the expression of these two miRNAs is lost in a majority of breast cancer patients who suffer relapse [139]. Consequently, loss of both of these miRNAs is associated with poor metastasis-free survival. This was followed by the suggestion that miR-31 and miR-34c might be the miRNAs that are upregulated in recurrent breast tumors [140]. A subsequent study confirmed the downregulation of miR-335 in recurrent tumors, and this miRNA was identified as a robust inhibitor of tumor reinitiation [141]. In a study that employed global miRNA together with mRNA expression profiling to list miRNAs that might have a prognostic value in determining distant relapse-free survival, several miRNAs were found to be prognostically important in ER-positive as well as ER-negative breast cancers [142]. When matched for the mRNA targets, the two miRNAs that stood out for their putative prognostic value were miR-210 and miR-128a. More recent data has connected miR-92a with better outcome and reduced tumor recurrence [143], and miR-9 with increased tumor recurrence [144]. An interesting observation was made in a study on miR-34a when its expression was examined in 1172 breast tumors [145]. First of all, it was detectable in most of the samples studied. The tumors with high expression of miR-34a represented aggressive breast cancers but the tumors with lower expression suffered from significantly increased tumor recurrence. Thus, this miRNA presented a novel and peculiar finding which needs to be explored further. Another miRNA down-regulated in recurrent breast tumors, miR-320, is believed to function through its regulation of phosphatase and tensin homolog (PTEN) [146].

As discussed before, breast cancer frequently metastasizes to bone, and that metastasis is one of the primary reasons for tumor recurrence. Several investigations have been carried out to uncover the miRNA regulation of breast cancer metastases that might be the reason for tumor relapse. In one such study that focused on bone metastasis of breast cancer, miR-21 and miR-181a were found to be enriched in bone metastatic breast cancers leading to poor prognosis [147]. This study primarily utilized miRNA microarray to distinguish the miRNA signature between 4 patients who represented recurrent breast cancer versus 4 breast cancer patients without recurrence. Later, the results were validated in bone marrow samples from 291 additional patients.

In the context of drug resistance and breast cancer recurrence, Bergamaschi and Katzenellenbogen [148] studied the tamoxifen-induced induction of 14-3-3ζ which confers tamoxifen resistance leading to cancer relapse. The study revealed a mechanistic role of miR-451 which was down-regulated by tamoxifen leading to derepression of its target 14-3-3ζ. The tamoxifen-resistant cells were marked by upregulated 14-3-3ζ and down-regulated miR-451. A more recent study has indicated that there is no single miRNA profile predictive of outcome following tamoxifen treatment [149]. This points to the limitations and challenges in the field of miRNA research and the need for more robust investigations.

EMT and its regulation by miRNAs are not novel information anymore. However, a recent study evaluated this connection with possible clinical relevance. This study found a regulation of mesenchymal marker vimentin by miR-30a [150]. Since vimentin is associated with EMT and an invasive phenotype, miR-30a correlated with reduced invasion and breast cancer aggressiveness. The clinical importance of this regulation was revealed with the observation that breast cancer patients with reduced levels of miR-30a had poor prognosis, increased metastases and worse prognosis. This study provided further evidence connecting EMT with increased breast cancer recurrence.

Table 2: miRNAs that influence breast tumor recurrence.

miRNA	Status in recurrent breast tumors	Reference
miR-9	Upregulated	[144]
miR-21	Upregulated	[147]
miR-30a	Downregulated	[150]
miR-31	Upregulated	[140]
miR-34a	Downregulated	[145]
miR-34c	Upregulated	[140]
miR-92a	Downregulated	[143]
miR-122	Upregulated	[151]
miR-125b	Upregulated	[152]
miR-126	Downregulated	[139]
miR-181a	Upregulated	[147]
miR-320	Downregulated	[146]
miR-335	Downregulated	[139, 141]
miR-451	Downregulated	[148]

Detection of miRNAs in circulation is a hot topic attracting attention in an attempt to predict the outcome of therapeutic regime as well as chances of tumor relapse. In one such recent study [151], more than 800 miRNAs were actually detected in the serum of breast cancer patients. After vigorous analyses, miR-122 stood out as the miRNA that was significantly induced in metastatic breast cancer patients with recurrence. Circulating miRNAs have also been evaluated in relation to resistance to chemotherapy, and miR-125b expression in circulation has been linked to increased chemoresistance [152]. This knowledge holds a lot of promise particularly for the early stage patients who can be monitored on a regular basis for the possible chances of cancer relapse which can then be handled clinically at an early stage. Although a significant advancement, use of circulatory miRNAs in clinical prognosis is still in its early stages which needs to be developed further [153].

The last few years have seen an exponential increase in the number of investigations focused on the functionality of miRNAs in breast cancer progression. There has also been an interest in studying miRNAs with possible implications in predicting breast cancer recurrence. Table 2 lists various miRNAs that have been shown to relate to recurrence of breast cancer. The area of research involving miRNAs is relatively new, but has captured the imagination of a large number of researchers. More robust investigations are needed to further exploit the potential of these tiny regulatory molecules.