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Risk Factors in Breast Cancer Progression and Current Advances in Therapeutic Approaches to Knockdown Breast Cancer

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Abstract

The complicated coding of tumorous cells requires emerging molecular biology tools for early diagnosis and for the better understandings of cancer progression. In spite of the advancement in diagnostic and therapeutic approaches to hit breast cancer, it is still a second major cause of cancerous deaths among women globally. In therapeutic vibes, deregulation in the expression of genes such as BRCA1, BRCA2, PIK3, RB, MDM2, TPK53 and HER2 involved in breast cancer prevalence. Furthermore, microRNAs such as miR-200, miR-27a, miR-182 and let-7 have been demonstrated that hold some potential hope to extricate from the complexity of cancerous cells. This review elaborates the different risk factors that lead to breast cancer progression and the current therapeutic approaches ongoing to tackle the tangled cellular behavior of cancerous cell. Moreover, for the better understandings of various signaling cascades involved in breast cancer development and to design effective therapies, researchers further needed to take interest in upcoming approaches including biophysics and nanotechnology based gene therapy and drug delivery.

Keywords: MicroRNAs; BRCA; Nanotechnology; Gene therapy; Molecular biology

Introduction

Breast cancer is the second major leading cause of cancerous deaths among women worldwide with poor prognosis and tangled cellular coding that requires in-depth understandings of signaling cascades involved in cell proliferation and cancer progression. Broadly breast cancer has 3 major types invasive, non-invasive and other include paget's disease of nipple that accounts 1-4% of breast cancer [1]. The most common symptoms associated with the onset of breast cancer are; appearance of lumps, redness, soreness, and compactness of dimple. The environmental factors have been reported as the major cause of the breast cancer after the genetic mutations. Most epidemiology researches have made the association between fat present in diet and breast cancer risks [2].

Breast cancer is the second major leading cause of death among women; more than one million cases of breast cancer have been documented globally. In the recent research on breast cancer prevalence 90,000 cases of breast cancer have been registered in Pakistan but due to the lack of suitable markers these cases are unable to diagnose. In Pakistan breast cancer accounts for 38.5% of other types of cancer in the country. Among Pakistani females the ratio of developing breast cancer is increasing at an alarming rate. About 10% of the breast cancer cases are diagnosed and treated while 75% patients do not get any treatment and after diagnosis die within five years. It is observed that early detection of breast cancer also increases the chances of survival up to 90% [3].

Different types of breast cancer caused by different types of mutations in genes mainly BRCA1, BRCA2, PIK3, RB, MDM2, TPK53 and HER2 that affects the body differently. Deregulation of expression of some genes like TPK53, MDM2 and RB play role in therapeutic vibes of breast cancer, research classified that 90% of breast cancer cause by genetic mutation in any of the two genes namely BRCA1 and BRCA2 [4]. To untangle the complexity of signaling cascades of cancerous cells, there is a need of complete molecular understandings of epigenetics and genetics events including the tumor suppressor and oncogenic miRNAs associated with the cancer development. miRNA plays important role in cellular homeostasis by regulating the apoptosis, cell differentiation and proliferation by number of events including gene silencing, translational inhibition and deregulation of targeted mRNA. miRNAs act as both tumor suppressor and oncogenic, the up-regulation of the oncogenic miRNAs such as miR-21, miR-27a and miR-182 down regulates the tumor suppressor miRNAs that leads to modulate the downstream signaling pathways and thus induce cancer. Nanotechnology based miRNA replacement therapies has a potential hope to treat breast cancer [5].

Emerging hybrid technologies and therapeutic approaches against breast cancer is the requirement of the time to support the traditional therapies such as immunotherapy, chemotherapy and radiotherapy. This review highlights the current effective therapeutic approaches including nanotechnology based drug delivery with controlled drug release at the site of disease and the use of natural drugs with their anti-cancerous and anti-oxidant properties [6].

Breast Cancer Awareness

Mostly countries in world are facing resources containment that confines accommodation to improve early diagnosis, detection and treatment of breast cancer. BHGI (breast cancer global initiative) combat to establish evidence-based, culturally appropriate and economically feasible guidelines that can also use in nations along confined health care supplies to promote breast cancer outcomes. In

highly developed countries, guidelines delimiting superlative approaches to initial diagnosis, detection and medication of breast cancer have also designated and annunciated [7].

The associated awareness research on breast cancer or experiences of breast cancer in cultural minority women of origin of Asia is unoccupied. Trendy evidences conjecture the women in Asia, especially those of women which are muslin beliefs are conceivable to be more unfamiliar to breast cancer [8].

In Pakistan breast cancer incidences are almost equal to European countries. In Pakistan most of women receive breast cancer diagnosis when disease reached to a advanced stage. Breast cancer and breast health in Pakistan is underreported [9].

Likely the strong cultural awareness towards female breasts, breast cancer and also its affiliation to breast self-examination, exist experience of patient having breast cancer, and the capability of breast cancer inmate to encounter not only along the consequence of disease but also with impingement on intimate relationships to husbands, extended and immediate family, is not unanticipated that there is also a scarcity of concentrated research of breast cancer in the Pakistan [10].

In Pakistan many women rejected the breast cancer possibility and overpass the lump of breast and lasted for long time more than two years. In such cases, Pakistani women wanted religious flotation from peers as contend strategy or communicated with homeopathic Medicare practitioner for medication of breast cancer in alternative to looking for proper medical advice [11]. In Pakistan also due to illiteracy and lack of resources women have not proper diagnosis, medication and detection of breast cancer, women also feel hesitation to tell about breast problems to other, and because of no awareness to breast cancer death rate of women is much higher in Pakistan [12].

Types of Breast Cancer

Different types of breast cancer have now been reported caused by different types of mutations in genes that affects the body differently in Figure 1. In invasive breast cancer, the affected cells of breast break out the duct and lobular walls and access to the fatty and connective tissues surrounding the duct in breast. It has been reported that in invasive breast cancer BRCA1 gene activity particularly decreased [13]. In noninvasive breast cancer, affected cells remain bounded with the duct of breast. It has been demonstrated recently that 90% of the non-invasive breast cancer is due to ductal carcinoma in situ that considered very common type of it. Lobular carcinoma considered as a marker for increase in breast cancer possibilities. In the case of lobular carcinoma in situ rapid increase of the number of cancerous cells occurs and it accounts 10-15% of the breast cancer [14].

Another type of breast cancer is paget's disease of nipple starts from the milk duct and metastatic to the skin of breast nipple and areola and accounts 1-4% of breast cancer. Mostly shave biopsy, surface biopsy, punch biopsy and wedge biopsy used for it diagnosis. Women with the Paget's disease of the nipple have poor characterizes of cancer. There is an association present between underlying invasive carcinoma and Paget's disease of the nipple [15]. Males also have chances of breast cancer, incidence for male breast cancer overall is 1%. Factors that influence breast cancer in male are family history, hormonal milieu and alternation in genetics. Different studies on breast cancer have shown that breast cancer in male is mostly associated with the alternation in estrogen-testosterone ratio (Figure 1) [16].

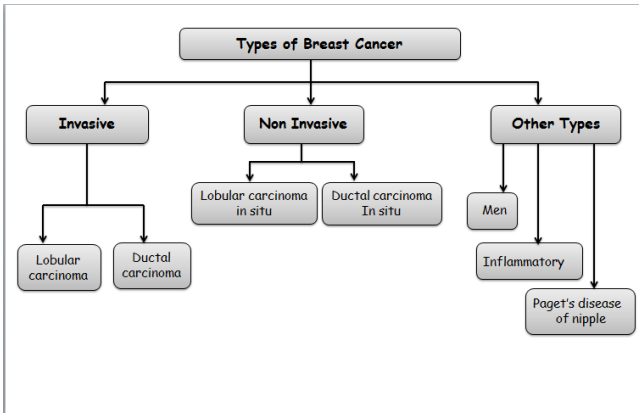

Figure 1: Types of breast cancer.

Molecular Aspects of Breast Cancer

In family linkage or due to the mutation in the genes, breast cancer is highly identified in BRCA1, BRCA2, PTEN and TP53, also there are some other genes that have been reported recently that are involved in DNA repairing like RAD59C, PALBL, ATM, CHEK2, ATM, BRTP1 also affiliated with modest breast cancer [4]. It has now been clear that signaling pathway of phosphatidyl inositol-3-kinase (PI3K) denationalize different cancer types. PIK3CA gene mutation in breast cancer consider for approximately 20%. PIK3CA gene mutation is 20% to 25% approximately has been reported for HER2 positive breast cancer, which is depending upon PI3K pathway [17]. HER2 is an epidermal growth factor constituent that receptor family has an activity of tyrosin kinase, resulting in the auto-phosphorylation of receptor in cytoplasmic domain that starts different pathways of signaling that leads to proliferation of cell and tumor-genesis. HER2 overexpression occurs 15-30% approximately in breast cancer and act as a predictive and prognostic biomarker for breast cancer [18].

IGF family biological activates not only the development of normal organism but also have implicated in tumorigenesis. This signaling family IGF consists of IGF ligands (IGF1 and 2), also have cell receptors (IR, IGF-1R and IGF-2R) and a binding protein group (IGFBPs). High levels of IGF-1 indicated as a constituent risk factor in development of breast cancer. Overexpression and activation of IGF-1R have been suspected in different cellular processes containing cell migration, attenuation and proliferation of cell survival. Transduction routes for IGF signaling are PI-3K and MAPK pathways, which act as a key moderator of cell propagation. Recently, it has been reported that MAPK44/42(ERK) act as an important constituent in resistance of MCF-7 apoptosis from cell to cell, which demonstrated the significance of ERK signaling in the prolonged endurance for breast cancer cells. Additionally, there is substantiation that JNK (c-Jun N-terminal kinase) signaling regulates IGF-1 negatively to cell proliferation in breast cancer [19].

BRCA1 and BRCA2 genes mutations have been demonstrated that elevates the risks of ovarian, breast and contralateral breast cancer. Approximate range for BRCA1 and BRCA2 mutation for the breast cancer is 40% to 87% and 18% to 88% have been reported [20]. Comparatively 30% of breast cancer is caused by tumor protein p53 (TP53) mutation but this constancy alternates extensively between

subclasses. Epigenetic and genetic changes have been determined in p53 activity regulators [21].

S-phase kinase protein-2 (Skp-2) role in breast cancer development

It has been reported recently that in breast cancer pathogenesis, F-box protein skp2 (S-phase kinase protein-2) plays important role. Skp2 related to system of ubiquitin-proteasome that plays important role in different biological processes by regulating the appropriate turn-over of proteins [22]. S-phase kinase associated protein-2 is a particular determinant of SCFskp2 E3 ligase that involved in progression of cell cycle by deregulating its target. p27 is a substrate for skp2, its lower level caused by Skp2 overexpression which shows expression of cancer in humans. Skp2 act as a prognostic marker in breast cancer. Apparently, evidences have also show that skp2 act as an important factor in cell growth, invasion, apoptosis and metastasis in breast cancer [23].

Different signaling pathways, for instance ERK (extracellular signal-regulated kinase) PI3K/Akt (phosphatidylinositol-3 kinase), PPARϒ (peroxisome proliferator-activated receptor-ϒ), mTOR and insulin growth factor-1 (IGF-1) signaling pathways have been originated for cross-talk to Skp2, which indicated that this cross-talk present between these signaling pathways and Skp2 plays substantial role in breast cancer occurrence [23]. Skp2 protein and mRNA protein both play exhilarated level in cell lines of breast cancer and also in primary breast tumor. Skp2 overexpression promotes growth of cancerous cells of breast. In recent studies it has been inaugurated that Skp2B interact to REA and then high level of Skp2B leads to low level of REA and indicates Skp2 overexpression enriched for breast cancer by modulating ER activity. Skp2 overexpression was encountered more commonly in tumor metastatic in axillary lymph nodes in case of breast cancer demonstrated that Skp2 stimulates breast tumor metastasis shown in Figure 2 [24].

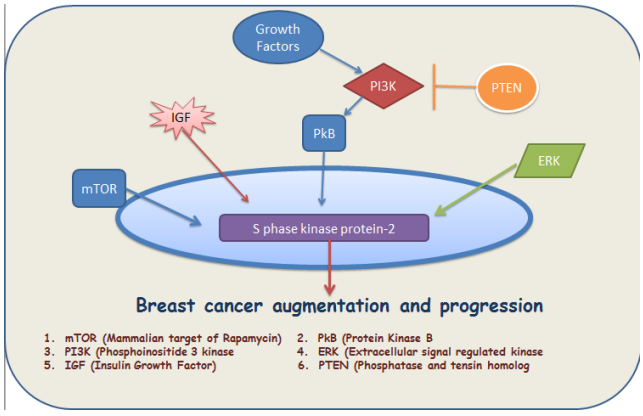

Figure 2: Skp-2 in breast cancer development.

MicroRNAs for Breast Cancer

Small single stranded functional RNAs having range between 19-25 nucleotides commonly known as microRNAs have been demonstrated as a biological active RNA subtype involved in various biological functions to regulate the cellular homeostasis by regulating cell differentiation, apoptosis and proliferation by the degradation of functionally active mRNAs. The biogenesis of microRNAs must be tightly regulated for the proper functioning of cell. It has been reported that any kind of de-regulation in the biogenesis of miRNAs effect the expression of several mRNAs associated with the particular miRNA and thus it leads to induce cancer [25]. Numbers of enzymes are involved in the synthesis of miRNA such as RNA Pol II forms the pri-miRNA and then the premature miRNA processed by number of enzymes to form mature miRNA shown in Figure 3. Reduced expression of any of these enzymes involved in the maturation of miRNAs leads to induce cancer [26].

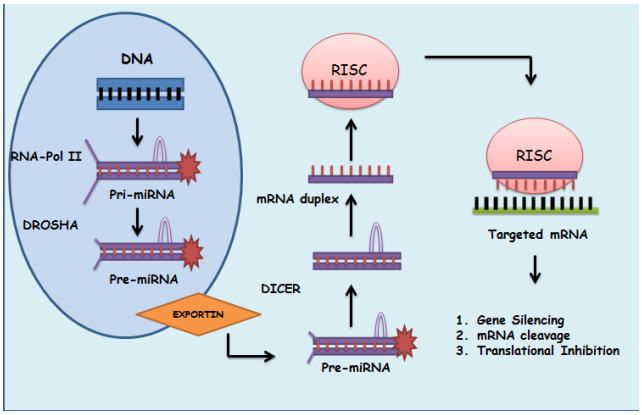

Figure 3: Biosynthesis of miRNA.

The miRNAs can act as both tumor suppressor miRNAs and oncogenic miRNAs. In breast cancer, the oncogenic miRNAs are up-regulated while the expression of tumor suppressor miRNAs is down regulated [27]. Numbers of events have been reported that leads to the aberrant function of miRNAs such as epigenetic factors, SNPs and defect in the maturation of mature miRNA pathway. Increased and decreased level of miRNAs can now be easily detected by the use of emerging molecular biology and sequencing techniques [28]. Expression of tumor suppressor miRNAs inhibit by the up regulated oncogenic miRNAs and thus the lower expression of tumor suppressor miRNAs leads to the augmentation of signal pathways involved in the progression of cancer (Table 1) [29].

MicroRNAs	Targeted Gene	Biological Function	Expression
let-7	H-Ras, HMGA2, PAK1	Initiate tumor growth, involved in cell differentiation and metastasis	Decreased

miRNA-200	ZEB1, ZEB2, HER3	Involved in tumor growth and cell differentiation	Decreased
miRNA-145	ER-α, N-Ras, RTKN, OCT4, MUC1	Initiate tumor growth, angiogenesis, metastasis, cell differentiation and metastasis	Decreased
miRNA-126	PITPNC1, MERTK,	Involved in metastatic angiogenesis	Deceased
miRNA-21	TPM1, PTEN, TIMP3, PDCD4	Involved in cancer metastasis	Increased
miRNA-182	RECK, FOXO1, MIM	Involved in cancer invasion	Increased
miRNA-27a	ZBTB10, HOXO1	Involved in angiogenesis and cell viability and	Increased
miRNA-155	SOCS1, FOXO3a	Involved in cell apoptosis and proliferation	Increased

Table 1: Tumor suppressor and oncogenic miRNAs linked with breast cancer are listed.

miRNAs as therapeutic tool for breast cancer

Three layered polyplex (microRNA) used as a targeted delivery system for breast cancer gene therapy. Gene therapy is use as a drug to treat diseases i.e., therapeutic delivery of nucleic acid into patient's cell. MicroRNA is small in size and has low molecular weight due to this property it has now became the promising therapeutic drugs in cancer treatment. Major challenge of miRNA is to attain specificity, affectivity and safe delivery to the cancerous cells. Therefore, use of three-layered polyplex with folic acid as a target to deliver miR-210 into breast cancer cells and thus it is useful to inhibit the breast cancer progression by this method [30].

Immunotherapy

Breast cancer has been considered as an immunologically silent, but now it is clear that the immune system has role in this disease [31]. Moreover, at the earliest stages of the disease, immunity to breast cancer begins in some patients prior to detection. Immune cells also emerged as a promising target against breast cancer as both the innate and adaptive immune system is necessary for the design and development of immunotherapies in breast cancer. The role of immunotherapies against cancerous cells refers as active and passive treatments shown in Figure 4 [32].

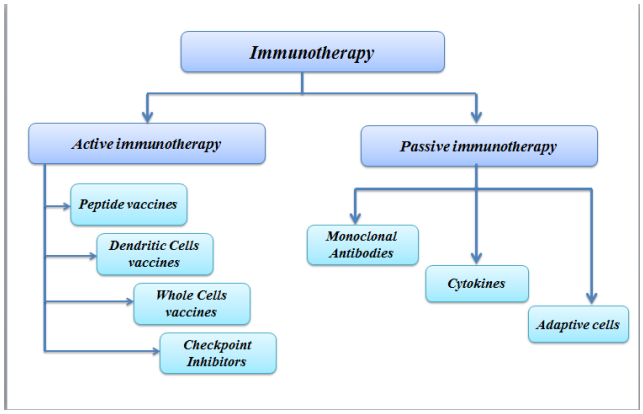

Figure 4: Immunotherapy and its role in breast cancer.

Immunotherapy encircles both vaccines and checkpoint blocking antibodies and both of these approaches are being examined as a future for the treatment of breast cancer. Vaccine therapy may be ideal to damage ductal carcinoma in situ (DCIS) by the activation of type I T-cells against DCIS antigens and thus inhibit its reoccurrence [33]. Some of the vaccines against breast cancer have been reported that use new approaches for its delivery such as liposome formulation and nanoparticles that further enhance the efficacy of vaccines (Table 2).

Vaccines	Immune Response	References
Dendritic cell based vaccines	Have known specificity for tumor associated-antigen and also generate its own immune response	[34]
Peptide based vaccines	These help to generate immune responses (including antibodies, helper T-cells and cytotoxic T lymphocytes CTLs) using antigenic epitopes	[35]
DNA based vaccines	It stimulates a 'physiological' immune response against antigens.	[36]
	These may deliver by new technology like nanotechnology and liposome.	
Whole-cell-based vaccines	These may generate antigen specific T cell responses	[37]
CD8+Tcell vaccines	These target immunosuppressive pathways allowing for greater anti-tumor response	[38]

Table 2: Some of the vaccines are listed.

Natural Cure for Treatment of Breast Cancer

For many centuries, plants and herbs have been used for medicinal purposes as they possess therapeutic properties to treat number of diseases including cancer. The main goal of these natural drugs is to retain the immune stimulating and anti-tumor properties by different

types of plants. The emerging research in the development of medicines has now more concern towards the use of herbal medicines because of the lower proportion of toxicity cause by these natural drugs. In different types of herbs, vast variety of active phytochemicals has been reported such as flavonoids, terpenoids, sulfides, ligands, lignans, polyphenolics, plant sterols and carotenoids possessing anti-oxidant properties. These phytochemicals either stimulate the protective enzyme (glutathione transferase) or it may prevent the cell growth. It it has been demonstrated that the extracts and juices of Amoora rohituka, Withania somnifera, Vaccinium macrocarpon and Dysoxylum binectariferum have anti-tumor properties and is useful for the treatment of breast cancer [39].

Common herbs for the treatment of breast cancer

Great progress has now been made in medicinal fields to fight against the life-threatening disease. Wide variety of natural herbs having anti-tumor properties have been identified that cause low toxicity (Table 3).

Natural drugs	Anti-cancer properties of natural drugs	References
Carotenoids	Carotenoid substances have vigorous antioxidants that exhibit different therapeutic activities, such as protecting against oxidative damage to cells, searching of free radicals, modulation of immune system and enzyme's activity regulation involved in cancer production and also simulates the activity of immune system.	[40]
Turmeric (*Curcuma longa)*	Curcumin (active ingredient of turmeric) has role in anticancerious activity due to its phenolic substances. Curcumin has inhibitory action in all phases like initiation, promotion and propagation of tumor.	[6]
Garlic (*Allium sativum)*	Garlic has Anti-cancer activity due to presence of polysulfide's and organic sulfides. Mechanism of anti-tumor activity stimulates the lymphocytes and macrophages. They also interfere with cancerous cells metabolism and kill the cancerous cells.	[41]
Black Cohosh (*Cimicifuga recemosa)*	Black cohosh has synergistic effects for patients of breast cancer when use in combination with chemotherapeutic agents.	[42]
Green Tea (*Camellia sinensis)*	Polyphenolic compounds show anti-tumor activity. Green tea also stimulates the necrosis and apoptosis of tumor cells and possess anti mutagenic activity. All these properties are due to the anti-oxidant activity of phenolic compounds present in green tea.	[43]
Burdock (*Arctium lappa)*	It may contain active ingredients that alter the oncogenes. Burdock seeds also contain Arctigenin that has an ability to inhibit tumor cells. Most important active ingredient is Tannin which is a phenolic compound and regulates the macrophages action and reduces the cancer propagation.	[44]

Table 3: Some of the effective natural herbs use for the treatment of breast cancer is listed.

Emerging Therapeutic Approaches to Hit Breast Cancer (Nano Based Drug Delivery)

Today breast cancer is arguably the most common cancer faced by females and world widely it is the second major cause of death in women. Certainly, this disease has gathered much attention in the field of pharmacology research. Modern chemotherapeutic treatments also use for the breast cancer treatment, but it has a limiting use because of number of limitations. Nanotechnology as compared to chemotherapy is a highly focused approach that may provide very effective and less toxic treatment. For the treatment of metastatic breast cancer, emerging nanotechnologies also guaranteed new approaches that require delivery of nanomaterials and thus it controls the release of a particular drug to the site of action [45]. An important step in identifying novel targets in breast cancer is provided by ability to profile molecular pathways in drug responsive and drug resistant tumors [46]. However, applications of diagnostic and therapeutic interventions require treatment related cognitive state, also determine the subgroup of breast cancer patients is still a challenge [47].

It has been reported that method of drug delivery system by the use of magnetic polyurethane is biocompatible and has lower toxicity; these magnetic polymers can be used as an external magnet to direct chemotherapeutic drugs to cancerous cells in body. For the successful treatment of cancer, nanotechnology-based combination drug delivery system also summarized facing challenges and perspectives i.e., in this approach enhanced cytotoxicity is mainly due to reduction of multidrug resistance and synergistic effects as a result it may reduce toxicity towards normal cells [48].

Conclusion

Breast cancer is a second major cause of cancerous death among females globally, deregulation of genes such as BRCA1, BRCA2, PIK3, RB, MDM2, TPK53 and HER2 are involved in breast cancer prevalence. Different oncogenic miRNAs also have been reported that leads to breast cancer progression. Different therapeutic approaches against breast cancer such as immunotherapies and the use of natural drugs are currently available. Inspite of all currently available treatments, there exist some limitations and side effects on healthy cells, while the nanotechnology based drug delivery and miRNA therapy have potential of targeted and controlled drug release to execute tumorous cells, for further advancement Biological scientists further needed to take interest in upcoming nanotechnology based approaches to untangle the complexity of cancerous cells.

References

1. Bodai BI, Tuso P (2015) Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. The Permanente Journal 19: 48.

2. Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK (2010) Various types and management of breast cancer: An overview. Journal of Advanced Pharmaceutical Technology & Research 1: 109.
3. Spurdle AB, Couch FJ, Parsons MT, McGuffog L, Barrowdale D, et al. (2014) Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. Breast Cancer Research 16: 3419.
4. Filippini SE, Vega A (2013) Breast cancer genes: beyond BRCA1 and BRCA2. Front Biosci (Landmark Ed), 18: 1358-1372.
5. Reddy KB (2015) MicroRNA (miRNA) in cancer. Cancer Cell International 15: 38.
6. Shareef M, Ashraf MA, Sarfraz M (2016) Natural cures for breast cancer treatment.
7. Tazhibi M, Feizi A (2014) Awareness levels about breast cancer risk factors, early warning signs, and screening and therapeutic approaches among Iranian adult women: a large population based study using latent class analysis. BioMed Research International 2014.
8. Peltzer K, Pengpid S (2014) Awareness of breast cancer risk among female university students from 24 low, middle income and emerging economy countries. Asian Pac J Cancer Prev 15: 7875.
9. Youlden DR, Cramb SM, Yip CH, Baade PD (2014) Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer Biology & Medicine 11: 101.
10. Asif HM, Sultana S, Akhtar N, Rehman JU, Rehman RU (2014) Prevalence, risk factors and disease knowledge of breast cancer in Pakistan. Asian Pac J Cancer Prev 15: 4411-4416.
11. Shaukat U, Ismail M, Mehmood N (2013) Epidemiology, major risk factors and genetic predisposition for breast cancer in the Pakistani population. Asian Pacific Journal of Cancer Prevention 14: 5625-5629.
12. Memon ZA, Shaikh AN, Rizwan S, Sardar MB (2013) Reasons for Patients Delay in Diagnosis of Breast Carcinoma in Pakistan. Asian Pacific Journal of Cancer Prevention 14: 7409-7414.
13. Cowell CF, Weigelt B, Sakr RA, Ng CK, Hicks J, et al. (2013) Progression from ductal carcinoma in situ to invasive breast cancer: revisited. Molecular Oncology 7: 859-869.
14. Whitaker-Worth DL, Carlone V, Susser WS, Phelan N, Grant-Kels JM (2000) Dermatologic diseases of the breast and nipple. Journal of the American Academy of Dermatology 43: 733-754.
15. Szpor J, Polak K, Dyduch G, Okon K, Hodorowicz-Zaniewska D, et al. (2015) Pigmented Paget's disease of the nipple. Polish Journal of Pathology: Official Journal of the Polish Society of Pathologists 66: 93-97.
16. Bouchardy Magnin C, Rapiti Aylward E, Fioretta G, Schubert H, Chappuis P, et al. (2013) Impact of family history of breast cancer on tumour characteristics, treatment, risk of second cancer and survival among men with breast cancer. Swiss Medical Weekly 143: w13879.
17. Loibl S, Von Minckwitz G, Schneeweiss A, Paepke S, Lehmann A, et al. (2014) PIK3CA mutations are associated with lower rates of pathologic complete response to anti–human epidermal growth factor receptor 2 (HER2) therapy in primary HER2-overexpressing breast cancer. Journal of Clinical Oncology 32: 3212-3220.
18. Iqbal N, Iqbal N (2014) Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. Molecular Biology International 2014.
19. Voudouri K, Berdiaki A, Tzardi M, Tzanakakis GN, Nikitovic D (2015) Insulin-like growth factor and epidermal growth factor signaling in breast cancer cell growth: focus on endocrine resistant disease. Analytical Cellular Pathology 2015.
20. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, et al. (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. Journal of the National Cancer Institute 105: 812-822.
21. Ziyaie D, Hupp TR, Thompson AM (2000) p53 and breast cancer. The Breast 9: 239-246.
22. Signoretti S, Di Marcotullio L, Richardson A, Ramaswamy S, Isaac B, et al. (2002) Oncogenic role of the ubiquitin ligase subunit Skp2 in human breast cancer. The Journal of Clinical Investigation 110: 633.
23. Sonoda H, Inoue H, Ogawa K, Utsunomiya T, Masuda TA, et al. (2006) Significance of skp2 expression in primary breast cancer. Clinical Cancer Research 12: 1215-1220.
24. Davidovich S, Ben-Izhak O, Shapira MA, Futerman B, Hershko DD (2008) Over-expression of Skp2 is associated with resistance to preoperative doxorubicin-based chemotherapy in primary breast cancer. Breast Cancer Research 10: R63.
25. Kodahl AR, Lyng MB, Binder H, Cold S, Gravgaard K, et al. (2014) Novel circulating microRNA signature as a potential non-invasive multi-marker test in ER-positive early-stage breast cancer: a case control study. Molecular Oncology 8: 874-883.
26. Ben-Hamo R, Efroni S (2015) MicroRNA regulation of molecular pathways as a generic mechanism and as a core disease phenotype. Oncotarget 6: 1594.
27. Tokumaru S, Suzuki M, Yamada H, Nagino M, Takahashi T (2008) let-7 regulates Dicer expression and constitutes a negative feedback loop. Carcinogenesis 29: 2073-2077.
28. Wang W, Luo YP (2015) MicroRNAs in breast cancer: oncogene and tumor suppressors with clinical potential. Journal of Zhejiang University Science B 16: 18-31.
29. Kurozumi S, Yamaguchi Y, Kurosumi M, Ohira M, Matsumoto H, et al. (2017) Recent trends in microRNA research into breast cancer with particular focus on the associations between microRNAs and intrinsic subtypes. Journal of Human Genetics 62: 15.
30. Bader AG, Brown D, Winkler M (2010) The promise of microRNA replacement therapy. Cancer Research 70: 7027-7030.
31. Disis ML, Stanton SE (2017) Immunotherapy in breast cancer: An introduction. The Breast.
32. Papaioannou NE, Beniata OV, Vitsos P, Tsitsilonis O, Samara P (2016) Harnessing the immune system to improve cancer therapy. Annals of Translational Medicine 4.
33. Milani A, Sangiolo D, Aglietta M, Valabrega G (2014) Recent advances in the development of breast cancer vaccines. Breast Cancer: Targets and Therapy 6: 159.
34. Nabekura T, Nagasawa T, Nakauchi H, Onodera M (2008) An immunotherapy approach with dendritic cells genetically modified to express the tumor-associated antigen, HER2. Cancer Immunology, Immunotherapy 57: 611-622.
35. Zaks TZ, Rosenberg SA (1998) Immunization with a peptide epitope (p369–377) from HER-2/neu leads to peptide-specific cytotoxic T lymphocytes that fail to recognize HER-2/neu+ tumors. Cancer Research 58: 4902-4908.
36. Prud'homme GJ (2005) DNA vaccination against tumors. The Journal of Gene Medicine 7: 3-17.
37. Keenan BP, Jaffee EM (2012) Whole cell vaccines—past progress and future strategies. In Seminars in Oncology, WB Saunders 39: 276-286.
38. Clifton GT, Litton JK, Arrington K, Ponniah S, Ibrahim NK, et al. (2017) Results of a Phase Ib Trial of Combination Immunotherapy with a CD8+ T Cell Eliciting Vaccine and Trastuzumab in Breast Cancer Patients. Annals of Surgical Oncology, pp: 1-7.
39. Donaldson MS (2004) Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutrition Journal 3: 19.
40. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, et al. (1996) Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. New England Journal of Medicine 334: 1145-1149.
41. Galeone C, Pelucchi C, Levi F, Negri E, Franceschi S, et al. (2006) Onion and garlic use and human cancer. The American Journal of Clinical Nutrition 84: 1027-1032.
42. Rockwell S, Liu Y, Higgins SA (2005) Alteration of the effects of cancer therapy agents on breast cancer cells by the herbal medicine black cohosh. Breast Cancer Research and Treatment 90: 233-239.

43. Zaveri NT (2006) Green tea and its polyphenolic catechins: medicinal uses in cancer and noncancer applications. Life Sciences 78: 2073-2080.

44. Chan YS, Cheng LN, Wu JH, Chan E, Kwan YW, et al. (2011) A review of the pharmacological effects of Arctium lappa (burdock). Inflammopharmacology 19: 245-254.

45. Jabir NR, Tabrez S, Ashraf GM, Shakil S, Damanhouri GA, et al. (2012) Nanotechnology-based approaches in anticancer research. International Journal of Nanomedicine 7: 4391.

46. Grobmyer SR, Zhou G, Gutwein LG, Iwakuma N, Sharma P, et al. (2012) Nanoparticle delivery for metastatic breast cancer. Maturitas 73: 19-26.

47. Davies E, Hiscox S (2011) New therapeutic approaches in breast cancer. Maturitas 68: 121-128.

48. Xie J, Lee S, Chen X (2010) Nanoparticle-based theranostic agents. Advanced Drug Delivery Reviews 62: 1064-1079.