Biomarkers for Breast Cancer

Subjects: Oncology

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Breast cancer is the most commonly diagnosed cancer type and the leading cause of cancer-related mortality in women worldwide. Breast cancer is fairly heterogeneous and reveals six molecular subtypes: luminal A, luminal B, HER2+, basal-like subtype (ER−, PR−, and HER2−), normal breast-like, and claudin-low. Breast cancer screening and early diagnosis play critical roles in improving therapeutic outcomes and prognosis. Mammography is currently the main commercially available detection method for breast cancer; however, it has numerous limitations. Therefore, reliable noninvasive diagnostic and prognostic biomarkers are required. Biomarkers used in cancer range from macromolecules, such as DNA, RNA, and proteins, to whole cells. Biomarkers for cancer risk, diagnosis, proliferation, metastasis, drug resistance, and prognosis have been identified in breast cancer. In addition, there is currently a greater demand for personalized or precise treatments; moreover, the identification of novel biomarkers to further the development of new drugs is urgently needed.

breast cancer biomarker diagnosis prognosis treatment

1. Introduction

Breast cancer is the most commonly diagnosed cancer type and the leading cause of cancer-related mortality in women worldwide [1]. It is estimated that there were approximately 2 million new cases and 627,000 breast cancer-related mortalities globally in 2018 [2][3]. Although the five-year relative survival rate for localized breast cancer is relatively high (80–92%), the survival rate dramatically declines to <25% for metastatic breast cancer [4]. Breast cancer is fairly heterogeneous; gene-expression profiling of breast cancer revealed six intrinsic molecular subtypes: luminal A (estrogen receptor (ER)+, progesterone receptor (PR)+, human epidermal growth factor receptor 2 (HER2)−, and Ki67−), luminal B (ER+, PR+, HER+/−, and Ki67+), HER2+, basal-like subtype (ER−, PR−, and HER2−), normal breast-like, and claudin-low (low expression of cellular adhesion genes) [5][6][7]. Triple-negative breast cancer (TNBC) belongs to either the basal-like or claudin-low subtypes [7]. Breast cancer subtypes differ in terms of clinical relevance, patterns of gene expression, selection of therapeutic strategies, responses to treatment, and prognosis [5][8][9]. Therefore, knowledge of the specific breast cancer subtype is important in guiding treatment decisions and predicting prognosis.

Breast cancer screening and early diagnosis play critical roles in improving therapeutic outcomes, leading to a better prognosis for breast cancer patients [10]. Mammography is currently the main commercially available detection method for breast cancer; however, it has numerous well-known limitations including low sensitivity of 25~59% for detecting cancer in dense breasts, which present commonly in younger women, as well as high rates of false-negatives and false positives, and 1–10% overdiagnosis [11][12][13]. Therefore, the effective management of

breast cancer during therapy or early detection depends on the availability of reliable noninvasive diagnostic, prognostic, and predictive biomarkers [14][15]. In addition, an increasing number of patients demand personalized or precise treatments; hence, the identification of novel biomarkers for diagnosis and prognosis and the development of new drugs is urgently required.

Biomarkers for cancer include substances released from the cancer cells themselves or by other tissues in response to tumors as well as physiological markers that can be visualized using imaging technology or detected by molecular technology [16][17]. Biomarkers are objective and quantifiable evaluations of biological states or diseases that can predict tumor behavior, prognosis, or treatment responses, thus playing an important role in the management of breast cancer [18][19]. They must be validated by human samples to ensure that they reflect the clinical outcome [20][21]. Because tumor cells are highly heterogeneous, a single biomarker might not have sufficient sensitivity and specificity to accurately predict cancer progression and metastasis, and a combination of multiple markers is more appealing.

With the rapid advancement of molecular signaling pathways and genetic signatures, including immunohistochemistry, next-generation sequencing, and targeted multigene, numerous clinically relevant biomarkers in tissue and/or blood (liquid biopsies) have been reported to aid in determining the risk of metastasis, prognosis, recurrence, treatment guidance, and drug resistance in breast cancer. Some of these have been used clinically [19][22][23][24]. However, they lack specificity and sensitivity. Therefore, the identification of novel and effective biomarkers is urgently required. In addition, there is an emerging development of immunotherapies for breast cancer, and it is important to identify reliable biomarkers for predicting who will benefit from immunotherapies.

2. Types of Biomarkers

Biomarkers used in cancer range from macromolecules, such as DNA, genetic mutations, RNA, and proteins to whole cells (Table 1 and Table 2). They can circulate in the blood as circulating mRNA, circulating free DNA, and circulating tumor cells, making liquid biopsies attractive for clinical use [17][25][26]. Two types of biomarkers are used for cancer treatment outcome: prognostic biomarkers are associated with clinical outcome and can inform whether a patient should be treated, and predictive biomarkers to guide a treatment that is effective only in a subtype of breast cancer [27][28][29]. Some biomarkers are already available in clinical practice, whereas some biomarkers have been validated in mouse models or clinical trials.

Table 1. Biomarkers discovered recently for breast cancer.

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
DNA	Immune response-related genes	may be used to identify patients with a good prognosis in	Measured the tissues from 819 breast cancer patients.	[30]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
	(*BTN3A2*, *CD2* and *TRBC1*)	HR−/HER2+ breast cancer.		
	Immunity genes (*APOBEC3G*, *CCL5*, *CCR2*, *CD2*, *CD27*, *CD3D*, *CD52*, *CORO1A*, *CXCL9*, *GZMA*, *GZMK*, *HLA-DMA*, *IL2RG*, *LCK*, *PRKCB*, *PTPRC*, and *SH2D1A*)	immunity gene expression was an important parameter for prognosis.	Tested on 225 breast tumor FFPE tissues.	[31]
	T helper type-1 gene signatures (*IFNG*, *STAT1*, *GRZM*, *CXCL9*)	are correlated with favorable clinical outcome, particularly in ER- tumors.		[32][33][34]
	methylated *14-3-3 σ*	as a blood-based biomarker for breast cancer diagnosis.	meta-analysis	[35]
	methylated *APC* and *RARβ*$_2$	might be valuable serum-based molecular markers for early detection of early-stage breast cancer, low grade tumors and TNBC.	Tested on serum samples from 121 breast cancer patients, 79 patients with benign breast diseases, and 66 healthy controls.	[36]
	S100P and *HYAL2* hypomethylation	as breast cancer biomarkers for early stage detection.	*S100P*: Validation I: 235 familial breast cancer cases and 206 controls; Validation II: 189 sporadic breast cancer cases and 189 controls;	[37][38]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
			Validation III: 156 sporadic breast cancer cases and 151 controls. *HYAL2*: first validation round: 338 breast cancer cases and 507 controls; second validation round: 189 breast cancer cases and 189 controls.	
	long noncoding RNA 299 gene (*LINC00299*) methylation	for early detection of TNBC in young women.	Examined blood samples of 154 TNBC cases and 159 breast cancer-free matched controls.	[39]
	ESR1 mutations	1. *ESR1* Y537S mutation promotes resistance to fulvestrant. 2. may have clinical utility in directing further endocrine therapy. 3. *ESR1* mutations are prevalent in ER-positive aromatase inhibitor-treated metastatic breast cancer predicting its prognosis.	1. Testing the blood samples of 195 patients from the PALOMA-3 cohort; 2. In the SoFEA trial, plasma samples of 162 patients were tested; in the PALOMA3 trial, plasma samples of 360 patients were tested. 3. In the BOLERO-2 cohort, 541 plasma samples were examined.	[40][41][42]
	TP53 mutation	associated with better prognosis in metaplastic breast	Examined the clinical outcomes data of 52 archived samples.	[43]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
		cancer with increased RFS and OS.		
	a 14-gene prognostic signature (*PFKL*, *P4HA2*, *GRHPR*, *SDC3*, *PPP1R15A*, *SIAH2*, *NDRG1*, *BTG1*, *TPD52*, *MAFF*, *ISG20*, *LALBA*, *ERRFI1*, and *VHL*)	could serve as a potential prognostic biomarker for breast cancer.	Clinical data from 1097 cases were obtained from the TCGA database. 113 adjacent normal samples and 1039 breast cancer patients were followed-up for ≥1 month.	[44]
	28-CpG based methylation panel	could independently predict the overall survival of breast cancer patients. Patients with high methylation risk were associated with tumor heterogeneity and poor survival.	The DNA methylation profile of The Cancer Genome Atlas Breast Invasive Carcinoma (TCGA-BRCA) included a total of 890 breast cancer samples. A total of 62, 118, 188, 70, and 58 breast cancer samples were included in GSE37754, GSE72245, GSE75067, GSE78754, and GSE72251. 40 normal breast samples and 80 breast cancer samples in GSE666952.	[45]
MicroRNAs	miR-21 and/or miR-221	can be successfully applied as breast cancer biomarkers.	Tested the sera of 50 patients with breast cancer, 25 fibroadenoma, and 25 healthy controls.	[46][47]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
	six miRNA signature, miR-21, miR-221, miR-210, miR-195, miR-145, and let-7a	for early detection of TNBC.	Examined 85 paired tumor tissues and sera with an equal number of adjacent normal tissue margins and normal sera from healthy women and 15 benign fibroadenomas.	[48]
	miR-21	promotes the transformation and development of breast cancer.	Examined on blood samples of 30 female patients with breast tumors and 30 with benign breast lesions	[49]
	Exosomal miR-1246 and miR-21	for detection of breast cancer.	Tested the plasma of 16 patients with breast cancer and 16 healthy control subjects.	[50]
	five-miRNA signature, miR-1246, miR-1307-3p, miR-4634, miR-6861-5p, and miR-6876-5p	for detection of early stage breast cancer.	Tested 1280 serum samples of breast cancer patients, 2836 serum samples from non-cancer controls, 451 from patients with other types of cancers, and 63 from patients with non-breast benign diseases.	[51]
	The eight-marker signature (miR-16, let7d, miR-103, miR-107, miR-148a, let-7i, miR-19b, and miR-22)	for early detection of breast cancer including younger women.	Tested plasma from 127 sporadic breast cancer cases and 80 healthy controls.	[52]

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	a 9-miRNA profile	for early detection of breast cancer.	Examined 116 blood samples including 36 with breast cancer.	[53]
	miR-1204	could be a novel prognostic/diagnostic biomarker for breast cancer patients.	Tested sera from 144 breast cancer patients and 38 healthy controls.	[54]
	combination of miR-181b-5p, miR-200b-3p, miR-200c-3p, and miR-203a-3p	could be potential diagnostic biomarkers for inflammatory breast cancer.	Examined tissue specimens of 18 non- inflammatory breast cancer and 17 inflammatory breast cancer patients.	[55]
	miR-140 and miR-196a	both miR-140 and miR-196a are promising biomarkers for the diagnosis of breast cancer.	Tested 110 cases of breast cancer and their adjacent non-tumor tissues.	[56]
	miR-26a/26b	may be useful markers of the progression of breast cancer.	Examined 29 pairs of fresh breast cancer and adjacent tissues.	[57]
	miR-26b	inhibited TNBC cell proliferation and tumor growth.	-	[58]
	miR-182	contributed to cell progression.	45 patients with breast cancer.	[59]

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	miR-224	inhibited proliferation and migration of breast cancer cells.	Examined serum samples from 45 patients with breast cancer.	[60]
	miR-124-3p	reduced breast cancer cell proliferation and metastasis.	Tested 30 breast cancer and normal breast tissues.	[61]
	miRNA-17 and miRNA-20b	resistance to taxol in breast cancer patients increased with the loss of miRNA-17 and miRNA-20b.	55 pairs of breast cancer tissues and adjacent normal tissues were examined.	[62]
	miR-18a	overexpression directly led to Dicer repression and confers paclitaxel resistance in TNBC.	Tested 20 TNBC patient tissues.	[63]
	miR-90b, 130a, 200b, and 452	contribute to chemoresistance.	-	[64]
	miRNAs 221 and 222	chemoresistance to fulvestrant, doxorubicin, or trastuzumab.	-	[64]
	miRNA 320a	chemoresistance to paclitaxel.	-	[64]
	miRNAs let-7, 181a and 145	chemoresistance to doxorubicin, tamoxifen, or epirubicin.	-	[64]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
	miRNA 125b	chemoresistance to tamoxifen, letrozole, anastrazole or fulvestrant.	-	[64]
	miR200c and miR489	downregulation of miR200c and miR489 were correlated with better prognosis.	-	[64]
	miR484 and miR4443	upregulation of miR484 and miR4443 were associated with better prognosis.	-	[64]
	miR520h and miR125b	upregulation of miR520h and miR125b were correlated with poor prognosis.	-	[64]
	miR125b and miR21	could be novel, noninvasive predictive markers for neoadjuvant chemotherapy response and prognosis in breast cancer.	Examined 118 stage II/III breast cancer patients and 30 healthy adult women.	[65]
	miR-106b	is a putative plasma marker for risk assessment in patients with breast cancer.	Examined the tissue and plasma samples from 173 patients with primary breast cancer and 50 women with fibroadenoma.	[66]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
	pre-miR-488	could be a novel prognostic biomarker for predicting recurrence in breast cancer patients.	Tested the blood from 356 female patients with breast cancer without distant metastases, preoperative therapy or previous treatment for various cancers, 330 invasive ductal carcinomas (IDC), 26 were ductal carcinomas in situ (DCIS), and 11 healthy volunteers.	[67]
	miR-130b	contributes to MDR through PI3K/Akt signaling pathway.	Tested 29 pairs of breast cancer tissues and their adjacent noncancerous tissues.	[68]
	miR-9	inhibit metastasis.	-	[69]
	miR-205	inhibit metastasis.	Tested on 40 pairs of TNBC and their adjacent normal breast tissues.	[70][71]
	miR-628	inhibit metastasis.	-	[72]
cicRNAs	hsa_circ_0001785	the potential diagnostic biomarker for breast cancer.	Examined the plasma of 57 breast cancer patients and 17 age-matched healthy individuals.	[73]
	Combination of hsa_circ_006054, hsa_circ_100219,	may be diagnostic biomarker for breast cancer.	Tested 51 breast cancer and adjacent normal tissues.	[74]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
	and hsa_circ_406697			
	hsa_circ_0001982	hsa_circ_0001982 knockdown suppressed breast cancer cell proliferation and invasion and induced apoptosis by targeting miR-143.	Examined 29 breast cancer tissues and adjacent normal tissues.	[75]
	circRNA-000911	enhanced expression of circRNA-000911 suppressed cell proliferation, migration and invasion, and promoted the apoptosis of breast cancer cells.	Human circRNA microarray analysis.	[76]
	circ-ABCB10	circ-ABCB10 knockdown suppressed the proliferation and increased apoptosis of breast cancer cells.	Tested 36 cancer and adjacent noncancerous tissues.	[77]
	circGFRA1	Knockdown of circGFRA1 inhibited proliferation and promoted apoptosis in TNBC.	Examined 51 TNBC tissues and their paired adjacent normal tissues.	[78]
	circ_0006528	may play a role in breast cancer	-	[79]

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		chemoresistance.		
Protein	4-test combination of TAP + CEA + CA125 + CA15-3	higher sensitivity than the traditional test, i.e., CEA, CA125, or CA15-3 and may be auxiliary used in early screening.	Tested on blood of 261 women with operable benign breast disease and 348 with breast cancer.	[80]
	TFF1, TFF2 and TFF3	for breast cancer screening.	Examined sera in 94 breast cancer patients and 84 health check females, and breast cancer tissues.	[81]
	Pleiotrophin (PTN)	PTN could be a potential biomarker for the presence of breast cancer.	Tested sera in 105 breast cancer patients and 40 healthy volunteers using ELISA. In addition, PTN expression was examined in 80 BC tissues in a nested case-control study by immunohistochemistry.	[82]
	Combination of miR-127-3p and HE4	Greatly improved the sensitivity of breast cancer diagnosis and may be a candidate biomarker for early detection and diagnosis of breast cancer.	Examined plasma in 102 patients with breast cancer, and 87 patients with benign breast tumors and 90 healthy volunteers as control.	[83]
	Combination of VEGF and CA 15-3	showed the highest usefulness in the diagnosis of early breast cancer.	Tested plasma in 100 breast cancer patients, and 50 patients with benign breast	[84]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
			tumors, and 50 healthy women as control.	
	Combination of AGR3 and AGR2	showed the potential usability of AGR3 and AGR2 as biomarkers for blood-based early detection of human breast cancer.	Examined 190 breast carcinomas and 39 normal breast tissues; 40 breast cancer and 40 healthy serum samples.	[85]
	COL11A1, COMP, and COL10A1	may be useful in diagnostic assessment for breast cancers	Discovery dataset: 50 healthy donors, 42 patients with benign breast disease, and 52 patients with invasive breast cancer; validation cohort: 52 healthy donors, 49 benign breast disease, and 66 invasive breast cancer.	[86]
	CA15-3 included in the diagnostic panel constituted of 4 protein peaks [m/z 3972, 6850, 8115 (Bc2), and 8949 (Bc3)]	distinguished invasive ductal carcinoma from healthy controls and benign breast diseases.	Tested the sera from 62 patients with invasive ductal carcinoma, and 47 non-cancerous individuals (16 healthy controls and 31 patients with benign breast diseases).	[87]
	Serum autoantigens (LGALS3, PHB2, MUC1 and GK2) in	had better diagnostic values compared with anti-CA 15-3 alone for	Examined the sera from 100 breast cancer patients and 50 healthy subjects.	[88]

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
	combination with CA 15-3	early-stage breast cancer.		
	A combination of six antigens, RAD50, PARD3, SPP1, NY-BR-62, and NY-CO-58	could discriminate breast cancer patients from healthy controls.	Tested the sera of 112 patients with breast cancer and 35 patients with no neoplasm (control group); Cancer and non-cancerous breast tissue samples were obtained from 17 female patients with primary breast carcinomas and 7 patients with fibrocystic disease.	[89]
	A combination of serum protein biomarkers and tumor associated	the benefit of the integration of SPB and TAAb for detecting	Using a retrospective cohort of sera from 18 participants with no breast diseases, 92 participants with benign breast	[90]

Cell Types	Prognosis/Treatment	References
T cells (Tregs)	better prognosis in lymph node negative, primary breast cancer patients including those with stages I–III.	[32][33][34][101][102][103]
CD8 T cells	were predictive for response to checkpoint inhibitors.	[104]
B cells	1. better prognosis in lymph node negative, primary breast cancer patients including those with stages I–III, ER- breast cancer, highly proliferating luminal B breast cancer, and 2. improved outcome in HR+ breast cancer.	[101][102][105][106]
Plasma cells	better prognosis in ER- breast cancer and highly proliferating luminal B	[106]

Cell Types	Prognosis/Treatment	References
	breast cancer.	
TILs	1. The frequency of TILs is usually high in the more aggressive breast cancer subtypes. TIL frequency was found to be a superior prognostic marker; 2. were predictive for response to checkpoint inhibitors, 3. was associated with improved responses to trastuzumab or lapatinib in HER2+ breast cancer.	[33][104][106][107][108]
Macrophages	associate with survival in basal-like breast cancer.	[103][108][109][110]
MDSCs	are correlated with poor survival in ER- tumors.	[109][110]
Neutrophils	1. are associated with poor breast cancer survival; 2. inhibiting leukotriene-generating enzyme arachidonate 5-lipoxygenase (Alox5) abrogates neutrophil pro-metastatic activity and consequently reduces metastasis.	[108][111]
NK cells	were found significantly depleted from peripheral blood compared to pretreatment levels after chemotherapy.	[102]
myeloid dendritic cell	improved outcome in HR+ breast cancer.	[105]
astrocytes	may provide new opportunities for effective anti-metastasis therapies, especially for brain metastasis patients.	[112]
Exosome	fibronectin	This liquid biopsy to detect fibronectin on	Tested on plasma samples from 70 disease-free	[99]

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and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2018, 4, 1553–1568.

Type	Biomarkers	Clinical Value	Clinical Validation/Research Design	References
		circulating extracellular vesicles could be a promising method to detect early breast cancer.	individuals, 240 breast cancer patients, 40 breast cancer patients after surgical resection, 55 patients with benign breast tumor, and 80 patients with non-cancerous diseases (thyroiditis, gastritis, hepatitis B, and rheumatoid arthritis.	
	Del-1	is a promising marker for identification of patients with early-stage breast cancer and distinguish breast cancer from benign breast tumors and noncancerous diseases.	Measured in plasma samples from 81 healthy controls, 269 patients with breast cancer, 50 breast cancer patients after surgical resection, 64 patients with benign breast tumors, and 98 patients with noncancerous diseases.	[100]

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