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Long non-coding RNAs and drug resistance in breast cancer patients: A scoping review

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Abstract

Breast cancer (BC) is the most prevalent cancer among women. Despite improvements in the detection and treatment of BC, drug resistance is widespread, making it the leading cause of cancer mortality in women. Long non-coding RNAs (lncRNAs) have been shown to play essential roles in regulating drug resistance in pre-clinical models. However, their clinical relevance remains largely unexplored. This review addresses this gap by identifying and examining lncRNAs with potential predictive value as biomarkers for drug resistance in BC cancer patients. A systematic search (last updated February 7, 2024) was conducted across five databases (Cochrane Library, Embase, PubMed, Scopus, and Web of Science) for research articles in English, published after 2010, involving BC patients who underwent treatment. Following the selection and review process, 66 studies were short-listed, and 185 unique lncRNAs linked to drug resistance in BC patients were identified. Notably, only five lncRNAs (*BCAR4*, *CCAT2*, *DSCAM-AS1*, *GAS5*, and *H19*) were reported in at least two independent studies, indicating the scarcity of replicated evidence in clinical cohorts. Receiver operating characteristic curve analysis for these five lncRNAs confirmed that *BCAR4*, *GAS5*, and *H19* expression levels have prognostic potential for predicting chemotherapy response. However, further validation is required before lncRNAs can be effectively utilized as prognostic markers in a clinical setting.

Keywords: Breast cancer; Long non-coding RNAs; Drug resistance; Biomarkers; Therapeutics

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1. Introduction

Cancer is a serious global health concern and a leading cause of death among non-communicable diseases.[1] Female breast cancer (BC) is the second most commonly diagnosed cancer worldwide, after lung cancer.[2] Among women, BC is the leading cause of cancer incidence (23.8%) and cancer mortality (15.4%).[2] BC is a heterogeneous disease and can be categorized in several different ways. In clinical practice, BC subtyping and subsequent management are primarily based on the presence or absence of three key pathological markers: Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2).

Therapeutic resistance is a significant contributor to BC mortality. In metastatic BC, over 90% of patients do not respond to chemotherapy.[3] Up to 88% of metastatic HER2-

positive patients have intrinsic resistance to trastuzumab, and while trastuzumab in combination with adjuvant chemotherapy improves the response rate, approximately 15% of patients will still develop resistance.[4] Similarly, around 30% of hormone receptor-positive (ER^+PR^+) BC patients treated with tamoxifen develop resistance within 10 years, primarily due to prolonged exposure.[5] Even in early-stage patients, approximately 30% will develop recurrence after chemotherapy.[6,7] The mechanisms underlying therapeutic resistance are not yet fully understood, representing a significant barrier to improved patient outcomes.

While most of the eukaryotic genome is transcribed, only a tiny proportion is translated into proteins.[8] Once thought to be transcriptional noise, long non-coding RNAs (lncRNAs) are now widely regarded to be important in the regulation of gene expression of complex organisms.[9] LncRNAs are transcripts longer than 200 nucleotides that are not translated into functional proteins.[10] They are a heterogeneous group with diverse properties, mechanisms, and functions that regulate key biological processes (BPs). LncRNA dysregulation is associated with various diseases, including cancer, autoimmune, cardiovascular, and neurodegenerative disorders.[11,12]

In BC, regulatory lncRNAs have been reported to have pivotal roles in cell proliferation, apoptosis, and metastasis.[13] Knockdown of H19 was reported to cause cell cycle arrest at G0/G1 and suppress cell migration and invasion in triple-negative BC cells (TNBC) via inhibition of p53 and restoring the transcription of *TNFAIP8*.[14] In addition, overexpression of the lncRNA GAS5 appears to promote apoptosis and inhibit cell proliferation by sponging miR-196a-5p and inhibiting the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway.[15] In the TNBC cell line MDA-MB-231, *AFAP1-AS1* was overexpressed, and its knockdown promoted apoptosis, inhibited proliferation, invasion, and migration through the Wnt/β-catenin signaling pathway. *AFAP1-AS1* knockdown also reduced the expression of β-catenin, phosphorylated glycogen synthase kinase 3, MYC, Snail family transcriptional repressor 2, Snail family transcriptional repressor 1, N-cadherin, and vimentin.[16] Although only a small fraction of lncRNAs have been experimentally studied to date, evidence suggests that they could play a significant role in cancer diagnosis, prognosis, and therapeutic development.

While various studies have investigated the mechanism of lncRNAs in BC treatment resistance, it remains inconclusive whether these *in vitro* findings can be reflected in clinical settings.[17,18] This scoping review aims to unveil the role of lncRNA in driving chemotherapeutic resistance among BC patients while also identifying potential genetic markers for drug resistance.

2. Methods

2.1. Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[19] were followed to design, analyze, and report the data obtained in this scoping review. The systematic search was independently conducted by JL and two other researchers (AKR and UDP) across five databases: PubMed, Embase, Cochrane Library, Web of Science, and Scopus.

2.2. Study selection

The initial systematic database search was conducted on July 1, 2022, and updated on August 26, 2022. A subsequent manual search of the reference lists of included studies was performed on February 7, 2024. The search terms used were "breast" AND "cancer" AND "lncRNA" AND "drug resistance" and synonyms. Depending on the database, the appropriate Medical Subject Headings were also used when available. Table S1 shows the whole search string used in each database. Search results from all databases were compiled, and duplicate references were removed in three stages: (i) An initial automated removal using the default EndNote X9 settings, (ii) manual verification and de-duplication, and (iii) a final automated check using Covidence software.[20] When the search was updated, additional de-duplication and removal of previously screened records were performed.[21] Only English original articles were included in the final selection for data analysis.

2.3. Inclusion and exclusion criteria

The inclusion criteria for this scoping review were: (i) Original research articles with data from BC patients, (ii) articles reporting data of BC patients who received treatment, (iii) research papers published after 2010, and (iv) papers written in English. The exclusion criteria were: (i) Not original research journal articles (e.g., reviews or conference abstracts), (ii) *in vitro* studies, or (iii) animal *in vivo* studies.

2.4. Data extraction and outcomes

The Covidence software was used to perform screening, full-text review, and data extraction. JL and AKR independently conducted the title and abstract as well as the full-text screening. Conflicts were resolved by a third independent reviewer (UDP). Data extraction was conducted by JL and reviewed by AKR. The extracted data included bibliographic details (e.g., authors, year of publication, and journal name), number of patients, patient details, treatment, lncRNA

measured, and the study's directionality. Three outcomes were extracted: (i) Patient response, (ii) patient survival, and (iii) diagnostic ability.

2.5. Enrichment analysis

The Metascape software (version 3.5)[22] was used to conduct gene ontology (GO), BP, and GO molecular functions (MF) enrichment analysis on the lncRNAs that were identified as being associated with chemoresistance. The NcPath tool (version 1.0)[23] was utilized to conduct the Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis based on the interactions between the identified lncRNAs and protein-coding genes. The RNAInter v4.0 database (http://www.rnainter.org/batch_search/)[24] was used to identify associated interactions with the lncRNAs identified in the literature search by more than one study. Interactions with a confidence score >0.5 were exclusively selected as the most reliable. The lncRNA set enrichment analysis (TLSEA, version 1.0) tool[25] was used to analyze disease association.

2.6. Prognostic analysis

The lncRNAs that were reported in at least two of the research articles were selected for cross-validation. Probe set IDs used for the lncRNAs analyzed were as follows: *BCAR4:* 235712_at*, *DSCAM-AS1:* 1562821_a_at*, *GAS5:* 228238_at*, and *H19:* 224348_s_at*. A corresponding probe set for *CCAT2* could not be identified. The validation of predictive biomarkers was performed through the receiver operating characteristic (ROC) plotter website (https://rocplot.org/).[26] Pathological complete response (pCR) and relapse-free survival (RFS) 5 years after treatment with endocrine therapy, anti-HER2 therapy, and chemotherapy were evaluated using default settings. The Mann–Whitney test assessed statistical significance between responders and non-responders, where $p<0.05$ was considered significant. For the pCR cohort ($n = 507$), responders included patients with no histological evidence of tumor remains after treatment, and non-responders were patients with residual tumor tissue. For the RFS cohort ($n = 163$), patients were classified into two groups based on survival status at the 5-year follow-up. Patients censored before 5 years were excluded. The area under the curve (AUC) is a combined measure of the sensitivity and specificity of the diagnostic; an AUC value >0.5 signifies that the lncRNA can statistically distinguish between responders and non-responders.

3. Results

3.1. Search results

A total of 4487 records were identified through the initial and the updated search. The search process is illustrated in Figure 1. Deduplication and removal of previously screened records were carried out as described by Bramer and Bain.[21] A total of 2205 studies were deemed irrelevant and excluded. Subsequently, the remaining 235 studies were assessed for eligibility, of which only 53 were selected for data extraction. A manual search was conducted on February 7, 2024, to identify the latest papers, leading to a further 13 relevant studies, resulting in a total of 66 articles included for data analysis.

3.2. Study characteristics

Of the 66 articles, most (38, 57.6%) focused on BC patients from China (Figure 2A), whereas only 11 articles included a patient population from multiple countries (Figure 2A). Most articles (30, 45.5%) analyzed all BC patients regardless of molecular markers (Figure 2B). Of specific subtypes of patients, ER-positive patients were the subject of nearly a third (19, 28.8%) of the studies. Only two articles (3.0%) were on HER2-negative BC patients (Figure 2B). Seven articles (10.6%) investigated the effects of trastuzumab, a monoclonal antibody against HER2, in HER2-positive patients (Figure 2B and C). Most studies (44, 66.7%) investigated the associations between lncRNAs and non-specific chemotherapy drugs, with 22 articles (33.3%) focusing on resistance to combination neoadjuvant chemotherapy. About one-third of the studies (25, 37.8%) examined resistance to endocrine therapy. Tamoxifen, a selective ER modulator commonly used to treat ER-positive BC, was the most common single drug (18, 27.3%) investigated. Only seven (10.6%) studies looked into targeted therapies, all of which focused on trastuzumab, a monoclonal antibody of HER2 (Figure 2C).

Among the 66 articles, 185 unique lncRNAs were identified as associated with drug resistance in BC patients. The characteristics of the 66 studies and the lncRNAs identified are provided in Table S2. Only five lncRNAs were reported in two or more studies, namely, *BCAR4*, *CCAT2*, *DSCAM-AS1*, *GAS5*, and *H19* (Figure 2D). While most articles measured the response to treatment (50, 75.8%) and patient survival (45, 68.2%), only 23 (34.8%) assessed the prognostic ability.

3.3. Enrichment analysis

This study identified 185 lncRNAs that were associated with poor prognosis in clinical samples of BC patients who underwent treatment. Enrichment analysis of GO, BP, and MF suggested that these lncRNAs were involved in regulatory ncRNA-mediated gene silencing, primarily through binding with microRNA (miRNA) (Figure 3A and Table S3). Most signaling pathway databases do not include information on lncRNAs, so the NcPath[25] was used to conduct the Kyoto Encyclopedia of

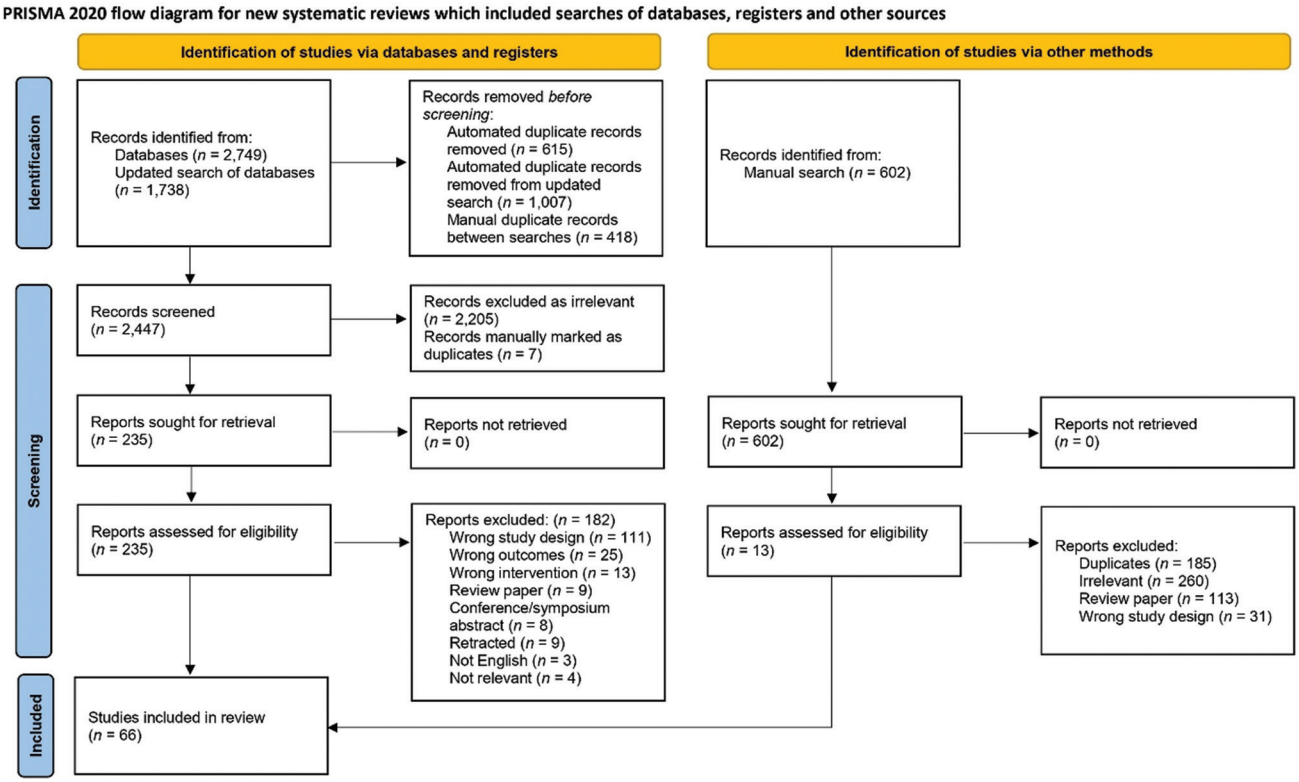

Figure 1. Preferred reporting items for systematic reviews flow diagram for systematic search of articles across five databases (PubMed, EMBASE, Cochrane, Scopus, and Web of Science)

Genes and Genomes pathway enrichment analysis based on experimentally validated ncRNA and protein-coding gene interactions. Pathways significantly enriched by these lncRNAs are associated with cell growth and proliferation (Figure 3B and Table S4). Interestingly, while these lncRNAs were primarily associated with BC, they were also enriched in other cancers such as gastric, colorectal, hepatocellular, and ovarian cancers (Figure 3B and C, Tables S4 and S5).

3.4. Long non-coding RNA-target interactions

Of the 185 lncRNAs identified, only five lncRNAs (*BCAR4*, *CCAT2*, *DSCAM-AS1*, *GAS5*, and *H19*) were reported in two or more studies. Using the RNAInter database,[26] 88 lncRNA interactions were identified with a confidence score >0.5 (Table S6). Among these, androgen receptor (AR), CCCTC-binding factor (CTCF), ESR1, forkhead box protein A1 (FOXA1), MYC, RNA polymerase II subunit A, POU class 5 homeobox 1, RELA proto-oncogene, and tumor protein p53 were common targets for at least two of the selected lncRNAs (Table 1). ESR1, which encodes ERα, interacts with all five lncRNAs (*BCAR4*, *CCAT2*, *DSCAM-AS*1, *GAS5*, and *H19*) (Table 1). AR, CTCF, FOXA1, and MYC also interacted with four of the five selected lncRNAs (Table 1). Concordant with the results of the pathway enrichment analysis (Figure 3B), the targets of the five selected lncRNAs are also involved in tumor progression (Table 1).

3.5. Prognostic analysis

The five lncRNAs were selected for further validation analysis using the ROCplot tool to evaluate their potential as predictive biomarkers for treatment in a larger patient cohort.[26] Cross-validation was only performed for *BCAR4*, *DSCAM-AS1*, *GAS5*, and *H19* since the probe set for *CCAT2* was not found. Furthermore, the pCR cohort's sample size for endocrine treatment was insufficient for analysis. Patients with no remaining tumor tissues (responders, n = 119) had a significantly higher expression of *BCAR4* and *GAS5* compared to patients with residual tumor tissues (non-responders, n = 388) after chemotherapy (p<0.05, Figure 4A and C). While the sensitivity and specificity are somewhat lacking, the expression of both *BCAR4* (AUC = 0.617, p=0.6 × 10^{-4}) and *GAS5* (AUC = 0.557, p=0.034) can differentiate between patients who respond to chemotherapy and resistant patients (Figure 4A and C).

The RFS cohort compared the lncRNA expression in patients who relapsed before 5 years (non-responders, n = 48) to patients still in remission at 5 years (responders,

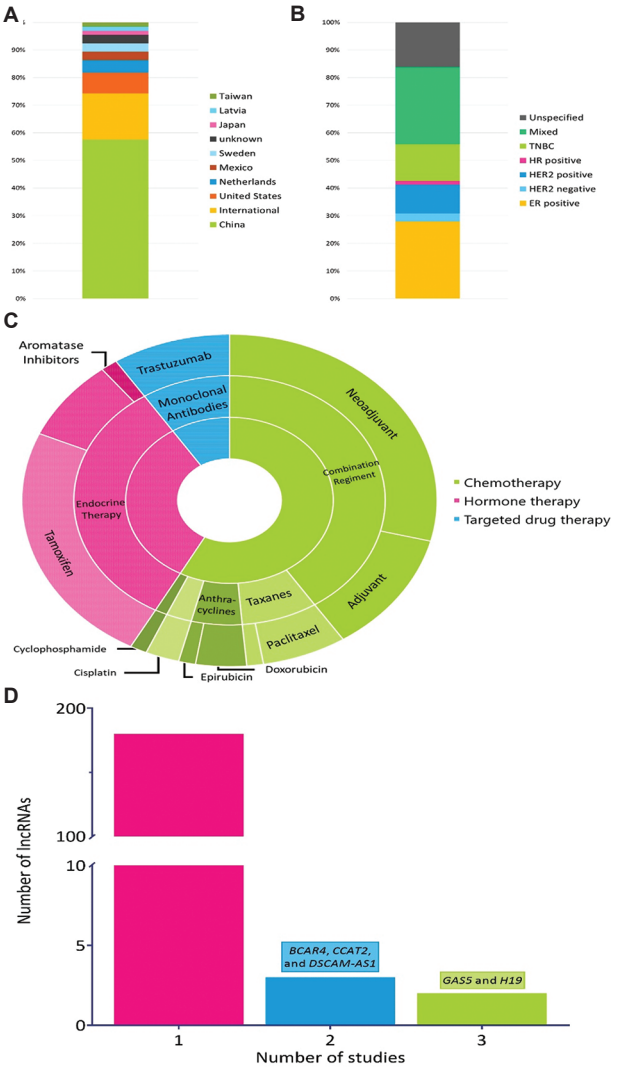

Figure 2. Study characteristics of the 66 research articles selected for this scoping review. (A) Relative distribution of the patient population by country. (B) Relative distribution of the breast cancer subtypes. "*Unspecified*" refers to a lack of molecular marker information regarding the patient samples. (C) Sunburst chart showing the relative distribution of treatments. (D) Bar chart showing the frequency distribution of lncRNAs across studies.

Abbreviations: ER: Estrogen receptor; HER2: Human epidermal growth factor 2; HR: Hormone receptor (ER or PR); lncRNA: Long non-coding RNA; PR: Progesterone receptor; TNBC: Triple-negative breast cancer.

n = 115) after chemotherapy. *GAS5* expression was higher in responders (p=0.0056) and can predict RFS status at five years after chemotherapy (AUC = 0.638, p=0.0016) (Figure 4G). *H19* expression was higher in relapsed patients (p=0.0011) and can predict RFS status at five years after chemotherapy (AUC = 0.662, p=1.6 × 10^{-4}) (Figure 4H).

4. Discussion

Drug resistance remains a significant challenge that impedes effective treatment and contributes to BC's high mortality. One method to address this is to move toward personalized medicine by identifying patients likely to benefit from a given therapy, thereby avoiding overtreatment, minimizing side effects, and enabling early intervention of alternative therapeutics for non-responders. Over the last two decades, lncRNAs have emerged as promising biomarkers for predicting drug response due to their frequent dysregulation in cancer, their tissue-specific expression, and detectability in bodily fluids.[45,46] Such non-invasive monitoring could complement existing imaging and molecular assays. Beyond their prognostic value, lncRNAs also represent attractive therapeutic targets. Approaches to modulate drug resistance-associated lncRNAs, including antisense oligonucleotides, small interfering RNAs, clustered regularly interspaced short palindromic repeats/Cas-mediated editing, and small-molecule inhibitors, are actively under investigation.[47,48] Notably, combining lncRNA-targeted strategies with conventional chemotherapy may produce synergistic effects, potentially reversing resistance and improving patient survival.[49]

4.1. Enrichment analysis

While lncRNAs can regulate a wide range of pathways through various mechanisms,[12,50] only the regulation of gene silencing via miRNA binding (Figure 3A) was identified in this review. Although this finding is statistically significant and miRNA sponging is a well-established lncRNA mechanism, it is unlikely to be the sole means by which lncRNAs modulate drug resistance. Rather than highlighting the primacy of miRNA silencing, this result more likely reflects the current paucity of functional annotations.

Our synthesis revealed that the drug resistance-associated lncRNAs were associated with genes regulating cell growth and proliferation, as the top enriched pathways include cell cycle, cellular senescence, mammalian/mechanistic target of rapamycin (mTOR) signaling pathway, mitogen-activated protein kinase (MAPK) signaling, FoxO signaling pathway, and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance (Figure 3B and Table S4). This suggests that lncRNAs could be particularly relevant as biomarkers for drugs targeting the cell cycle. Not only does the lncRNA-target interaction analysis reveal that the selected lncRNAs can interact with key transcription factors that drive tumor

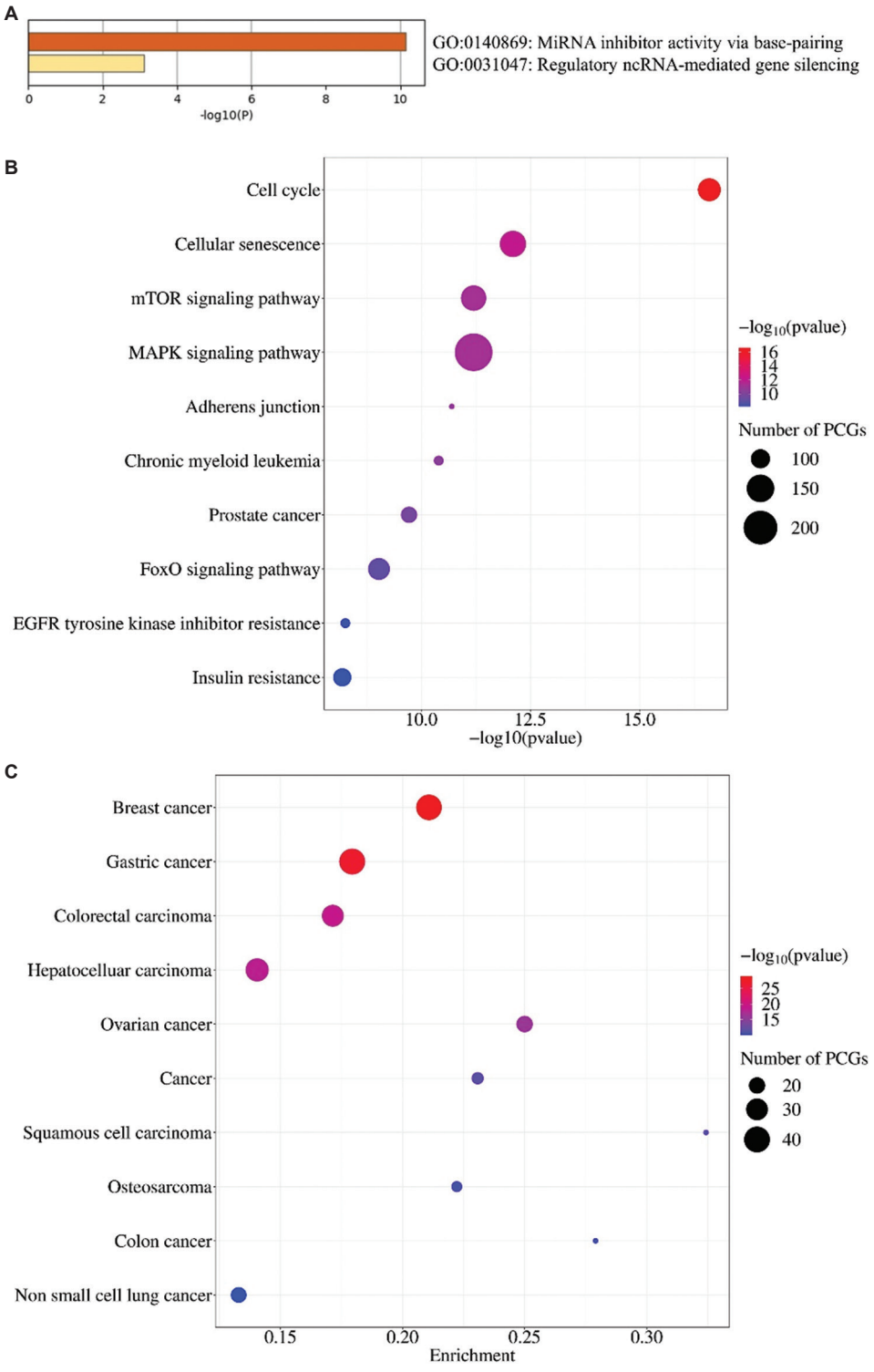

Figure 3. Gene enrichment of the 185 distinct lncRNAs identified by the scoping review, showing (A) gene ontology (GO), biological processes, and GO molecular function gene set enrichment analysis using Metascape; and (B) the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis using NcPath. Only the top 10 pathways are displayed. (C) Gene set enrichment analysis for disease association using TLSEA. Only the top 10 associations are shown.

Abbreviations: EGFR: Epidermal growth factor receptor; lncRNA: Long non-coding RNA; MAPK: Mitogen-activated protein kinase; miRNA: MicroRNA; mTOR: Mammalian/mechanistic target of rapamycin; ncRNA: Non-coding RNA; PCG: Protein coding gene; TLSEA: The lncRNA set enrichment analysis.

Table 1. List of targets common to at least two of the selected long non-coding RNAs

Target	lncRNAs	Target function	References
AR	*CCAT2*, *DSCAM-AS1*, *GAS5*, *H19*	Proliferation, DNA damage repair, cell cycle regulation, metastasis	27,28
CTCF	*CCAT2*, *DSCAM-AS1*, *GAS5*, *H19*	Proliferation, apoptosis, epithelial-mesenchymal transition	29-31
ESR1	*BCAR4*, *CCAT2*, *DSCAM-AS1*, *GAS5*, *H19*	Proliferation	32
FOXA1	*BCAR4*, *CCAT2*, *DSCAM-AS1*, *GAS5*	Proliferation, cell cycle regulation	33,34
MYC	*BCAR4*, *CCAT2*, *GAS5*, *H19*	Proliferation, cell cycle regulation, angiogenesis, epithelial-mesenchymal transition, metastasis	35-37
POLR2A	*BCAR4*, *GAS5*	Transcription, proliferation, apoptosis	38
POU5F1	*GAS5*, *H19*	Embryonic stem cells transcription factor, cell growth, metastasis	39-41
RELA	*BCAR4*, *GAS5*	Nuclear factor kappa B transcription factor subunit, proliferation, apoptosis	42,43
TP53	*GAS5*, *H19*	Cell cycle arrest, proliferation, apoptosis	44

Abbreviations: AR: Androgen receptor; CTCF: CCCTC-binding factor; ESR1: Estrogen receptor 1; FOXA1: Forkhead box protein A1; MYC: MYC proto-oncogene; POLR2A: RNA polymerase II subunit A; POU5F1: POU class 5 homeobox 1; RELA: RELA proto-oncogene; TP53: Tumor protein p53.

development (Table 1), but pre-clinical studies have also demonstrated their ability to regulate the expression of key proteins and related signaling pathways in BC.[51] Disease gene set enrichment of the identified lncRNAs also showed enrichment of other cancers besides BC (Figure 3B and C). While lncRNAs are generally more tissue-specific, some lncRNAs are more ubiquitous. LncRNAs are differentially expressed in various cancers[52] and can also regulate drug resistance.[18,53] For example, *H19* dysregulation is associated with multiple cancers and resistance, including cervical,[54] colorectal,[55] endometrial,[56] gastric,[57] ovarian,[58] non-small cell lung cancer,[59] and gliomas.[60] This suggests that the lncRNAs identified in this review could be pan-cancer driver lncRNAs and potentially be involved in resistance to common chemotherapeutic drugs across multiple cancers.

4.2. Selected long non-coding RNAs

Of the 185 lncRNAs identified, only five lncRNAs (*BCAR4*, *CCAT2*, *DSCAM-AS1*, *GAS5*, *H19*) were reported by two or more studies (Figure 2D and Table S2). The overexpression of *BCAR4*, *CCAT2*, *DSCAM-AS1*, and *H19* was associated with poor clinical prognosis. *GAS5* downregulation was associated with drug resistance. *ESR1* can interact with all five of the short-listed lncRNAs (Table 1) and thus potentially be a biomarker for resistance to therapies targeting the ER. Four lncRNAs (*CCAT2*, *DSCAM-AS1*, *GAS5*, and *H19*) of the five short-listed lncRNAs were found to interact with the AR and the transcription factor CTCF (Table 1). Expression of AR has been reported to be prevalent in BC patients, particularly in ER$^+$ patients, as up to 90% of them also express AR.[61,62] Notably, AR is an attractive target for treating BC, given the availability of AR inhibitors with proven efficacy and documented safety, thereby facilitating the expedited integration into clinical practice.[61,63-65] In addition, AR is reported to be capable of cross-talk with other key signaling pathways and proteins, such as PI3K-Akt, mTOR, and FOXA1,[34,63] which were also identified within this enrichment analysis. The role of AR in BC is yet to be fully understood, but it is very likely to be context-specific. As lncRNAs are also highly specific, further research into their relationship could prove fruitful. CTCF is a transcriptional repressor involved in chromatin organization, and its aberrant binding pattern is associated with cancer.[29,30,66] The expression of CTCF can be modulated by estrogen and causes the aberrant expression of various genes, such as *BAX, MYC, Nm23-H1,* and *TP53,* in BC.[29,30,67-69] The interaction between four of the selected lncRNAs with transcriptional factors CTCF, FOXA1, and MYC suggests another mechanism by which lncRNAs can modulate gene expression to drive resistance beyond the competitive endogenous binding with miRNAs.

4.3. Role of *BCAR4* and *DSCAM-AS1* in tamoxifen resistance

In ER$^+$ patients, overexpression of *BCAR4* and *DSCAM-AS1* was associated with tamoxifen resistance (Table S2). In MCF-7 cells, the knockdown of *DSCAM-AS1* was found to downregulate several cell cycle-related genes, including *BCL2*, *CDC6*, *E2F7*, *ESR1*, *FEN1*, and *TOP2A*.[70] Experiments by Ma *et al.*[71] demonstrated that overexpression of *DSCAM-AS1* inhibited apoptosis and caused cell cycle G1/S arrest by silencing miR-137, which in turn binds to the 3'UTR of the *EPS8* signaling adaptor gene. Experiments in ZR-75-1 and MCF7 BC cells found that *BCAR4* induced tamoxifen resistance through the phosphorylation of erb-B2 receptor tyrosine kinase 2 (also known as HER2).[72] The activation of HER2 signaling led to the downstream activation of Akt and extracellular signal-regulated kinase (ERK) ½.[72]

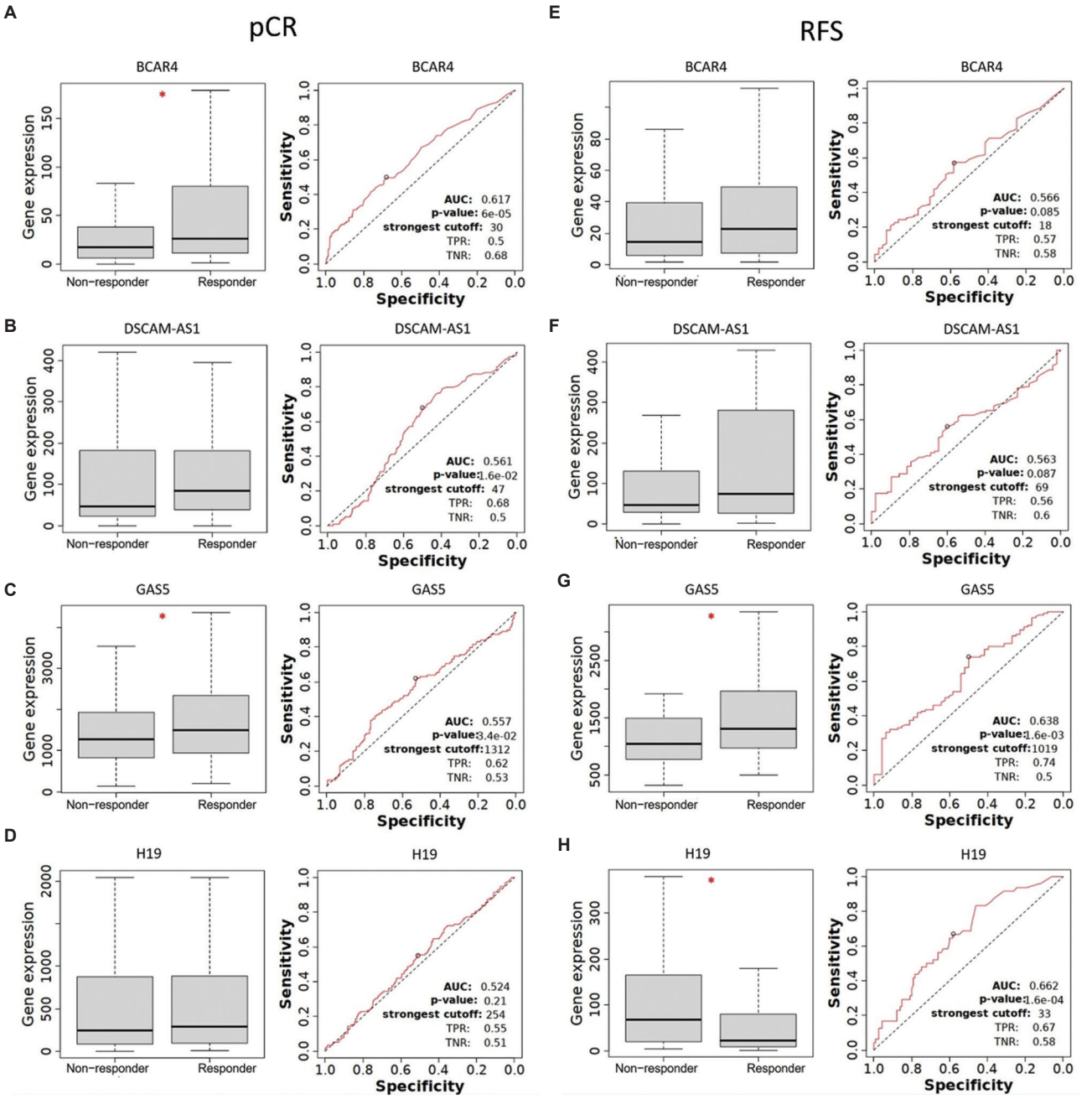

Figure 4. Boxplots and receiver operating characteristic curves of pathological complete response (pCR) for (A) *BCAR4*, (B) *DSCAM-AS1*, (C) *GAS5*, and (D) *H19* for chemotherapy resistance in and relapse-free survival at 5 years for (E) *BCAR4*, (F) *DSCAM-AS1*, (G) *GAS5*, and (H) *H19*. Red *denotes Mann–Whitney test $p<0.05$.
Abbreviations: AUC: Area under the curve; TNR: True negative rate; TPR: True positive rate.

The activation of downstream signaling from growth factor receptor tyrosine kinases such as HER2 and EGFR correlates with tamoxifen resistance.[73] Although co-targeting both ER and HER2 can be beneficial in the clinical setting, clinical trials involving EGFR tyrosine kinase inhibitors and tamoxifen in endocrine-resistant ER$^+$ BC have not been very promising.[73-76] While *BCAR4* and *DSCAM-AS1* expression could not predict the RFS status of all pooled BC patients undergoing endocrine therapy, anti-HER2 therapy, or chemotherapy (Figures 4E, F, S1, and S2), there is evidence to suggest that these lncRNAs might be helpful in stratifying patients who will benefit

from dual combination targeted treatment.

Pre-clinical work also suggests that *BCAR4* could be a valuable biomarker for a combination of lapatinib and tamoxifen treatment in *BCAR4* high/*HER2* low patients, as the activation of *HER2* is not necessarily reflected at the transcriptional level.[72] *BCAR4* was reported to drive trastuzumab resistance by sponging miR-665 and thus upregulating Yes-associated protein 1, resulting in downstream transforming growth factor beta signaling.[77] Several clinical trials have reported that there is no benefit to HER2-targeted therapy in most $ER^+/HER2^-$ patients; however, there is a significant minority (10–15%) of patients that may benefit; however, biomarkers to stratify these patients have yet to be identified.[78]

While high *BCAR4* expression is associated with tamoxifen resistance in ER^+ patients,[72,79] the ROC analysis of the pCR cohort found that high *BCAR4* expression was significantly associated with remission when treated with chemotherapy (Figure 4A). While this finding needs to be independently verified, this discrepancy could be due to *BCAR4* having a different role in different subgroups of BC patients or in response to other drugs. Interestingly, Gan *et al.*[80] report that overexpression of *BCAR4* in locally advanced BC may predict resistance to neoadjuvant chemotherapy, but only when using the Response Evaluation Criteria in Solid Tumors 1.1 evaluation system and not pathological response or the Miller–Payne score. Thus, while promising, more research is clearly needed, especially on the effect of combination treatments and on the differences between BC subtypes.

4.4. Role of *GAS5* in drug resistance

Low *GAS5* expression is associated with drug resistance (Table S2). *GAS5* expression was found to predict response to chemotherapy significantly (Figure 4C and G). While the AUC is not very high, it is worth noting that even established biomarkers, such as HER2 for trastuzumab therapy, do not exhibit particularly high AUC values (p=8.4 × 10^{-4}, AUC = 0.629).[81] This supports the use of *GAS5* as a biomarker for chemoresistance. Various experiments in MCF-7 cells demonstrated that *GAS5* regulates doxorubicin resistance by binding competitively to miR-221-3p, preventing its inhibition of dickkopf Wnt signaling pathway inhibitor 2 (activator of the Wnt/β-catenin signaling pathway) and its downstream targets β-catenin, c-Myc, cyclin D1, and adenosine triphosphate binding cassette subfamily B member 1.[82] *GAS5* promotes apoptosis in paclitaxel and cisplatin-resistant MDA-MB-231 cells.[83] It is reported that *GAS5* mediates this by inhibiting miR-378a-5p, thus upregulating suppressor of fused homolog, a negative regulator of the Hedgehog signaling pathway.[83] Furthermore, low *GAS5* expression was associated with anti-HER2 therapy resistance and can be used as a prognostic biomarker for RFS at 5 years (AUC = 0.797, p=8.7 × 10^{-4}, Figure S3). Mechanistically, experiments in trastuzumab-resistant SKBR-3 cells demonstrated that *GAS5* knockdown leads to the upregulation of miR-21 and the subsequent downregulation of *PTEN*.[84] Lapatinib upregulates *GAS5* through the mTOR pathway and abrogates trastuzumab resistance.[84] Based on pre-clinical work, *GAS5* seems to regulate multiple pathways dependent on the different drugs investigated and is a candidate therapeutic target to circumvent multidrug-resistant BC.

4.5. Role of *H19* in drug resistance

Upregulation of *H19* is associated with drug resistance to multiple drugs (Table S2). It has been suggested that the lncRNA *H19* can modulate drug resistance in numerous ways.[85] Knockdown of *H19* resensitized doxorubicin-resistant MCF-7 cells to doxorubicin, epirubicin, pirarubicin, and paclitaxel.[86] Zhu *et al.*[86] showed this was mediated through the upregulation of cullin-4A, an ubiquitin ligase component, and downstream multidrug resistance (MDR) proteins MDR1 and MDR4. The negative regulation of poly(ADP-ribose) polymerase 1 also mediated doxorubicin resistance.[87] *H19* can also drive paclitaxel resistance by activating the Wnt/β-catenin pathway; H19 upregulates *YWHAZ* via competitive endogenous binding of miR-340-3p.[88] H19 recruits enhancer of zeste homolog 2 to methylate the promoter and suppress the expression of B-cell leukemia/lymphoma 2 protein-interacting killer, thus inhibiting apoptosis when treated with paclitaxel.[89] In TNBC cells, paclitaxel resistance was demonstrated to be regulated by *H19* inhibition of apoptosis through the Akt signaling pathway.[90] Furthermore, *H19* can predict patients' RFS status 5 years after chemotherapy (AUC = 0.662, p=1.6 × 10^{-4}, Figure 4H). Taken together, the involvement of *H19* in various chemoresistance pathways and the validation of its diagnostic ability in patients suggest that *H19* is a good candidate biomarker, primarily since exosomal *H19* in the serum can be utilized.[91]

The *H19* lncRNA has also been shown to regulate the resistance of other targeted therapeutic drugs in cellular models. In endocrine resistance, *H19* can promote autophagy by reducing methylation of the Beclin1 promoter by the S-adenosylhomocysteine hydrolase/DNA methyltransferase 3 beta axis[92] and can promote epithelial–mesenchymal transition via the Wnt/β-catenin pathway.[93] Knockdown of *H19* restored trastuzumab sensitivity in SKBR3 cells.[94] However, ROC analysis indicated that *H19* expression could not predict patient response to endocrine or anti-HER2 therapy (Figure S4). Nevertheless, this could

be due to limitations in the patient cohort. Most of the patients were treated with multiple agents, and the number of patients in the targeted therapy arms was sparse.

4.6. Role of *CCAT2* in drug resistance

High *CCAT2* expression is associated with resistance in patients who received the CMF (cyclophosphamide, methotrexate, and 5-fluorouracil [5FU]) regimen (Table S2). Zhou *et al.*[95] reported that *CCAT2* mediates 5FU resistance in BC via the mTOR pathway. *CCAT2* is also known to regulate the Wnt/β-catenin signaling pathway via interaction with the Transcription Factor 7-like 2 transcription factor.[96,97] In BC, *CCAT2* is positively associated with MYC, which is also a downstream target of the Wnt/β-catenin pathway.[97-99] In tamoxifen-resistant MCF-7 cells, the knockdown of *CCAT2* promoted apoptosis via the ERK/MAPK pathway[100] and the miR-145-5p/Akt3/mTOR axis.[101] Thus, *CCAT2* may also be a biomarker of tamoxifen resistance in BC patients. However, a recent paper reported that the subcellular distribution of *CCAT2* can affect its role in luminal BC.[102] Exogenous cytoplasmic *CCAT2* was found to inhibit cell proliferation by inhibiting miR-221/222, which in turn led to the upregulation of p27, a cell cycle inhibitor.[102] Meanwhile, nuclear overexpression of *CCAT2* promotes cell proliferation and stemness by upregulating *OCT4-PG1* expression.[102] This highlights the need for more research into the importance of lncRNA cellular localization and its relevance in patients. It also raises an important question—would non-invasive collection methods, such as serum or exosomal lncRNAs, be sufficient as reliable biomarkers?

4.7. Research gaps

Despite the expanding body of research investigating the role of lncRNAs in BC drug resistance; this review highlights the lack of clinically validated evidence in patient cohorts. Out of 185 lncRNAs, <3% (n = 5) were independently replicated, with only *H19* and *GAS5* reported in three separate studies—the highest level of recurrence observed (Figure 2D). Such sparse corroboration is a significant limitation that hinders the translation of pre-clinical discoveries into clinical applications.

Among the 185 lncRNAs identified as associated with drug resistance in this review, less than half (n = 88) were annotated in Metascape,[24] and only eight (*CARMN*, *GAS5*, *H19*, *KCNQ1OT1*, *MALAT1*, *MAPT-AS1*, *MIAT*, and *OIP5-AS1*) had GO annotations (Table S3). While the analysis of proteins interacting with drug resistance-related lncRNAs showed enrichment of various BPs, particularly cell cycle-related pathways (Figure 3B), direct lncRNA annotations of the identified drug resistance-related lncRNAs yielded only two enriched terms: miRNA inhibitor activity via base-pairing and regulatory ncRNA-mediated gene silencing (Figure 3A). This striking underrepresentation highlights the lack of established functional annotations in the burgeoning field of lncRNA research. Most of the drug resistance-associated lncRNAs identified in patients are not well-characterized, and altogether, this suggests that more research into the functions of lncRNAs as a whole group is required. Addressing this gap is essential to bridge mechanistic insights from *in vitro* studies to the development of robust biomarkers and/or therapeutics.

This review has identified lncRNAs associated with resistance to several common BC therapeutics. However, it is interesting to note that the roles of lncRNAs in the resistance of other therapeutics, such as antibody–drug conjugates, kinase inhibitors, or immune checkpoint inhibitors, were not found (Figure 2C). Most BC patients are diagnosed with ER$^+$ BC,[103] and tamoxifen is the most common targeted therapy for this subtype. However, while 23.7% of the studies focused on resistance to tamoxifen, there were also no studies using other ER$^+$ targeted therapeutics such as cyclin-dependent kinase 4/6 inhibitors, mTOR inhibitors, or PI3K inhibitors (Figure 2C). The lack of efficacious targeted therapy for TNBC, the most aggressive BC subtype, underscores the importance of identifying patients who will benefit from chemotherapy and newer therapies, such as immune checkpoint inhibitors, that target cell death receptor 1. As previously discussed, high *BCAR4* expression is reported to be associated with chemoresistance,[80] which contradicts the ROC analysis of the pCR cohort (Figure 4A). This mismatch may be due to the small sample size (n = 48) of the Gan *et al.* study,[80] or to the different chemotherapy regimens or mixed BC patients in the pCR cohort. Furthermore, it is rare for patients to receive monotherapy in current clinical practice, making it more complicated to link a specific gene to individual drug response. Nonetheless, as this review indicates, lncRNAs are viable biomarkers in patients, and our synthesis underscores the need for more research into the roles of lncRNAs, especially in smaller subgroups of patients and with newer therapeutics.

5. Conclusion

Long non-coding RNAs play vital roles in the drug resistance of BC patients through various pathways, especially cell cycle-related pathways such as the PI3K/Akt/mTOR and Wnt/β-catenin signaling. There is evidence that lncRNAs have the potential to be good prognostic markers for therapeutic management. However, this review reveals a striking scarcity of reproducible, clinically validated findings. Among candidate drug resistance-related lncRNAs, only *BCAR4*, *CCAT2*, *DSCAM-AS1*, *GAS5*, and

H19 have been repeatedly associated with drug resistance in patient cohorts, though their utility as biomarkers or therapeutic targets requires further validation. Notably, *GAS5* and *H19* emerge as the most promising candidates due to their recurrent validation across studies, warranting prioritization in translational research to confirm their roles in BC drug resistance and advance them toward clinical application. Bridging this gap between pre-clinical discovery and patient-centered validation will be pivotal in harnessing lncRNAs for personalized therapy.

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Conflict of interest

The authors declare that they have no competing interests.

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References

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the global burden of disease study 2013. *Lancet*. 2015;385(9963):117-171.

   doi: 10.1016/s0140-6736(14)61682-2

2. Bray F, Laversanne M, Sung H, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263.

   doi: 10.3322/caac.21834

3. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. *J Pathol*. 2005;205(2):275-292.

   doi: 10.1002/path.1706

4. Nahta R, Esteva FJ. HER2 therapy: Molecular mechanisms of trastuzumab resistance. *Breast Cancer Res*. 2006;8(6):215.

   doi: 10.1186/bcr1612

5. Haque MM, Desai KV. Pathways to endocrine therapy resistance in breast cancer. *Front Endocrinol (Lausanne)*. 2019;10:573.

   doi: 10.3389/fendo.2019.00573

6. Cosentino G, Plantamura I, Tagliabue E, Iorio MV, Cataldo A. Breast cancer drug resistance: Overcoming the challenge by capitalizing on microRNA and tumor microenvironment interplay. *Cancers (Basel)*. 2021;13(15):3691.

   doi: 10.3390/cancers13153691

7. Early Breast Cancer Trialists' Collaborative G, Peto R, Davies C, *et al*. Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432-444.

   doi: 10.1016/S0140-6736(11)61625-5

8. Djebali S, Davis CA, Merkel A, *et al*. Landscape of transcription in human cells. *Nature*. 2012;489(7414): 101-108.

   doi: 10.1038/nature11233

9. Mattick JS, Amaral PP, Carninci P, *et al*. Long non-coding RNAs: Definitions, functions, challenges and recommendations. *Nat Rev Mol Cell Biol*. 2023;24(6):430-447.

   doi: 10.1038/s41580-022-00566-8

10. Ulitsky I, Bartel DP. LincRNAs: Genomics, evolution, and mechanisms. *Cell*. 2013;154(1):26-46.

    doi: 10.1016/j.cell.2013.06.020

11. Schmitz SU, Grote P, Herrmann BG. Mechanisms of long noncoding RNA function in development and disease. *Cell Mol Life Sci*. 2016;73(13):2491-2509.

    doi: 10.1007/s00018-016-2174-5

12. Statello L, Guo CJ, Chen LL, Huarte M. Author correction: Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol*. 2021;22(2):159.

    doi: 10.1038/s41580-021-00330-4

13. Zhang T, Hu H, Yan G, *et al*. Long non-coding RNA and breast cancer. *Technol Cancer Res Treat*. 2019;18:1533033819843889.

doi: 10.1177/1533033819843889

14. Li Y, Ma HY, Hu XW, *et al*. LncRNA H19 promotes triple-negative breast cancer cells invasion and metastasis through the p53/TNFAIP8 pathway. *Cancer Cell Int*. 2020;20:200.

doi: 10.1186/s12935-020-01261-4

15. Li S, Zhou J, Wang Z, Wang P, Gao X, Wang Y. Long noncoding RNA GAS5 suppresses triple negative breast cancer progression through inhibition of proliferation and invasion by competitively binding miR-196a-5p. *Biomed Pharmacother*. 2018;104:451-457.

doi: 10.1016/j.biopha.2018.05.056

16. Zhang K, Liu P, Tang H, *et al*. AFAP1-AS1 promotes epithelial-mesenchymal transition and tumorigenesis through Wnt/β-catenin signaling pathway in triple-negative breast cancer. *Front Pharmacol*. 2018;9:1248.

doi: 10.3389/fphar.2018.01248

17. Du T, Shi Y, Xu S, Wan X, Sun H, Liu B. Long non-coding RNAs in drug resistance of breast cancer. *Onco Targets Ther*. 2020;13:7075-7087.

doi: 10.2147/OTT.S255226

18. Liu K, Gao L, Ma X, *et al*. Long non-coding RNAs regulate drug resistance in cancer. *Mol Cancer*. 2020;19(1):54.

doi: 10.1186/s12943-020-01162-0

19. Page MJ, McKenzie JE, Bossuyt PM, *et al*. [The PRISMA 2020 statement: An updated guideline for reporting systematic reviews declaración PRISMA 2020: Una guía actualizada para la publicación de revisiones sistemáticas]. *Rev Panam Salud Publica*. 2022;46:e112.

doi: 10.26633/RPSP.2022.112

20. In: Innovation VH, editor. *Covidence Systematic Review Software*. Melbourne. Available from: https://www.com/covidence.org/australia [Last accessed on 2024 Mar 24].

21. Bramer W, Bain P. Updating search strategies for systematic reviews using EndNote. *J Med Libr Assoc*. 2017;105(3):285-289.

doi: 10.5195/jmla.2017.183

22. Zhou Y, Zhou B, Pache L, *et al*. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nat Commun*. 2019;10(1):1523.

doi: 10.1038/s41467-019-09234-6

23. Li Z, Zhang Y, Fang J, *et al*. NcPath: A novel platform for visualization and enrichment analysis of human non-coding RNA and KEGG signaling pathways. *Bioinformatics*. 2023;39(1):btac812.

doi: 10.1093/bioinformatics/btac812

24. Kang J, Tang Q, He J, *et al*. RNAInter v4.0: RNA interactome repository with redefined confidence scoring system and improved accessibility. *Nucleic Acids Res*. 2022;50(D1):D326-D332.

doi: 10.1093/nar/gkab997

25. Li J, Li Z, Wang Y, Lin H, Wu B. TLSEA: A tool for lncRNA set enrichment analysis based on multi-source heterogeneous information fusion. *Front Genet*. 2023;14:1181391.

doi: 10.3389/fgene.2023.1181391

26. Fekete JT, Győrffy B. ROCplot.org: Validating predictive biomarkers of chemotherapy/hormonal therapy/anti-HER2 therapy using transcriptomic data of 3,104 breast cancer patients. *Int J Cancer*. 2019;145(11):3140-3151.

doi: 10.1002/ijc.32369

27. Michmerhuizen AR, Spratt DE, Pierce LJ, Speers CW. ARe we there yet? Understanding androgen receptor signaling in breast cancer. *NPJ Breast Cancer*. 2020;6:47.

doi: 10.1038/s41523-020-00190-9

28. Kolyvas EA, Caldas C, Kelly K, Ahmad SS. Androgen receptor function and targeted therapeutics across breast cancer subtypes. *Breast Cancer Res*. 2022;24(1):79.

doi: 10.1186/s13058-022-01574-4

29. Oh S, Oh C, Yoo KH. Functional roles of CTCF in breast cancer. *BMB Rep*. 2017;50(9):445-453.

doi: 10.5483/bmbrep.2017.50.9.108

30. Segueni J, Noordermeer D. CTCF: A misguided jack-of-all-trades in cancer cells. *Comput Struct Biotechnol J*. 2022;20:2685-2698.

doi: 10.1016/j.csbj.2022.05.044

31. Kakani P, Dhamdhere SG, Pant D, *et al*. Hypoxia-induced CTCF promotes EMT in breast cancer. *Cell Rep*. 2024;43(7):114367.

doi: 10.1016/j.celrep.2024.114367

32. Miziak P, Baran M, Błaszczak E, *et al*. Estrogen receptor signaling in breast cancer. *Cancers (Basel)*. 2023;15(19):4689.

doi: 10.3390/cancers15194689

33. Liu N, Wang A, Xue M, Zhu X, Liu Y, Chen M. FOXA1 and FOXA2: The regulatory mechanisms and therapeutic implications in cancer. *Cell Death Discov*. 2024;10(1):172.

doi: 10.1038/s41420-024-01936-1

34. Metovic J, Borella F, D'Alonzo M, *et al*. FOXA1 in breast cancer: A luminal marker with promising prognostic and predictive impact. *Cancers (Basel)*. 2022;14(19):4699.

doi: 10.3390/cancers14194699

35. Bhin J, Yemelyanenko J, Chao X, *et al*. MYC is a clinically significant driver of mTOR inhibitor resistance in breast cancer. *J Exp Med*. 2023;220(11):e20211743.

doi: 10.1084/jem.20211743

36. Gao FY, Li XT, Xu K, Wang RT, Guan XX. c-MYC mediates

the crosstalk between breast cancer cells and tumor microenvironment. *Cell Commun Signal*. 2023;21(1):28.

doi: 10.1186/s12964-023-01043-1

37. Fallah Y, Brundage J, Allegakoen P, Shajahan-Haq AN. MYC-driven pathways in breast cancer subtypes. *Biomolecules*. 2017;7(3):53.

doi: 10.3390/biom7030053

38. Muste Sadurni M, Saponaro M. Deregulations of RNA pol II subunits in cancer. *Appl Biosci*. 2023;2(3):459-476.

doi: 10.3390/applbiosci2030029

39. Chai Y, Shi Y. Exosomal POU5 F1 derived from TNBC promotes cancer progression by regulating M2 macrophage polarization via inhibiting TRAF6 ubiquitination and activating AKT in macrophage. *Cell Biol Toxicol*. 2025;41(1):95.

doi: 10.1007/s10565-025-10041-7

40. Gwak JM, Kim M, Kim HJ, Jang MH, Park SY. Expression of embryonal stem cell transcription factors in breast cancer: Oct4 as an indicator for poor clinical outcome and tamoxifen resistance. *Oncotarget*. 2017;8(22):36305-36318.

doi: 10.18632/oncotarget.16750

41. Cai S, Geng S, Jin F, Liu J, Qu C, Chen B. POU5F1/Oct-4 expression in breast cancer tissue is significantly associated with non-sentinel lymph node metastasis. *BMC Cancer*. 2016;16:175.

doi: 10.1186/s12885-015-1966-6

42. Zaher DM, Abdin SM, Semreen MH, *et al*. Identifying the impact of RelA overexpression in triple-negative breast cancer cells using mass spectroscopy-based proteomics and metabolomics analysis. *Chem Biodivers*. 2025:e00717.

doi: 10.1002/cbdv.202500717

43. Xia W, Bacus S, Husain I, *et al*. Resistance to ErbB2 tyrosine kinase inhibitors in breast cancer is mediated by calcium-dependent activation of RelA. *Mol Cancer Ther*. 2010;9(2):292-299.

doi: 10.1158/1535-7163.MCT-09-1041

44. Shahbandi A, Nguyen HD, Jackson JG. TP53 mutations and outcomes in breast cancer: Reading beyond the headlines. *Trends Cancer*. 2020;6(2):98-110.

doi: 10.1016/j.trecan.2020.01.007

45. Shi T, Gao G, Cao Y. Long noncoding RNAs as novel biomarkers have a promising future in cancer diagnostics. *Dis Markers*. 2016;2016:9085195.

doi: 10.1155/2016/9085195

46. Bolha L, Ravnik-Glavač M, Glavač D. Long noncoding RNAs as biomarkers in cancer. *Dis Markers*. 2017;2017:7243968.

doi: 10.1155/2017/7243968

47. Jiang MC, Ni JJ, Cui WY, Wang BY, Zhuo W. Emerging roles of lncRNA in cancer and therapeutic opportunities. *Am J Cancer Res*. 2019;9(7):1354-1366.

48. Fathi Dizaji B. Strategies to target long non-coding RNAs in cancer treatment: Progress and challenges. *Egypt J Med Hum Gen*. 2020;21(1):41.

doi: 10.1186/s43042-020-00074-4

49. Peng L, Jiang J, Tang B, Nice EC, Zhang YY, Xie N. Managing therapeutic resistance in breast cancer: From the lncRNAs perspective. *Theranostics*. 2020;10(23):10360-10377.

doi: 10.7150/thno.49922

50. Jin H, Du W, Huang W, *et al*. lncRNA and breast cancer: Progress from identifying mechanisms to challenges and opportunities of clinical treatment. *Mol Ther Nucleic Acids*. 2021;25:613-637.

doi: 10.1016/j.omtn.2021.08.005

51. Zangouei AS, Zangoue M, Taghehchian N, *et al*. Cell cycle related long non-coding RNAs as the critical regulators of breast cancer progression and metastasis. *Biol Res*. 2023;56(1):1.

doi: 10.1186/s40659-022-00411-4

52. Cabanski CR, White NM, Dang HX, *et al*. Pan-cancer transcriptome analysis reveals long noncoding RNAs with conserved function. *RNA Biol*. 2015;12(6):628-642.

doi: 10.1080/15476286.2015.1038012

53. Saadh MJ, Rasulova I, Almoyad MAA, *et al*. Recent progress and the emerging role of lncRNAs in cancer drug resistance; Focusing on signaling pathways. *Pathol Res Pract*. 2024;253:154999.

doi: 10.1016/j.prp.2023.154999

54. Peng L, Yuan XQ, Liu ZY, *et al*. High lncRNA H19 expression as prognostic indicator: Data mining in female cancers and polling analysis in non-female cancers. *Oncotarget*. 2017;8(1):1655-1667.

doi: 10.18632/oncotarget.13768

55. Sun F, Liang W, Qian J. The identification of CRNDE, H19, UCA1 and HOTAIR as the key lncRNAs involved in oxaliplatin or irinotecan resistance in the chemotherapy of colorectal cancer based on integrative bioinformatics analysis. *Mol Med Rep.* 2019;20(4):3583-3596.

doi: 10.3892/mmr.2019.10588

56. Zhang L, Wang DL, Yu P. LncRNA H19 regulates the expression of its target gene HOXA10 in endometrial carcinoma through competing with miR-612. *Eur Rev Med Pharmacol Sci*. 2018;22(15):4820-4827.

doi: 10.26355/eurrev_201808_15617

57. Chen JS, Wang YF, Zhang XQ, *et al*. H19 serves as a diagnostic biomarker and up-regulation of H19 expression

contributes to poor prognosis in patients with gastric cancer. *Neoplasma*. 2016;63(2):223-230.

doi: 10.4149/207_150821N454

58. Zheng ZG, Xu H, Suo SS, *et al*. The essential role of H19 contributing to cisplatin resistance by regulating glutathione metabolism in high-grade serous ovarian cancer. *Sci Rep.* 2016;6:26093.

doi: 10.1038/srep26093

59. Pan R, Zhou H. Exosomal transfer of lncRNA H19 promotes erlotinib resistance in non-small cell lung cancer via miR-615-3p/ATG7 axis. *Cancer Manag Res*. 2020;12:4283-4297.

doi: 10.2147/CMAR.S241095

60. Guan N, Wang R, Guo WS, Lai YJ, Zhang YD, Cheng YY. Long non-coding RNA H19 regulates the development of gliomas through the Wnt/β-catenin signaling pathway. *Eur Rev Med Pharmacol Sci*. 2019;23(10):4243-4253.

doi: 10.26355/eurrev_201905_17929

61. Collins LC, Cole KS, Marotti JD, Hu R, Schnitt SJ, Tamimi RM. Androgen receptor expression in breast cancer in relation to molecular phenotype: Results from the Nurses' health study. *Mod Pathol*. 2011;24(7):924-931.

doi: 10.1038/modpathol.2011.54

62. Kensler KH, Regan MM, Heng YJ, *et al*. Prognostic and predictive value of androgen receptor expression in postmenopausal women with estrogen receptor-positive breast cancer: Results from the breast international group trial 1-98. *Breast Cancer Res*. 2019;21(1):30.

doi: 10.1186/s13058-019-1118-z

63. Anestis A, Zoi I, Papavassiliou AG, Karamouzis MV. Androgen receptor in breast cancer-clinical and preclinical research insights. *Molecules*. 2020;25(2):358.

doi: 10.3390/molecules25020358

64. Dai C, Ellisen LW. Revisiting androgen receptor signaling in breast cancer. *Oncologist*. 2023;28(5):383-391.

doi: 10.1093/oncolo/oyad049

65. Lehmann BD, Bauer JA, Chen X, *et al*. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767.

doi: 10.1172/JCI45014

66. Fang C, Wang Z, Han C, *et al*. Cancer-specific CTCF binding facilitates oncogenic transcriptional dysregulation. *Genome Biol*. 2020;21(1):247.

doi: 10.1186/s13059-020-02152-7

67. Lee JY, Mustafa M, Kim CY, Kim MH. Depletion of CTCF in breast cancer cells selectively induces cancer cell death via p53. *J Cancer*. 2017;8(11):2124-2131.

doi: 10.7150/jca.18818

68. Docquier F, Farrar D, D'Arcy V, *et al*. Heightened expression of CTCF in breast cancer cells is associated with resistance to apoptosis. *Cancer Res*. 2005;65(12):5112-5122.

doi: 10.1158/0008-5472.CAN-03-3498

69. Wong KM, Song J, Wong YH. CTCF and EGR1 suppress breast cancer cell migration through transcriptional control of Nm23-H1. *Sci Rep.* 2021;11(1):491.

doi: 10.1038/s41598-020-79869-9

70. Sun W, Li AQ, Zhou P, *et al*. DSCAM-AS1 regulates the G_1/S cell cycle transition and is an independent prognostic factor of poor survival in luminal breast cancer patients treated with endocrine therapy. *Cancer Med*. 2018;7(12):6137-6146.

doi: 10.1002/cam4.1603

71. Ma Y, Bu D, Long J, Chai W, Dong J. LncRNA DSCAM-AS1 acts as a sponge of miR-137 to enhance Tamoxifen resistance in breast cancer. *J Cell Physiol*. 2019;234(3):2880-2894.

doi: 10.1002/jcp.27105

72. Godinho MF, Wulfkuhle JD, Look MP, *et al*. BCAR4 induces antioestrogen resistance but sensitises breast cancer to lapatinib. *Br J Cancer*. 2012;107(6):947-955.

doi: 10.1038/bjc.2012.351

73. Lei JT, Gou X, Seker S, Ellis MJ. ESR1 alterations and metastasis in estrogen receptor positive breast cancer. *J Cancer Metastasis Treat*. 2019;5:38.

doi: 10.20517/2394-4722.2019.12

74. Mehta A, Tripathy D. Co-targeting estrogen receptor and HER2 pathways in breast cancer. *Breast*. 2014;23(1):2-9.

doi: 10.1016/j.breast.2013.09.006

75. Baselga J, Albanell J, Ruiz A, *et al*. Phase II and tumor pharmacodynamic study of gefitinib in patients with advanced breast cancer. *J Clin Oncol*. 2005;23(23):5323-5333.

doi: 10.1200/JCO.2005.08.326

76. Osborne CK, Neven P, Dirix LY, *et al*. Gefitinib or placebo in combination with tamoxifen in patients with hormone receptor-positive metastatic breast cancer: A randomized phase II study. *Clin Cancer Res*. 2011;17(5):1147-1159.

doi: 10.1158/1078-0432.CCR-10-1869

77. Ye X, Liu Q, Qin X, *et al*. BCAR4 facilitates trastuzumab resistance and EMT in breast cancer via sponging miR-665 and interacting with YAP1. *FASEB J*. 2024;38(7):e23589.

doi: 10.1096/fj.202301617RR

78. Mazumder A, Shiao S, Haricharan S. HER2 activation and endocrine treatment resistance in HER2-negative breast cancer. *Endocrinology*. 2021;162(10):bqab153.

doi: 10.1210/endocr/bqab153

79. Godinho MF, Sieuwerts AM, Look MP, *et al*. Relevance of BCAR4 in tamoxifen resistance and tumour aggressiveness

of human breast cancer. *Br J Cancer*. 2010;103(8):1284-1291.

doi: 10.1038/sj.bjc.6605884

80. Gan FJ, Li Y, Xu MX, *et al*. LncRNA BCAR4 expression predicts the clinical response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. *Cancer Biomark*. 2021;32(3):339-351.

doi: 10.3233/CBM-210048

81. Xuan J, Liu Y, Zeng X, Wang H. Sequence requirements for miR-424-5p regulating and function in cancers. *Int J Mol Sci*. 2022;23(7):4037.

doi: 10.3390/ijms23074037

82. Chen Z, Pan T, Jiang D, *et al*. The lncRNA-GAS5/miR-221-3p/DKK2 axis modulates ABCB1-mediated adriamycin resistance of breast cancer via the Wnt/β-catenin signaling pathway. *Mol Ther Nucleic Acids*. 2020;19:1434-1448.

doi: 10.1016/j.omtn.2020.01.030

83. Zheng S, Li M, Miao K, Xu H. lncRNA GAS5-promoted apoptosis in triple-negative breast cancer by targeting miR-378a-5p/SUFU signaling. *J Cell Biochem*. 2020;121(3): 2225-2235.

doi: 10.1002/jcb.29445

84. Li W, Zhai L, Wang H, *et al*. Downregulation of LncRNA GAS5 causes trastuzumab resistance in breast cancer. *Oncotarget*. 2016;7(19):27778-27786.

doi: 10.18632/oncotarget.8413

85. Zhang X, Luo M, Zhang J, *et al*. The role of lncRNA H19 in tumorigenesis and drug resistance of human cancers. *Front Genet*. 2022;13:1005522.

doi: 10.3389/fgene.2022.1005522

86. Zhu QN, Wang G, Guo Y, *et al*. LncRNA H19 is a major mediator of doxorubicin chemoresistance in breast cancer cells through a cullin4A-MDR1 pathway. *Oncotarget*. 2017;8(54):91990-92003.

doi: 10.18632/oncotarget.21121

87. Wang Y, Zhou P, Li P, Yang F, Gao XQ. Long non-coding RNA H19 regulates proliferation and doxorubicin resistance in MCF-7 cells by targeting PARP1. *Bioengineered*. 2020;11(1):536-546.

doi: 10.1080/21655979.2020.1761512

88. Yan L, Yang S, Yue CX, *et al*. Long noncoding RNA H19 acts as a miR-340-3p sponge to promote epithelial-mesenchymal transition by regulating YWHAZ expression in paclitaxel-resistant breast cancer cells. *Environ Toxicol*. 2020;35(9):1015-1028.

doi: 10.1002/tox.22938

89. Si X, Zang R, Zhang E, *et al*. LncRNA H19 confers chemoresistance in ERα-positive breast cancer through epigenetic silencing of the pro-apoptotic gene *BIK*. *Oncotarget*. 2016;7(49):81452-81462.

doi: 10.18632/oncotarget.13263

90. Han J, Han B, Wu X, *et al*. Knockdown of lncRNA H19 restores chemo-sensitivity in paclitaxel-resistant triple-negative breast cancer through triggering apoptosis and regulating Akt signaling pathway. *Toxicol Appl Pharmacol*. 2018;359:55-61.

doi: 10.1016/j.taap.2018.09.018

91. Wang X, Pei X, Guo G, *et al*. Exosome-mediated transfer of long noncoding RNA H19 induces doxorubicin resistance in breast cancer. *J Cell Physiol*. 2020;235(10):6896-6904.

doi: 10.1002/jcp.29585

92. Wang J, Xie S, Yang J, *et al*. The long noncoding RNA H19 promotes tamoxifen resistance in breast cancer via autophagy. *J Hematol Oncol*. 2019;12(1):81.

doi: 10.1186/s13045-019-0747-0

93. Gao H, Hao G, Sun Y, Li L, Wang Y. Long noncoding RNA H19 mediated the chemosensitivity of breast cancer cells via Wnt pathway and EMT process. *Onco Targets Ther*. 2018;11:8001-8012.

doi: 10.2147/OTT.S172379

94. Sun Z, Zhang C, Wang T, Shi P, Tian X, Guo Y. Correlation between long non-coding RNAs (lncRNAs) H19 expression and trastuzumab resistance in breast cancer. *J Cancer Res Ther*. 2019;15(4):933-940.

doi: 10.4103/jcrt.JCRT_208_19

95. Zhou D, Gu J, Wang Y, Luo B, Feng M, Wang X. Long noncoding RNA CCAT2 reduces chemosensitivity to 5-fluorouracil in breast cancer cells by activating the mTOR axis. *J Cell Mol Med*. 2022;26(5):1392-1401.

doi: 10.1111/jcmm.17041

96. Pirlog R, Drula R, Nutu A, Calin GA, Berindan-Neagoe I. The roles of the colon cancer associated transcript 2 (CCAT2) long non-coding RNA in cancer: A comprehensive characterization of the tumorigenic and molecular functions. *Int J Mol Sci*. 2021;22(22):12491.

doi: 10.3390/ijms222212491

97. Cai Y, He J, Zhang D. Long noncoding RNA CCAT2 promotes breast tumor growth by regulating the Wnt signaling pathway. *Onco Targets Ther*. 2015;8:2657-2664.

doi: 10.2147/OTT.S90485

98. Redis RS, Sieuwerts AM, Look MP, *et al*. CCAT2, a novel long non-coding RNA in breast cancer: Expression study and clinical correlations. *Oncotarget*. 2013;4(10):1748-1762.

doi: 10.18632/oncotarget.1292

99. Sarrafzadeh S, Geranpayeh L, Tasharrofi B, *et al*. Expression study and clinical correlations of MYC and CCAT2 in breast cancer patients. *Iran Biomed J*. 2017;21(5):303-311.

doi: 10.18869/acadpub.ibj.21.5.303

100. Cai Y, He J, Zhang D. [Suppression of long non-coding RNA CCAT2 improves tamoxifen-resistant breast cancer cells' response to tamoxifen]. *Mol Biol (Mosk)*. 2016;50(5): 821-827.

doi: 10.7868/S0026898416030046

101. Moradi F, Mohajerani F, Sadeghizadeh M. CCAT2 knockdown inhibits cell growth, and migration and promotes apoptosis through regulating the hsa-mir-145-5p/AKT3/mTOR axis in tamoxifen-resistant MCF7 cells. *Life Sci*. 2022;311(Pt B):121183.

doi: 10.1016/j.lfs.2022.121183

102. Xie H, Guo Y, Xu Z, *et al*. Dual function of CCAT2 in regulating luminal subtype of breast cancer depending on the subcellular distribution. *Cancers (Basel)*. 2023;15(2):538.

doi: 10.3390/cancers15020538

103. Acheampong T, Kehm RD, Terry MB, Argov EL, Tehranifar P. Incidence trends of breast cancer molecular subtypes by age and race/ethnicity in the US from 2010 to 2016. *JAMA Netw Open*. 2020;3(8):e2013226.

doi: 10.1001/jamanetworkopen.2020.13226