Clinical Theragnostic Relationship between Drug-Resistance Specific miRNA Expressions, Chemotherapeutic Resistance, and Sensitivity in Breast Cancer: A Systematic Review and Meta-Analysis

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Review

Abstract: Awareness of breast cancer has been increasing due to early detection, but the advanced disease has limited treatment options. There has been growing evidence on the role of miRNAs involved in regulating the resistance in several cancers. We performed a comprehensive systematic review and meta-analysis on the role of miRNAs in influencing the chemoresistance and sensitivity of breast cancer. A bibliographic search was performed in PubMed and Science Direct based on the search strategy, and studies published until December 2018 were retrieved. The eligible studies were included based on the selection criteria, and a detailed systematic review and meta-analysis were performed based on PRISMA guidelines. A random-effects model was utilised to evaluate the combined effect size of the obtained hazard ratio and 95% confidence intervals from the eligible studies. Publication bias was assessed with Cochran’s Q test, I² statistic, Orwin and Classic fail-safe N test, Begg and Mazumdar rank correlation test, Duval and Tweedie trim and fill calculation and the Egger’s bias indicator. A total of 4584 potential studies were screened. Of these, 85 articles were eligible for our systematic review and meta-analysis. In the 85 studies, 188 different miRNAs were studied, of which 96 were upregulated, 87 were downregulated and 5 were not involved in regulation. Overall, 24 drugs were used for treatment, with doxorubicin being prominently reported in 15 studies followed by Paclitaxel in 11 studies, and 5 drugs were used in combinations. We found only two significant HR values from the studies (miR-125b and miR-4443) and our meta-analysis results yielded a combined HR value of 0.748 with a 95% confidence interval of 0.508–1.100; p-value of 0.140. In conclusion, our results suggest there are different miRNAs involved in the regulation...
of chemoresistance through diverse drug genetic targets. These biomarkers play a crucial role in guiding the effective diagnostic and prognostic efficiency of breast cancer. The screening of miRNAs as a theragnostic biomarker must be brought into regular practice for all diseases. We anticipate that our study serves as a reference in framing future studies and clinical trials for utilising miRNAs and their respective drug targets.

**Keywords:** miRNAs; chemoresistance; breast cancer; systematic review; meta-analysis

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**1. Introduction**

Breast cancer is the most prevalent type of cancer in women worldwide [1]. This makes it a cause of increasing concern, and it is important to address this issue. It was estimated that 41,070 breast cancer deaths occurred in women during 2017 in the USA alone, making it the second-leading cause of cancer-related death in women [1]. A large number of breast cancer patients are from developing countries as compared to Western countries, mainly due to their increasing populations [2]. In developed countries, breast cancer is often diagnosed early and treated accordingly; developing countries have higher death rates due to delayed diagnosis and improper access to healthcare [2]. Regardless of this, in developed countries breast cancer is second to lung cancer for cancer-related deaths in women [2]. Asia has 44% of the world’s breast cancer deaths, with 39% of overall new breast cancer cases diagnosed [2]. In India, breast cancer has been ranked as the foremost cancer among the Indian female population [3]. Approximately 25% of female cancer cases in the country are breast cancer [4,5]. The rate of incidence was found to be 25.8 in 100,000 women, and the mortality rate was 12.7 per 100,000 women (2017 statistics) [3]. The highest rate of incidence was found to be in Delhi (41 per 100,000 women) followed by Chennai (37.9 per 100,000 women), Bangalore (34.4 per 100,000 women) and Thiruvananthapuram district (33.7 per 100,000 women) [3]. When the mortality-to-incidence ratio was analysed, it was found to reach 66 in rural registries and 8 in urban registries [3]. Another troubling concern about the scenario of breast cancer in India is the increased incidence of disease in younger Indian women (between the ages of 30 and 40) [3–5]. Presently, almost 48% of breast cancer patients in India are below 50 years of age [4,5]. There is an increasing trend of breast cancer in women between the ages of 25 to 40 in the past 25 years [4,5].

At present, breast cancer is classified into four types: (1) Luminal A (classical hormone-positive tumours); (2) Luminal B (hormone-positive with higher ki 67 and poorer prognosis); (3) Triple-negative (ER/PR/HER neu negative); and (4) Her 2 neu overexpressing [6,7]. Currently, several treatments are available for breast cancer, and these include: surgical resection [8], which is often followed by radiotherapy [9], hormone replacement therapy (differs in pre-menopausal and post-menopausal women) [10], targeted therapies [11], immunotherapy [12] and chemotherapeutic drugs [13]. There are a number of chemotherapeutic drugs that are commonly in use and have distinct mechanisms of action, such as anthracyclines (e.g., doxorubicin [14] and epirubicin [15]), taxanes (e.g., Paclitaxel [16,17], docetaxel [16]), alkylating agents (e.g., cyclophosphamide (CTX) [18], carboplatin [17]), trastuzumab—a monoclonal antibody targeted against Her 2 neu [17], anti-metabolites (e.g., 5-fluorouracil (5-FU)) [18], and hormonal agents (e.g., tamoxifen, estradiol (E2), fulvestrant, anastrazole, letrozole).

Conventional chemotherapeutics for breast cancer treatment comprise cytotoxic [19], hormonal [20], and immunotherapeutic agents [21]. Both in neoadjuvant and adjuvant instances, the effectiveness of the chemotherapeutics is limited by resistance developed in the tumour tissue. This is mainly due to the various genetic and epigenetic changes found in cancer cells, and the resistance thus conferred may be intrinsic or acquired [22]. Like most other tumour cells, breast cancer cells exhibit the phenomenon of multi-drug resistance (MDR) [23]. MDR is characterized by a combination of mechanisms including, P-glycoprotein (P-gp) [20], multidrug-resistance-associated protein 1 (MRP1) and breast cancer resistance protein (BCRP) of the ATP-binding cassette (ABC)
membrane transporter family, which efflux a diverse range of anticancer drugs from the tumour cells [23,24]. Other notable mechanisms that simultaneously contribute to MDR are enhanced aldehyde dehydrogenase (ALDH) activity, up-regulation of anti-apoptotic B-cell lymphoma-2 (Bcl-2) family proteins and abnormal activation of signalling pathways such as PI3K (phosphatidylinositol 3-kinase)/Akt, Notch, Hedgehog and Wnt pathways [25–27]. These mechanisms are predominantly showcased in CSCs (cancer stem cells).

The recent surge in the number of cancer cases along with the development of drug resistance in a large number of tumours has pushed the direction of cancer research towards new arenas that provide the grounds for the development of more effective personalised medicine treatment. MicroRNAs (miRNAs) pave the way for this by being potential biomarkers for early cancer detection, and could also help in designing a more specific treatment plan by helping in the analysis of drug resistance and sensitivity [28]. Various studies have been conducted highlighting the effect of miRNAs in chemotherapeutic resistance in cancers such as gastric cancer [29], breast cancer [30], cervical cancer [31], colorectal cancer [32], lung cancer [33], oral cancer [34], ovarian cancer [35], pancreatic cancer [36], prostate cancer [37] and skin cancer [38].

In one study it was found that there was increased resistance to docetaxel in breast cancer tissues having decreased expression of miR-638, and the restoration of miR-638 in these tissues led to apoptosis and enhanced sensitivity to docetaxel [39]. Microarray miRNA expression analysis in OHT (4-hydroxytamoxifen) showed the overexpression of eight miRNA genes, namely, miR-221, miR-222, miR-181, miR-203, miR-375, miR-32, miR-171, and miR-213, as compared to regular MCF-7 cell line conferring resistance [40]. Furthermore, seven miRNAs were under-expressed in OHT cells: miR-342, miR-484, miR-21, miR-24, miR-27, miR-23 and miR-200. miR-221 and miR-222 were also found to be up-regulated in HER2/neu-positive primary human breast cancer cells [40].

When an MCF7 (Michigan Cancer Foundation-7 cell line treated with VP-16 (etoposide) was compared with the untreated parent MCF7 cell line, it was observed that 17 miRNAs had abnormal levels of expression; the majority of them were up-regulated, whereas miR-326, miR-429, miR-187, miR-7, and miR-92-2 showed decreased expression [41]. The results were verified by RT-PCR, and it was concluded that these miRNAs could be specific regulators of MRP1 (multidrug-resistance-associated protein) and play a critical role in MDR (multiple drug resistance) [41].

A clinical study comparing the effects of the drug tamoxifen versus tamoxifen plus breast radiotherapy, carried out on 71 lymph-node-negative (LNN) breast cancer patients, revealed that the up-regulation of miRNA-301 in co-operation with SKA2 (spindle kinetochore-associated complex subunit 2) increased proliferation, migration, invasion and tumour formation through the regulation of key signalling pathways including PTEN, FOXF2 and Col2A1 [42]. According to another study, high levels of miRNA-210 expression in plasma was observed to be associated with trastuzumab resistance in HER-2 (human epidermal growth factor receptor 2)-positive breast cancer patients [43]. Xiang Ao and his colleagues examined 55 pairs of breast cancer tissues and adjacent normal tissues in total, and found that resistance to taxol in breast cancer patients increased with the loss of miRNA-17 and miRNA-20b, by the up-regulation of nuclear receptor co-activator 3 (NCOA3) levels [44].

Over the years, several studies have focused on the role of various miRNAs in the chemotherapeutic resistance or sensitivity in breast cancer. However, none of these studies have been able to conclusively define the exact mechanism by which these miRNAs are involved in chemo-sensitivity/resistance. Through this study, we aim to provide insight into the association of the expression of specific miRNAs with breast-cancer-related chemotherapeutic drug resistance and sensitivity, thereby making it relevant in a clinical setting. Further, this study paves the way to devise new treatment strategies targeting these miRNAs, and developing alternate ways to counter the occurrence of chemo-resistance in breast cancer. This study was carried out with the aid of tools including meta-analysis and systematic review.
2. Methods

To obtain studies to perform the meta-analysis, two databases were extensively used: PubMed and Science Direct. This systematic review required articles related to the chemotherapeutic resistance specific to miRNA in breast cancer. To obtain relevant papers, the selection was performed using of the following MeSH (Medical Subject Heading) terms: “miRNA” or “microRNA”, “drug resistance” and “breast cancer”. To further refine the process of selection, only papers published within 2012–2018 were selected. This systematic review and meta-analysis study adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [45].

The study search ended on (31 December 2018). After the initial screening process, additional studies were obtained via the reference section of relevant articles. The relevance of articles was determined by reading the title and abstract followed by the analysis of the complete text. The search was conducted in an orderly and elaborate manner, and was designed to meet the requirements of the study.

2.1. Selection Criteria

Studies that were to be used in the systematic review and meta-analysis had to adhere to certain selection criteria. These criteria were of two types: inclusion criteria and exclusion criteria. The inclusion criteria set the guidelines for the studies that could be included in the analysis process and included the following factors:

1. An analysis of the association between miRNA and breast cancer;
2. Studies with both breast cancer patients as well as in vitro studies with cell lines;
3. Studies that focused on cancer tissues that had resistance to some form of therapy;
4. Reporting of miRNA profiling platforms;
5. Information about the genes or pathways involved in chemotherapeutic resistance or sensitivity;
6. Inclusion of some in vitro assays to analyse the expression of miRNA or gene-related studies.

Some studies were not considered because of certain exclusion criteria. These included studies that were not in the English language, did not involve drug resistance in breast cancer, studies involving microbes and those focusing only on long non-coding (Inc) RNA. Additionally, review articles, editorials and studies with only in vitro or only breast cancer patient samples were excluded.

2.2. Data Analysis

The studies were evaluated separately by both authors (RJ and MRM), and further elaboration was performed with the help of corresponding authors. All articles were subject to the exclusion and inclusion criteria. An MS Excel worksheet (Master) was used to structurally store all the information obtained from the studies that qualified for final inclusion. After a complete survey of full-text and supplementary material, the data from all the studies were broken down under the following important headings: First author, Year of publication, Patients information, Location of the study, Ethnicity, Gender, Drug used, Clinical stages, Number of samples, Lymph node metastasis, Cell lines used, miRNA(s) involved, miRNA profiling platform and Drug pathways or gene associated. A number of biochemical and molecular assays were used to qualitatively and quantitatively analyse the miRNA expression in various studies. The frequency of their usage in all studies were compared and duly represented in a graphical form.

For further qualification of the studies, they had to pass a set of criteria that ensured a degree of quality control [46–48]. Two of the authors (RJ and MRM) critically assessed the quality of eligible articles for epidemiological studies based on some checklists derived from Dutch Cochrane Centre represented by Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [49]. The studies that were finally selected had to meet all the criteria as determined by the authors. This process of
sorting all the information obtained was a step that was crucial to ensure efficient examination of the studies.

2.3. Publication Bias

On the basis of a few distinct methods, two of the authors (RJ and MRM) individually assessed the risk of bias [50–54]. This included the number of patients, year of publication, study period, study location and diagnostic procedure. With the information obtained from the eligible studies, the reviewers arrived at a decision [55–59]. Egger’s and Begg’s bias indicator tests were employed to infer the publication bias along with the inverted funnel plot [60–63]. The effect size of statistically non-significant, unpublished and small studies was addressed using classic [64] and Orwin [65] fail-safe N tests. Duval and Tweedie’s trim and fill calculation was also performed to compute the new size effect, after the removal of an extremely positive and small study, until a symmetric funnel plot was obtained [66]. A third reviewer was consulted to resolve any disagreement regarding the decision of the team.

2.4. Statistical Analysis

We used the Comprehensive Meta-Analysis (CMA) 3.0 software for the meta-analysis and calculated the hazard ratios (HRs) with 95% confidence intervals (CIs). Cochran’s Q test and Higgins’ $I^2$ statistic [67] were used to obtain the heterogeneity, and statistical significance was defined as a p-value less than 0.01. A fixed-effect model [67] or random-effects model [68] was used to calculate 95% CI in cases where significant heterogeneity was not observed. The overall standard deviation (SD) of each sample from the main sample was calculated using the statistical Z-test.

3. Results

The eligible studies for our systematic review and meta-analysis through search results identified are shown in the form of the flow chart in Figure 1. Of the 4584 potential studies, 600 were screened for further proceeding and 92 articles were analysed in depth. Finally, 85 studies were found to be confined to the inclusion and exclusion criteria and the eligible studies involved 5159 tissues. The main characteristics of the patients are represented in Table 1. The systematically reviewed articles met all the criteria, and of the 85 articles included only 6 had hazard ratios and 95% confidence intervals and among these 3 articles denoted them directly in the article and 3 were extracted from Kaplan–Meier curves through online software. Between the 85 articles published, 57 were from China, 9 were from the USA, 5 were from Japan, 3 were from India, 2 each were from France, Italy and Taiwan, and there was 1 from each of Argentina, Canada, Finland, South Korea and Spain. Thirty studies used frozen tissues samples, 15 studies used formalin fixed paraffin embedded (FFPE) samples, 6 studies used core needle biopsy and 1 used blood sample. Meanwhile, 33 studies did not mention the type of material used.
Figure 1. Flowchart of our literature search.
### Table 1. Main characteristics of the included studies.

| Author                        | Ethnicity (Patient) | Period of Study                  | Drug(s)                                    | Clinical Stages | No. of Samples (Cancer/Normal) | miRNA | miRNA Profiling Platform |
|-------------------------------|---------------------|----------------------------------|--------------------------------------------|-----------------|--------------------------------|-------|--------------------------|
| Lin X et al. (2017) [69]      | Chinese             | 2001 to 2006 and 2015            | docetaxel                                  | 2 stages (I–II and III) | 74 4 60 0 138/83               | 34a   | GeneSpring GX (Agilent Technologies, Capital Biochip Corporation) |
| Zhao G et al. (2017) [39]     | Chinese             | January 2012 to November 2015    | docetaxel                                  | NM NM NM NM NM | 78/78                         | 638   | qRT-PCR- SYBR Premix ExTaqTM (Takara, USA) |
| Nakano M et al. (2017) [70]   | Japanese            | NM                               | methotrexate                               | 3 stages (I, I–II, II, II–III) | 1 21 1 NM 19/19                | 25-3p and 125a-3p | Mx3000P (Stratagene, La Jolla, CA) |
| Miao Y et al. (2017) [71]     | Chinese             | January 2014 to March 2016       | doxorubicin                                | NM NM NM NM NM | 29/29                         | 130b  | SYBR Green qRT-PCR master mix (TaKaRa, Otsu, Shiga, Japan) |
| Chen M-J et al. (2017) [72]   | Taiwanese           | NM                               | tamoxifen                                  | NM NM NM NM NM | 36a                           | 148a, 152 | ABI 7900 and SYBR@Select Master Mix (Applied Biosystems) |
| Yang F et al. (2017) [73]     | Chinese             | 2012–2015                        | docetaxel                                  | NM NM NM NM NM | 24/24                         | 346   | ABI 7300 real-time PCR machine (Applied Biosystems, USA) |
| Gong J-P et al. (2016) [74]   | Chinese             | July 2010 to June 2014           | Paclitaxel                                 | NM NM NM NM NM | 40a                           | 24    | TaqMan™ MicroRNA Assays (Applied Biosystems; Thermo Fisher Scientific, Inc.) |
| Ao X et al. (2016) [44]       | Chinese             | 2009–2011                        | taxol                                      | 3 stages (II, III and III–IV) | 0 12 18 25 55/55             | 17 and 20b | SYBR on the CFX96 system (Bio-Rad) |
| Zhu J et al. (2016) [75]      | Chinese             | 2005–2009                        | tamoxifen                                  | 3 stages (II, III and III–IV) | 0 8 22 22 73/19            | 27b-3p | SYBR on the CFX96 system (Bio-Rad) |
| Chen X et al. (2016) [76]     | Chinese             | January 2010 to February 2015    | docetaxel, epirubicin and vinorelbine      | NM NM NM NM NM | 55/26                         | 25a, 34a, 90b, 130a, 139, 140, 149, 197, 209b, 210, 222, 425, 452, 574, 671, 744, 1246, 1268a, 3179, 3613, 4258, 4298, 4644, 6780b, 7107 and 7847 | SYBR®Advantage®qPCR Premix, Light cycler system (Roche, Australia) |
| Damiano V et al. (2016) [77]  | Italian             | 2000–2010                        | anthracycline, anthracycline + taxane and CMF | 2 stages (I–II and III) | 2 48 0 51a 200c  | TaqMan normalizer (Applied Biosystems, ThermoFisher Scientific) |
| Jana S et al. (2016) [78]     | Indian              | NM                               | NM NM NM NM NM NM | 35/35                 | 216b  | SYBR green detection system |
| Wang D et al. (2016) [79]     | Chinese             | 2010–2015                        | doxorubicin                                | NM NM NM NM NM | 21a                           | 222   | SYBR Premix Ex Taq system (Roche, Australia) |
### Table 1. Cont.

| Author               | Ethnicity (Patient) | Period of Study | Drug(s)               | Clinical Stages | No. of Samples (Cancer/Normal) | miRNA | miRNA Profiling Platform |
|----------------------|---------------------|-----------------|-----------------------|-----------------|-------------------------------|-------|--------------------------|
| Xu X et al. (2016)   | NM                  | 2011–2014       | docetaxel             | NM              | 37/37                         | 125a-3p | SYBR Premix ExTaqTM (Takara, USA) |
| Chen X et al. (2016) | Chinese             | January 2010 to February 2015 | epirubicin           | 3 stages (I, II and III) | 10 32 4 0 | 76a | 4443 | MiR-X miRNA qRT-PCR SYBR Kit (638314; Clontech Laboratories, USA) |
| Gao M et al. (2016)  | Chinese             | NM              | doxorubicin           | NM              | 55/21                         | 145    | NCode VILO miRNA cDNA Synthesis Kit and the EXPRESS SYBR GreenER miRNA qRT-PCR Kit, respectively (Invitrogen, Carlsbad, CA, USA) |
| Thakur S et al. (2016) | Indian             | NM              | NM                    | 2 stages (I–II and III–IV) | 47 38 | 100/100 | TaqMan Universal Master Mix kit (Applied Biosystems, USA) |
| Hu Y et al. (2016)   | Chinese             | June 2014 to June 2015 | docetaxel, doxorubicin and cyclophosphamide | 3 stages (II, III and III–IV) | 0 7 19 4 | 30a | 205 | TaqMan assays (Life Technologies) |
| Sha L-Y et al. (2016) | Chinese             | NM              | epirubicin plus Paclitaxel | NM              | 20/20                         | 18a    | TaqMan MicroRNA Assay Kit (Applied Biosystems) |
| Chen X et al. (2016) | Chinese             | 2008–2013       | doxorubicin           | 4 stages (I, II, III and IV) | 37 64 12 3 | 114/114 | 489 | SYBR Primescr1 miRNA RT PCR Kit (TaKaRa, Dalian, China) |
| Venturatti L et al. (2016) | Argentinians       | 2008–2014       | trastuzumab and lapatinib | 4 stages (I, II, III and IV) | 5 9 3 2 | 19a | 16 | TaqMan®MicroRNA assay (Ambion) |
| Gu X et al. (2016)   | Chinese             | January 2010 to December 2013 | epirubicin and docetaxel | 2 stages (II and III) | NM 82/60 | 451 | miScript SYBR Green PCR Kit (Qiagen, Hilden, Germany) and a real-time LightCycler PCR (Roche Molecular Biochemicals, Mannheim, Germany) |
| Zhong S et al. (2016) | Chinese             | January 2010 to February 2015 | docetaxel, epirubicin and vinorelbine | 3 stages (I, II and III) | 6 8 9 0 | 23a | Affymetrix GeneChip miRNA 4.0 Array |
| Zhang B et al. (2015) | Chinese             | NM              | Paclitaxel           | NM              | 36/36                         | 100    | Realplex Real-time PCR Detection System (Eppendorf, Beijing, China) |
### Table 1. Cont.

| Author                        | Ethnicity (Patient) | Period of Study                          | Drug(s)                        | Clinical Stages | No. of Samples (Cancer/Normal) | miRNA | miRNA Profiling Platform                                      |
|-------------------------------|---------------------|------------------------------------------|--------------------------------|-----------------|--------------------------------|-------|---------------------------------------------------------------|
| Shen R et al. (2015) [91]     | Chinese             | Between January 2006 to December 2011    | tamoxifen                      | NM              | NM                             | NM    | 18<sup>a</sup>                                               | 155   | SYBR Green PCR master mix (TaKaRa) on the ABI 7500HT System |
| Yu X et al. (2015) [92]       | Chinese             | NM                                       | tamoxifen and fulvestrant      | NM              | NM                             | NM    | 20/20                                                       | 214   | MiScript SYBR Green PCR kit (Qiagen)                         |
| Zhou S et al. (2015) [93]     | Chinese             | March 2014 to June 2015                  | cisplatin                      | NM              | NM                             | NM    | 40/40                                                       | 27a    | FastStart Universal SYBR Green Master (Roche, Switzerland)  |
| Zheng Y et al. (2015) [94]    | Chinese             | NM                                       | doxorubicin                    | NM              | NM                             | NM    | 30/30                                                       | 181b   | TaqMan MicroRNA assays kit (Applied Biosystems, USA)       |
| Ye Z et al. (2015) [95]       | Chinese             | NM                                       | cisplatin                      | NM              | NM                             | NM    | 85/85                                                       | 221    | SYBR Green (Takara)                                         |
| Mattos-Arruda L-D et al. (2015) [96] | Spaniards        | 2005–2011                                | trastuzumab, anthracyclines, taxanes | NM              | NM                             | NM    | 85<sup>a</sup>                                               | 21     | LightCycler 480 Real-Time PCR System (Roche)                |
| Lu L et al. (2015) [97]       | Chinese             | Not mentioned                            | doxorubicin, cyclophosphamide and fluorouracil | 2 stages (II–III) | NM | NM | NM | NM | 40<sup>a</sup> | 134 | SYBR PrimeScript miRNA RT-PCR Kit (Takara, Japan) |
| Zhang H-d et al. (2015) [98]  | Chinese             | 2012–2015                                | docetaxel                      | 2 stages (I–II and III) | 18 | 17 | 0 | 35<sup>a</sup> | 139 | TaqMan MicroRNA Assay Kit (assay ID: miR-139-5p: 002289, and RNU6B: 001093), (Applied Biosystems, Life Technologies) |
| He H et al. (2015) [99]       | Chinese             | October 2012 to January 2015             | cisplatin                      | NM              | NM                             | NM    | 70/70                                                       | 944    | ABI PRISM 7900 Sequence Detection System (Applied Biosystems) with SYBR Green (TaKaRa, Japan) |
| Ikeda K et al. (2015) [100]   | Japanese            | Not mentioned                            | tamoxifen                      | NM              | NM                             | NM    | 40/16                                                       | 378a-3p | TaqMan microRNA assays (Applied Biosystems, CA, USA)       |
| Wu J et al. (2015) [101]      | Chinese             | January 2005 to December 2006            | before therapy                 | NM              | NM                             | NM    | 39<sup>a</sup>                                               | Let7a   | Real-time quantitative reverse transcription PCR (qRT-PCR) |
| Author                          | Ethnicity (Patient) | Period of Study | Drug(s)                                      | Clinical Stages | No. of Samples (Cancer/Normal) | miRNA | miRNA Profiling Platform                                      |
|--------------------------------|---------------------|-----------------|----------------------------------------------|-----------------|-------------------------------|-------|-------------------------------------------------------------|
| Takahashi R et al. (2015)      | Japanese            | 1996–2000       | docetaxel                                    | 1 stage (II-III) | NM 26 NM 26/9                  | 27b   | TaqMan MicroRNA Assays (Applied Biosystems)                  |
| Niu J et al. (2015)            | Chinese             | 1 January 2009 to 31 December 2010 | doxorubicin                                | 2 stages (I-II and III-IV) | 49 13 | 62a | 181a MyiQ Real-Time PCR Detection System (Bio-Rad)  |
| Su C-M et al. (2015)           | Taiwanese           | NM              | Paclitaxel                                   | 2 stages (I and I-II) | 36 110 NM NM 146a | 520fh | Applied Biosystems 7900 Fast Real-Time PCR                  |
| Boulbes D et al. (2015)        | American            | NM              | trastuzumab, fluorouracil, epirubicin and cyclophosphamide | NM NM NM NM NM | 50a has-520b-5p, 532-3p, 548n and 34a-3p | miRNA microarray (version 4.0, microRNACHIPv4) |
| Manvati S et al. (2015)        | Indian              | NM              | docetaxel                                    | 3 stages (I, II and III) | NM NM NM NM 46/46 | 24-2 | TaqMan microRNA assays (Applied Biosystems)                |
| Kang L et al. (2015)           | Chinese             | NM              | Paclitaxel                                   | 4 stages (I, II, III and IV) | 11 18 12 4 | 45a | TaqMan MicroRNA Assay kit (Applied Biosystems, Foster City, CA, USA) |
| Lu M et al. (2015)             | Chinese             | 2009–2010       | tamoxifen                                    | 3 stages (I, II and III) | 159 32 NM 400/243 | 484 | SYBR Premix Ex Taq System (TaKaRa)                        |
| Ye F-G et al. (2015)           | Chinese             | September 2013   | gemcitabine                                  | 3 stages (I, II and III) | 159 32 NM 400/243 | 484 | SYBR Premix Ex Taq System (TaKaRa)                        |
| Vilquin P et al. (2015)        | French              | NM              | letrozole, anastrazole, tamoxifen and fulvestrant | 3 stages (I, II and III) | 4 18 23 0 | 65/65 | 125b ExiLENT SYBR Green Master Mix and CFX96 (BioRad, Marne-la-Coquette, France) |
| Ujihara T et al. (2015)        | Japanese            | NM              | tamoxifen                                    | NM NM NM NM NM | 19a | 574-3p | triplicate TaqMan microRNA assays (Applied Biosystems, CA, USA) |
| Cui J et al. (2014)            | Chinese             | NM              | tamoxifen                                    | NM NM NM NM NM | 873 | RNeasy Mini kit (Qagen, Hilden, Germany) or TRIzol (Invitrogen) reagent. SYBR Green PCR Master Mix reagents using an ABI Prism 7700 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) |
Table 1. Cont.

| Author                  | Ethnicity (Patient) | Period of Study                  | Drug(s)            | Clinical Stages                  | No. of Samples (Cancer/Normal) | miRNA                                                                 | miRNA Profiling Platform                                                                 |
|-------------------------|---------------------|----------------------------------|--------------------|----------------------------------|-------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Lv J et al. (2014) [113]| Chinese             | 2008–2009                        | doxorubicin        | NM                               | NM                            | 31, 125b-1, 141, 145, 196b, 147, 200a, 200c, 370, 429, 491-3p, 576, 760, 765 and Let-7a | ABI 7900 PCR System (Applied Biosystems, USA) using Power SYBR Green PCR Master Mix (2X, Applied Biosystems) |
| He X et al. (2014) [114]| Chinese             | NM                               | cisplatin          | 4 stages (I, II, III and IV)     | 15 + 17                        | 85<sup>a</sup>                                                                 | TRizol reagent (Invitrogen) miRNA microarray chip (v.10.0, Exiqon, Vedbaek, Denmark) |
| Winsel S et al. (2014) [115]| Norwegians         | May 1995 to December 1998       | Taxol              | NM                               | NM                            | 378a-3p                                                                 | RNeasy Mini Kit (Qiagen) TaqMan Universal Master Mix II, no PNG (Applied Biosystems, Foster City, CA, USA) |
| Hu J et al. (2014) [116]| Chinese             | NM                               | NM                 | 4 stages (I, II, III and IV)     | 20                            | 119<sup>a</sup>                                                                 | TRizol Reagent (Invitrogen) and the miRNeasy Mini Kit (QIAGEN) |
| He DX et al. (2014) [117]| Chinese             | NM                               | doxorubicin, Paclitaxel | NM                               | NM                            | 320a                                                                 | All-in-One miRNA qRT-PCR detection kit (GeneCopoeia, Rockville, MD, USA) |
| He DX et al. (2014) [118]| Chinese             | NM                               | doxorubicin, Paclitaxel | NM                               | NM                            | 149                                                                 | All-in-One miRNA qRT-PCR detection kit (GeneCopoeia, Rockville, MD, USA). Briefly, total RNA was extracted from MCF-7/WT and ADM cells with TRizol (Invitrogen, Carlsbad, CA, USA) |
| Ouyang M et al. (2014) [119]| Chinese           | 2011 (January–October)        | doxorubicin        | NM                               | NM                            | 108-5p, 21-3p, 31-5p, 125b-3p, 130a-3p, 155-5p, 181a-5p, 181b-5p, 183-5p, 195-5p and 451a | Total RNA was harvested using TRizol (Invitrogen) and miRNeasy mini kit (QIAGEN). SYBR Premix EX TaqTM II kit (Takara, Dalian, China) |
| Luo ML et al. (2014) [120]| Chinese             | NM                               | PiB                | NM                               | NM                            | 200                                                                 | Total RNA was isolated from miRNeasy kit (Qagen) and reversely transcribed by miScript PCR starter kit |
| Author | Ethnicity (Patient) | Period of Study | Drug(s) | Clinical Stages | No. of Samples | miRNA | miRNA Profiling Platform |
|--------|---------------------|-----------------|---------|----------------|----------------|-------|------------------------|
|        |                     |                 |         | Total stages   | I   | II  | III | IV |                       |                       |
|        |                     |                 |         |                | 103 | 104 | 105 | 106 |                       |                       |
| Jiang L et al. (2014) [121] | Chinese | NM | doxorubicin | NM | NM | NM | NM | NM | 489 | Total RNA was prepared using TRIZol (Beyotime, China) according to the manufacturer’s instructions. |
| Ye XM et al. (2014) [122] | Chinese | NM | trastuzumab/Herceptin | NM | NM | NM | NM | NM | 375 | Total RNA was extracted from each cell line using TRIZol reagent (Invitrogen, USA) |
| Zhu Y et al. (2013) [123] | Chinese | NM | doxorubicin | 2 stages (I and II) | 34 | 9 | NM | NM | 43a | Total RNA was extracted from each cell line using TRIZol reagent (Invitrogen, Carlsbad, CA, USA) |
| Ye X et al. (2014) [122] | Chinese | NM | trastuzumab | NM | NM | NM | NM | NM | 221 | Total RNA from each cell line was extracted by TRIZol reagent (Invitrogen, USA) |
| Yang G et al. (2013) [124] | Chinese | NM | doxorubicin | 2 stages (I and II) | 9 | 8 | NM | NM | 30a | Total cellular RNA from tissues and cultured cells were isolated using a TRIZol Reagent (Invitrogen) |
| Pichiorri F et al. (2013) [125] | Americans | NM | fulvestrant | NM | NM | NM | NM | NM | 180/57 | TaqMan PCR kit (Applied Biosystems) and 7900HT Sequence Detection System (Applied Biosystems) |
| Wang H-J et al. (2013) [126] | Chinese | January 2010 to December 2011 | Paclitaxel, 5-FU, epirubicin and cyclophosphamide | NM | NM | NM | NM | NM | 19/19 | ABI 7900HT system (Applied Biosystems) |
| Ji S et al. (2013) [127] | Chinese | 2007–2009 | taxol + doxorubicin + cyclophosphamide | NM | NM | NM | NM | NM | 67/67 | QRT-PCR |
| Hu H et al. (2013) [128] | Chinese | October 2003 to July 2010 | topotecan, etoposide, doxorubicin, docetaxel and cyclophosphamide | NM | NM | NM | NM | NM | 39/39 | Conventional TaqMan PCR (Bio-Rad) |
| Masuda M et al. (2011) [129] | Japanese | NM | estradiol (E2) | NM | NM | NM | NM | NM | 41a | PCR was performed in ABI7500 Real-Time PCR System (Applied Biosystems, Foster city, CA, USA) |
Table 1. Cont.

| Author              | Ethnicity (Patient) | Period of Study | Drug(s)                                               | Clinical Stages | No. of Samples (Cancer/Normal) | miRNA                | miRNA Profiling Platform                                                                 |
|---------------------|---------------------|-----------------|-------------------------------------------------------|-----------------|--------------------------------|----------------------|------------------------------------------------------------------------------------------|
| Li X et al. (2012)  | Chinese             | 2008–2010       | doxorubicin, cyclophosphamide (CTX) and 5-fluorouracil (5-FU) | 1 stage (II)    | 0 38 0 0 38/38                  | 34a                  | SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA)                   |
| Lv K et al. (2012)  | Chinese             | 2002–2010       | Paclitaxel, vincristine                               | NM              | NM 38 0 0 38/38                  | 34a                  | Real-time PCR was performed using the TaqMan MicroRNA Reverse Transcription Kit and the Fast Real-Time PCR System (Applied Biosystems, Carlsbad, CA, USA) |
| Wang H et al. (2012)| Chinese             | 2009–2010       | 5-FU (5-fluorouracil)                                | 2 stages (II and III) | 0 35 21 0 56/10            | 34a                  | miRNA-specific TaqMan MicroRNA Assays (Applied Biosystems)                               |
| Jung E-J et al. (2012) | Americans, Koreans | 2007–2011       | trastuzumab, Paclitaxel, fluorouracil, cyclophosphamide and epirubicin | 3 stages (I, II and III) | 33 31 8 0 72/72                      | 34a                  | TaqMan MicroRNA Assay kit (Applied Biosystems, Foster City, Calif)                       |
| Chen J et al. (2011)| Chinese             | 2008–2009       | doxorubicin                                           | NM              | NM 39a 0 39/39                  | 34a                  | Real-time PCR was performed using SYBR Green PCR Master Mix (Applied Biosystems, USA) on the Stepone plus system (Applied Biosystems, USA) |
| Zhu Y et al. (2011) | Chinese             | 2004–2011       | NM                                                     | 3 stages (II, III and IV) | 44 29 4 77/77                      | 34a                  | Mature miRNA expression analysis was conducted using a TaqMan MicroRNA Assays (Applied Biosystems) |
| Zhao Y et al. (2011)| NM                  | 2004–2011       | tamoxifen                                             | NM              | NM 29/15                       | 34a                  | mirVana miRNA isolation kit (Ambion Inc., Austin, TX, USA) or from FFPE tissues using the miRNeasy FFPE Kit (Qagen, Valencia, CA, USA) |
| Gong C et al. (2011)| Chinese             | 2008–2009       | trastuzumab (Herceptin)                               | NM              | NM 32a 0 32/32                  | 34a                  | Total RNA was harvested using TRIzol (Invitrogen) and the RNeasy minikit (Qagen) according to the manufacturer’s instructions. |
Table 1. Cont.

| Author                   | Ethnicity (Patient) | Period of Study | Drug(s)                  | Clinical Stages                      | No. of Samples (Cancer/Normal) | miRNA            | miRNA Profiling Platform                                      |
|--------------------------|--------------------|-----------------|--------------------------|--------------------------------------|--------------------------------|------------------|---------------------------------------------------------------|
| Shi W et al. (2011) [42] | NM                 | NM              | NM                       | 3 stages (I, II and III)              | 8 33 30 NM                     | 71a              | 301 Standard TaqMan MicroRNA Assay (Applied Biosystems)        |
| Cittelly D et al. (2010) [137] | Americans          | 1978–1993       | Tamoxifen                | 3 stages (I, II and III)              | 72 346 322 NM                   | 791a             | 342 miRVANA RNA Isolation System (Ambion)                     |
| Liang Z et al. (2010) [41] | Americans          | NM              | VP-16, Mitoxantrone      | 3 stages (I, III and IV)              | 5 NM 10 (III and IV) 10 (III and IV) | 35a              | 326 Total RNA was extracted from 70% to 85% confluence of MCF-7 and MCF-7/VP cells with TRIzol (Invitrogen, Carlsbad, CA, USA) |
| Maillot G et al. (2009) [138] | NM                 | NM              | Tamoxifen                | 2 stages (III and IV)                | NM 5 10                         | 15a              | 21, 23b, 26a, 26b, 27b, 181a, 181b and 208c miRNA microarray analysis was performed as described by Castoldi and colleagues |
| Iorio M et al. (2009) [139] | Italians            | NM              | NM                       | NM                                   | NM 76a                         | 205              | TaqMan MicroRNA Reverse Transcription kit and TaqMan MicroRNA Assay were used to detect and quantify mature microRNA-205 (Applied Biosystems) |
| Miller T et al. (2008) [40] | Americans          | NM              | Tamoxifen                | NM                                   | NM 76a                         | 221 and 222     | The miRNA microarray was performed at the Ohio State University Comprehensive Cancer Center Microarray Core Facility |
| Yu F et al. (2007) [140] | Chinese            | NM              | Epirubicin               | NM                                   | NM 25a                         | Let-7            | NM                                                             |
| Li G et al. (2016) [141] | Chinese            | 2001–2002       | Tamoxifen                | NM                                   | NM 57/57                       | 1254             | mirVana miRNA isolation kit (Ambion) using stem-loop RT primers and analysed by qPCR (TaqMan, TaKaRa) |
| Yu S-J et al. (2018) [142] | Chinese            | 2003–2009       | Paclitaxel and carboplatin | 2 stages (II and III)               | NM 28 44 NM                     | 110/110          | 200a-5p 7900HT Fast Real-Time PCR System (Applied Biosystems) |
| Lee J-W et al. (2017) [143] | South Korean       | NM              | Doxorubicin              | 2 stages (I–II and III–IV)           | 28 NM 21 NM                     | 50/50            | 708-3p High-Capacity cDNA Reverse Transcription Kit (Life Technologies) |
### Table 1. Cont.

| Author                  | Ethnicity (Patient) | Period of Study       | Drug(s)                        | Clinical Stages | No. of Samples (Cancer/Normal) | miRNA | miRNA Profiling Platform                          |
|-------------------------|---------------------|-----------------------|--------------------------------|-----------------|-------------------------------|-------|---------------------------------------------------|
| Si W et al. (2018) [144] | Chinese             | NM                    | Paclitaxel                     | 3 stages (I, II and III) | 15/38/53 0/106/106 | 20a   | SYBR Premix Ex Taq (TaKaRa, RR420A)              |
| Cheng S et al. (2018) [145] | Chinese            | NM                    | cisplatin and doxorubicin      | NM              | NM/31/57 | 137   | ABI Prism 7900HT thermal cycler (Applied Biosystems, Foster City, CA, USA) |
| Hu G et al. (2018) [146]  | Chinese             | August 2013 to December 2015 | doxorubicin                    | NM              | NM/30 | 125b  | ABI PRISM 7900 Sequence Detection system (Applied Bioystems) |

NM: Not Mentioned; a: only cancer tissue; CMF: Cyclophosphamide, Methotrexate, Fluorouracil.
A total of 22 cell lines were used in the 85 studies, and MCF-7, SKBR3, T47D and MDA-MB-231 cell lines were the most frequently included, with MCF-7 used in 33 studies. Zhao Y et al. (2011) used the highest number of cell lines in a single study [135].

Overall, 188 miRNAs were studied in our systematic review and meta-analysis, conjointly 96 miRNAs were upregulated and 87 miRNAs were downregulated. Elevated expression of miR-18a, 21, 21-3p, 29a, 31, 34a, 34c-5p, 124, 125b, 130b, 137, 138, 138-5p, 139, 139-5p, 140, 140-3p, 141, 149, 149-3p, 155-5p, 181a-5p, 181b, 181b-5p, 181d, 183-5p, 197, 197-3p, 200a-5p, 200c, 205, 210, 210-3p, 221, 222, 378a-3p, 423, 423-5p, 520h, 574, 574-3p, 663, 671, 671-5p, 744, 744-5p, 944, 1246, 1268a, 3178, 3613, 3613-5p, 4258, 4298, 4438, 4443, 4644, 6780b, 6780b-3p, 7107, 7107-5p, 7847, 7847-3p, Let-7a and Lin28 and redundant expression of miR-7, 10b-5p, 17, 20a, 20b, 21, 24-2, 25, 25-3p, 27b, 31-5p, 34a-3p, 103, 125a-3p, 125b-5p, 128, 134, 145, 148a, 149, 181a, 191, 195, 195-5p, 200c, 210, 221, 222, 301a, 320a, 375, 424, 451, 489, 520b-5p, 532-3p, 548n, 574-3p, 708-3p, 873 and Let-7a were associated with chemotherapeutic resistance and increased expression of miR-16, 27a, 34a, 128, 148a, 152, 155, 210, 221, 346, 484 and Let-7 and reduced expression of miR-21, 24, 23b, 26a, 26b, 27b, 27b-3p, 34a, 100, 125a-3p, 125b-1, 130a-3p, 139, 145, 181a, 181b, 195, 200, 200c, 205, 214, 216b, 218, 301, 320a, 326, 342, 370, 378a-3p, 451a, 489, 576-3p, 638, 760, 765, 1254, Let-7 and Let-7a were associated with chemosensitivity.

Five miRNAs were differentially regulated and four miRNAs (i.e., miR-90b, 130a, 200b and 452) contributed to chemoresistance. miR-491-3p did not have any impact on chemoresistance or sensitivity. Chemotherapeutic resistance and chemosensitivity were boosted by the miRNAs through drug-regulated cellular pathways. In total, 26 drugs were studied in the included articles: 5-FU, anastrozole, cisplatin, cyclophosphamide, docetaxel, doxorubicin, E2, epirubicin, etoposide, fulvestrant, gemcitabine, lapatinib, letrozole, methotrexate, mitoxanthrone, Paclitaxel, PiB, tamoxifen, topotecan, trastuzumab, vinorelbine and combinations such as cisplatin plus doxorubicin, epirubicin plus Paclitaxel, Paclitaxel plus carboplatin, taxol plus doxorubicin plus Cyclophosphamide, Methotrexate, Fluorouracil (CMF), and anthracycline plus taxane were studied, and radiotherapy was also observed in one study.

miRNA Pathway Relation

The miRNA and pathways involved in chemoresistance and chemosensitivity are represented in Tables 2 and 3, respectively.
Table 2. Pathways involved in chemoresistance.

| Drug          | miRNA | Gene/Pathway                  | Drug          | miRNA | Gene/Pathway                  |
|---------------|-------|-------------------------------|---------------|-------|-------------------------------|
| 5-FU          | 134   | ABCC1                         | 5-FU          | 125b  | EMT                           |
| anastrozole   | 424   | Akt/mTOR pathway              | 5-FU          | 125b  | Transcription factor E2F3     |
| anthracycline | 200c  | ZEB1                          | anthracycline | 21    | IL-6/STAT3/NF-κB/PI3K pathway.|
| anthracycline + taxane | 200c  | ZEB1                          | cisplatin     | 944   | Bcl2/BNI3P                    |
| CMP           | 200c  | ZEB1                          | cisplatin and doxorubicin | 137   | FSTL1/integrin β3/Wnt         |
| CTX           | 134   | ABCC1                         | CTX           | 125b  | EMT                           |
| docetaxel     | 451   | NM                            | CTX           | 663   | HSPG2                         |
| docetaxel     | 24-2  | YWHAZ, TP53, SMAD3, ESR1 and CREBBP | docetaxel    | 663   | HSPG2                         |
| doxorubicin   | 145   | MRP1                          | doxorubicin   | 130b  | PTEN/PI3K/Akt                 |
| doxorubicin   | 320a  | TRPC5, NFATC3 and ETS-1 gene  | doxorubicin   | 222   | PTEN/Akt/cyclin-dependent kinase (p27) pathway |
| doxorubicin   | 149   | GlcNAc-NDST1                  | doxorubicin   | 181b  | MMP/caspase pathway           |
| doxorubicin   | 103   | NCL                           | doxorubicin   | 663   | HSPG2                         |
| doxorubicin   | 222   | NCL                           | doxorubicin   | 31    | MAPK signalling pathway, cytokine–cytokine receptor interaction |
| doxorubicin   | 134   | ABCC1                         | doxorubicin   | 141   | MAPK signalling pathway, cytokine–cytokine receptor interaction |
| doxorubicin   | 181a  | STAT3/NG-kB/MSK1              | doxorubicin   | 200c  | MAPK signalling pathway, cytokine–cytokine receptor interaction |
| doxorubicin   | 10b-5p| PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes | doxorubicin | 181b-5p | PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes |
| doxorubicin   | 125b-3p| PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes | doxorubicin | 183-5p | PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes |
| doxorubicin   | 155-5p| PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes | doxorubicin | 195-5p | PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes |
| doxorubicin   | 181a-5p| PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes | doxorubicin | 21-3p | PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes |
| doxorubicin   | 31-5p | PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes | E2            | 124   | EGFR                          |
| doxorubicin   | 200c  | MDR1 mRNA                     | E2            | 29a   | EGFR                          |
| doxorubicin   | 708-3p| ZEB1/CDH2/vimentin            | E2            | 21    | EGFR                          |
| doxorubicin   | 125b  | HAX-1                         | E2            | 181d  | EGFR                          |
| E2            | 301a  | EGFR                          | E2            | 34c-5p| EGFR                          |
| Drug     | miRNA | Gene/Pathway         | Drug       | miRNA | Gene/Pathway         |
|----------|-------|----------------------|------------|-------|----------------------|
| E2       | 20a   | EGFR                 | epirubicin | 4443  | TIMP2                |
| E2       | 149   | EGFR                 | epirubicin + Paclitaxel | 18a   | Dicer                |
| E2       | 17    | EGFR                 | epirubicin | 125b  | EMT                  |
| E2       | 25    | EGFR                 | etoposide | 663   | HSPG2                |
| E2       | 191   | EGFR                 | fulvestrant | 125b | Akt/mTOR pathway     |
| E2       | 27b   | EGFR                 | letrozole  | 205   | Akt/mTOR pathway     |
| E2       | 148a  | EGFR                 | Paclitaxel | 520h  | DAPK2                |
| E2       | 210   | EGFR                 | Paclitaxel | Lin28 | p21, RB, cyclin B1, Akt and Let-7 miRNA |
| E2       | 7     | EGFR                 | Paclitaxel | 125b  | EMT                  |
| epirubicin | Let7a | H-RAS/HMGA2          | Paclitaxel and carboplatin | 200a-5p | TP53INP1/YAP1 |
| epirubicin | Let7a | H-RAS/HMGA2          | tamoxifen  | 222   | p27Kip1              |
| epirubicin | 451   | NM                   | tamoxifen  | 221   | p27Kip1              |
| fulvestrant | 21    | NCL                  | taxanes    | 21    | IL-6/STAT3/NF-κB/PI3K pathway |
| methotrexate | 25-3p | ADAR1/DHFR          | taxol      | 378a-3p | Triggered receptor tyrosine kinase–MAP kinase pathway signalling, suppression of Aurora B kinase |
| methotrexate | 125a-3p | ADAR1/DHFR           | topotecan  | 663   | HSPG2                |
| Paclitaxel | 320a  | TRPC5 gene; NFATC3gene; ETS-1 gene | trastuzumab | 21    | IL-6/STAT3/NF-κB/PI3K pathway |
| Paclitaxel | 149   | GlcNAc-NDST1         | trastuzumab | 221   | PTEN                 |
| Paclitaxel | 20a   | MAPK1/c-Myc          | trastuzumab | 21    | PTEN                 |
| tamoxifen | 574-3p | CLTC                 | vincristine | Lin28 | p21, RB, cyclin B1  |
| tamoxifen | 873   | CDK3, Erx            |           |       |                      |
| tamoxifen | 424   | Akt/mTOR pathway     |           |       |                      |
| taxol     | 17    | NCOA3                |           |       |                      |
| taxol     | 20b   | NCOA3                |           |       |                      |
| trastuzumab | 221  | NCL                  |           |       |                      |
| trastuzumab | 375  | IGF1R                |           |       |                      |

*anthracycin: epirubicin/doxorubicin; EMT: Epithelial-Mesenchymal Transition.
| Drug                  | miRNA | Gene/Pathway          | miRNA | Gene/Pathway          |
|----------------------|-------|-----------------------|-------|-----------------------|
| CTX                  | 205   | VEGF/FGF2             | 34a   | Notch 1               |
| cisplatin            | 218   | BRCA1                 | CTX   | 34a                   |
| doxorubicin          | 489   | Smad3, EMT            | cisplatin | 27a   | BAK-SMAC/DIABLO-XIAP Pathway |
| doxorubicin          | 181a  | Bcl-2                 | cisplatin | 221  | BIM/Bcl-2/Bax/Bak        |
| docetaxel            | 34a   | C22ORF28              | docetaxel | 346  | SRCIN1                 |
| docetaxel            | 638   | STARD10               | doxorubicin | 196b | MAPK signalling pathway, cytokine–cytokine receptor interaction |
| docetaxel            | 125a-3p | BRCA1               | doxorubicin | 200a | MAPK signalling pathway, cytokine–cytokine receptor interaction |
| doxorubicin          | 195   | Raf-1                 | doxorubicin | 34a  | Notch 1               |
| docetaxel            | 139   | Notch 1               | doxorubicin | 451a | PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes |
| docetaxel            | 27b   | ENPP1                 | doxorubicin | 429  | MAPK signalling pathway, cytokine–cytokine receptor interaction |
| docetaxel            | 205   | VEGF/FGF2             | gemcitabine | 484  | CDA/Cyclin-dependent kinase |
| doxorubicin          | 145   | MAPK signalling pathway, cytokine–cytokine receptor interaction | lapatinib | 16   | CCNJ/FUBP1             |
| doxorubicin          | 370   | MAPK signalling pathway, cytokine–cytokine receptor interaction | tamoxifen | 148a | ALCAM                  |
| doxorubicin          | 576-3p | MAPK signalling pathway, cytokine–cytokine receptor interaction | tamoxifen | 152  | ALCAM                  |
| doxorubicin          | 760   | MAPK signalling pathway, cytokine–cytokine receptor interaction | tamoxifen | Let-7 | MAPK/Akt, ER-α36       |
| doxorubicin          | 765   | MAPK signalling pathway, cytokine–cytokine receptor interaction | tamoxifen | 155  | SOCS6-STAT3 signalling pathway |
| doxorubicin          | 125b-1 | MAPK signalling pathway, cytokine–cytokine receptor interaction | taxol + doxorubicin + cyclophosphamide | 128  | Bax                     |
| doxorubicin          | Let-7a | MAPK signalling pathway, cytokine–cytokine receptor interaction | trastuzumab | 16   | CCNJ/FUBP1             |
Table 3. Cont.

| Drug       | miRNA  | Gene/Pathway                                      | Drug       | miRNA  | Gene/Pathway                                      |
|------------|--------|---------------------------------------------------|------------|--------|---------------------------------------------------|
| doxorubicin| 130a-3p| PTEN/Akt, MAPK, RhoA, FOXO3 and PDCD4 genes       | doxorubicin| 205    | VEGF/FGF2                                        |
| epirubicin | Let-7  | HMGA2                                             |            |        |                                                   |
| fulvestrant| 214    | UCP2/PI3K-Akt-mTOR pathway                        |            |        |                                                   |
| mitoxantrone| 326   | MRP-1                                             |            |        |                                                   |
| Paclitaxel | 24     | ABCB9                                             |            |        |                                                   |
| Paclitaxel | 34a    | Notch 1                                           |            |        |                                                   |
| Paclitaxel | 100    | mTOR                                             |            |        |                                                   |
| PiB        | 200    | Pin1                                              |            |        |                                                   |
| tamoxifen  | 342    | Cyclin B1, p53, BRCA1 gene                        | tamoxifen  | 27b-3p | NR5A2/CREB1                                      |
| tamoxifen  | 378a-3p| GOLT1A                                            | tamoxifen  | 320a   | ARPP-19/ERGr, c-Myc, Cyclin D1                    |
| tamoxifen  | 21     | Estrogen-dependent cellular functions             | tamoxifen  | 181a   | Estrogen-dependent cellular functions             |
| tamoxifen  | 181b   | Estrogen-dependent cellular functions             | tamoxifen  | 200c   | Estrogen-dependent cellular functions             |
| tamoxifen  | 23b    | Estrogen-dependent cellular functions             | tamoxifen  | 26a    | Estrogen-dependent cellular functions             |
| tamoxifen  | 26b    | Estrogen-dependent cellular functions             | tamoxifen  | 27b    | Estrogen-dependent cellular functions             |
| tamoxifen  | 1254   | CCAR1                                             | tamoxifen  | 214    | UCP2/PI3K-Akt-mTOR pathway                        |
| VP-16      | 326    | MRP-1                                             |            |        |                                                   |

Anthracyclin: epirubicin/doxorubicin.
The relationship between miRNA expression and patient survival was assessed by meta-analysis. Breast cancer (BC) patients had elevated expressions of miR-125b (HR = 6.350, 95% CI = 1.211–33.297), 484 (HR = 0.375, 95% CI = 0.193–0.730), 520h (HR = 1.233, 95% CI = 0.890–1.707), 4443 (HR = 0.721, 95% CI = 0.529–0.983) and downregulated expression of miR-200c (HR = 0.433, 95% CI = 0.102–1.829), 489 (HR = 0.703, 95% CI = 0.415–1.191). An extensive examination found that 89 out of 95 articles did not mention the HR and 95% confidence interval values and of the six remaining articles, only three mentioned them in their manuscript and three HR values were obtained from Kaplan–Meier curve through online software. So, 89 studies were excluded from our meta-analysis due to insufficient data. Cumulatively, a meta-analysis was done for six studies encompassing 852 samples (Figure 2).

An unbiased correlation was observed from Begg and Mazumdar rank collection test results. Regarding Duval and Tweedie’s trim and fill calculation for the fixed-effect model, the point estimate and 95% confidence interval for the combined studies was 0.83921 (0.69115–1.01899). Under the random-effects model, the point estimate and 95% confidence interval for the combined studies was 0.79909 (0.50575–1.26256). Using trim and fill, these values were unchanged. Egger’s regression intercepted at −0.132 with 95% CI from −5.141 to 4.877; t = 0.07, p = 0.945. The 1-tailed p-value was 0.47237, and the 2-tailed p-value was 0.94473. The funnel plot is represented in Figure 3.

**Figure 2.** Forest plot of the studies included in our meta-analysis. BC: breast cancer.
miRNAs were estimated 0.662 (0.403–1.087) and 0.904 (0.487–1.678), respectively. On observing the results obtained since only a small fraction of papers were used to give results of the whole, leading to the biasing of the results. There is a possibility of our interpretation being wrong in the context of heterogeneous disease.

4.1. Role of miRNAs in Guiding Diagnosis and Prognosis

We extracted the prognosis results of six miRNAs from six different studies. Among the selected miRNAs, two miRNAs (miR200c and miR489) were downregulated and the remaining four miRNAs (miR484, miR4443, miR520h and miR125b) were upregulated. Both downregulated miRNAs were associated with better prognosis; similarly, both miRNAs (miR484 and miR4443) from the overexpressed miRNAs were expressed as better prognosis whereas miR520h and miR125b were associated with poor prognosis.

The overall hazard ratio (95% CI) of the prognostic significance was 0.78 (0.508–1.100) at a p-value of 0.140 which was analysed by random-effect model. This overall combined sized effect estimate indicates that the miRNAs decreased the likelihood of death of breast cancer patients by 22%. This means an HR value >1 indicates an increased risk of breast cancer survival whereas an HR <1 indicates a decreased risk of breast cancer patient survival. The Z-value of the overall effect size was −1.476. The individual overall hazard ratios (95% CIs) of upregulated and downregulated miRNAs were estimated 0.662 (0.403–1.087) and 0.904 (0.487–1.678), respectively. On observing the
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overall effect size of the individual subgroups, the significant prognosis was associated with a good prognosis, and hence the miRNAs could be considered as better prognostic biomarkers for breast cancer patients.

The Z-value of upregulated and downregulated miRNAs for the null hypothesis test (the mean risk ratio of which is 1.0) were −1.636 and −0.319, respectively. Both the differently expressed miRNA subgroups were associated with lower risk of death in breast cancer patients and hence we cannot accept the null hypothesis that the risk is lower in both differently expressed miRNAs. Similar to our study, two other studies have studied the subgroup analysis of higher and lower expressed miRNAs in meta-analysis studies of the prognosis of melanoma and nasopharyngeal carcinoma patient survival. Those studies demonstrated different risk levels among the subgroups, whereas in our study both subgroups exhibited better prognosis for cancer patients. More studies are required to obtain better prognostic significance of miRNAs in breast cancer patients [147].

4.2. Current Challenges

Systematic reviews and meta-analytic studies face a number of challenges when investigating the theragnostic relationship between miRNA and chemotherapeutic response in breast cancer. The primary limiting factor for detailed analysis and clinically applicable insights/results is the scarcity of data. The literature in this specific niche of breast cancer treatment is sparse, with few high-quality studies being available for comparison and analysis. This challenge is exacerbated by the lack of homogeneity between similar studies. The variance in study parameters and the methodology makes assessment difficult by introducing uncertainty in the reliability of the results. Furthermore, a large number of studies have explored this topic via the use of in-vitro models, which cannot be directly applied to clinical theragnostics. The lack of well-documented, large-scale, patient-based clinical studies is a significant challenge faced by this study. Furthermore, the mechanisms of miRNA and chemotherapeutic response are not currently understood in detail, requiring further assessment in the future if meta-analytic studies are to provide conclusions viable for application in the clinical sphere.

The strengths of our paper include its large set of research papers, varied results in terms of miRNAs and pathways that show a change in function in cancerous cells. The result of this exhaustive analysis has provided us with a large number of miRNAs that can be focused on for prognostic or diagnostic purposes. Many miRNAs play a role in regulating many vital cellular pathways, and these regulations are observed to be significantly potentiated or deregulated during treatment with chemotherapeutics.

A single miRNA can regulate multiple genes, and this regulation down the cascade can affect many pathways. Many reports have independently observed several genes or pathways as targets of many miRNAs. Of those, the treatment of doxorubicin has been frequently observed to affect the PTEN/Akt and MAPK signalling pathways, and increases chemoresistance (Table 3). In the case of miRNA 21 which is also an oncomiR, treatment with Fulvestrant; Selective Estrogen Receptor Degrader (SERD) or trastuzumab (HER2 antagonist) leads to downregulation, affecting the EMT. Whereas treatment with tamoxifen; Selective Estrogen Receptor Modulators (SERM) downregulates the expression of miRNA-21 via estrogen-dependent functions, leading to chemosensitivity.

In case of miRNAs 221 and 222, the treatment with fulvestrant, doxorubicin or trastuzumab also leads to the downregulation with increased expression of ABC transporters. The treatment with Paclitaxel leads to the downregulation of miRNA 320a with downregulation of TRPC5, Nfatc3 and the FTS-1 genes, ultimately causing chemoresistance. miRNA 125b is upregulated when treated with tamoxifen, letrozole, anastrazole or fulvestrant due to its interaction with the Akt/mTOR pathway, leading to chemoresistance. The same pattern is observed when treatment of 5-FU, Paclitaxel and cyclophosphamide is applied, which affects the EMT pathway; or when 5-FU is used, which affects the transcription factor E2F3.

miRNAs Let-7, 181a and 145 are also majorly downregulated when treated with drugs like doxorubicin, tamoxifen, or epirubicin, with increases in chemosensitivity. Thus, myriad miRNAs take centre stage in the search for theragnostic miRNAs indicating drug resistance. However, Our study has
tried its best to bridge the gaps, and serves as a benchmark for further clinical studies in personalized treatment research.

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