Molecular studies of breast cancer in Iran: A Systematic Review

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Abstract

Background: The present study aimed to review the existing cellular and molecular research systematically carried out in the field of breast cancer in Iran. This study was part of a big project, which evaluated a variety of studies conducted on breast cancer in Iran.

Methods: All molecular articles about breast cancer in Iran which were published from January 2005 to October 21, 2015 were included. English and Persian databases consisted of Web of Science, PubMed, Scopus, Scientific Information Database (SID) and IranMedex. Finally of 3331 abstracts, a total of 379 articles, including 219 English and 160 Persian papers related to molecular studies were included in this study.

Results: After initial evaluations, 240 studies were included. Molecular studies conducted in Iran were divided into four main groups based on their focus. They evaluated breast cancer susceptibility genes, Prognosis and clinicopathologic features of the patients, compounds with therapeutic properties, and diagnosis. Moreover, ethical statements in manuscripts were investigated.

Conclusions: Result of this review showed that most of the researches in Iran categorize to 4 main subjects. The majority of the studies in Iran were conducted sporadically and with small sample sizes. Stronger studies would require the development of more biological banks and execution of multicenter comprehensive projects defined with orientation to main problems of Breast Cancer patients in the country.

Background

Studies on cancer, especially breast cancer, are extensively ongoing throughout the world. Many Iranian research centers and universities are also working in this field. The present study aimed to review the existing cellular and molecular research carried out in the area of breast cancer in Iran. This study was part of comprehensive research, which evaluated a variety of studies conducted on breast cancer in Iran. The articles reviewed in this study involved molecular studies on genetic susceptibility, diagnosis, Prognosis, survival, therapeutic compounds and clinicopathologic features of breast cancer.

Genetic mutations have a significant role in increasing the risk of breast cancer. In addition to BRCA1/2, low-penetrance genes are also effective in the development of this cancer (1). Therefore, this study sought to collect data on various examined genes from different ethnic groups in Iran. Knowing about the researches which are focusing on genetic mutations in Iran, will make an essential contribution toward decision-making about the design of future studies. On the other hand, since the frequency of younger patients (< 50 years) with breast cancer is higher in Iran compared to western countries (2), the Iranian population might have a particular mutation pattern that affects the risk of breast cancer in younger individuals.

Genotype-phenotype relationship is another critical subject in cancer research. These studies include evaluating the association of genotype and phenotype with the response to treatment and type of clinicopathologic features of patients. Such studies investigated the role of mutations, gene expressions, or epigenetic changes in various subgroups of affected people (3, 4).

Herbal medicine and new medications are among the important aspects of drug discovery that many researchers are interested in (5). Vast geographic area and a combination of various animal and plant species in Iran (6) persuade researchers to investigate new anticancer medications. The microbial metabolite, chemical, or synthetic compounds with anticancer properties are another source for drug discovery.

According to the category mentioned above of breast cancer studies and due to the limited budget of research in this country, it is crucial to categorize breast cancer studies. To best of our knowledge, there is not a comprehensive study discussing the mentioned issues. As a result, this systematic review could shed light on the whole picture of studies about the breast cancer molecular susceptibility, treatment, Prognosis, survival and diagnosis in Iran during a decade. It may help organizing the research resources in future.

Methods

This study was part of a big project evaluating different aspects of breast cancer in Iran. All articles about breast cancer in Iran which were published within a specific period were included and divided into five subgroups. The process of the systematic review was then followed in each subset. Details of the methodology are as follows:

Search Strategy

All articles published from January 2006 to October 21, 2015, were included. To achieve the most comprehensive search results from electronic medical databases, keywords were extracted from the Medical Subject Headings (MeSH) of PubMed. Online English international electronic databases consisted of Web of Science, PubMed, and Scopus. English search formula was "breast cancer" OR "breast carcinoma" OR "breast tumor" OR "breast neoplasm" AND Iran. Scientific Information Database (SID) and IranMedex. Since using a combined formula was not possible in Persian search, the keywords, including the Persian equivalents of breast tumor, breast cancer, breast carcinoma, and breast neoplasm, and Iran was searched separately and combined with each other. A total of 1986 English and 1345 Persian abstracts were included.

Data screening

After excluding duplicate articles keywords, three experienced persons in the field of breast cancer screened the initial search results and divided them into five subgroups of epidemiology and risk factors, genetics, prevention, diagnosis and treatment, and rehabilitation. After excluding duplicate and unrelated articles based on title and abstract, 763 English and 572 Persian abstracts were included in those categories. Since some articles were allocated to more than one group, the total of 1646 eligible items entered the process of the systematic review. More details have been published in the previous publication of this project.(7)

Totally 379 articles included in a molecular subgroup. Full texts of the selected papers were found and, on some occasion, an e-mail was sent to corresponding authors to get the necessary information. Three reviewers used a checklist to appraise the full texts of selected articles critically. The reviewers discussed and resolved any cases of disagreement.

Data extraction

After reviewing all selected articles, the necessary information was extracted and entered into the study characteristics sheet. Because of the wide variation in the methodology and presented results of the studies chosen, an Excel sheet was used for data extraction. The first part of the datasheet contained general information about the first author, number of authors, title, study design, year of publication, year of the study (midpoint), city and place of the study, study population, sample type, total sample size, and ethnicity, sex, and age of the participants. The second and third parts of data consisted of the method of research and main results, respectively.

Three persons extracted all articles. The manager of the research team organised the three extracted forms in one sheet. The main objective of this study was to clarify the distribution of breast cancer researches in Iran. Therefore, no studies were excluded due to low quality. Duplicate and unrelated articles were excluded from the study. For better quality assessment of the articles, all their limitations were highlighted by entering NA (not assigned) in relevant columns of the results tables.

Data analysis

In the third step, the extracted data were analyzed. Due to the variety in study fields, the results were categorized according to study designs. The reviewed articles were categorized into five groups, including susceptibility, treatment with the different type of compounds, Prognosis, survival and clinicopathologic features, and diagnosis. However, 17 studies could not be included in any of the mentioned groups. They were, hence, not inserted in the tables but described in the text.

This research has been approved in Breast Cancer Research Center Ethical Committee with ethical code number "IR.ACECR.IBCRC.REC.1394.54"

Results

A total of 379 articles, including 219 English and 160 Persian papers, were found eligible. After initial evaluations, 139 studies were excluded from the systematic review due to irrelevance ($n = 37$), unavailability of full text ($n = 14$), duplicates ($n = 54$), irrelevance of publication date ($n = 12$), inaccessibility ($n = 5$), and poster ($n = 3$), review studies ($n = 12$), or note articles ($n = 2$). Ultimately, 240 studies were included. (Fig. 1) Duplicates found during this phase were articles published in both Persian and English languages. The reviewed articles were categorized into five groups according to their main themes. The results of the analysis of the papers in each group were as follows:

Susceptibility

Table 1 summarises the studies in Iran which examined genes related to breast cancer susceptibility. Based on these studies, susceptibility genes were divided into three groups, including high, intermediate, and low penetrance genes. Accordingly, from a total of 62 studies, 21 examined high-penetrance genes, four studied intermediate-penetrance genes, and 38 investigated low-penetrance genes. Moreover, 47 studies were conducted on blood samples, nine on tissue samples, three on blood and tissue samples, and three on cell lines.

Table 1
Studies focusing on susceptibility genes in breast cancer

NO.	City of Study	Type of sample	Total Sample Size	Case	Ctrl	Sex	Gene /Protein Name	PG	GENE/Protein Alterations	Ref.
1	Zahedan	Blood	479	262	217	F	APOBEC3	L	Deletion	(40)
2	Ahvaz	Blood	70	38	32	F	BRCA1	H	185delAG exon2,617delT exon11	(41)
3	Mashhad	Blood	68	39	29	F	BRCA1	H	185delAG, 5382insC, unclarified mutations in the 251 bp fragment of exon 11	(42)
4	Kerman	Blood	30	-	-	F/M	BRCA1	H	c.1017delA, c.969InsC, c.999T > A, c.792A > C, c.825G > C, c.822T > A, c.1068A > G, c.969A > T, c.966T > C	(43)
5	Isfahan	Blood	61	41	20	F	BRCA1 BRCA2	H	185 del AG, 5382 ins C, 1476 del G, 3889 del AG 6033-34 ins GT, 6174 del T	(44)
6	Tehran	Blood	150	100	50	F	BRCA1 BRCA2	H	p.Asn1403His, p.Gly1140Ser, p.Ile26Val, p.Leu1418X, p.Glu23Gln, p.Leu3X, p.Asn1403Asp, p.Lys581X, p.Pro938Arg, p.Thr77Arg, p.Leu6Val, p.Arg7Cys, p.Leu15Ile, p.Ser177Thr, IVS7 + 83(-TT), IVS8 -70(-CATT), IVS2 + 9(G > C), IVS1-20(G > A), IVS1-8(A > G), p.Met1Ile, IVS2 + 24(A > G), IVS5-8 (A > G), IVS2(35-39)TTcctatGAT, IVS13 + 9 G > C p.Glu1391Gly, 1994-1995(InsA), IVS6-70(T > G) p.Val1852Ile	(14)
7	Tehran	Blood	5 families	-	-	F	BRCA1 BRCA2	H	Misssense, Intronic Loss, New Mutation Misssense, Intronic Loss, New Mutation	(45)
8	Kermanshah	FFPE	30	-	-	F	BRCA1	H	exon5, 11 B	(46)
9	Shiraz	Blood	505	305	200	F	BRCA1 BRCA2	H	5382insC, 185delAG 6174delT	(47)
10	Mashhad	Blood	142	42	100	F	BRCA1 exons	H	was not present in the control families or BC-free twin.	(48)
11	Tehran	Blood	7	3	4	F/M	BRCA2	H	rs80359352	(49)
12	Tehran	Blood	87	67	20	NA	BRCA2 BRCA1	H	c.4415_4418delAGAA, c.6033_6034insGT g.5075-53C > T, g.*381_389del9ins29	(50)
13	Shiraz	Blood	1457	-	1057	NA	CAT	L	C-262T (rs1001179)	(8)
	Abarku			-	200					
	Yasoj			-	200					
14	Rafsanjan	Blood	136	36	100	F	CCR5	L	MutationΔ32	(51)
15	Ahvaz	Tissue	120	60	60	NA	C-kit	L	Protein Expression	(52)
16	Isfahan	Blood	190	90	100	F	Collagenase IV	L	C1562T	(53)
17	Tabriz	Blood	200	100	100	F	CYP1A1	L	A2455G	(54)
18	Mashhad	Blood	200	100	100	F	CYP2D6	L	CYP2D6*4 (1846G to A)	(55)
19	Isfahan	Blood	216	108	108	F	EGFR	L	14, 16, 17, 18, 19, 20, 21 repeats	(56)
20	Tehran	Tissue	297	150	147	F	ER-α	I	A908G(K303R)	(57)
21	Tehran	Blood	297	150	147	F	ER-α	L	codon325(CCC > CCG)	(58)
22	Tehran	Blood	297	150	147	F	ESR1 exon 1	L	T 392 C	(59)
23	Tabriz	Blood	200	100	100	F	FGFR2 Tp53	L H	Rs1219684 Rs1042522	(60)
24	Isfahan	Blood	468	206	262	F	GATA3	L	CT Dinucleotide Repeat in intron 3	(61)
25	Ilam	Blood	77	31	46	F	GST	L	GSTM1-null, GSTT1-null, GSTP1	(62)
26	Zahedan	Blood	286	134	152	F	GSTM1	I	Null Genotype	(63)
NO.: Number, Ctrl: control group, PG: Penetrance group, Ref.: Reference.										

NO.	City of Study	Type of sample	Total Sample Size	Case	Ctrl	Sex	Gene /Protein Name	PG	GENE/Protein Alterations	Ref.
							GSTP1		IleVal and ValVal Genotypes	
							GSTT1		Null Genotype	
27	Shiraz	Blood	212	106	106	F	GSTZ1	L	G-1002A, Gly42Arg Polymorphism	(64)
28	Shiraz	Blood	175	89	86	F	HLA	L	HLA-A24, HLA-A1	(65)
29	Tehran	Blood	180	100	80	F	HLA-class II	L	DRB/DQA1/DQB1	(66)
30	Zahedan	Blood	439	236	203	F	hsa-miR-146a	L	rs2910164 G > C	(67)
							hsa-miR-499		rs3746444 T > C	
							hsa-miRNA-196a2		rs11614913 C > T	
							hsa-miRNA-196a2		rs185070757 T > G	
31	Isfahan	Blood	200	100	100	F	IGF1	L	allell 11, 16, 17, 18, 19, 20, 21, 22, 23	(68)
32	Tehran	Blood	455	-	140	F/M	IL-1 α , IL-1 β , IL-1 β , IL-1R, IL-1RA, TNF- α , TNF- α , IL-12, IL-6, IL-6, IL-2, IL-2, IFN- γ , IL-4, IL-4, IL-	L	C-889T, C-511T, C3962T, CPst-I1970T, CMspa-I 11100T, A-308G, A-238G, A-1188C, C-174G, A nt565G, G-330T, G166T, AUTR5644T, G-1098T, C-590T, C-33T, A1902G, A-1082G, C-819T, A-592C, C Codon 10 T, C Codon 25 G	(69)
	Yazd			-	121					
	Sistan			-	98					
	Balochistan			-	96		4, IL-4RA, IL-10, IL-10, IL-10, TGF- β , TGF- β			
33	Shiraz	Blood	320	203	117	F	Leptin	L	G-2548A	(70)
34	Mashhad	Blood	183	106	77	F	MDR1	L	C3435T	(71)
35	Tehran	Blood	94	54	40	F	MDR1	L	C3435T	(72)
36	Kermanshah & Ilam	Tissue	100	50	50	NA	mt tRNAPhe/Pro	L	C182T, 194insT, 285insA, 16342delT, 302insC, C309T, C16069T	(73)
37	Tehran	Blood	592	282	310	NA	MTR	I	A2756G	(74)
38	Shahrekord	Blood	275	135	140	NA	p53	H	Arg72Pro(Codon 72 exon 4)	(75)
39	Tabriz	Tumor	102	102	-	NA	P53	H	codon160(ATG > AAG)exon5,codon163(ATC > AAG) exon5,codon193(CAT > AAT),codon195(ATC > TTC),codon195(ATC > AAC),codon198(GAA > TAA),codon220(TAT > TGT),codon213(CGA > CTA),codon214(CAT > CGT)	(76)
40	Isfahan	Tissue & Blood	192	96	96	F	p53	H	codon 72 (Arg/Arg,Pro/Pro,Arg/Pro)	(77)
41	Tabriz	Tissue	391	221	170	F	p53	H	intron 3, 16 bp Polymorphism	(78)
42	Tehran	Blood	92	49	43	F	PTEN	H	IVS4	(79)
43	Tehran	Tissue	137	137	-	F	RAR β 2 & ER α	L	hypermethylation frequencies	(80)
44	Shiraz	Blood	459	278	181	F	SDF-1	L	A30G	(81)
45	Tabriz	Tissue	35	18	17	F	Survivin	L	Survivin, Survivin Δ Ex3, Survivin3b, Survivin2b	(82)
46	Shiraz	Blood	220	110	110	F	TGF β 1	L	haplotypes "GTGCCGC" AND "GCGCCGC"	(83)
47	Tabriz	Blood	225	126	99	F	TP53	H	codon72 Arg/Pro	(84)
48	Tehran	Blood	296	140	156	F	VDR	L	FokI (FF, ff, Ff), BsmI (BB, bb, Bb)	(85)
49	Tabriz	Blood & Tissue	409	206	203	F	WRAP53	L	rs2287499	(86)
50	Shiraz	Blood	373	186	187	F	XRCC1	L	Arg399Gln	(87)

NO.: Number, Ctrl: control group, PG: Penetrance group, Ref.: Reference.

NO.	City of Study	Type of sample	Total Sample Size	Case	Ctrl	Sex	Gene /Protein Name	PG	GENE/Protein Alterations	Ref.
51	Shiraz	Blood	802	407	395	F	XRCC5	L	VNTR	(88)
							XRCC6		T-991C	
52	Shiraz	Blood	724	362	362	F	XRCC7 G6721T	I	rs7003908	(89)
53	Tehran	Blood & Tissue	85	50	35	NA	DBC2	L	methylation	(90)
54	Isfahan	Tissue	73	53	20	NA	PTEN	H	promoter methylation	(91)
55	Tehran	Blood	113	63	50	F	BRCA1	H	Gly1140Ser, Ileu15Ieu, Ileu26Ieu, Glu23Gln, Leu3stop codon, Pro9Arg, Leu6Val, Arg7Cys, Ser177Val,	(92)
									IVS7 + 83(TT), IVS8 -70(CATT), IVS2 + 9(GC), IVS1-20(GA), IVS1-8(AG), IVS2 + 24(AG)	
							BRCA2		Glu1391Gly	
56	Kermanshah and Ilam	Blood	205	101	104	F/M	MMP-9	L	Promoter Polymorphism at C-1562T	(93)
57	Zahedan	Blood	165	72	93	F	IL-18	L	IL-18 – 607 C/A Polymorphism	(63)
58	Tehran	Blood	150	100	50	NA	BRCA1/2	H	Multiple Mutation	(94)
59	Tabriz	Blood	190	95	95	F	MDM2	L	309T/G Polymorphism	(95)
60	Ahvaz	Cell Lines	1	1	-	NA	IL23, IL27	L	Downregulation	(96)
61	Tehran	Cell Lines	-	-	-	-	Aurora-C	L	Overexpression/ Amplification	(97)
62	Shiraz	Cell Lines	-	-	-	-	Heme Oxygenase-1	L	Overexpression	(98)
NO.: Number, Ctrl: control group, PG: Penetrance group, Ref.: Reference.										

Thirteen studies focused on BRCA 1/2 genes. The total sample size in these studies was 1413 cases and controls and five families. While six studies determined the sequencing of all the exons of these two genes, the others examined their specific areas. P53, from the high-penetrance group of genes, was also observed in six studies. Few (mainly one) studies assessed other genes. The largest sample size (1457 participants) belonged to a study on the CAT gene (8).

The majority of studies were conducted in Tehran (n = 18), Shiraz (n = 11), and Tabriz (n = 8). None of the studies investigated the survival rate of mutation carriers.

Prognosis, survival and clinicopathologic features

Another group of studies investigated the relationship of gene or miRNA expressions, mutations, and epigenetic changes with clinicopathological characteristics and invasiveness of the disease (Table 2). The majority of these studies compared the tumor tissue with the adjacent healthy tissue. Most studies focused on the relationship of these genes with clinicopathological features of the tumor. Such features included stage, grade, tumor size, number of affected lymph nodes, and invasiveness of the disease. Moreover, 35 studies examined the expression of mRNA and proteins, nine assessed nucleotide changes in genes, one assessed the expression of miRNAs, two investigated immune cells, and three examined epigenetic modifications and their relationship with clinicopathological features of the disease. There was a significant relationship between the age of diagnosis and the expression of six genes (HER2, BRCA1, P53, RARβ2, PR, ER). Tumor size was also significantly related to the expression of five genes and/or proteins (EMSY, MYC, HER2, TOP2A, CD10). Natural killer (NK) cells, catalase and superoxide dismutase activity, and expression of mir21, P53, Ki67, E-cadherin, and BRCA1 were found to have significant relationships with the stage of the disease. Twelve studies identified significant associations between tumor grade and 22 genes/proteins including Bcl-2, E-cadherin, FGFR1, ADAM9, IKBKB, PRDM14, MTDH, MYC, HER2, CCND1, TOP2A, CDC6, CD10, BRCA 1, hTERT, p53, PSA, Telomerase, Hsp70, HER2, MHC I and ICAM-I (9–20).

Table 2
Studies focusing on genes related to prognosis, survival and clinicopathologic f

NO.	Gene /Protein name	GENE/Protein Alterations	city of study	Type of sample	total sample size	Case	control	sex	Age	A	B	C	D	E	F	G
1	Chromosome 17	Aneusomy	Tehran	Tissue	30	*	*	F							*	
2	(HER-2)/ neu	Over expression	Mashhad	Tissue	196	196	non	F	*							
3	EMSY protein	Expression and localization	Tehran	Tissue	116	116	non	F		*						
4	Bcl-2	Over expression	Tabriz	Tissue	40	21	19	NA				*				
5	GSTT1, GSTM1, GSTZ1, and GSTO2 (detoxifying genes) XRCC1, XRCC6 and XRCC7 (DNA repair genes)	Poly morphisms	Shiraz		101		non									
6	MMP-9 promoter polymorphism	(C-1562T) poly morphism	Isfahan	Blood	280	180	100	F								
7	ATM	Down regulation	Tehran	Tissue	129	119	10	F								
	cyclin D1	Over expression														
8	MiR-21	Over expression	Tehran	Tissue	59	59	*	NA							*	
	MiR-342 and MiR-205	Down regulation														
9	UBE2Q1 (ubiquitin-conjugating enzyme E2Q family member 1)	Over expression	Shiraz	Tissue specimens	26	26	non	F								
10	UBE2Q1	Over expression	Shiraz	MDA-MB-468 cell line	*	*	*	*								
11	E-cadherin (CDH1)	Down regulation by promoter methylation	Tabriz	tissue samples	100	50	50	F				*			*	
12	Bcl-2/Bax Ratio	Increase	Tabriz	Tow paclitaxelresistance cell lines	*	*	*	*					*			
	Caspase-8	Increase											*			
	Caspase-9	Decrease											*			
13	CCND1, HER2 AND AIB1	Over expression	Tehran	Tissue	170	85	85	F								

A: Tumor Size, B: Histological Type, C: Grade, D:Drug Resistance, E: Lymph Node Status, F: Stage, G: BC Occurrence, H: Occupation, I: Body Mass Index, J: Lep Status, Q: HER-2 Status, R: TNBC Status, S: Lymph Node Metastasis, T: Metastasis, U: Risk of Cancer, V: Recurrence on Tamoxifen Treatment, W: MAI, X: Fam

NO.	Gene /Protein name	GENE/Protein Alterations	city of study	Type of sample	total sample size	Case	control	sex	Age	A	B	C	D	E	F	G
	NCOR1	Down regulation														
14	FGFR1, ADAM9, IKBKB, PRDM14, MTDH, MYC, HER2,	amplification	Tehran	FFPE tumor blocks	170	85	85	F				*				
	CCND1, TOP2A	amplification										*				
	CDC6	amplification										*				
15	CD10	Expression	Mashhad	paraffin blocks	150	100	50			*		*				
16	MDR1	Expression	Tehran	Tissue	54	54	non	F								
	MRP1	Expression														
17	MDR1	Poly morphism	Tehran	Tissue & Blood	104	54	50	F					*			
18	ST6Gal1, Cox-2, HB-EGF	Over expression	Kashan	Tissue	108	54	54									
19	P16ink4a	Promoter methylation	Isfahan	Blood	140	70	70	F	*		*				*	
20	MUC2	Over expression	Tehran	Blood, Bone marrow	70	50	20	F/M								
21	BRCA 1	Down regulation	Tehran, Ardebil	Tumor samples	27	27	non	F				*				
22	BRCA 1	Down regulation, Localization	Tehran	Tumor	156	156	non	F	*		*	*				
23	hTERT	Over expression	Tabriz	Blood and Tumor	65	65	non	F				*			*	
24	IL-12	Over expression	Tehran	Blood	76	50	26	NA								
	CD4+ lymphocyte	Decrease														
25	Gelatinase B	Poly morphism	Isfahan	Blood	190	90	100	F								
26	MMP-9	Down regulation	Isfahan	Blood	98	98	non	F								
27	MMP-3	Poly morphism	Isfahan	Blood	180	120	60	F								
28	p53	expression	Rasht	Tissue samples	465	465	non		*			*				
29	active MMP9	plasma concentration	Isfahan	Blood	220	100	120	F								
		Poly morphism c-t														

A: Tumor Size, B: Histological Type, C: Grade, D:Drug Resistance, E: Lymph Node Status, F: Stage, G: BC Occurrence, H: Occupation, I: Body Mass Index, J: Lep Status, Q: HER-2 Status, R: TNBC Status, S: Lymph Node Metastasis, T: Metastasis, U: Risk of Cancer, V: Recurrence on Tamoxifen Treatment, W: MAI, X: Fam

NO.	Gene /Protein name	GENE/Protein Alterations	city of study	Type of sample	total sample size	Case	control	sex	Age	A	B	C	D	E	F	G
30	RARβ2	Hyper	Tehran	Tissue	137	137	non	F	*							
		metilation														
31	PSA	Down	Tabriz	Tissue	100	50	50	F				*			*	
		regulation														
	Telomerase	High activity										*			*	
32	HER2	Expression	Tehran	Tissue	140	140	non	NA			*			*		
33	PTEN	Mutation	Tehran	Blood & Tissue	107	72	35	NA								
34	Hsp70	Expression	Khouzestan	Tissue	47	47	non	NA				*				
		and localization														
35	MDM 2	Expression	Tehran	Tissue	75	75	non	F						*	*	
36	HER2	Expression	Khorasan	Tissue	339	339		F				*				
	p53	Down												*		
		regulation														
	PR	Expression												*		
37	CD16+	Decrease	Tehran	Blood & Tissue	23	9	9	F								
	D14+/HLA-DR+	Decrease										*				
38	Dicer	Down	Tabriz	tissue sample	140	70	70									
		reulation														
39	HIC1	Promoter	Shiraz	frozen tissue,	81	81	non				*			*		
		Hyper		blood samples												
		methylation														
	RASSF1A	Promoter									*					
		Hyper														
		methylation														
40	MHC I and ICAM-I	expression	Tehran	Tissue	50	25	25					*				
41	ALDH1	activity	Tehran	Tissue	121	121	non									
42	Superoxide Dismutase and Catalase	activity	Tehran	Blood	100	50	50	F							*	
43	ki67	Over	Sabzevar	Tissue	80	80	non	F/M			*				*	
		expression														
44	p53	expression	Sabzevar	Tissue	80	80	non								*	

A: Tumor Size, B: Histological Type, C: Grade, D:Drug Resistance, E: Lymph Node Status, F: Stage, G: BC Occurrence, H: Occupation, I: Body Mass Index, J: Lep Status, Q: HER-2 Status, R: TNBC Status, S: Lymph Node Metastasis, T: Metastasis, U: Risk of Cancer, V: Recurrence on Tamoxifen Treatment, W: MAI, X: Fam

NO.	Gene /Protein name	GENE/Protein Alterations	city of study	Type of sample	total sample size	Case	control	sex	Age	A	B	C	D	E	F	G
45	CYP2D6 polymorphism	CYP2D6*4 poly morphism	Yazd	Tissue	101	101	non	F								
46	Her-2, p53	expression	Ahvaz	tissue/ blood	299	299	non	F			*					
	PR, ER	expression							*		*					
47	ER-α	NA	Birjand	tissue	51	51	non	F								
A: Tumor Size, B: Histological Type, C: Grade, D:Drug Resistance, E: Lymph Node Status, F: Stage, G: BC Occurrence, H: Occupation, I: Body Mass Index, J: Lep Status, Q: HER-2 Status, R: TNBC Status, S: Lymph Node Metastasis, T: Metastasis, U: Risk of Cancer, V: Recurrence on Tamoxifen Treatment, W: MAI, X: Fam																

Seven studies also showed significant relationships between EMSY protein, MiR 21, CD 10, HER2, MDM2, P53, PR and HIC1 expression and number of affected lymph nodes (12, 19, 21–25)(The list of significant genes (n = 9) is shown in Table 2. The relationship between six genes including IL-12, Gelatinase B, MMP-9, MMP-3 and p53 and metastasis was significant in these studies (19, 26–30) Of the two studies evaluating the relationship between gene expression and response to chemotherapy; one found the relationship between MRP1and metastasis to be significant (31).

Treatment

The third group of studies focused on the therapeutic effects of different compounds, including herbal extracts, medicinal compounds, nanoparticles, and bacteria, on breast cancer (Table 3). Some of these studies (n = 104) assessed the effects of various compounds on the expression of specific genes involved in apoptosis or cell proliferation. The most studied compounds are drug conjugate to Trastuzumab and nanoparticle forms of doxorubicin (32–39). Of these, four were conducted on human samples and 20 on rats or mice (in-vivo). The studies mainly involved cells and cell lines (particularly MCF7). Most studies (n = 42) used MTT assay to determine the effects of various compounds on specific genes, mainly cell proliferation and apoptosis pathway genes.

Table 3
Iranian studies focusing on herbal, microbial, chemical, or synthetic compounds with anticancer properties.

No.	Type of Study	Gene /Protein/ Cell Activity	Drug /Extract/ Component name	Cell Line, Tissue, Animal model name	Effect	Ref.
1	Effect of Components		Astrodaucus persicus (Boiss.) Drude	T47D cell line	Prolifration ↓(insignificantly)	(32)
			Doxorubicin	T47D cell line	Prolifration ↓	
2	Effect of Components	cyclin D1	Crocine (from Crocus sativus L.)	Rats	↓ Expression	(122)
3	Effect of Components		Marrubium persicum	MCF-7 cell line	Prolifration ↓	(123)
4	New Technologies		trastuzumab-multiwalled carbon nanotubes	SK-BR-3 cell line	↓ Cell viability	(33)
			trastuzumab-multiwalled carbon nanotubes	MCF-7 cell line	No effect on Cell viability	
			trastuzumab-diphtheria toxin	SK-BR-3 cell line	↓ Cell viability	
			trastuzumab-diphtheria toxin	MCF-7 cell line	No effect on Cell viability	
5	New Technologies		Silver Nanoparticles and Ions	Parent and tamoxifen-resistant T47D cell lines	↓ Cell viability	(124)
6	Effect of Components		Cadmium and Copper Chloride	MDA-MB468 cell line	↓ Cell viability	(125)
7	Effect of Components	BRCA1, ATM, Bak, p53, p21	Silibinin	MCF7 Cell line	↑ Genes Expression, ↓ Cell Prolifration, ↑ Cell Apoptosis	(126)
		Bcl-xl			↓ Gene Expression	
8	New Technologies		2-(3,5-Dihydroxyphenyl)-6-hydroxybenzothiazole	MDA-MB-231	↑ Apoptosis, Arrest of Prolifration	(127)
9	New Technologies		Dimethyl-5-acetyl-4-methyl-6-(4-methylphenylimino)-6H-thiopyran-2,3-dicarboxylate	MCF-7 cell line	↓ proliferation	(128)
10	New Technologies		A naphthalene-fused (a-alkoxycarbonyl)methylene-g-butyrolactone (methyl 2-[7-hydroxy-2-oxonaphtho[1,2-b]furan-3(2H)-yliden]acetate)	MCF-7 cell line	↓ proliferation	(129)
11	New Technologies		2-(3,5-Dihydroxyphenyl)-6-Hydroxybenzothiazole	MCF-7 cell line	↓ Prolifration	(130)
12	New Technologies		¹⁷⁷ Lu-DOTA-trastuzumab	MCF-7 cell line	↓ Cell viability	(34)
13	Effect of Components		¹⁷⁷ Lu-DOTA-trastuzumab	SKBr3 and MCF7 cell lines	↓ Cell viability	(35)
14	Effect of Components		Silimarin and Doxorubicin	MCF-7 cell line	↑Apoptosis	(36)
15	Effect of Components		Baneh and Doxorubicin	T47D cell line	↑Apoptosis	(37)
16	Effect of Components	cyclin D1, cdk4, CyclinA, cdk2	Baneh	T47D cell line	↓ Expression	(131)
		Cyclin E, cdk1, CyclinB1			↑Expression	
17	Effect of Components		Crab Shell	MCF-7 cell line	↓Prolifration (↑Apoptosis, ↓Nitric oxide level)	(132)

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Jan 2005-Oct2015

1986 English Citation(s)

1345 Persian Citation(s)

No.	Type of Study	Gene /Protein/ Cell Activity	Drug /Extract/ Component name	Cell Line, Tissue, Animal model name	Effect	Ref.
18	Effect of Components	Mre11	Lithium chloride	T47D cell line	↓ DNA repair, ↓ Expression	(133)
19	Effect of Components	Mre11	Lithium chloride	T47D cell line	↓ DNA repair, ↓ Expression	(134)
20	Effect of Components	Nrf2, Ho1, MDR1	letulin and dextrorubicin	MDA-MB 231	↑ Cell death	(135)
			luteolin-loaded nanoparticles		↓ Expression	
21	Effect of Components		Viola tricolor(EtOAc, <i>n</i> -butanol, and H2O fractions and Hydroalcoholic extract)	Neuro2a mouse neuroblastoma and MCF-7 cell line and normal L929 cells	↑ Cell death, ↑Apoptosis(caspase-dependent)	(136)
22	Effect of Components		Metformin	MCF-7, BT-474, SK-BR-3 and MDA-MB-231 cell lines +/- Paclitaxel	No effect on Cell viability and paclitaxel cytotoxicity	(137)
23	Effect of Components		ZnO nanoparticles	Du145 and T-47D cell lines	Significant lethal effects	(138)
			ZnO-MTCP and ZnO-CuMTCP	Du145 and T-47D cell lines	No cytotoxic effects	
			ZnO-MTCP + UV light exposure	T-47D cell line	↓ Survival	
24	Effect of Components		palladium(II) complex +/- calf thymus DNA	T-47D cell line	↓ Cell proliferation	(139)
25	Effect of Components		AuNP-Conjugated/ Non-conjugated 2-amino-4H-chromene-3-carbonitrile	T-47D cell line	↓ Cell viability	(140)
26	Effect of Components		Noscapine and papaverine	MCF-7 and MDA-MB-231 cell lines	↑Apoptosis of CSCs	(141)
27	Effect of Components		(1)polypyridyl-based copper(II) complexes [Cu(tpy)(dppz)](NO3)2 and (2)polypyridyl-based copper(II) complexes [Cu(tptz)2](NO3)2	MCF-7 cell line	↑Apoptosis	(142)
28	Effect of Components		ethanolic extract of Alpinia galanga rhizome	MCF-7 cell line	↓ Cell viability	(143)
29	Biomarkers	PDE9	inhibitor BAY 73-6691	MCF-7 and MDA-MB-468 cell lines	↓ Expression, ↓cell proliferation, ↑Apoptosis	(144)
30	Effect of Components	Survivin	Piperine	Triple-negative breast cancer cells in vitro and in vivo	Inhibition of Survivin, ↑Apoptosis	(145)
31	Effect of Components		Mitoxantrone (MX) + ionizing radiation and photodynamic therapy	MCF-7 cell line	↑ Cell death, ↓ Cell viability	(146)
32	Biomarkers	FBXO39		MCF-7 cell line	Expressed	(147)
		TDRD4, FBXO39		MDA-MB-231 cell line	Expressed	
		FBXO39	RHOXF1 shRNA	invasive ductal carcinoma samples and MDA-MB-231 cell line	↑Expression	
		FBXO39	RHOXF1 shRNA	MCF-7 cell line	↓ Expression	
		TDRD4	RHOXF1 shRNA	MDA-MB-231 cell line	↑Expression	
33	Effect of Components		SN38 (7-ethyl-10-hydroxyl camptothecin) and SN38-NPs	4T1 breast cancer cells and xenograft balb/c animal	↑Cytotoxicity	(148)

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Jan 2005-Oct2015
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34	Effect of Components		Myrsinane-type compounds: 3,7,14,15-tetraacetyl-5-propanoyl-13(17)-epoxy-8,10(18)-myrsinadiene (1) and 3,7,10,14,15-pentaacetyl-5-butanoyl-13,17-epoxy-8-myrsinene (2)	MCF-7 and MDA-MB 468 cell lines	Moderate Cytotoxicity	(149)
			Jatrophane-type diterpene: 5,6-epoxy-8,9,15-triacetyl-3-benzoyl-14-oxo-jatropha-11(E)-ene (3)		Weak Cytotoxicity	
35	Effect of Components		artemisinin + Miconazole + Butyric acid + Iron sulfate	4T1 breast cancer cells	↑Apoptosis	(150)
36	Effect of Components		pegylated liposomal <i>trans</i> -anethole	MCF-7 and T47D cell lines	↑Cytotoxicity	(151)
37	New Technologies	Th1, Th2 and Treg	(TNF-α/CD40L)-MSCs + DCs	4T1 injected BALB/c mouse	↓ Expression, ↓Tumor progression,↑Survival	(152)
38	Effect of Components	HER-2	recombinant λ phage C-Myc tagged	SKBR-3 and MCF-7 cell lines	↓Cell growth	(153)
39	Effect of Components		[Cd2(Dic)41.5(MeOH)2(H2O)]n (Dic = diclofenac sodium)	MCF7,T24,L-929 and A-549 cell lines	↓Cell proliferation	(154)
			[Cd2(Dic)41.5(MeOH)2(H2O)]n in comparison with Dic and Cd2	MCF7,T24 cell lines	↑Cytotoxicity	
40	Effect of Components		Equol(metabolite of the soybean isoflavone daidzein)	MDA-MB231(IC50:252 μM) and T47D(IC50 228 μM)	↓ Cell proliferation	(155)
				MDA-MB-231(IC50 50 μM and T47D(IC50 50 μM)	↑Radiation-induced apoptosis	
41	New Technologies		methotrexate–human serum albumin nanoparticles(MTX–HSA NPs) with luteinizing-hormone releasing hormone(LHRH)	Female Balb/c mice bearing 4T1 cell line	↑ Survival	(156)
42	Biomarkers	MMP-3,MMP-9 and TIMP-1 cell lines		Female Balb/c mice bearing adenocarcinoma breast tumor + Candida Albicans, Female BALB/c mice was infected Candida Albicans and Female Balb/c mice bearing adenocarcinoma breast tumor	↑Secretion	(157)
		MMP-2		Female Balb/c mice bearing adenocarcinoma breast tumor + Candida Albicans and Female BALB/c mice was infected Candida Albicans	↓Secretion	
43	Effect of Components	Extracellular Signal-Regulated Kinases 1/2 (ERK) and phospho-ERK	DOX	MDA-MB-231 (ER-) cell line	↓ Expression	(158)
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Jan 2005-Oct2015						
1986 English Citation(s)						
1345 Persian Citation(s)						

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		Extracellular Signal-Regulated Kinases 1/2 and phospho-ERK	DOX	MCF-7 (ER+) cell line	↑ Expression	
		Extracellular Signal-Regulated Kinases 1/2 (ERK) and phospho-ERK	DOCT	MDA-MB-231 (ER-) cell line	↓ Expression	
		Extracellular Signal-Regulated Kinases 1/2 (ERK) and phospho-ERK	DOCT	MCF-7 (ER+) cell line	↑ Expression	
44	Immunotherapy-Immunology	HER2	anti-HER2 mAbs 1T0, 2A8 and both trastuzumab, 1T0 and 2A8	BT474 cell line	↓Cell proliferation significant synergistic ↓Cell proliferation	(38)
45	Effect of Components		Proline-rich heptapeptide 11a–b and 11i–j	HL60,MCF7 and A549 cell lines	little or no effect on cell viability	(159)
			Proline-rich heptapeptide 11e	A549 and MCF7 cell lines	little or no effect on cell viability	
			Proline-rich heptapeptide 11d and 11 h	MCF7 cell line	60% effect on cell viability	
			Proline-rich heptapeptide 11c and 11 g	MCF7 cell line	10% effect on cell viability	
46	Effect of Components	EGFR	ASOND-loaded chitosan particles	T47D cell line	Downregulated expression	(160)
			ASOND-loaded thiolated particles		↓ Expression	
47	Effect of Components		13-S-hydroxyoctadecadienoic acid (13(S)-HODE)	MCF7 and MDA-MB-231 cell lines	↓Cell growth, induce apoptosis	(161)
48	Effect of Components	15-Lipoxygenase-1	Trichostatin A (TSA)	MCF7 and MDA-MB-231 cell lines	↓ Cell viability and cell growth, induce apoptosis	(162)
49	Effect of Components		Methanol extract of Salvia chloroleuca,n-hexane and CH2Cl2	MCF-7 cell line	↓ Cell viability	(163)
			CH2Cl2		Apoptosis	
			Total methanol extract of S. chloroleuca,n-hexane,CH2Cl2EtOAc, n-BuOH, and H2O		↓Cell growth	
50	Effect of Components	miR-145	Chitosan polyplex nanoparticles	MCF-7 cell line	↓Cell proliferation	(164)
51	Effect of Components		(pH-sensitive)MTO PEG-PMMI- CholC6 and CHEMS-based bearing niosomes	HUVEC,OVCAR-3 and MCF-7 Cell lines	↑Antiproliferative activity	(165)
			(pH-sensitive)MTO conventional, PEG-PMMI-CholC6 and CHEMS-based bearing niosomes	HUVEC,OVCAR-3 and MCF-7 Cell lines	↑ Cytotoxicity	
			(pH-sensitive)MTO conventional, PEG-PMMI-CholC6 and CHEMS-based bearing niosomes	OVCAR-3 and MCF-7 Cell lines	↓ Cell viability	
52	Effect of Components		Valproic acid (VPA)	MCF-7 cell line	↓Cell viability, Apoptosis	(166)
		Telomerase	Valproic acid (VPA)		↓Activity	
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Jan 2005-Oct2015						
1986 English Citation(s)						
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		Bax/Bcl-2	Valproic acid (VPA)		↑Bax and ↓Bcl-2 expression and ↑Bax/Bcl-2 ratio	
		Telomerase activity & ↑in Bax/Bcl-2 ratio			significant correlation	
53	Effect of Components		Scrophularia oxysepala(n-hexane extract)	MCF-7 cell line	no cytotoxic effects	(167)
			Scrophularia oxysepala(dichloromethae and methanol extract)		↓Cell growth, ↓ viability, apoptosis	
54	Effect of Components	p53	Boswellia Thurifera Gum Methanol Extract	MDA-MB-231 cell line	↑Expression, cytotoxic effect	(168)
55	Effect of Components		docetaxel-coated Fe3O4 MNPs	4 T1 cell line	↑Cell death than docetaxel alone	(169)
56	Effect of Components		Lactobacillus plantarum enriched with selenium nanoparticles(SeNPs)	FemaleBALB/c mice with 4T1 cell line	↓Growth rate of tumors, ↓Rate of death, ↑ Survival	(169)
		IFN-γ, TNF-α and IL-2	Lactobacillus plantarum enriched with selenium nanoparticles(SeNPs)	Female BALB/c mice with 4T1 cell line	↑Production, ↑NK cells cytotoxicity	
		LDH			↓Production	
57	Effect of Components		Selenium nanoparticle(SeNPs)-enriched Lactobacillus brevis	Female BALB/c mice with 4T1 cell line	↓Growth rate of tumors, ↓Rate of death, ↑ Survival, ↑Tumor necrosis, ↓Metastasis	(170)
		IFN-γ and IL-17			↑Production, ↑NK cells cytotoxicity	
		LDH and ALP			↓Production	
58	Effect of Components		Biogenic Selenium Nanoparticles	Female BALB/c mice with 4T1 cell line	↓Growth rate of tumors, ↓Rate of death, ↑ Survival	(171)
		IFN-γ, IL-12, IL-2, and TNF-α			↑production	
59	Immunotherapy-Immunology		TGFαL3-SEB	4T1 cell line	↑Antitumor activities	(172)
60	Effect of Components		Curcumin-loaded NIPAAm-MAA	MCF-7 cell line	More cytotoxic effect and efficiently ↓cell growth than curcumin alone	(173)
61	Effect of Components	Autocrine hGH (Human growth hormone)	Arsenic trioxide (ATO)	MCF7-hGH than MCF-7 cell line	↑Expression, ↓ Cell viability, ↓ colony formation, ↑Apoptosis	(174)
62	Effect of Components		Lactobacillus Rhamnosus, cisplatin, Lactobacillus Rhamnosus + cisplatin	Female BALB/c Mice	↓Growth rate of tumors	(175)
63	Effect of Components	IFN-γ	aqueous extract of Carica papaya leaves	Female BALB/c Mice	↑Expression, ↓Growth rate of tumors	(175)
		IL- 4			↓Expression	
64	Effect of Components	HER2	Silybin	SKBR3 cell line	↓Cell growth, ↓Expression	(176)

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65	Effect of Components		Neutra Charged liposomes-encapsulated Doxorubicin	MDA-MB-231 cell line	More cytotoxic effect than Negative Charged liposomes-encapsulated Doxorubicin and free Doxorubicin	(39)
66	Effect of Components		Artemisia absinthium L.(Grown at high height)	MCF7 cell line	↑Cytotoxicity than others	(177)
67	Effect of Components		Acetazolamide	T47-D cell line	No effect on apoptosis and cell cycle arrest	(178)
68	Effect of Components		Methanolic extract of Avicennia marina	MDA-MB231 cell line	↓Cell growth and induce apoptosis more than other extraction	(179)
			Ethanollic extract of Avicennia marina		↑Cytotoxicity more than other extraction	
69	Effect of Components		Letrozole loaded lipid nanocapsules (LNCs)	MCF7 cell line	↓Cytotoxicity in comparison with free letrozole	(180)
70	Effect of Components	CD83	Melphalan alkylating + TNF-α and MCM	MCF7 cell line	↑Expression, ↓Phagocytosis, polarized immune responses to DC1 phenotype triggering TH1 responses	(181)
71	Effect of Components		Ethanollic Extract of ginger fresh extract (Zingiber)	MCF7 cell line	↓Cell growth, Cytotoxic effect, induce apoptosis	(182)
72	Effect of Components	Telomerase	Curcuma longa n-hexane extract	MCF7 cell line	↓Expression, ↓Cell growth	(183)
73	Effect of Components		Saffron	MCF7 cell line	↓Cell viability, induce apoptosis	(184)
74	Effect of Components		Lactobacillus Reuteri	Female BALB/c Mice	↓Growth rate of tumors, ↑Weight, ↑Survival, ↑Tumor Cell death	(185)
75	Biomarkers	interlukin-6 (IL-6) and Vascular endothelial growth factor (VEGF)	Rest-tumor-exercise(RTE) and Rest-tumor-rest (RTR) Rest-tumor-rest (RTR) and Exercise-tumor-rest (ETR)	Female BALB/c with MC4L2 cell line	↑Expression ↑Growth rate of tumors	(186)
76	Biomarkers	2H1-TP, KALA-2H1-TP and KALA-2H1-NLS-TP	histone H1-based recombinant fusion peptide	ZR-75-1 cell line(P control) MDA-MB-231 cell line(N control)	No significant cytotoxicity effect and cell viability	(187)
77	Immunotherapy-Immunology	INF-γ and IL-4	Lip-DOPE-P5-MPL	Female BALB/c mice with TUBO cells	No immunological responses and antitumor effect	(188)
78	New Technologies	MUC1 antigen	USPIO-C595	MCF-7, MDA-MB-231 and LNCap cell lines, BALB/c mice with MUC1-positive breast tumor	↑Uptake	(189)
79	New Technologies		2-aryl-3-nitro-2H-chromenes 4a-u,2-aryl-3-nitro-2H-chromenes 4 l	MCF-7 cell line	↑Activity ,↑↑↑Activity compare with Etoposide	(190)

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			2-aryl-3-nitro-2H-chromenes 4a,4b,4c,4d,4e,4f,4 g,4h,4j,4 k,4 l,4 m,4n,4o,4p,4r and 4 s	T-47D cell line	↑Cytotoxicity compare with etoposide	
			2-aryl-3-nitro-2H-chromenes 4a-u instead of 4i,2-aryl-3-nitro-2H-chromenes 4b	MDA-MB-231 cell line	↑Activity, ↑↑Activity compare with Etoposide	
			2-aryl-3-nitro-2H-chromenes 4 h and 4 l	MDA-MB-231 cell line	↑Caspase-3 activity, ↓ Cell viability and cell growth, ↑apoptosis	
			2-aryl-3-nitro-2H-chromenes 4 h and 4 l	MCF-7 cell line	↓ Cell viability and cell growth, ↑apoptosis	
80	New Technologies	IL-2	pCDNA-2 hinge CAR-OX40	MCF-7 and NIH3T3 cell line	↑Expression	(191)
			pCDNA-2 hinge CAR and pCDNA-2 hinge CAR-OX40	T-47D cell line	↑Expression	
			pCDNA3.1/HYGRO(+)	A-431 cell line	↑Expression	
81	Effect of Components		lactobacillus acidophilus ATCC4356 strain	Female BALB/c mice	↑proliferation of immune cells, ↑survival rate compare with control mice	(192)
		IFnγ			↑Expression	
		IL4			↓Expression	
82	Immunotherapy-Immunology		gp96N-terminal/Her2/GFP	Female BALB/c mice with TUBO cells	↓ therapeutic potentials of Her2 DNA vaccine	(193)
		Ifnγ,IL4	gp96N-terminal/Her2/GFP	TUBO cell-raised tumor extract	↑ Proliferation compare with pHer2- or pCT/Her2-vaccinated animals	
		CD4+/CD8+	gp96N-terminal/Her2/GFP	TUBO cell-raised tumor extract	↑Expression in the order of pNT/Her2 > pCT/Her2 > pHer2	
82	New Technologies		GP96 + Her2/Her2	Female BALB/c mice with TUBO cells	better in part I↑Growth rate of tumors, better in part II↑Growth rate of tumors,	(194)
		CD4 + CD25 + Foxp3+	pHer2 + pGP96-vaccinated animals		↓Expression	
		Ifnγ,IL4	pHer2 + pGP96		↑Induce response, ↑proliferation, ↑Expression	
		CD4+	pHer2 + pGP96-vaccinated miceand pHer2-vaccinated mice		↑Expression	
84	Immunotherapy-Immunology	IL-4	T7-phage nanoparticles	Female BALB/c mice (H-2d haplotype) with TUBO cells	↑Expression compare with control	(195)
		IgG antibodies	T7-p66 Chimeric Nanoparticles		↑Expression against T7 capsids in all T7 nanoparticle-immunized mice	
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		Ifn γ	T7-p66 Chimeric Nanoparticles		$\uparrow$ Expression	
85	New Technologies		2-amino-4-aryl-4H-benzo[h or f]chromene-3-carbonitrile 4 h and 4e	BT20 cell line	$\downarrow$ Cell proliferation	(196)
		Src kinase	2-amino-4-aryl-4H-benzo[h or f]chromene-3-carbonitrile 4d, 4i, 4 m, and 4n	BT20 cell line	$\uparrow$ Inhibitory activity	
86	Biomarkers	IGF-1, HGF, VEGF and IL-8		ASCs (Adipose derived stem cells)	$\uparrow$ Expression	(197)
87	Biomarkers	IL-10 and TGF-b1		ASCs (Adipose derived stem cells)	Higher expressions	(198)
		IL-4, TGF-b1, IL-10, CCR4 and CD25		PBLs (peripheral blood lymphocytes)		
88	Immunotherapy-Immunology		TSA-P1-24 and A-P1-15	BT-20, BT-474, MDA-MB-361, MDA-MB-453, MDA-MB-468, MCF-7, T-47D, SK-BR-3, and Mel III cell lines	$\uparrow$ Immune response	(199)
89	Immunotherapy-Immunology (DNA VAccine)	Anti-HER2 antibody	fECD DNA	Female BALB/c mice	Induce anti Her2 antibody response	(200)
			HER2 DNA subdomains (DI, DII, DIII, and DIV)			
				BT474 cell line		
90	Immunotherapy-Immunology		Tumoral ASCs	T cells	$\uparrow$ CD4 + CD25 + CD127LowFoxp3 + and CD4 + CD25-CD127LowFoxp3 + Treg subsets	(201)
		IL-4 and IL-10			$\uparrow$ Expression	
		IFN- γ			$\downarrow$ Expression	
91	Immunotherapy-Immunology		Radiation		Higher chromatid radiosensitivity	(202)
			Radiation	lymphocytes	Higher background SCE	
92	Radiosensitivity		Radiation	leukocytes	higher apoptosis induction, DNA damage	(203)
93	Effect of Components	Bcl-2, procaspase3 and procaspase9	Econazole Nitrate	MCF-7 cell line	$\downarrow$ Expression	(204)
94	Effect of Components		menadione	trastuzumab-sensitive SKBR3 cells	$\uparrow$ level of ROS, $\downarrow$ level of GSH	(205)
			menadione + trastuzumab	trastuzumab-sensitive SKBR3 cells	no effect on ROS, $\downarrow$ level of GSH	
			menadione	trastuzumab-resistant SKBR3 cells	$\downarrow$ level of ROS and GSH	
			menadione + trastuzumab	trastuzumab-resistant SKBR3 cells	no effect on ROS, $\downarrow$ level of GSH	
95	Immunotherapy-Immunology				Higher CD8 + T cells frequency	(206)
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1345 Persian Citation(s)						

No.	Type of Study	Gene /Protein/ Cell Activity	Drug /Extract/ Component name	Cell Line, Tissue, Animal model name	Effect	Ref.
		granzyme B		micro-metastatic dLN	Lower frequency of CD4 + in macro-metastatic dLN than micro-metastatic dLN	
		CXCL10			Higher expression	
					No difference	
96	New Technologies	Dopamine Receptor D2	Bromocriptine	MCF-7 CELLS	↑ Apoptosis	(207)
97	Effect of Components	Adenosine Receptors	Adenosine	MDA-MB468 and MCF-7 cells	↑ Cell growth	(208)
98	Effect of Components	cell growth	Zingiber	MCF-7 and L929 cells	Cytotoxic effects on tumor cells, Negative cytotoxic effect on normal cells	(209)
99	Biomarkers	mir145	mir145 vector	MCF10A/MCF7	↑ expression levels of miR-145 in MCF10A	(210)
100	Effect of Components	RARB, BRCA1, RASSF1A	folate and other one-carbon related nutrients	149 participants with primary breast cancer	↑ Frequency of tumors with methylation status at RARB and BRCA1 genes.	(211)
101	Effect of Components	Telomerase Activity	Zinc, Selenium and Copper	T47D cells and 56 breast cancer patients	Paradoxical relationship between trace elements levels with telomerase activity in tumor tissue	(212)
102	Effect of Components	Cell Growth	LACTOBACILLUS RHAMNOSUS	INBRED BALB/C MICE	↑ Immune system responses against tumor	(213)
103	Effect of Components	cell growth	Newcastle Disease Virus	MCF-7 cell line	oncolytic effect of NDV-AF2240 against the MCF-7 cell line	(214)
104	Effect of Components	Tumor Mass Status, intra Tumor CD4/CD8 ratio of the mammary tumor	Candida Albicans Infections (Candidiasis)	Balb/C Mice	immunosuppressive effects of candida albicans on proliferation of lymphocytes	(215)
Web of Science, PubMed, Scopus, SID, IranMedex						
Jan 2005-Oct2015						
1986 English Citation(s)						
1345 Persian Citation(s)						

Diagnosis

The fourth group included 9 studies with applications in breast cancer diagnosis. The majority of these studies compared various molecular methods such as differential PCR (216), multiplex PCR (217), Real-Time RT-PCR (218), quantitative reverse transcription-PCR (qRT-PCR) and multiplex ligation-dependent probe amplification (MLPA) (219) to immunohistochemistry. Kadivar et al. evaluated inter- and intraobserver reproducibility of assessment of HER2/neu immunostaining in invasive breast cancer (220). One of the studies introduced a developed label-free electrochemical miRNA biosensor based on employing methylene blue (MB) which confirmed by electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) methods (221). Other study developed a High-Performance Liquid Chromatography (HPLC) method for assessment of ErbB1 and ErbB2 genes amplification (222). Salimi et al. evaluate the gene amplification using dual-colour primed in situ labelling (PRINS) in comparison with fluorescence in situ hybridization (FISH) (223). Conjugation of monoclonal antibodies to SPIO informed as a useful method for the detection of tumor cells in the other study (224).

The fifth group comprised 18 studies that could not be assigned to any of the abovementioned groups. They examined various issues including functional mechanisms of genes (225–231) animal models of the disease (232–235), familial breast cancer assessment (236–238), tumor environment simulation (239) and informatics studies (240, 241). One study optimised a method to prepare liposomes containing HER2/Neu-derived peptide as a vaccine delivery system for breast cancer (242).

Ethical considerations

Out of the 240 selected studies, 174 studies were conducted on human or animal samples. However, only 53.45% of these papers (n = 53) had ethical approval, and the rest did not address ethical issues (the other 71 studies did not consider ethical issues, either).

Discussion

Cellular and molecular studies conducted on breast cancer in Iran were divided into five groups: I) focusing on breast cancer susceptibility genes, II) genes affecting prognosis and survival, III) genes affecting therapeutic effects of different compounds on different grades of breast cancer cell lines, IV) studying about genes affecting breast cancer diagnosis, and V) studies which are focus on functional mechanisms of genes and establishment of animal models of breast cancer, respectively.

Studies in the first group investigated either germline or somatic mutations. Most of the researches were about BRCA1/2 gene. Most of the investigations on other susceptible genes did not consider family history. The critical problem in these studies was patient sampling difficulties and collecting clinical data and follow up variables. It seems that further studies on family pedigrees and germline mutations are required to confirm the role of mutations in susceptibility to cancer. Moreover, establishment and strengthening the cancer biobanks are very important which has been neglected these years (243) but, it is growing today.

In spite of increasing attention to the regulatory role of miRNAs, few of the reviewed studies focused on this subject. Most of them have shown the gene expression alteration in breast cancer. Further studies on large sample sizes in different populations would, hence, help clarify the relationship between miRNAs and various stages of cancer pathogenesis. Moreover investigating their targeting potency is recommended.

Numerous studies in the world have examined the effects of epigenetic changes on cancer. However, the number of such studies is very limited in Iran. Among all of the studied HIC 1 promoter hypermethylation was correlated with nodal involvement and tumor size. Since most epigenetic changes occur due to environmental and non-genetic factors (22, 67, 164), studying the subject in sporadic patients can help clarify the role of the environment in the incidence of cancer. Moreover, these changes may affect the invasiveness of cancer or its response to medications (244, 245).

Hence, it is essential to conduct further studies to clarify susceptibility genes and their relationship with prognosis. Such studies will lead to the discovery of new genes or gene panels and facilitate decision-making during the treatment of patients with breast cancer. Conducting these studies in populations from different geographical locations is highly essential. However, most studies in Iran have been sporadic and with limited sample sizes. The majority of these studies have not assessed the patient survival rate or different subgroups of breast cancer separately. Performing reliable studies in this field would require access to not only the patients' clinical data but also biological banks and systems for regular collection and storage of biological samples. Limited reports of such banks are available in the country (e.g. BCRC-BB)(243). Moreover, since limited research resources are available, more extensive studies cannot be easily performed.

Another problem is that the majority of studies are researcher-oriented. Determining research priorities in specific fields by relevant institutions, e.g. the Ministry of Health or various universities, and aggregating and integrating the results of multi-center studies would probably yield stronger and more valid results. However, sporadic studies in single centers will not help the expansion of the boundaries of knowledge.

The majority of studies on the effects of herbal and medicinal compounds were at cell level or on mice. Considering the high therapeutic potentials of these compounds, the great interest of pharmaceutical companies in the screening and discovery of new medications based on the geographical area, vegetation cover, and microorganism populations in Iran, more serious studies in this field may be essential.

This review also assessed the ethical considerations in the selected articles. The absence of ethical approval, despite its necessity, indicates two points. Firstly, ethical approvals were not mandatory for biological studies before 2015 in Iran, and many researchers did not consider it as an essential issue in non-clinical studies. Now, the Ministry of Health has obliged researchers to obtain approval from an ethics committee. Secondly, and more importantly, it is evident that journals publishing such papers had no strict rules about the absence of ethical approval. In these cases, most of the researcher might have had ethical approval but did not provide the data due to journal policies. Considering the current policies in ethical aspects of researches in Iran, It is expected that this issue is modified in future studies.

Conclusion

Molecular Studies conducted in Iran between 2005–2015 evaluated breast cancer susceptibility genes, Prognosis, survival and clinicopathologic features of the patients, compounds with therapeutic properties, diagnosis and other issues. The majority of these studies were conducted sporadically and with small sample sizes. More qualified multi-center studies would require the development of biological banks and providing data from breast cancer patients with different characteristics. Moreover, considering the limitations of research funding and the importance of increasing knowledge about Iranian population Genetics, It seems that financial support by health system providers in this field is necessary.

Abbreviations

SID: Scientific Information Database

BRCA1/2: BReast CAncer genes 1 and 2

MeSH: Medical Subject Headings

NA: Not Assigned

CAT: CATalase

mRNA: Messenger RNA

miRNA: microRNA

NK: Natural Killer

MTT: [3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide]

FFPE: Formalin-Fixed Paraffin-Embedded

PCR: Polymerase Chain Reaction

qRT-PCR: quantitative Reverse Transcription-PCR

MLPA: Multiplex Ligation-dependent Probe Amplification

MB: Methylene Blue

EIS: Electrochemical Impedance Spectroscopy

CV: Cyclic Voltammetry

HPLC: High-Performance Liquid Chromatography

PRINS: Primed In Situ Labeling

FISH: Fluorescence In Situ Hybridization

SPIO: Super Paramagnetic Iron Oxide

HIC1: Hypermethylated In Cancer 1

APOBEC3: Apolipoprotein B mRNA-Editing enzyme, Catalytic polypeptide-like 3

CCR5: C-C Chemokine Receptor type 5

CYP1A1: Human cytochrome P450 1A1

CYP2D6: Human Cytochrome P450 2D6

EGFR: Epidermal Growth Factor Receptor

ESR1: Estrogen Receptor 1

FGFR2: Fibroblast Growth Factor Receptor 2

GATA3: GATA Binding Protein 3

GSTM1: Glutathione S-Transferase Mu 1

GSTP1: Glutathione S-Transferase Pi gene

GSTT1: Glutathione S-Transferase (GST) Theta 1

GSTZ1: Glutathione S-Transferase Zeta 1

HLA: Human Leukocyte Antigen

IGF1: Insulin-like Growth Factor 1

IL: Interleukin

MDR1: Multidrug Resistance Protein 1

SDF-1: Stromal cell-Derived Factor 1

TGF- β 1: Transforming growth factor beta 1

VDR: Vitamin D Receptor

WRAP53: WD Repeat Containing Antisense To TP53

XRCC: X-ray Repair Cross-Complementing

DBC2: Deleted in Breast Cancer

PTEN: Phosphatase and Tensin homologue

MMP-9: Matrix MetalloPeptidase 9

MDM2: Murine Double Minute 2

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors. This research has been approved in Breast Cancer Research Center Ethical Committee with ethical code number "IR.ACECR.IBCRC.REC.1394.54"

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

RE managed the group and was responsible for the literature search, manuscript categorization, data extraction, writing manuscript. SHD and ZES participated in the literature search, data extraction, and preparation of tables and rechecking the data. TO was responsible for data extraction and rechecking the data. SH and KM managed the team in developing the idea in all steps of research including search, data extraction, preparing tables, writing the manuscript. All authors have participated in providing the first draft of the manuscript and they have approved the final version.

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