Prognostic role of microRNAs in breast cancer: A systematic review

Eleni Zografos[1], Flora Zagouri[2], Despoina Kalapanida[2], Roubini Zakopoulou[2], Anastasios Kyriazoglou[2], Kleoniki Apostolidou[2], Maria Gazouli[1] and Meletios-Athanasios Dimopoulos[2]

[1]Department of Basic Medical Sciences, Laboratory of Biology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[2]Department of Clinical Therapeutics, Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Correspondence to: *Eleni Zografos, email: el_zogra@hotmail.com*

ABSTRACT

MicroRNAs (miRNAs) have been found to play an important role in breast cancer, functioning either as potential oncogenes or tumor suppressor genes, but their role in the prognosis of patients remains unclear. The aim of the present review study is to highlight recent preclinical and clinical studies performed on both circulating and tissue-specific miRNAs and their potential role as prognostic markers in breast cancer. We systematically searched the PubMed database to explore the prognostic value of miRNAs in breast cancer. After performing the literature search and review, 117 eligible studies were identified. We found that 110 aberrantly expressed miRNAs have been associated with prognosis in breast cancer. In conclusion, the collective data presented in this review indicate that miRNAs could serve as novel prognostic tools in breast cancer, while the clinical application of these findings has yet to be verified.

INTRODUCTION

Breast carcinoma is the leading cause of cancer death in women worldwide [1]. According to the GLOBOCAN 2018 worldwide estimates of cancer incidence and mortality, in 2018, about 2,088,849 new cases were diagnosed and approximately 626,679 women were predicted to die from the disease [2]. These data support the need to develop more efficient strategies for preventive intervention, evaluation of therapy, and prediction of prognosis [3].

Undoubtedly, TNM staging is of great prognostic value; however, considering all the limitations of the currently available prognostic strategies, it is overall recognized that new affordable more accurate methods indicative of molecular characteristics of tumors are needed to achieve personalized treatment [4]. Still, it remains difficult to achieve these goals, because of the absence of refined (sensitive and specific) biomarkers for disease monitoring and for addressing breast cancer on an individual basis.

MicroRNAs are a small class of endogenous, evolutionarily conserved, single-stranded noncoding RNAs, with a length of approximately 19–24 nucleotides [5]. Interaction between miRNAs and mRNAs, within the 3′untranslated region of the target genes, leads to the degradation or inhibition of mRNA translation [6]. In the past few years, miRNAs have attracted considerable attention in the cancer research field, due to their regulatory actions in multiple levels [7, 8]. Depending on the target gene that they regulate, miRNAs can either serve as "tumor suppressor miRs" by repressing oncogenes or as "onco-miRs" by targeting tumor suppressor genes. However, a number of miRNAs play both tumor suppressor and onco-miR roles depending on the cellular context and tumor type [9].

Particularly in breast cancer, microRNAs (miRNAs or miRs) have been proposed as promising biomarkers because they can be readily detected in tumor biopsies (non-circulating miRNAs) and can also be identified in blood, plasma, serum, and saliva (circulating miRNAs) [10].

Furthermore, circulating miRNAs are bound to lipoproteins such as HDL, are associated with Argonaute 2 (Ago2) protein, or are packaged into exosome-like microparticles, micro-vesicles, and apoptotic bodies [11]. Therefore, they are protected from endogenous RNAase activity, and hence they are reliable.

Several lines of evidence have proven that in breast cancer, the expression levels of miRNAs are altered due to key mechanisms, such as epigenetic control, transcription factors, or the effect of mutated proteins [10]. According to previous publications [12], miRNAs are considered as tumor suppressive or protective when they are down-regulated in cancer compared to their normal counterpart, or else, they are termed oncogenic miRNAs or onco-miRs. In this context, miRNAs are increasingly recognized as promising biomarkers, given the fact that they are easy to isolate, and they maintain their structural stability under different conditions of sample processing and isolation. A prognostic biomarker should indicate a patient's outcome, for example disease recurrence or disease progression, independent of the treatment regimen that was followed, and they are highly desirable for personalized or precise patient treatment [13].

The aim of the present review is to highlight recent preclinical and clinical studies performed on both circulating and tissue-specific miRNAs and therefore to identify their potential role as prognostic markers in breast cancer. We will particularly focus on the potential role of miRNAs in breast cancer prognosis, and on how miRNAs have the potential to answer actual clinical needs, such as identification of biomarkers for prognosis, in order to achieve the goal of individualized breast cancer treatment.

RESULTS

The search strategy retrieved 192 articles. Of these articles, 42 were irrelevant, 11 were reviews, eight (8) were meta-analyses, six (6) were retracted articles, three (3) were not in English, three (3) were duplicates, two (2) were comments and 117 were eligible. The aforementioned steps concerning the selection of studies are illustrated in detail in Figure 1. Therefore, a total of 117 articles were eligible for this systematic review and the prognostic role of 110 miRNA molecules is described (Table 1). Furthermore, we retrieved five studies, in which authors have identified six distinct microRNA signatures with prognostic value in breast cancer (Table 2).

According to our results, presented in Table 1, the majority of publications have not taken into account the distinct breast cancer subtypes during the development of their research protocol, since in 60.8% of studies breast cancer samples were not classified. The remaining 25.8% focused on Triple Negative Breast Cancer (TNBC) samples or involved Luminal A (5.0%), Luminal B (1.7%) and HER2-positive (1.7%) breast cancer samples. Of note, 5.0% of the selected studies accessed the prognostic value of miRNAs through experiments performed on breast

cancer cell lines. Different detection methods, as well as different sample types were used for the detection of the prognostic miRNA expression levels (i.e., paraffin-fixed, formalin-fixed, freshly frozen tumors, plasma or serum). Concerning the detection methods, quantitative reverse transcriptase real-time polymerase chain reaction (qRT-PCR) was used in 35,8% of the eligible studies, while in 21,7% of the studies qRT-PCR was performed along with Microarray analysis. Additionally, next generation Sequencing technologies (9,2%), in situ hybridization techniques (9,2%), luciferase report assays (6,7%) or a combination of various techniques (10,8%) were employed.

DISCUSSION

We conducted a comprehensive systematic literature review to unfold the utility of miRNA biomarkers that can be evaluated for predicting prognosis in breast cancer patients. We have identified 117 studies that investigate the potential correlation between miRNA profile expression in breast cancer tissue and in the circulation and their possible use as prognostic factors. Interestingly, most of the miRNAs found to be associated with prognosis in breast cancer, were assessed in only a single study. Six miRs (miR-10b, miR-200b, miR-21, miR-203, miR-375, and miR-210) were evaluated in at least four studies and the discussion will be mainly focused on these molecules, based on an effort to merely provide some important information on the most commonly researched molecules in accordance with our systematic literature review.

MiR-21 is one of the most extensively studied cancer-related miRNAs and its aberrant expression and deregulation may play a pivotal role in the majority of cancers [14]. miR-21 may serve as a key regulator of oncogenic processes, including tumor growth, migration, and invasion [15], through targeting the pro-apoptotic phosphatase and tensin homolog (PTEN) and promoting tumor cell proliferation [16]. According to our initial search results, we retrieved 12 studies [16-27] and four meta-analyses [28-31] focusing on the prognostic value of miR-21, which collectively provide robust evidence that miR-21 up-regulation is associated with poor outcomes in cancer patients.

Mir-210 has multiple functions in cancer cells and is involved in angiogenesis, cell cycle regulation, DNA damage repair, mitochondrial metabolism, and immune response [32]. According to our search results, including seven studies [33-39], high expression of miR-210 has been significantly associated with poor survival in patients with breast cancer. Notably, single miR-210 assay has been proposed as an independent prognostic factor in this disease.

Concerning miR-10b, it has been presented as a potential biomarker that could play a predictive role in lymph node metastases occurrence across TNBC and

in the incidence of high-grade tumors in non-TNBC cases [17]. Elevated expression of miR-10b in breast tumor tissue samples has been associated with adverse outcome, which is further supported from data derived from in vitro studies [40]. Finally, a survival analysis of 230 breast tissue samples has shown that high levels of miR-10b result to a short relapse free survival (RFS) of breast cancer, acting as an independent prognostic factor of RFS [41]. Our results, emphasize the oncogenic role of miR-10b and indicate that its high expression may be correlated with poor survival in breast cancer, while a recent metanalysis further strengthens our findings [30].
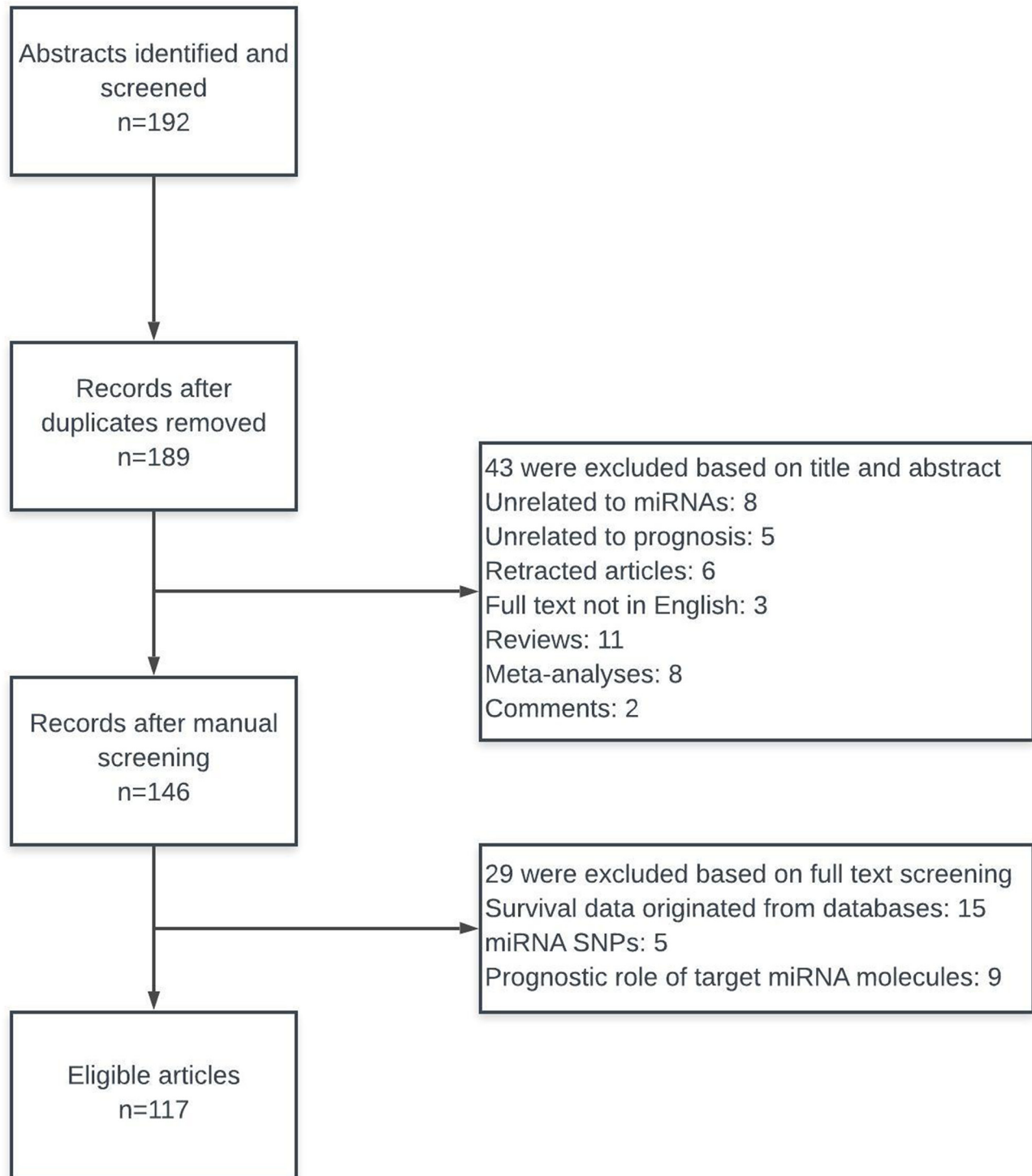

Figure 1: Flow diagram of the study selection process.

Table 1: List of prognostic microRNAs in breast cancer

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
let-7	BC not classified	qRT-PCR	potential prognostic biomarker as altered levels of miR-let-7 are associated with metastases risk	tumor suppressor	serum	[56]
let-7-3p	TNBC	NGS, qRT-PCR	independent prognostic factor for OS, DFS	onco-miR	FFPE	[57]
let-7b	luminal subtype	qRT-PCR, LNA-ISH, TMAs	independent prognostic factor for OS associated with luminal tumors	tumor suppressor	FFPE	[58]
let-7c/miR-99a/miR-125b cluster	estrogen-dependent BC cell line	Nanostring, qRT-PCR, luciferase assay	potential prognostic factor for OS in the luminal A subtype	tumor suppressor	cell lines	[59]
miR-1	ER-positive, stage IV BC	PCR, microarray, ISH, IHC	independent worse prognostic factor of DFS and BC-specific survival associated with stage, lymph node metastasis, distant metastasis, histological grade, ER status, PR status and Ki-67	onco-miR	FFPE	[60]
miR-7	BC not classified	qRT-PCR	potential prognostic factor for OS, DFS predictive of an adverse response to tamoxifen therapy	onco-miR	fresh frozen tissue, cell lines	[61]
miR-9	TNBC, BC not classified	qRT-PCR	prognostic factor of DFS and DMFS, OS	onco-miR	FFPE, fresh frozen tissue, cell lines	[62, 63]
miR-10b	BC not classified, TNBC	qRT-PCR	independent prognostic factor for DFS associated with distant metastasis, occurrence in TNBC, associated with genico-obstetric history	onco-miR	FFPE, fresh frozen tissue, cell lines	[17, 40, 41, 64]
miR-15a	TNBC	qRT-PCR	prognostic factor for OS, DFS	tumor suppressor	fresh frozen tissue	[65]
miR-16	triple possitive BC	qRT-PCR, Western blot, luciferase report assay, MTS assay	potentially tumor suppressive effect on cancer progression of ER positive breast cancers, impairment of cell proliferation	tumor suppressor	FFPE	[45]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-19a	newly diagnosed IBC stage III, IBC stage IV, non-IBC stage II-IV and HER2+ BC	qRT-PCR	potential prognostic factor for OS, DFS in patients with metastatic HER2(+) IBC.	tumor suppressor	serum, cell lines	[66]
miR-19b	BC not classified	qRT-PCR	prognostic factor for OS associated with distant metastasis and TNM stage	onco-miR	fresh frozen tissue, cell lines	[67]
miR-20b-5p	BC not classified	microRNA arrays	potential prognostic factor for DFS, correlated with the presence of breast tumor interstitial fluid	onco-miR	FFPE, interstitial breast tumor fluids, serum	[68]
miR-21	stage II/III BC, HER2 positive, TNBC	qRT-PCR, microarray, luciferase report assay	independent prognostic factor of OS, DFS, prognostic biomarker for resistance to trastuzumab, to predict lymph node metastases occurrence in TNBC, to predict high grade in non TNBC possible, prognostic factor in daughter of patients, associated with genico-obstetric history	onco-miR	FFPE, serum, fresh frozen tissue, cell lines	[16-27]
miR-22	BC not classified	qRT-PCR, ISH, luciferase report assay	potential prognostic factor for OS, DFS, associated with EMT/metastasis	both	FFPE, cell lines	[69, 70]
miR-24-2*.	BC cell lines	qRT-PCR	associated with tumor suppressive activity through the suppression of cellular survival	tumor suppressor	cell lines, fresh frozen mouse tissue	[71]
mir-24-3p	BC not classified (stage I-III)	Nanostring technology	potential prognostic biomarker of occult metastasis	onco-miR	plasma	[72]
miR-27a	BC not classified	ISH, IHC	independent prognostic factor for OS, DFS	onco-miR	FFPE	[73]
miR-27b-3p	TNBC	qRT-PCR	independent prognostic factor for OS, DMF survival	onco-miR	FFPE	[74]
miR-29a	BC not classified	qRT-PCR, microarray	asocciated with poor response and chemotherapy resistance	onco-miR	FFPE, cell lines	[75]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-29b	lobular and ductal subtypes	qRT-PCR	prognostic factor for OS, DFS	tumor suppressor	fresh frozen tissue	[76, 77]
miR-30a	TNBC	NGS, qRT-PCR, microarray, luciferase assay	independent prognostic factor for OS, DFS	tumor suppressor	FFPE, cell lines	[57, 78]
miR-30a-3p	TNBC	qRT-PCR	prognostic factor for OS, RFS	tumor suppressor	FFPE	[57]
miR-30a-5p	TNBC	NGS	prognostic factor for OS, RFS	tumor suppressor	FFPE	[57]
miR-30c-5p	TNBC	qRT-PCR	prognostic factor for RFS	tumor suppressor	FFPE	[57]
miR-30e*	ESR1-/ ERBB2- tumors	microarray, ISH	prognostic factor for DFS	tumor suppressor	fresh frozen tissue	[79]
miR-34a	BC not classified TNBC	qRT-PCR, TMAs	prognostic factor for OS, associated with response and chemotherapy resistance	both	FFPE, plasma, cell lines	[75, 80, 81]
miR-34b	TNBC	qRT-PCR	prognostic factor for OS, DFS	onco-miR	FFPE	[82]
miR-34c	TNBC	qRT-PCR	independent risk factor for OS	tumor suppressor	Plasma	[81]
miR-93-5p	BC not classified	microRNA arrays	potential prognostic factor for DFS, correlated with the presence of breast tumor interstitial fluid	onco-miR	FFPE, interstitial breast tumor fluids, serum	[68]
miR-95-3p	TNBC	qRT-PCR	prognostic factor for OS, RFS in patients treated with anthracycline-based chemotherapy	onco-miR	FFPE	[57]
miR-96	BC cell lines	qRT-PCR	potential prognostic factor for OS associated with EMT and regulation of growth factors involved in G1/S-phase transition	onco-miR	cell lines	[44]
miR-99a	BC not classified	qRT-PCR	potential prognostic factor for OS, independent risk factor for breast cancer	tumor suppressor	serum	[83]
miR-122	BC not classified (stage II-III)	qRT-PCR, NGS	potential prognostic factor for disease relapse, predictor of metastasis	onco-miR	serum	[84]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-124	BC not classified	qRT-PCR	prognostic factor for OS associated with advanced TNM stage, lymph node metastasis and poorer pathological differentiation, associated with age at diagnosis (>50 years old)	tumor suppressor	FFPE, fresh frozen tissue	[85, 86]
miR-125a-5p	BC not classified	microarray, qRT-PCR, luciferase assay, ISH, IHC	potential prognostic factor for OS, progression-free survival (PRS)	tumor suppressor	serum, cell lines	[87]
miR-125b	HER2 positive BC, stage II/III	qRT-PCR, ISH	prognostic factor for OS, DFS, associated with aromatase inhibitor esistant breast cancers	onco-miR	FFPE, serum, cell lines	[26, 88, 89]
miR-126-5p	BC not classified	microRNA arrays	potential prognostic factor for DFS	onco-miR	FFPE, interstitial breast tumor fluids, serum	[68]
miR-127	BC not classified	qRT-PCR	prognostic factor of OS	tumor suppressor	fresh frozen tissue, cell lines	[90]
miR-128-3p	TNBC	qRT-PCR	prognostic factor for RFS	tumor suppressor	FFPE	[57]
miR-129-5p	BC not classified	qRT-PCR, luciferase report assay	potential prognostic factor for OS, DFS, associated with EMT	tumor suppressor	FFPE, fresh frozen tissue, cell lines	[91]
miR-133a	BC not classified	qRT-PCR, TMA, ISH, Luciferase assay	potential prognostic factor for DFS associated with migration and invasion	tumor suppressor	FFPE, fresh frozen tissue, cell lines	[92]
miR-140	BC not classified	qRT-PCR, microarray	asocciated with poor response and chemotherapy resistance	onco-miR	FFPE, cell lines	[75]
miR-141	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS associated with circulating tumor cells status	onco-miR	plasma	[33, 34]
miR-143	Triple possitive BC	qRT-PCR, Western blot, luciferase report assay, MTS assay	potentially tumor suppressive effect on cancer progression of ER positive breast cancers, impairment of cell proliferation	tumor suppressor	FFPE	[45]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-144	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS	tumor suppressor	plasma	[34]
miR-145	BC not classified	qRT-PCR	potential prognostic factor for DFS, OS (3-year survival rate)	tumor suppressor	fresh frozen tissue	[93, 94]
miR-146a	BRCA1-deficient TNBC tumors	qRT-PCR	potential prognostic factor for OS	tumor suppressor	FFPE, cell lines	[95]
miR-148a	TNBC	qRT-PCR, microarray	potential prognostic factor for OS associated with metastasis	tumor suppressor	Cell lines, mouse models	[96]
miR-155	TNBC, BC not classified	qRT-PCR, microarray, luciferase report assay	prognostic factor of DMFS, associated with lymph node metastasis	both	FFPE, fresh frozen tissue, cell lines	[62, 97]
miR-182	BC not classified, TNBC	qRT-PCR	potential prognostic factor to predict lymph node metastases occurrence in TNBC, associated with genico-obstetric history, related with hormonal receptors	onco-miR	FFPE, serum	[17, 98]
miR-183/182/96 cluster	BC not classified	qRT-PCR, ISH	potential prognostic factor for OS, DFS	onco-miR	breast tissues not classified, cell lines	[99]
miR-187	BC not classified	TMA, ISH	independent prognostic factor FOR breast cancer–specific survival (BCSS)	onco-miR	FFPE, cell lines	[100]
miR-193b	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS	onco-miR	plasma	[34]
miR-195-5p	BC not classified	microRNA arrays	potential prognostic factor for DFS	onco-miR	FFPE, interstitial breast tumor fluids, serum	[68]
miR-199a-5p	TNBC	NGS	prognostic factor for OS	tumor suppressor	FFPE	[57]
miR-199b-5p	BC not classified (-II stage)	qRT-PCR, assays in vitro	potential prognostic factor for OS associated with TNM stage and lymph node metastasis	tumor suppressor	fresh frozen tissue and cell lines	[101]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-200a	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS, associated with circulating tumor cells status, potential to detect the onset of metastasis	onco-miR	plasma	[33, 34]
miR-200b	BC not classified	qRT-PCR, microRNA arrays, ISH, TMA, luciferase report assay	potential prognostic factor for OS (independent), PFS associated with advanced clinical stage, metastasis, cell proliferation, apoptosis, cell cycle distribution and circulating tumor cells status, potential to detect the onset of metastasis	both	FFPE, plasma, cell lines	[33, 34, 46, 47]
miR-200c	BC not classified	qRT-PCR, microRNA arrays	prognostic factor of OS, DFS, potential to detect the onset of metastasis, associated with circulating tumor cells status	onco-miR	fresh frozen tissue, plasma	[33, 34, 102]
miR-200c/141 cluster	BC not classified, TNBC	qRT-PCR, CAT reporter assay, siRNA transfection, Western blot	poor prognostic factor in TNBC, promoting metastasis	onco-miR	FFPE, cell lines, xenograft animal model	[103]
miR-203	BC not classified, ER positive BC	microRNA arrays, qRT-PCR, Western blot, luciferase report assay, MTS assay	potential prognostic factor for OS, PFS associated with EMT and circulating tumor cells status	both	FFPE, plasma, cell lines	[33, 34, 44, 45]
miR-203-5p	TNBC	NGS	prognostic factor for OS	onco-miR	FFPE	[57]
miR-203a	ductal in situ, invasive ductal and lobular carcinoma	qRT-PCR	potential prognostic marker associated with increased stage in invasive lobular carcinomas	tumor suppressor	FFPE	[104]
miR-204	BC not classified	qRT-PCR	potential prognostic factor for OS, DFS, correlated with chemotherapeutic resistance	tumor suppressor	FFPE	[105]
miR-205	BC not classified	qRT-PCR, LNA-ISH, TMAs, IHC	potential prognostic factor for OS associated with tumours of ductal morphology, for OS and DFS in early breast cancer	tumor suppressor	FFPE	[21, 58]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-206	BC not classified	qRT-PCR, luciferase report assay	potential prognostic factor for OS	both	fresh frozen tissue, cell lines	[94, 106, 107]
miR-210	early first primary BC, TNBC	qRT-PCR, microarray	independent prognostic factor for OS, DFS, associated with poor clinical outcome in ER-positive, tamoxifen-treated BC patients, involved in cell proliferation, migration and invasion, Potential to detect the onset of metastasis prior to clinical diagnosis, associated with circulating tumor cells status	onco-miR	FFPE, fresh frozen tissue, plasma, cell lines (Breast cancer and tumor-educated macrophages)	[33-39]
miR-210-3p	BC cell lines	qRT-PCR	potential prognostic factor for OS associated with EMT and regulation of growth factors involved in G1- to S-phase transition	onco-miR	cell lines	[44]
miR-215	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS, Potential to detect the onset of metastasis prior to clinical diagnosis	tumor suppressor	plasma	[34]
miR-218	BC not classified	qRT-PCR	prognostic factor for OS associated with lymph node metastases, higher grades,	tumor suppressor	fresh frozen tissue	[108]
miR-221	BC not classified	qRT-PCR	prognostic factor for DFS, OS, RFS	onco-miR	FFPE, fresh frozen tissue, cell lines	[41, 63, 109]
miR-221-3p	TNBC	qRT-PCR	prognostic factor for DFS	tumour suppressor	FFPE, cell lines	[110]
miR-222	BC not classified	qRT-PCR, TMA	potential prognostic factor related to lymph node metastasis, down-regulation of the estrogen receptor, EMT, tumor progression, poor response and chemotherapy resistance	onco-miR	FFPE, fresh frozen tissue, cell lines	[75, 109]
miR-222-3p	BC not classified	qRT-PCR, microarray	independent prognostic factor for DFS postoperatively	onco-miR	serum	[111]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-301a	BC not classified, TNBC	qRT-PCR, microarray, ISH	prognostic factor for DFS, OS	onco-miR	FFPE	[112, 113]
miR-320a	BC not classified	chromogenic ISH	potential prognostic factor for OS for invasive breast cancer	tumor suppressor	FFPE	[114]
miR-324-5p	TNBC	NGS	prognostic factor for OS	onco-miR	FFPE	[57]
miR-329	BC not classified	qRT-PCR	independent prognostic factor for OS	tumor-suppressor	serum, fresh frozen tissue, cell lines	[115]
miR-330-3p	BC not classified	qRT-PCR	potential prognostic factor for OS	onco-miR	fresh frozen tissue	[116]
miR-339-5p	BC not classified	qRT-PCR, TMA, ISH	independent prognostic factor for OS, DFS	tumor suppressor	FFPE, cell lines	[117]
miR-361-5p	BC not classified, TNBC	TMAs, ISH	prognostic factor for DFS	tumor suppressor	FFPE	[118]
miR-365	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS	miR-365, onco-miR	plasma	[34]
miR-370	BC not classified	qRT-PCR, TMA	potential prognostic factor for DFS	onco-miR	FFPE	[119]
miR-374a	BC not classified, IDC stage II	qRT-PCR, TMAs, Luciferase assay, MTT assays, IHC	potential prognostic factor for DFS, contributes to tumorigenicity and progression	onco-miR	FFPE, fresh frozen tissue, cell lines, xenograft mouse models	[120, 121]
miR-375	BC not classified, stage II-III locally advanced and IBC patients	qRT-PCR, microRNA arrays, NGS	potential prognostic factor for OS, PFS associated with circulating tumor cells status, related to hormonal receptors	both	serum, plasma	[33, 34, 84, 98]
miR-409-3p	BC not classified	qRT-PCR	independent prognostic factor for OS associated with advanced TNM stage, lymph node metastasis, and poorer pathological differentiation	tumor suppressor	fresh frozen tissue	[122]
miR-423	BC not classified	qRT-PCR, microarray	asocciated with poor response and chemotherapy resistance	onco-miR	FFPE, cell lines	[75]
miR-429	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS	miR-429 onco-miR	plasma	[34]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-451	BC cell lines	qRT-PCR	potential factor associated with cell survival and endocrine resistance	tumor suppressor	cell lines	[123]
miR-454	BC not classified (stage I-III)	TMA, ISH	potential prognostic factor for OS (especially in TNBC) and DFS, associated with response to anthracycline	onco-miR	FFPE	[124]
miR-454-3p	BC not classified	microRNA arrays	potential prognostic factor for DFS	onco-miR	FFPE, interstitial breast tumor fluids, serum	[68]
miR-486-5p	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, Potential to detect the onset of metastasis prior to clinical diagnosis	tumor suppressor	plasma	[34]
miR-493	TNBC	TMAs, ISH	prognostic factor for DFS	tumour suppressor	FFPE	[125]
miR-494	node-negative BC	ISH	8.5-fold risk of breast cancer death (association trend-not clinical significance)	tumour suppressor	fresh frozen tissue	[126]
miR-497	BC not classified, TNBC	qRT-PCR, luciferase assay	potential prognostic factor for OS	tumor suppressor	fresh frozen tissue, cell lines, orthotopic mouse models	[127, 128]
miR-548c-5p	TNBC	qRT-PCR, ISH	independent prognostic factor for OS, DFS	onco-miR	FFPE	[39]
miR-574	BC not classified	qRT-PCR, microarray	asocciated with poor response and chemotherapy resistance	onco-miR	FFPE, cell lines	[75]
miR-574-3p	BC not classified	qRT-PCR, NGS	potential prognostic factor for OS, DFS	tumor suppressor	FFPE	[129]
miR-588	BC not classified	qRT-PCR	prognostic factor of OS	tumour suppressor	fresh frozen tissue, cell lines	[130]
miR-590-3p	BC cell lines	qRT-PCR, luciferase report assay	associated with breast cancer cells viability, growth and apoptosis	tumor suppressor	cell lines	[131]
miR-597	BC not classified	qRT-PCR	prognostic factor of OS	tumor suppressor	fresh tissue	[132]
miR-601	BC not classified	qRT-PCR	prognostic factor for DFS associated with cell proliferation and metastasis	tumor suppressor	FFPE, cell lines	[133]

*(**Continued**)*

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-638	BC not classified, BRCA1-deficient TNBC tumors	qRT-PCR	independent prognostic factor for OS associated with lymph node metastasis and TNM stage	tumor suppressor	FFPE, fresh frozen, cell lines	[95, 134]
miR-644a	BC cell lines	qRT-PCR, luciferase report assay	associated with tumor progression and distant metastasis-free survival	tumor suppressor	cell lines	[135]
miR-660-5p	BC not classified	qRT-PCR, NGS	potential prognostic factor for OS, DFS	onco-miR	FFPE	[129]
miR-711	BC not classified	qRT-PCR	independent prognostic factor for OS, DFS, associated with breast cancer cells' proliferation, colony formation, invasion	onco-miR	FFPE, cell lines	[136]
miR-744	BC not classified	qRT-PCR, microarray	associated with poor response and chemotherapy resistance	onco-miR	FFPE, cell lines	[75]
miR-801	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS associated with circulating tumor cells status	onco-miR	plasma	[33, 34]
miR-874	BC not classified	qRT-PCR	prognostic factor for OS	tumour suppressor	fresh frozen tissue, cell lines	[137]
miR-940	IDC, TNBC	qRT-PCR	prognostic factor for OS	tumor suppressor	serum	[138]
miR-1179	BC not classified	RT-PCR	independent prognostic factor for OS	tumor suppressor	breast tissue not classified, cell lines	[139]
miR-1247-5p	BC not classified	qRT-PCR	independent prognostic indicator for DFS, OS	tumor suppressor	FFPE, fresh frozen tissue, cell lines	[140, 141]
miR-1260	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS	onco-miR	plasma	[34]
miR-1274a	BC not classified	microRNA arrays, qRT-PCR	potential prognostic factor for OS, PFS	onco-miR	plasma	[34]
miR-1274b	BC not classified	microRNA arrays	potential prognostic factor for DFS	onco-miR	FFPE, interstitial breast tumor fluids, serum	[68]

(*Continued*)

Prognostic microRNA	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-1825	BC not classified	microRNA arrays	potential prognostic factor for DFS	onco-miR	FFPE, interstitial breast tumor fluids, serum	[68]
miR-3178	BC not classified	qRT-PCR, microarray	associated with poor response and chemotherapy resistance	onco-miR	FFPE, cell lines	[75]
miR-4653-3p	HR+ BC (stage I~III)	qRT-PCR	potential prognostic biomarker for DFS for patients treated with adjuvant tamoxifen	tumor suppressor	FFPE	[142]
miR-6780b	BC not classified	qRT-PCR, microarray	associated with poor response and chemotherapy resistance	onco-miR	FFPE, cell lines	[75]

Abbreviations: quantitative reverse transcriptase real-time polymerase chain reaction (qRT-PCR), In situ hybridization (ISH), locked nucleic acid probe in situ hybridization (LNA-ISH), Immunohistochemistry (IHC), epithelial-mesenchymal transition (EMT), formalin-fixed paraffin embedded (FFPE), Next Generation Sequencing (NGS), overall survival (OS), relapse free survival (RFS), disease free survival (DFS), progress free survival (PFS), breast cancer (BC), triple negative breast cancer (TNBC), Inflammatory breast cancer (IBC), Invasive Ductal Carcinoma (IDC), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER2).

MiR-200 family members function as regulators of the epithelial to mesenchymal transition (EMT), which is one of the initial steps in tumor metastasis [42]. Specifically, miR-200b and miR-203 have both been characterized as tumor suppressors in multiple breast tumor types [43]. However, there seems to be an inconsistency in the existing literature, since we retrieved two studies that have found that higher expression of circulating miR-200b and miR-203 are associated with worse outcome [33, 34], further substantiated by a study on breast cancer cell lines [44]. However, other studies on breast cancer tissue samples and cell lines presented inverse results [45-47]. These discrepancies exhibit the diverse regulatory roles of miR-200 family members, depending on the cellular context and type of biological sample (blood VS tissue), and highlight the potential prognostic impact of these EMT regulating miRNA molecules in breast cancer.

Furthermore, our search retrieved five studies that have found six miRNA signatures to be useful for predicting the outcome of breast cancer [48-52]. Coordinated regulation of multiple miRNAs of potential prognostic value, has helped researchers identify panels of prognostic microRNAs for breast cancer. The discovery of microRNA expression signatures shows considerable promise for determining the prognosis of individuals with breast cancer. Similar miRNA signatures have been identified in a variety of other cancers, including acute myeloid leukemia, chronic lymphocytic leukemia, colon cancer, pancreatic cancer, and non-small cell lung cancer [53]. These reports highlight that this class of RNA molecules is showing substantial potential to be used as prognostic biomarkers for cancer.

Among the limitations of this effort, it should be stressed that this process was essentially driven by the search algorithm, which focused mainly on titles of the published literature, in an effort to provide more relevant results. Furthermore, clear heterogeneity was observed in our results, due to differences in patient characteristics (ethnicity, age, tumor stage, grade and subtype) and the use of different isolation and detection methods, cut-off values for miRNA expression levels, sample preparation methods and sample types (i.e., paraffin-fixed, formalin-fixed, freshly frozen tumors, plasma or serum).

Based on the results of this systematic review, we consider that miRNA detection may address the need for independent, easily accessible, prognostic molecular markers for breast cancer management in clinical practice, by assessing the impact of aberrant miRNA expression on patients' survival. Our work sums up all the available data on prognostic miRNAs and can also act as a valuable reference point for future studies. Furthermore, while prognostic studies can assist in answering important questions concerning specific patient outcomes, their vigorous and careful design is a necessary condition for ensuring the reliability of results [54]. It should be stressed out that the thorough validation of prognostic factors is a necessary and unavoidable process in order to maximize

Table 2: List of prognostic microRNA signatures in breast cancer

miRNA signature	Breast cancer type	Detection method	Prognostic value	Role	Biological sample	References
miR-183-5p, miR-194-5p, miR-1285-5p signature	BC not classified	microarrays, qRT-PCR	potential prognostic factor for OS in young breast cancer patients (age <35 years)	miR-183-5p onco-miR miR-194-5p onco-miR miR-1285-5p tumor suppressor	FFPE	[48]
miR-21, miR-30c, miR-181a, miR-181c, miR-125b, miR-7, miR-200a, miR-135b, miR-22 and miR-200c signature	HR positive, HER2 negative	qRT-PCR	potential prognostic factor for DRFS	10-miRNA-based classifier as a prognostic model	FFPE	[49]
miR-155, miR-493, miR-30e and miR-27a signature	TNBC	qRT-PCR, IHC	potential prognostic factor for OS associated with taxanes resistance	miR-155 tumor suppressor miR-493 tumor suppressor miR-30e onco-miR miR-27a onco-miR	FFPE	[50]
miR-16, 155, 125b, 374a signature	TNBC	qRT-PCR	potential prognostic factor for OS	miR-16 tumor suppressor miR-155 tumor suppressor miR-125b onco-miR miR-374a tumor suppressor	FFPE	[51]
miR-16, 125b, 374a, 374b, 421, 655, 497 signature	TNBC	qRT-PCR	potential prognostic factor for DDFS	miR-16 tumor suppressor miR-125b onco-miR miR-374a tumor suppressor miR-374b tumor suppressor miR-421 onco-miR miR-655 onco-miR miR-497 tumor suppressor	FFPE	[51]
miR-191-5p, miR-214-3p, miR-451a, and miR-489 signature	BC not classified	qRT-PCR, microarray	independent prognostic factor for OS, DFS	miR-191-5p onco-miR miR-214-3p tumor suppressor miR-451a tumor suppressor miR-489 tumor suppressor	FFPE, cell lines	[52]

Abbreviations: breast cancer (BC), quantitative reverse transcriptase real-time polymerase chain reaction (qRT-PCR), formalin-fixed paraffin embedded (FFPE), overall survival (OS), distant disease-free survival (DDFS), distant recurrence free survival (DRFS).

certainty in predicting future breast cancer patients' outcomes. Therefore, extensive validation studies focusing on particular miRNAs or miRNA signatures should be performed to relate baseline clinical and experimental variables to outcome. Eventually, all the reviewed molecular studies may help in bringing prognostic miRNAs closer to the clinical practice.

MATERIALS AND METHODS

Methods of search strategy and study eligibility

This systematic review was conducted in accordance with the PRISMA guidelines [55] and in line with the a priori protocol agreed on and signed by EZ and FZ. Eligible studies were sought in PubMed without any restriction of publication language; the end-of-search date was January 28, 2019. The following search algorithm was used: breast[ti] AND (carcinoma OR carcinomas OR cancer OR cancers OR neoplasm OR neoplasms) AND (microRNA[ti] OR miR[ti] OR miRNA[ti] OR microRNAs[ti] OR miRs[ti] OR miRNAs[ti]) AND (prognosis[ti] OR prognostic[ti] OR survival[ti] OR outcome[ti] OR mortality[ti]). Eligible articles included studies examining the prognostic role of microRNAs in breast cancer. Only prospective and retrospective studies as well as case reports were considered eligible. In instances where multiple (overlapping) publications stemming from the same study were identified, the larger size study and the one with longer follow-up were included, unless the reported outcomes were mutually exclusive. Authors working independently and blindly to each other in pairs (E.Z., F.Z.) performed the selection of eligible studies; in case of disagreement, consensus with the whole team was reached.

Data extraction

The extraction of data comprised general information, including the name of the miRNA molecule, the breast cancer type in which its expression was determined, method of detection, the sample type that was used, its prognostic value in breast cancer, its function in cancer (onco-miR or tumor suppressor-miR) and the author-year of publication. Data were independently extracted and analyzed by a pair of reviewers (E.Z. and F.Z.), with one reviewer being blinded to the other; if needed, the final decision was reached by a team consensus.

Eligible literature met the following criteria: (1) measured miR expression levels in tumor or blood samples or human cell lines and (2) only articles in English. Publications were excluded if they had one or more of the following criteria: (1) studies referring to the prognostic role of single nucleotide polymorphisms (SNPs) in miRNA genes affecting their function; (2) studies that refer to the prognostic role of target miRNA molecules (molecules regulated by miRs); (3) studies based solely on a bioinformatics approach or a computational algorithm, with survival data originated from databases without subsequent biological validation and (4) review papers, meta-analyses, comments, letters or duplicate publications.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

REFERENCES

1. World Health Organization. Media Centre-Cancer (Fact Sheet). https://www.who.int/mediacentre/factsheets/fs297/en/. 2017. Accessed Feb 1 2017.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68:394–424. https://doi.org/10.3322/caac.21492. [PubMed]

3. Hinestrosa MC, Dickersin K, Klein P, Mayer M, Noss K, Slamon D, Sledge G, Visco FM. Shaping the future of biomarker research in breast cancer to ensure clinical relevance. Nat Rev Cancer. 2007; 7:309–15. https://doi.org/10.1038/nrc2113. [PubMed]

4. Nalejska E, Mączyńska E, Lewandowska MA. Prognostic and predictive biomarkers: tools in personalized oncology. Mol Diagn Ther. 2014; 18:273–84. https://doi.org/10.1007/s40291-013-0077-9. [PubMed]

5. Wang J, Zhang KY, Liu SM, Sen S. Tumor-associated circulating microRNAs as biomarkers of cancer. Molecules. 2014; 19:1912–38. https://doi.org/10.3390/molecules19021912. [PubMed]

6. Yoruker EE, Aydoğan F, Gezer U, Saip P, Dalay N. Analysis of circulating microRNAs during adjuvant chemotherapy in patients with luminal A breast cancer. Mol Clin Oncol. 2015; 3:954–58. https://doi.org/10.3892/mco.2015.567. [PubMed]

7. McGuire A, Brown JA, Kerin MJ. Metastatic breast cancer: the potential of miRNA for diagnosis and treatment monitoring. Cancer Metastasis Rev. 2015; 34:145–55. https://doi.org/10.1007/s10555-015-9551-7. [PubMed]

8. Goh JN, Loo SY, Datta A, Siveen KS, Yap WN, Cai W, Shin EM, Wang C, Kim JE, Chan M, Dharmarajan AM, Lee AS, Lobie PE, et al. microRNAs in breast cancer: regulatory roles governing the hallmarks of cancer. Biol Rev Camb Philos Soc. 2016; 91:409–28. https://doi.org/10.1111/brv.12176. [PubMed]

9. Muluhngwi P, Klinge CM. Identification of miRNAs as biomarkers for acquired endocrine resistance in breast cancer. Mol Cell Endocrinol. 2017; 456:76–86. https://doi.org/10.1016/j.mce.2017.02.004. [PubMed]

10. Bertoli G, Cava C, Castiglioni I. MicroRNAs: New Biomarkers for Diagnosis, Prognosis, Therapy Prediction and Therapeutic Tools for Breast Cancer. Theranostics. 2015; 5:1122–43. https://doi.org/10.7150/thno.11543. [PubMed]

11. Arroyo JD, Chevillet JR, Kroh EM, Ruf IK, Pritchard CC, Gibson DF, Mitchell PS, Bennett CF, Pogosova-Agadjanyan EL, Stirewalt DL, Tait JF, Tewari M. Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma. Proc Natl Acad Sci U S A. 2011; 108:5003–08. https://doi.org/10.1073/pnas.1019055108. [PubMed]

12. Liu Y, Zhang Y, Li Q, Li J, Ma X, Xing J, Rong S, Wu Z, Tian Y, Li J, Jia L. MiRNAs Predict the Prognosis of Patients with Triple Negative Breast Cancer: A Meta-Analysis. PLoS One. 2017; 12:e0170088. https://doi.org/10.1371/journal.pone.0170088. [PubMed]

13. Li G, Hu J, Hu G. Biomarker Studies in Early Detection and Prognosis of Breast Cancer. Adv Exp Med Biol. 2017; 1026:27–39. https://doi.org/10.1007/978-981-10-6020-5_2. [PubMed]

14. Pfeffer SR, Yang CH, Pfeffer LM. The Role of miR-21 in Cancer. Drug Dev Res. 2015; 76:270–77. https://doi.org/10.1002/ddr.21257. [PubMed]

15. Selcuklu SD, Donoghue MT, Spillane C. miR-21 as a key regulator of oncogenic processes. Biochem Soc Trans. 2009; 37:918–25. https://doi.org/10.1042/BST0370918. [PubMed]

16. Dong G, Liang X, Wang D, Gao H, Wang L, Wang L, Liu J, Du Z. High expression of miR-21 in triple-negative breast cancers was correlated with a poor prognosis and promoted tumor cell in vitro proliferation. Med Oncol. 2014; 31:57. https://doi.org/10.1007/s12032-014-0057-x. [PubMed]

17. Medimegh I, Omrane I, Privat M, Uhrhummer N, Ayari H, Belaiba F, Benayed F, Benromdhan K, Mader S, Bignon IJ, Elgaaied AB. MicroRNAs expression in triple negative vs non triple negative breast cancer in Tunisia: interaction with clinical outcome. PLoS One. 2014; 9:e111877. https://doi.org/10.1371/journal.pone.0111877. [PubMed]

18. Yan LX, Huang XF, Shao Q, Huang MY, Deng L, Wu QL, Zeng YX, Shao JY. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. RNA. 2008; 14:2348–60. https://doi.org/10.1261/rna.1034808. [PubMed]

19. Qian B, Katsaros D, Lu L, Preti M, Durando A, Arisio R, Mu L, Yu H. High miR-21 expression in breast cancer associated with poor disease-free survival in early stage disease and high TGF-beta1. Breast Cancer Res Treat. 2009; 117:131–40. https://doi.org/10.1007/s10549-008-0219-7. [PubMed]

20. Lee JA, Lee HY, Lee ES, Kim I, Bae JW. Prognostic Implications of MicroRNA-21 Overexpression in Invasive Ductal Carcinomas of the Breast. J Breast Cancer. 2011; 14:269–75. https://doi.org/10.4048/jbc.2011.14.4.269. [PubMed]

21. Markou A, Yousef GM, Stathopoulos E, Georgoulias V, Lianidou E. Prognostic significance of metastasis-related microRNAs in early breast cancer patients with a long follow-up. Clin Chem. 2014; 60:197–205. https://doi.org/10.1373/clinchem.2013.210542. [PubMed]

22. Toraih EA, Mohammed EA, Farrag S, Ramsis N, Hosny S. Pilot Study of Serum MicroRNA-21 as a Diagnostic and Prognostic Biomarker in Egyptian Breast Cancer Patients. Mol Diagn Ther. 2015; 19:179–90. https://doi.org/10.1007/s40291-015-0143-6. [PubMed]

23. Usmani A, Shoro AA, Memon Z, Hussain M, Rehman R. Diagnostic, prognostic and predictive value of MicroRNA-21 in breast cancer patients, their daughters and healthy individuals. Am J Cancer Res. 2015; 5:2484–90. [PubMed]

24. Yan LX, Liu YH, Xiang JW, Wu QN, Xu LB, Luo XL, Zhu XL, Liu C, Xu FP, Luo DL, Mei P, Xu J, Zhang KP, Chen J. PIK3R1 targeting by miR-21 suppresses tumor cell migration and invasion by reducing PI3K/AKT signaling and reversing EMT, and predicts clinical outcome of breast cancer. Int J Oncol. 2016; 48:471–84. https://doi.org/10.3892/ijo.2015.3287. [PubMed]

25. Yadav P, Mirza M, Nandi K, Jain SK, Kaza RC, Khurana N, Ray PC, Saxena A. Serum microRNA-21 expression as a prognostic and therapeutic biomarker for breast cancer patients. Tumour Biol. 2016; 37:15275–82. https://doi.org/10.1007/s13277-016-5361-y. [PubMed]

26. Liu B, Su F, Chen M, Li Y, Qi X, Xiao J, Li X, Liu X, Liang W, Zhang Y, Zhang J. Serum miR-21 and miR-125b as markers predicting neoadjuvant chemotherapy response and prognosis in stage II/III breast cancer. Hum Pathol. 2017; 64:44–52. https://doi.org/10.1016/j.humpath.2017.03.016. [PubMed]

27. Badr M, Said H, Louka ML, Elghazaly HA, Gaballah A, Atef Abd El Mageed M. MicroRNA-21 as a predictor and prognostic factor for trastuzumab therapy in human epidermal growth factor receptor 2-positive metastatic breast cancer. J Cell Biochem. 2019; 120:3459–66. https://doi.org/10.1002/jcb.27620. [PubMed]

28. Pan F, Mao H, Deng L, Li G, Geng P. Prognostic and clinicopathological significance of microRNA-21 overexpression in breast cancer: a meta-analysis. Int J Clin Exp Pathol. 2014; 7:5622–33. [PubMed]

29. Wang Y, Zhang Y, Pan C, Ma F, Zhang S. Prediction of poor prognosis in breast cancer patients based on microRNA-21 expression: a meta-analysis. PLoS One. 2015; 10:e0118647. https://doi.org/10.1371/journal.pone.0118647. [PubMed]

30. Tang Y, Zhou X, Ji J, Chen L, Cao J, Luo J, Zhang S. High expression levels of miR-21 and miR-210 predict unfavorable survival in breast cancer: a systemic review and meta-analysis. Int J Biol Markers. 2015; 30:e347–58. https://doi.org/10.5301/jbm.5000160. [PubMed]

31. Jinling W, Sijing S, Jie Z, Guinian W. Prognostic value of circulating microRNA-21 for breast cancer: a systematic review and meta-analysis.

Artif Cells Nanomed Biotechnol. 2017; 45:1–6. https://doi.org/10.1080/21691401.2016.1216856. [PubMed]

32. Qin Q, Furong W, Baosheng L. Multiple functions of hypoxia-regulated miR-210 in cancer. J Exp Clin Cancer Res. 2014; 33:50. https://doi.org/10.1186/1756-9966-33-50. [PubMed]

33. Madhavan D, Zucknick M, Wallwiener M, Cuk K, Modugno C, Scharpff M, Schott S, Heil J, Turchinovich A, Yang R, Benner A, Riethdorf S, Trumpp A, et al. Circulating miRNAs as surrogate markers for circulating tumor cells and prognostic markers in metastatic breast cancer. Clin Cancer Res. 2012; 18:5972–82. https://doi.org/10.1158/1078-0432.CCR-12-1407. [PubMed]

34. Madhavan D, Peng C, Wallwiener M, Zucknick M, Nees J, Schott S, Rudolph A, Riethdorf S, Trumpp A, Pantel K, Sohn C, Chang-Claude J, Schneeweiss A, Burwinkel B. Circulating miRNAs with prognostic value in metastatic breast cancer and for early detection of metastasis. Carcinogenesis. 2016; 37:461–70. https://doi.org/10.1093/carcin/bgw008. [PubMed]

35. Camps C, Buffa FM, Colella S, Moore J, Sotiriou C, Sheldon H, Harris AL, Gleadle JM, Ragoussis J. hsa-miR-210 Is induced by hypoxia and is an independent prognostic factor in breast cancer. Clin Cancer Res. 2008; 14:1340–48. https://doi.org/10.1158/1078-0432.CCR-07-1755. [PubMed]

36. Rothé F, Ignatiadis M, Chaboteaux C, Haibe-Kains B, Kheddoumi N, Majjaj S, Badran B, Fayyad-Kazan H, Desmedt C, Harris AL, Piccart M, Sotiriou C. Global microRNA expression profiling identifies MiR-210 associated with tumor proliferation, invasion and poor clinical outcome in breast cancer. PLoS One. 2011; 6:e20980. https://doi.org/10.1371/journal.pone.0020980. [PubMed]

37. Toyama T, Kondo N, Endo Y, Sugiura H, Yoshimoto N, Iwasa M, Takahashi S, Fujii Y, Yamashita H. High expression of microRNA-210 is an independent factor indicating a poor prognosis in Japanese triple-negative breast cancer patients. Jpn J Clin Oncol. 2012; 42:256–63. https://doi.org/10.1093/jjco/hys001. [PubMed]

38. Bleckmann A, Leha A, Artmann S, Menck K, Salinas-Riester G, Binder C, Pukrop T, Beissbarth T, Klemm F. Integrated miRNA and mRNA profiling of tumor-educated macrophages identifies prognostic subgroups in estrogen receptor-positive breast cancer. Mol Oncol. 2015; 9:155–66. https://doi.org/10.1016/j.molonc.2014.07.023. [PubMed]

39. Boukerroucha M, Josse C, ElGuendi S, Boujemla B, Frères P, Marée R, Wenric S, Segers K, Collignon J, Jerusalem G, Bours V. Evaluation of BRCA1-related molecular features and microRNAs as prognostic factors for triple negative breast cancers. BMC Cancer. 2015; 15:755. https://doi.org/10.1186/s12885-015-1740-9. [PubMed]

40. Chang CH, Fan TC, Yu JC, Liao GS, Lin YC, Shih AC, Li WH, Yu AL. The prognostic significance of RUNX2 and miR-10a/10b and their inter-relationship in breast cancer. J Transl Med. 2014; 12:257. https://doi.org/10.1186/s12967-014-0257-3. [PubMed]

41. Eissa S, Matboli M, Shehata HH, Essawy NO. MicroRNA-10b and minichromosome maintenance complex component 5 gene as prognostic biomarkers in breast cancer. Tumour Biol. 2015; 36:4487–94. https://doi.org/10.1007/s13277-015-3090-2. [PubMed]

42. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, Vadas MA, Khew-Goodall Y, Goodall GJ. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nat Cell Biol. 2008; 10:593–601. https://doi.org/10.1038/ncb1722. [PubMed]

43. Mongroo PS, Rustgi AK. The role of the miR-200 family in epithelial-mesenchymal transition. Cancer Biol Ther. 2010; 10:219–22. https://doi.org/10.4161/cbt.10.3.12548. [PubMed]

44. Fisher JN, Terao M, Fratelli M, Kurosaki M, Paroni G, Zanetti A, Gianni M, Bolis M, Lupi M, Tsykin A, Goodall GJ, Garattini E. MicroRNA networks regulated by all-trans retinoic acid and Lapatinib control the growth, survival and motility of breast cancer cells. Oncotarget. 2015; 6:13176–200. https://doi.org/10.18632/oncotarget.3759. [PubMed]

45. Yu X, Zhang X, Dhakal IB, Beggs M, Kadlubar S, Luo D. Induction of cell proliferation and survival genes by estradiol-repressed microRNAs in breast cancer cells. BMC Cancer. 2012; 12:29. https://doi.org/10.1186/1471-2407-12-29. [PubMed]

46. Ye F, Tang H, Liu Q, Xie X, Wu M, Liu X, Chen B, Xie X. miR-200b as a prognostic factor in breast cancer targets multiple members of RAB family. J Transl Med. 2014; 12:17. https://doi.org/10.1186/1479-5876-12-17. [PubMed]

47. Yao Y, Hu J, Shen Z, Yao R, Liu S, Li Y, Cong H, Wang X, Qiu W, Yue L. MiR-200b expression in breast cancer: a prognostic marker and act on cell proliferation and apoptosis by targeting Sp1. J Cell Mol Med. 2015; 19:760–69. https://doi.org/10.1111/jcmm.12432. [PubMed]

48. Hironaka-Mitsuhashi A, Matsuzaki J, Takahashi RU, Yoshida M, Nezu Y, Yamamoto Y, Shiino S, Kinoshita T, Ushijima T, Hiraoka N, Shimizu C, Tamura K, Ochiya T. A tissue microRNA signature that predicts the prognosis of breast cancer in young women. PLoS One. 2017; 12:e0187638. https://doi.org/10.1371/journal.pone.0187638. [PubMed]

49. Gong C, Tan W, Chen K, You N, Zhu S, Liang G, Xie X, Li Q, Zeng Y, Ouyang N, Li Z, Zeng M, Zhuang S, et al. Prognostic Value of a BCSC-associated MicroRNA Signature in Hormone Receptor-Positive HER2-Negative Breast Cancer. EBioMedicine. 2016; 11:199–209. https://doi.org/10.1016/j.ebiom.2016.08.016. [PubMed]

50. Gasparini P, Cascione L, Fassan M, Lovat F, Guler G, Balci S, Irkkan C, Morrison C, Croce CM, Shapiro CL, Huebner K. microRNA expression profiling identifies a four microRNA signature as a novel diagnostic and prognostic biomarker in triple negative breast cancers. Oncotarget.

2014; 5:1174–84. https://doi.org/10.18632/oncotarget.1682. [PubMed]

51. Cascione L, Gasparini P, Lovat F, Carasi S, Pulvirenti A, Ferro A, Alder H, He G, Vecchione A, Croce CM, Shapiro CL, Huebner K. Integrated microRNA and mRNA signatures associated with survival in triple negative breast cancer. PLoS One. 2013; 8:e55910. https://doi.org/10.1371/journal.pone.0055910. [PubMed]

52. Chen X, Wang YW, Zhu WJ, Li Y, Liu L, Yin G, Gao P. A 4-microRNA signature predicts lymph node metastasis and prognosis in breast cancer. Hum Pathol. 2018; 76:122–32. https://doi.org/10.1016/j.humpath.2018.03.010. [PubMed]

53. Grady WM, Tewari M. The next thing in prognostic molecular markers: microRNA signatures of cancer. Gut. 2010; 59:706–08. https://doi.org/10.1136/gut.2009.200022. [PubMed]

54. Halabi S, Owzar K. The importance of identifying and validating prognostic factors in oncology. Semin Oncol. 2010; 37:e9–18. https://doi.org/10.1053/j.seminoncol.2010.04.001. [PubMed]

55. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009; 6:e1000100. https://doi.org/10.1371/journal.pmed.1000100. [PubMed]

56. Elghoroury EA, ElDine HG, Kamel SA, Abdelrahman AH, Mohammed A, Kamel MM, Ibrahim MH. Evaluation of miRNA-21 and miRNA Let-7 as Prognostic Markers in Patients With Breast Cancer. Clin Breast Cancer. 2018; 18:e721–26. https://doi.org/10.1016/j.clbc.2017.11.022. [PubMed]

57. Turashvili G, Lightbody ED, Tyryshkin K, SenGupta SK, Elliott BE, Madarnas Y, Ghaffari A, Day A, Nicol CJ. Novel prognostic and predictive microRNA targets for triple-negative breast cancer. FASEB J. 2018; fj201800120R. https://doi.org/10.1096/fj.201800120R. [PubMed]

58. Quesne JL, Jones J, Warren J, Dawson SJ, Ali HR, Bardwell H, Blows F, Pharoah P, Caldas C. Biological and prognostic associations of miR-205 and let-7b in breast cancer revealed by in situ hybridization analysis of micro-RNA expression in arrays of archival tumour tissue. J Pathol. 2012; 227:306–14. https://doi.org/10.1002/path.3983. [PubMed]

59. Bailey ST, Westerling T, Brown M. Loss of estrogen-regulated microRNA expression increases HER2 signaling and is prognostic of poor outcome in luminal breast cancer. Cancer Res. 2015; 75:436–45. https://doi.org/10.1158/0008-5472.CAN-14-1041. [PubMed]

60. Minemura H, Takagi K, Miki Y, Shibahara Y, Nakagawa S, Ebata A, Watanabe M, Ishida T, Sasano H, Suzuki T. Abnormal expression of miR-1 in breast carcinoma as a potent prognostic factor. Cancer Sci. 2015; 106:1642–50. https://doi.org/10.1111/cas.12808. [PubMed]

61. Uhr K, Sieuwerts AM, de Weerd V, Smid M, Hammerl D, Foekens JA, Martens JW. Association of microRNA-7 and its binding partner CDR1-AS with the prognosis and prediction of 1st-line tamoxifen therapy in breast cancer. Sci Rep. 2018; 8:9657. https://doi.org/10.1038/s41598-018-27987-w. [PubMed]

62. Jang MH, Kim HJ, Gwak JM, Chung YR, Park SY. Prognostic value of microRNA-9 and microRNA-155 expression in triple-negative breast cancer. Hum Pathol. 2017; 68:69–78. https://doi.org/10.1016/j.humpath.2017.08.026. [PubMed]

63. Cheng CW, Yu JC, Hsieh YH, Liao WL, Shieh JC, Yao CC, Lee HJ, Chen PM, Wu PE, Shen CY. Increased Cellular Levels of MicroRNA-9 and MicroRNA-221 Correlate with Cancer Stemness and Predict Poor Outcome in Human Breast Cancer. Cell Physiol Biochem. 2018; 48:2205–18. https://doi.org/10.1159/000492561. [PubMed]

64. Parrella P, Barbano R, Pasculli B, Fontana A, Copetti M, Valori VM, Poeta ML, Perrone G, Righi D, Castelvetere M, Coco M, Balsamo T, Morritti M, et al. Evaluation of microRNA-10b prognostic significance in a prospective cohort of breast cancer patients. Mol Cancer. 2014; 13:142. https://doi.org/10.1186/1476-4598-13-142. [PubMed]

65. Shinden Y, Akiyoshi S, Ueo H, Nambara S, Saito T, Komatsu H, Ueda M, Hirata H, Sakimura S, Uchi R, Takano Y, Iguchi T, Eguchi H, et al. Diminished expression of MiR-15a is an independent prognostic marker for breast cancer cases. Anticancer Res. 2015; 35:123–27. [PubMed]

66. Anfossi S, Giordano A, Gao H, Cohen EN, Tin S, Wu Q, Garza RJ, Debeb BG, Alvarez RH, Valero V, Hortobagyi GN, Calin GA, Ueno NT, et al. High serum miR-19a levels are associated with inflammatory breast cancer and are predictive of favorable clinical outcome in patients with metastatic HER2+ inflammatory breast cancer. PLoS One. 2014; 9:e83113. https://doi.org/10.1371/journal.pone.0083113. [PubMed]

67. Li C, Zhang J, Ma Z, Zhang F, Yu W. miR-19b serves as a prognostic biomarker of breast cancer and promotes tumor progression through PI3K/AKT signaling pathway. Onco Targets Ther. 2018; 11:4087–95. https://doi.org/10.2147/OTT.S171043. [PubMed]

68. Halvorsen AR, Helland Å, Gromov P, Wielenga VT, Talman MM, Brunner N, Sandhu V, Børresen-Dale AL, Gromova I, Haakensen VD. Profiling of microRNAs in tumor interstitial fluid of breast tumors - a novel resource to identify biomarkers for prognostic classification and detection of cancer. Mol Oncol. 2017; 11:220–34. https://doi.org/10.1002/1878-0261.12025. [PubMed]

69. Pandey AK, Zhang Y, Zhang S, Li Y, Tucker-Kellogg G, Yang H, Jha S. TIP60-miR-22 axis as a prognostic marker of breast cancer progression. Oncotarget. 2015; 6:41290–306. https://doi.org/10.18632/oncotarget.5636. [PubMed]

70. Chen B, Tang H, Liu X, Liu P, Yang L, Xie X, Ye F, Song C, Xie X, Wei W. miR-22 as a prognostic factor targets glucose transporter protein type 1

in breast cancer. Cancer Lett. 2015; 356:410–17. https://doi.org/10.1016/j.canlet.2014.09.028. [PubMed]

71. Martin EC, Elliott S, Rhodes LV, Antoon JW, Fewell C, Zhu Y, Driver JL, Jodari-Karimi M, Taylor CW, Flemington EK, Beckman BS, Collins-Burow BM, Burow ME. Preferential star strand biogenesis of pre-miR-24-2 targets PKC-alpha and suppresses cell survival in MCF-7 breast cancer cells. Mol Carcinog. 2014; 53:38–48. https://doi.org/10.1002/mc.21946. [PubMed]

72. Khodadadi-Jamayran A, Akgol-Oksuz B, Afanasyeva Y, Heguy A, Thompson M, Ray K, Giro-Perafita A, Sánchez I, Wu X, Tripathy D, Zeleniuch-Jacquotte A, Tsirigos A, Esteva FJ. Prognostic role of elevated mir-24-3p in breast cancer and its association with the metastatic process. Oncotarget. 2018; 9:12868–78. https://doi.org/10.18632/oncotarget.24403. [PubMed]

73. Tang W, Zhu J, Su S, Wu W, Liu Q, Su F, Yu F. MiR-27 as a prognostic marker for breast cancer progression and patient survival. PLoS One. 2012; 7:e51702. https://doi.org/10.1371/journal.pone.0051702. [PubMed]

74. Shen S, Sun Q, Liang Z, Cui X, Ren X, Chen H, Zhang X, Zhou Y. A prognostic model of triple-negative breast cancer based on miR-27b-3p and node status. PLoS One. 2014; 9:e100664. https://doi.org/10.1371/journal.pone.0100664. [PubMed]

75. Chen X, Lu P, Wang DD, Yang SJ, Wu Y, Shen HY, Zhong SL, Zhao JH, Tang JH. The role of miRNAs in drug resistance and prognosis of breast cancer formalin-fixed paraffin-embedded tissues. Gene. 2016; 595:221–26. https://doi.org/10.1016/j.gene.2016.10.015. [PubMed]

76. Shinden Y, Iguchi T, Akiyoshi S, Ueo H, Ueda M, Hirata H, Sakimura S, Uchi R, Takano Y, Eguchi H, Sugimachi K, Kijima Y, Natsugoe S, Mimori K. miR-29b is an indicator of prognosis in breast cancer patients. Mol Clin Oncol. 2015; 3:919–23. https://doi.org/10.3892/mco.2015.565. [PubMed]

77. Papachristopoulou G, Papadopoulos EI, Nonni A, Rassidakis GZ, Scorilas A. Expression Analysis of miR-29b in Malignant and Benign Breast Tumors: A Promising Prognostic Biomarker for Invasive Ductal Carcinoma With a Possible Histotype-Related Expression Status. Clin Breast Cancer. 2018; 18:305–312.e3. https://doi.org/10.1016/j.clbc.2017.11.007. [PubMed]

78. Cheng CW, Wang HW, Chang CW, Chu HW, Chen CY, Yu JC, Chao JI, Liu HF, Ding SL, Shen CY. MicroRNA-30a inhibits cell migration and invasion by downregulating vimentin expression and is a potential prognostic marker in breast cancer. Breast Cancer Res Treat. 2012; 134:1081–93. https://doi.org/10.1007/s10549-012-2034-4. [PubMed]

79. D'Aiuto F, Callari M, Dugo M, Merlino G, Musella V, Miodini P, Paolini B, Cappelletti V, Daidone MG. miR-30e* is an independent subtype-specific prognostic marker in breast cancer. Br J Cancer. 2015; 113:290–98. https://doi.org/10.1038/bjc.2015.206. [PubMed]

80. Peurala H, Greco D, Heikkinen T, Kaur S, Bartkova J, Jamshidi M, Aittomäki K, Heikkilä P, Bartek J, Blomqvist C, Bützow R, Nevanlinna H. MiR-34a expression has an effect for lower risk of metastasis and associates with expression patterns predicting clinical outcome in breast cancer. PLoS One. 2011; 6:e26122. https://doi.org/10.1371/journal.pone.0026122. [PubMed]

81. Zeng Z, Chen X, Zhu D, Luo Z, Yang M. Low Expression of Circulating MicroRNA-34c is Associated with Poor Prognosis in Triple-Negative Breast Cancer. Yonsei Med J. 2017; 58:697–702. https://doi.org/10.3349/ymj.2017.58.4.697. [PubMed]

82. Svoboda M, Sana J, Redova M, Navratil J, Palacova M, Fabian P, Slaby O, Vyzula R. MiR-34b is associated with clinical outcome in triple-negative breast cancer patients. Diagn Pathol. 2012; 7:31. https://doi.org/10.1186/1746-1596-7-31. [PubMed]

83. Li J, Song ZJ, Wang YY, Yin Y, Liu Y, Nan X. Low levels of serum miR-99a is a predictor of poor prognosis in breast cancer. Genet Mol Res. 2016; 15. https://doi.org/10.4238/gmr.15038338. [PubMed]

84. Wu X, Somlo G, Yu Y, Palomares MR, Li AX, Zhou W, Chow A, Yen Y, Rossi JJ, Gao H, Wang J, Yuan YC, Frankel P, et al. De novo sequencing of circulating miRNAs identifies novel markers predicting clinical outcome of locally advanced breast cancer. J Transl Med. 2012; 10:42. https://doi.org/10.1186/1479-5876-10-42. [PubMed]

85. Dong LL, Chen LM, Wang WM, Zhang LM. Decreased expression of microRNA-124 is an independent unfavorable prognostic factor for patients with breast cancer. Diagn Pathol. 2015; 10:45. https://doi.org/10.1186/s13000-015-0257-5. [PubMed]

86. Oltra SS, Peña-Chilet M, Vidal-Tomas V, Flower K, Martinez MT, Alonso E, Burgues O, Lluch A, Flanagan JM, Ribas G. Methylation deregulation of miRNA promoters identifies miR124-2 as a survival biomarker in Breast Cancer in very young women. Sci Rep. 2018; 8:14373. https://doi.org/10.1038/s41598-018-32393-3. [PubMed]

87. Hsieh TH, Hsu CY, Tsai CF, Long CY, Chai CY, Hou MF, Lee JN, Wu DC, Wang SC, Tsai EM. miR-125a-5p is a prognostic biomarker that targets HDAC4 to suppress breast tumorigenesis. Oncotarget. 2015; 6:494–509. https://doi.org/10.18632/oncotarget.2674. [PubMed]

88. Luo Y, Wang X, Niu W, Wang H, Wen Q, Fan S, Zhao R, Li Z, Xiong W, Peng S, Zeng Z, Li X, Li G, et al. Elevated microRNA-125b levels predict a worse prognosis in HER2-positive breast cancer patients. Oncol Lett. 2017; 13:867–74. https://doi.org/10.3892/ol.2016.5482. [PubMed]

89. Vilquin P, Donini CF, Villedieu M, Grisard E, Corbo L, Bachelot T, Vendrell JA, Cohen PA. MicroRNA-125b upregulation confers aromatase inhibitor resistance and is a novel marker of poor prognosis in breast cancer. Breast Cancer Res. 2015; 17:13. https://doi.org/10.1186/s13058-015-0515-1. [PubMed]

90. Wang S, Li H, Wang J, Wang D, Yao A, Li Q. Prognostic and biological significance of microRNA-127 expression

in human breast cancer. Dis Markers. 2014; 2014:401986. https://doi.org/10.1155/2014/401986. [PubMed]

91. Yu Y, Zhao Y, Sun XH, Ge J, Zhang B, Wang X, Cao XC. Down-regulation of miR-129-5p via the Twist1-Snail feedback loop stimulates the epithelial-mesenchymal transition and is associated with poor prognosis in breast cancer. Oncotarget. 2015; 6:34423–36. https://doi.org/10.18632/oncotarget.5406. [PubMed]

92. Wu ZS, Wang CQ, Xiang R, Liu X, Ye S, Yang XQ, Zhang GH, Xu XC, Zhu T, Wu Q. Loss of miR-133a expression associated with poor survival of breast cancer and restoration of miR-133a expression inhibited breast cancer cell growth and invasion. BMC Cancer. 2012; 12:51. https://doi.org/10.1186/1471-2407-12-51. [PubMed]

93. Liu HT, Xu YT, Li HY, Zhao J, Zhai HY, Chen Y. Loss of microRNA-145 expression is involved in the development and prognosis of breast cancer complicated by type 2 diabetes mellitus. Int J Biol Markers. 2016; 31:e368–74. https://doi.org/10.5301/jbm.5000220. [PubMed]

94. Quan Y, Huang X, Quan X. Expression of miRNA-206 and miRNA-145 in breast cancer and correlation with prognosis. Oncol Lett. 2018; 16:6638–42. https://doi.org/10.3892/ol.2018.9440. [PubMed]

95. Zavala V, Pérez-Moreno E, Tapia T, Camus M, Carvallo P. miR-146a and miR-638 in BRCA1-deficient triple negative breast cancer tumors, as potential biomarkers for improved overall survival. Cancer Biomark. 2016; 16:99–107. https://doi.org/10.3233/CBM-150545. [PubMed]

96. Xu X, Zhang Y, Jasper J, Lykken E, Alexander PB, Markowitz GJ, McDonnell DP, Li QJ, Wang XF. MiR-148a functions to suppress metastasis and serves as a prognostic indicator in triple-negative breast cancer. Oncotarget. 2016; 7:20381–94. https://doi.org/10.18632/oncotarget.7953. [PubMed]

97. Kong W, He L, Richards EJ, Challa S, Xu CX, Permuth-Wey J, Lancaster JM, Coppola D, Sellers TA, Djeu JY, Cheng JQ. Upregulation of miRNA-155 promotes tumour angiogenesis by targeting VHL and is associated with poor prognosis and triple-negative breast cancer. Oncogene. 2014; 33:679–89. https://doi.org/10.1038/onc.2012.636. [PubMed]

98. Ali OS, Shabayek MI, Seleem MM, Abdelaziz HG, Makhlouf DO. MicroRNAs 182 and 375 Sera Expression as Prognostic Biochemical Markers in Breast Cancer. Clin Breast Cancer. 2018; 18:e1373–79. https://doi.org/10.1016/j.clbc.2018.07.020. [PubMed]

99. Song C, Zhang L, Wang J, Huang Z, Li X, Wu M, Li S, Tang H, Xie X. High expression of microRNA-183/182/96 cluster as a prognostic biomarker for breast cancer. Sci Rep. 2016; 6:24502. https://doi.org/10.1038/srep24502. [PubMed]

100. Mulrane L, Madden SF, Brennan DJ, Gremel G, McGee SF, McNally S, Martin F, Crown JP, Jirström K, Higgins DG, Gallagher WM, O'Connor DP. miR-187 is an independent prognostic factor in breast cancer and confers increased

101. Fang C, Wang FB, Li Y, Zeng XT. Down-regulation of miR-199b-5p is correlated with poor prognosis for breast cancer patients. Biomed Pharmacother. 2016; 84:1189–93. https://doi.org/10.1016/j.biopha.2016.10.006. [PubMed]

102. Tuomarila M, Luostari K, Soini Y, Kataja V, Kosma VM, Mannermaa A. Overexpression of microRNA-200c predicts poor outcome in patients with PR-negative breast cancer. PLoS One. 2014; 9:e109508. https://doi.org/10.1371/journal.pone.0109508. [PubMed]

103. Jin T, Suk Kim H, Ki Choi S, Hye Hwang E, Woo J, Suk Ryu H, Kim K, Moon A, Kyung Moon W. microRNA-200c/141 upregulates SerpinB2 to promote breast cancer cell metastasis and reduce patient survival. Oncotarget. 2017; 8:32769–82. https://doi.org/10.18632/oncotarget.15680. [PubMed]

104. Gomes BC, Martins M, Lopes P, Morujão I, Oliveira M, Araújo A, Rueff J, Rodrigues AS. Prognostic value of microRNA-203a expression in breast cancer. Oncol Rep. 2016; 36:1748–56. https://doi.org/10.3892/or.2016.4913. [PubMed]

105. Li W, Jin X, Zhang Q, Zhang G, Deng X, Ma L. Decreased expression of miR-204 is associated with poor prognosis in patients with breast cancer. Int J Clin Exp Pathol. 2014; 7:3287–92. [PubMed]

106. Li Y, Hong F, Yu Z. Decreased expression of microRNA-206 in breast cancer and its association with disease characteristics and patient survival. J Int Med Res. 2013; 41:596–602. https://doi.org/10.1177/0300060513485856. [PubMed]

107. Hesari Z, Nourbakhsh M, Hosseinkhani S, Abdolvahabi Z, Alipour M, Tavakoli-Yaraki M, Ghorbanhosseini SS, Yousefi Z, Jafarzadeh M, Yarahmadi S. Down-regulation of NAMPT expression by mir-206 reduces cell survival of breast cancer cells. Gene. 2018; 673:149–58. https://doi.org/10.1016/j.gene.2018.06.021. [PubMed]

108. Ahmadinejad F, Mowla SJ, Honardoost MA, Arjenaki MG, Moazeni-Bistgani M, Kheiri S, Teimori H. Lower expression of miR-218 in human breast cancer is associated with lymph node metastases, higher grades, and poorer prognosis. Tumour Biol. 2017; 39:1010428317698362. https://doi.org/10.1177/1010428317698362. [PubMed]

109. Falkenberg N, Anastasov N, Rappl K, Braselmann H, Auer G, Walch A, Huber M, Höfig I, Schmitt M, Höfler H, Atkinson MJ, Aubele M. MiR-221/-222 differentiate prognostic groups in advanced breast cancers and influence cell invasion. Br J Cancer. 2013; 109:2714–23. https://doi.org/10.1038/bjc.2013.625. [PubMed]

110. Deng L, Lei Q, Wang Y, Wang Z, Xie G, Zhong X, Wang Y, Chen N, Qiu Y, Pu T, Bu H, Zheng H. Downregulation of miR-221-3p and upregulation of its target gene PARP1 are prognostic biomarkers for triple negative breast cancer patients and associated

with poor prognosis. Oncotarget. 2017; 8:108712–25. https://doi.org/10.18632/oncotarget.21561. [PubMed]

111. Wang Y, Yin W, Lin Y, Yin K, Zhou L, Du Y, Yan T, Lu J. Downregulated circulating microRNAs after surgery: potential noninvasive biomarkers for diagnosis and prognosis of early breast cancer. Cell Death Discov. 2018; 4:21. https://doi.org/10.1038/s41420-018-0089-7. [PubMed]

112. Yu H, Li H, Qian H, Jiao X, Zhu X, Jiang X, Dai G, Huang J. Upregulation of miR-301a correlates with poor prognosis in triple-negative breast cancer. Med Oncol. 2014; 31:283. https://doi.org/10.1007/s12032-014-0283-2. [PubMed]

113. Zheng JZ, Huang YN, Yao L, Liu YR, Liu S, Hu X, Liu ZB, Shao ZM. Elevated miR-301a expression indicates a poor prognosis for breast cancer patients. Sci Rep. 2018; 8:2225. https://doi.org/10.1038/s41598-018-20680-y. [PubMed]

114. Yang H, Yu J, Wang L, Ding D, Zhang L, Chu C, Chen Q, Xu Z, Zou Q, Liu X. miR-320a is an independent prognostic biomarker for invasive breast cancer. Oncol Lett. 2014; 8:1043–50. https://doi.org/10.3892/ol.2014.2298. [PubMed]

115. Li P, Dong J, Zhou X, Sun W, Huang H, Chen T, Ye B, Zheng Z, Lu M. Expression patterns of microRNA-329 and its clinical performance in diagnosis and prognosis of breast cancer. Onco Targets Ther. 2017; 10:5711–18. https://doi.org/10.2147/OTT.S147974. [PubMed]

116. Wang H, Chen SH, Kong P, Zhang LY, Zhang LL, Zhang NQ, Gu H. Increased expression of miR-330-3p: a novel independent indicator of poor prognosis in human breast cancer. Eur Rev Med Pharmacol Sci. 2018; 22:1726–30. https://doi.org/10.26355/eurrev_201803_14587. [PubMed]

117. Wu ZS, Wu Q, Wang CQ, Wang XN, Wang Y, Zhao JJ, Mao SS, Zhang GH, Zhang N, Xu XC. MiR-339-5p inhibits breast cancer cell migration and invasion in vitro and may be a potential biomarker for breast cancer prognosis. BMC Cancer. 2010; 10:542. https://doi.org/10.1186/1471-2407-10-542. [PubMed]

118. Cao ZG, Huang YN, Yao L, Liu YR, Hu X, Hou YF, Shao ZM. Positive expression of miR-361-5p indicates better prognosis for breast cancer patients. J Thorac Dis. 2016; 8:1772–79. https://doi.org/10.21037/jtd.2016.06.29. [PubMed]

119. Sim J, Ahn H, Abdul R, Kim H, Yi KJ, Chung YM, Chung MS, Paik SS, Song YS, Jang K. High MicroRNA-370 Expression Correlates with Tumor Progression and Poor Prognosis in Breast Cancer. J Breast Cancer. 2015; 18:323–28. https://doi.org/10.4048/jbc.2015.18.4.323. [PubMed]

120. Li JY, Zhang Y, Zhang WH, Jia S, Kang Y, Tian R. Effects of differential distribution of microvessel density, possibly regulated by miR-374a, on breast cancer prognosis. Asian Pac J Cancer Prev. 2013; 14:1715–20. https://doi.org/10.7314/APJCP.2013.14.3.1715. [PubMed]

121. Zhang J, He Y, Yu Y, Chen X, Cui G, Wang W, Zhang X, Luo Y, Li J, Ren F, Ren Z, Sun R. Upregulation of miR-374a promotes tumor metastasis and progression

by downregulating LACTB and predicts unfavorable prognosis in breast cancer. Cancer Med. 2018; 7:3351–62. https://doi.org/10.1002/cam4.1576. [PubMed]

122. Cao GH, Sun XL, Wu F, Chen WF, Li JQ, Hu WC. Low expression of miR-409-3p is a prognostic marker for breast cancer. Eur Rev Med Pharmacol Sci. 2016; 20:3825–29. [PubMed]

123. Bergamaschi A, Katzenellenbogen BS. Tamoxifen downregulation of miR-451 increases 14-3-3ζ and promotes breast cancer cell survival and endocrine resistance. Oncogene. 2012; 31:39–47. https://doi.org/10.1038/onc.2011.223. [PubMed]

124. Cao ZG, Li JJ, Yao L, Huang YN, Liu YR, Hu X, Song CG, Shao ZM. High expression of microRNA-454 is associated with poor prognosis in triple-negative breast cancer. Oncotarget. 2016; 7:64900–09. https://doi.org/10.18632/oncotarget.11764. [PubMed]

125. Yao L, Liu Y, Cao Z, Li J, Huang Y, Hu X, Shao Z. MicroRNA-493 is a prognostic factor in triple-negative breast cancer. Cancer Sci. 2018; 109:2294–301. https://doi.org/10.1111/cas.13644. [PubMed]

126. Gurvits N, Autere TA, Repo H, Nykänen M, Kuopio T, Kronqvist P, Talvinen K. Proliferation-associated miRNAs-494, -205, -21 and -126 detected by in situ hybridization: expression and prognostic potential in breast carcinoma patients. J Cancer Res Clin Oncol. 2018; 144:657–66. https://doi.org/10.1007/s00432-018-2586-8. [PubMed]

127. Liu J, Zhou Y, Shi Z, Hu Y, Meng T, Zhang X, Zhang S, Zhang J. microRNA-497 Modulates Breast Cancer Cell Proliferation, Invasion, and Survival by Targeting SMAD7. DNA Cell Biol. 2016; 35:521–29. https://doi.org/10.1089/dna.2016.3282. [PubMed]

128. Zhong H, Yang J, Zhang B, Wang X, Pei L, Zhang L, Lin Z, Wang Y, Wang C. LncRNA GACAT3 predicts poor prognosis and promotes cell proliferation in breast cancer through regulation of miR-497/CCND2. Cancer Biomark. 2018; 22:787–97. https://doi.org/10.3233/CBM-181354. [PubMed]

129. Krishnan P, Ghosh S, Wang B, Li D, Narasimhan A, Berendt R, Graham K, Mackey JR, Kovalchuk O, Damaraju S. Next generation sequencing profiling identifies miR-574-3p and miR-660-5p as potential novel prognostic markers for breast cancer. BMC Genomics. 2015; 16:735. https://doi.org/10.1186/s12864-015-1899-0. [PubMed]

130. Yu M, Zhang X, Li H, Zhang P, Dong W. MicroRNA-588 is downregulated and may have prognostic and functional roles in human breast cancer. Med Sci Monit. 2017; 23:5690–96. https://doi.org/10.12659/MSM.905126. [PubMed]

131. Abdolvahabi Z, Nourbakhsh M, Hosseinkhani S, Hesari Z, Alipour M, Jafarzadeh M, Ghorbanhosseini SS, Seiri P, Yousefi Z, Yarahmadi S, Golpour P. MicroRNA-590-3P suppresses cell survival and triggers breast cancer cell apoptosis via targeting sirtuin-1 and

deacetylation of p53. J Cell Biochem. 2019; 120:9356–68. https://doi.org/10.1002/jcb.28211. [PubMed]

132. Zhang XY, Liu DJ, Yuan RB, Zhang DH, Li SR, Zhang SH, Zhang LY. Low expression of miR-597 is correlated with tumor stage and poor outcome in breast cancer. Eur Rev Med Pharmacol Sci. 2018; 22:456–60. https://doi.org/10.26355/eurrev_201801_14195. [PubMed]

133. Hu JY, Yi W, Wei X, Zhang MY, Xu R, Zeng LS, Huang ZJ, Chen JS. miR-601 is a prognostic marker and suppresses cell growth and invasion by targeting PTP4A1 in breast cancer. Biomed Pharmacother. 2016; 79:247–53. https://doi.org/10.1016/j.biopha.2016.02.014. [PubMed]

134. Li M, Wang J, Liu H. Downregulation of miR-638 promotes progression of breast cancer and is associated with prognosis of breast cancer patients. Onco Targets Ther. 2018; 11:6871–77. https://doi.org/10.2147/OTT.S182034. [PubMed]

135. Raza U, Saatci Ö, Uhlmann S, Ansari SA, Eyüpoğlu E, Yurdusev E, Mutlu M, Ersan PG, Altundağ MK, Zhang JD, Doğan HT, Güler G. Şahin Ö. The miR-644a/CTBP1/ p53 axis suppresses drug resistance by simultaneous inhibition of cell survival and epithelial-mesenchymal transition in breast cancer. Oncotarget. 2016; 7:49859–77. https://doi.org/10.18632/oncotarget.10489. [PubMed]

136. Hu JY, Yi W, Zhang MY, Xu R, Zeng LS, Long XR, Zhou XM, Zheng XS, Kang Y, Wang HY. MicroRNA-711 is a prognostic factor for poor overall survival and has an oncogenic role in breast cancer. Oncol Lett. 2016; 11:2155–63. https://doi.org/10.3892/ol.2016.4217. [PubMed]

137. Zhang L, Yan DL, Yang F, Wang DD, Chen X, Wu JZ, Tang JH, Xia WJ. DNA methylation mediated silencing of microRNA-874 is a promising diagnosis and prognostic marker in breast cancer. Oncotarget. 2017; 8:45496–505. https://doi.org/10.18632/oncotarget.17569. [PubMed]

138. Liu W, Xu Y, Guan H, Meng H. Clinical potential of miR-940 as a diagnostic and prognostic biomarker in breast cancer patients. Cancer Biomark. 2018; 22:487–93. https://doi.org/10.3233/CBM-171124. [PubMed]

139. Li WJ, Xie XX, Bai J, Wang C, Zhao L, Jiang DQ. Increased expression of miR-1179 inhibits breast cancer cell metastasis by modulating Notch signaling pathway and correlates with favorable prognosis. Eur Rev Med Pharmacol Sci. 2018; 22:8374–82. https://doi.org/10.26355/eurrev_201812_16535. [PubMed]

140. Zeng B, Li Y, Feng Y, Lu M, Yuan H, Yi Z, Wu Y, Xiang T, Li H, Ren G. Downregulated miR-1247-5p associates with poor prognosis and facilitates tumor cell growth via DVL1/Wnt/β-catenin signaling in breast cancer. Biochem Biophys Res Commun. 2018; 505:302–08. https://doi.org/10.1016/j.bbrc.2018.09.103. [PubMed]

141. Zhang P, Fan C, Du J, Mo X, Zhao Q. Association of miR-1247-5p expression with clinicopathological parameters and prognosis in breast cancer. Int J Exp Pathol. 2018; 99:199–205. https://doi.org/10.1111/iep.12287. [PubMed]

142. Zhong X, Xie G, Zhang Z, Wang Z, Wang Y, Wang Y, Qiu Y, Li L, Bu H, Li J, Zheng H. MiR-4653-3p and its target gene FRS2 are prognostic biomarkers for hormone receptor positive breast cancer patients receiving tamoxifen as adjuvant endocrine therapy. Oncotarget. 2016; 7:61166–82. https://doi.org/10.18632/oncotarget.11278. [PubMed]