Demiroglu Science University Florence Nightingale Journal of Transplantation 2022;7(1-2):7-13
doi: 10.5606/dsufnjt.2022.3

The role of oxytocin and prolactin in breast carcinogenesis and breast cancer prognosis: A mini-review

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ABSTRACT

It has long been a challenge for modern medical research to grasp and compose a sustainable treatment plan for all the different types of breast cancer for all patients with very different backgrounds in terms of their age, menopausal status, past pregnancies, body mass index, and genetics. Estrogen and progesterone have long been recognized as prominent hormones in the classification and treatment of many types of breast cancer. This review article focuses on the potential of implementing oxytocin and prolactin as yet other forthcoming factors, whose importance has been revealed by medical research conducted more promisingly in the last few decades, for approaching the classification and treatment algorithm of breast cancer, by briefly reviewing the plethora of studies published on the topic.

Keywords: Breast cancer, hormone receptor-negative breast cancer, hormone receptor-positive breast cancer, oxytocin receptor, oxytocin, prolactin.

Breast cancer has long been recognized as the most common cancer diagnosed in women;[1] however, as of 2020, having accounted for 12% of all new cancer cases each year, the World Health Organization now claims it to be the most common cancer diagnosed globally.[2] By the end of 2022, it is estimated that in the United States there will be 287,850 new cases of invasive mammary carcinomas, alongside 51,400 new cases that are non-invasive. On a positive note, death rates have been decreasing in breast cancer since 2007 with a rate of 1% dropping every year between 2013 and 2018, which is thought to be a result of scientific advancements in treatment approaches and the earlier detection of cases due to a more widespread protocol in screenings conducted.[1] Despite significant advances in cancer research and drug development initiatives, the five-year relative survival rate in metastatic breast cancer remains at 27%.[3]

Before we get into the details of how breast cancer is posing a challenge to modern healthcare in our society, we need to understand the fundamentals of the subject. The human breast is primarily made up of two types of tissues: Glandular and stromal. Glandular tissues consist of milk-producing glands (lobules) connected to and drained by the ducts (the milk passages) and are surrounded by fat and fibrous connective tissue collectively named stromal.[4] The mammary gland is also one of the few organs in the human body that completes its developmental stages postnatally through a tightly regulated process of differentiation through stages of pubertal growth, pregnancy, lactation, and involution and a dysregulation occurring during any of these stages may contribute to breast carcinogenesis in patients.[5]

The majority of tumors that develop inside the human breast are non-cancerous, such as fibrocystic changes, in which accumulated packets of fluid in the glands make up cyst, and a scar-like connective tissue formation in the stroma cause lumpiness, tenderness, and/or breast pain for the patient.[5] According to its site, breast cancer can be classified into non-invasive and invasive subtypes, where the invasiveness is denoted by the breaking of the cancer cells through the ducts, and the lobular walls of the breast to invade the surrounding stromal tissue. Amongst the types of breast cancer that are non-invasive, ductal carcinoma

Received: October 16, 2022
Accepted: November 03, 2022
Published online: December 05, 2022

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Cite this article as:
Yücel U, Erbaş O. The role of oxytocin and prolactin in breast carcinogenesis and breast cancer prognosis: a mini-review. D J Tx Sci 2022;7(1-2):7-13.

in situ (DCIS) is the most common type, making up almost 90% of cases. Lobular carcinoma *in situ* (LCIS) on the other hand, develops within the milk-producing glands of the breast and is considered to be a marker for increased risk of malignancy in the future.[6] Genetically, breast cancer is classified into four types: Human epidermal growth factor receptor 2 positive (HER2+), which is also known as ERBB2 in humans; Luminal A, where the tumor is also stained positive in immunohistological assays for estrogen receptor (ER), may or may not have also been shown to express the progesterone receptor (PR) but is shown not to express the ERBB2, while also not portraying high levels of mitotic activity (Ki67 levels below 14%); Luminal B, where on top of the findings seen for luminal A, ERBB2 may also have been tested positive and the Ki67 value of the tumor (denoting mitotic activity) is seen above 14%[7] and finally the triple-negative type of breast cancer, where none of the receptors mentioned above (ER, PR, ERBB2) are seen expressed in the tumor and the mitotic activity is also seen high (Ki67 levels above 14%).[8] Understanding this taxonomy is key for reviewing the plethora of research that has been conducted on the topic and is essential to manage treatment approaches in clinical settings.

Breast cancer is known to be a multifaceted disease that involves a patient's genetics and many environmental factors; however, the role of certain human hormones such as estrogen, progesterone, oxytocin, and prolactin in the propagation and the pathogenesis of the disease has long been a topic of research in breast cancer. Human prolactin hormone was for the first time seen to be potentially linked with breast cancer when in the 1990s, a study showed that the activation of the human prolactin receptor (PRLR) in transgenic mice induced mammary carcinomas.[9] Oxytocin receptor, on the other hand, a member of G-protein coupled receptors of the A/rhodopsin family is known to be found highly expressed in breast carcinomas ever since the late 1990s.[10-12] This mini-review article focuses on the roles of prolactin and oxytocin in breast cancer in relation to their receptor expression in the tumors, and the therapeutic indications of utilizing the scientific findings made in regard.

OXYTOCIN

Oxytocin is a cyclic nonapeptide with a C-terminal amide and a disulfide bond between its two cysteine residues it elicits many responses throughout the body, including its functions in both the central and peripheral nervous systems, regulating social bonding, and sexual activity, stress, maternal behavior, uterus contractions, and milk ejection.[13] The role of oxytocin in breast carcinogenesis has been an important topic for research in the field, especially since childbearing and breastfeeding have been found to be protective factors against breast cancer; processes during which it plays a crucial role.[14,15] It's also found that people who have birthed no children at all during the course of their lives have a higher risk of developing breast cancer, compared to those who have given birth at one point.[16-18] Oxytocin is also produced through nipple stimulation, where it facilitates the alleviation of radical oxygen species from the acinar glands through distention, by the means of myoepithelial cell contractions.[16]

The physiologic aspect

During pregnancy, breast development picks up the pace and the mammary glands start to undergo complete remodeling in order to mature into a functional milk-secreting organ with the lactation cycle.[19] As weaning commences and the baby is introduced to solid foods after the age of six months, the glands then regress into a resting state called involution.[20] It is found through studies conducted on lactating rats, that oxytocin has a role in maintaining the status of the glands, delaying involution with influence on cell growth and differentiation.[21-24] In all breasts, whether they are neoplastic or in healthy condition, cells that are from both myoepithelial and epithelial origins produce and secrete oxytocin, creating local autocrine and paracrine loops to enhance the effects of mammotropic hormones, inducing proliferation seen both *in vitro* and *in vivo* settings,[25] and also, postpartum.[26]

Role in carcinogenesis

The research on this topic has not been conclusive and comprehensive enough to reveal the full depth of the involvement of oxytocin in breast cancer, but the findings thus far point to an elusive fact that oxytocin and its effects produced through its signaling

pathways, in different mechanisms, both mitigate and promote the carcinogenic and metastatic processes of mammary tumors. Research conducted on MDA-MB-231 cell lines, which are of triple-negative breast cancer origin, demonstrated how overexpression of oxytocin receptors is linked to the migration and metastasis of cancer cells, while also facilitating epidermal growth factor (EGF) sensitivity.[27] In another study where oxytocin receptor overexpressing tumors were used in Gene Set Enrichment Analysis (GSEA), genes that enable the potential for the proliferation of cancer cells, disease progression, and ERBB2+ carcinogenesis were found upregulated. It was also deduced during the same study that oxytocin receptor overexpression created a set of circumstances on a cellular level that facilitates tumor growth and metastasis - this was found through the transplantation of oxytocin receptor overexpressing tumor fragments (E0771) into the fourth mammary glands of oxytocin receptor overexpressing and wild-type mice to check for tumor growth and tumor weight after 15 days-subsequently, results from the oxytocin receptor overexpressing mice were found to be much higher than what was observed in the wild-type samples.[28]

Another study conducted on mice, on the other hand, involved seven different groups of mice undergoing separate treatments of oxytocin administration, exercise training - which also enhances the endogenic oxytocin secretion in mammals - and atosiban administration (oxytocin antagonist) for two weeks. Results in this study and, the Western blot assays conducted to evaluate the Akt and ERK protein expression in the mice involved, showed that high plasma oxytocin levels served the purpose of decreasing the levels of Akt and ERK expression in samples, which are long-known to be proteins serving as parts of the Phosphatidylinositol-3-kinase (PI3K/AKT) and mitogen-activated protein kinase (MAPK) pathways; these are both involved in the regulation of growth, an increase in number, lifespan, and the potential to move and invade in their surroundings for cells, and they are both found activated in a wide range of human cancers. Inhibition of both of these proteins through exercise training or oxytocin administration is concluded to be correlated with the inhibition of tumor growth in the study at hand.[29]

There are in general more than ten cell lines of human breast cancer that express the oxytocin receptor on a protein or on a messenger ribonucleic acid (mRNA) level, including, but not limited to MCF7, MDA-MB-231, T47D, BT20, and BTEC, which is a non-cancer stromal cell line derived from the endothelial cells from human breast carcinoma sample.[30-32] A review of the effects of oxytocin analog administration on various human breast cancer cell lines *in vitro*[19] demonstrated that MCF7 cells incubated in fetal calf serum (FCS) without the presence of estrogen (E2) at 2.5% concentration levels, showed stimulation of cancer cell proliferation,[32] which was also seen together with the stimulation of cell migration in BTEC cells, incubated in a serum-free environment or an FCS solution on 10% concentration.[33] However, on cell lines such as T47D, MDA-MB-231, TS/A (mouse sample), and CMT-U27 (canine sample) a clear inhibition of cell proliferation was observed.[34,35] These contradictory results are potentially stemming from factors such as the variability of gene expression for oxytocin receptors that would be induced by hormonal levels, the composition of the serum samples used, and other environmental changes during different experiments conducted.[36,37]

PROLACTIN

Another important hormone that has proven itself to be a worthy highlight in breast cancer research in recent years is prolactin. Prolactin is a neuroendocrine hormone produced primarily in the adenohypophysis, by the lactotroph cells in the gland but also in the breasts, uterus, prostate, lymph cells, and placenta decidua.[38] It stimulates deoxyribonucleic acid (DNA) synthesis, epithelial cell proliferation, and more notably, breast development in human physiology and it exerts all its effects on the human body through its interactions with the prolactin receptor.[39] It is a key hormone in the mediation of breast tissue growth and differentiation as well as the process of lactation.[40] The prolactin receptor is a member of the cytokine receptor superfamily with three main domains: One located extracellularly for ligand binding, a short section that crosses the cell membrane and an extension into the cytosol meant for interaction with signaling molecules.[41] It is found upregulated in up to 80%

of all breast cancer cells.[42] The prolactin receptor interacts with several signaling pathways like the JAK2/STAT5, MAPK, and the PI3K to promote the proliferation and survival of cancer cells as well as interact with their dynamics of cytoskeletal structures.[40] Through its receptor, prolactin reduces the efficacy of available treatments for breast cancer by antagonizing the cytotoxic effects of chemotherapeutic agents.[43] Signaling pathways like MAPK and PI3K constitute a major intermediate by which sex steroids interact with cytoskeletal structures, more prominently the actin backbone of the cell.[40] Similarly, the interactions of prolactin with these pathways allow the cancer cells to modify the spatial organization of these filaments including their links with membrane-anchoring structures, to achieve local and distant metastases, especially within T47D, ZR75-1 and MCF7 cancer cell lines.[44]

Large prospective epidemiologic studies, such as the Nurses' Health Study[45] and the European Prospective Investigation into Cancer and Nutrition (EPIC) study,[46] showed how higher prolactin serum levels predicted an increase in breast cancer risk for the patient, independent of estrogen levels. Other epidemiological studies have shown a correlation between higher prolactin levels and higher mammographic density upon clinical inquiries, which is an important independent contributor to a significantly increased risk of getting diagnosed with breast cancer - especially for aggressive estrogen receptor-positive (ER+) type in postmenopausal women.[47-49] In addition to these effects of circulating prolactin, also locally elevated levels contribute to breast cancer development and progression by inducing ductal abnormalities and epithelial hyperplasia.[50]

Like many other cancer types, 80% of *in vivo* breast carcinomas examined in these handfuls of studies, induced by prolactin administrations, exhibit alterations of the Ras pathway, and copy number amplifications and activating mutations of KRAS; while the remaining 20% show elevated pAKT (phosphorylated RAC - α serine/threonine kinase, an indicator of poor prognosis in invasive breast cancer[51] levels, demonstrating consistency with mutations in the PI3K pathway. It is evident that, as seen through many studies conducted, prolactin induces proliferation and cell turnover in breast tissue.[52-55] However, it is also seen to influence epithelial stem cell or progenitor cell activity, and in combination with estrogen and progesterone, this increased stem cell activity is thought to be associated with an augmented Wnt signaling to serve as cell populations that are meant to be cancer cells of origin.[56] Through these findings, it can be easily deduced that prolactin and its receptor play a vital role in carcinogenesis, but there have been findings to have contrasted this idea: A study conducted using prolactin receptor neutralizing antibodies as monotherapy on breast cancer patients (75% of whom had ER+ subtypes of breast cancer), found no clinical significance of this treatment on disease progression.[57]

Some studies have found that inhibiting the effects of prolactin summarized above can enhance the sensitivity of breast cancer cells to other types of cancer medication, and rather not as an option for monotherapy.[58] It has to be also duly noted that, in the studies examined within the premises of this review, especially in regard to prolactin, a great heterogeneity among the sample characteristics was also present, where many important confounding factors, such as the age, body mass index, age at menarche and menopause for the patients enlisted, the duration of their postmenopausal period and hormone use varied widely, making it more difficult to draw conclusive results from a combination of studies showing consistent or contradicting results. As opposed to one study,[46] that had displayed certain data samples, indicating an apparent correlation *in situ* between higher prolactin levels in the serum and an increased risk of breast cancer, six other studies had data sets that were found to be demonstrating no correlation at all.[45,46,59-62]

In conclusion, breast cancer is surely a complicated entity posing crucial challenges for modern medicine still. Through our preconceived, textbook notion of understanding breast cancer, hormonal factors like estrogen and progesterone were already well established, even engraved into the classification of this disease. However, many pieces of modern medical research show other hormones like oxytocin and prolactin also to be playing roles just as important as those of estrogen and progesterone. Oxytocin is found to help relieve reactive oxygen species from the

breast tissue, enhance the effects of exercise training on a treatment course and inhibit cell proliferation on cell lines such as T47D, MDA-MB-231, TS/A, and CMT-U27. It is also found to be driving cell migration, metastasis and facilitating EGF sensitivity, creating a microenvironment that promotes mammary tumor growth and metastasis. Prolactin on the other hand is demonstrated to facilitate DNA synthesis, epithelial cell proliferation, and the survival of cancer cells. It is found to be upregulated in up to 80% of all cancer types and it interacts with signaling pathways such as JAK2/STAT5, PI3K, and MAPK to influence cytoskeletal structure dynamics in the cell to interact with membrane-anchoring structures to finally allow tumor cells to arrive at local and distant metastases sights. Many epidemiological studies demonstrate higher levels of serum prolactin to be correlated with a higher risk for a patient getting breast cancer while locally elevated levels are also shown to contribute to disease progression. However, introducing prolactin inhibition as monotherapy for breast cancer patients is clearly revealed to be clinically ineffective, which goes out to show that none of these hormones examined during this study alone hold the keys to breast cancer treatment and cure. There is also a huge amount of research that still needs to be done on the role of oxytocin and prolactin in oncogenesis and disease progression, and these hormones still need to be better integrated into a complex mesh of algorithms that we use to define and approach the treatment of various types of breast cancer.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. "Breast Cancer Facts and Statistics." Breast Cancer Facts and Statistics. Available at: https://www.breastcancer.org/facts-statistics.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. doi: 10.3322/caac.21660.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30. doi: 10.3322/caac.21590.
4. Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK. Various types and management of breast cancer: An overview. J Adv Pharm Technol Res 2010;1:109-26.
5. Desprez PY, Lin CQ, Thomasset N, Sympson CJ, Bissell MJ, Campisi J. A novel pathway for mammary epithelial cell invasion induced by the helix-loop-helix protein Id-1. Mol Cell Biol 1998;18:4577-88. doi: 10.1128/MCB.18.8.4577.
6. Masood S. Breast cancer subtypes: Morphologic and biologic characterization. Womens Health (Lond) 2016;12:103-19. doi: 10.2217/whe.15.99.
7. He L, Lv Y, Song Y, Zhang B. The prognosis comparison of different molecular subtypes of breast tumors after radiotherapy and the intrinsic reasons for their distinct radiosensitivity. Cancer Manag Res 2019;11:5765-75. doi: 10.2147/CMAR.S213663.
8. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-74. doi: 10.1073/pnas.191367098.
9. Wennbo H, Gebre-Medhin M, Gritli-Linde A, Ohlsson C, Isaksson OG, Törnell J. Activation of the prolactin receptor but not the growth hormone receptor is important for induction of mammary tumors in transgenic mice. J Clin Invest 1997;100:2744-51. doi: 10.1172/JCI119820.
10. Cassoni P, Sapino A, Fortunati N, Munaron L, Chini B, Bussolati G. Oxytocin inhibits the proliferation of MDA-MB231 human breast-cancer cells via cyclic adenosine monophosphate and protein kinase A. Int J Cancer 1997;72:340-4. doi: 10.1002/(sici)1097-0215(19970717)72:2<340::aid-ijc23>3.0.co;2-i.
11. Cassoni P, Sapino A, Stella A, Fortunati N, Bussolati G. Presence and significance of oxytocin receptors in human neuroblastomas and glial tumors. Int J Cancer 1998;77:695-700. doi: 10.1002/(sici)1097-0215(19980831)77:5<695::aid-ijc6>3.0.co;2-q.
12. Bussolati G, Cassoni P, Ghisolfi G, Negro F, Sapino A. Immunolocalization and gene expression of oxytocin receptors in carcinomas and non-neoplastic tissues of the breast. Am J Pathol 1996;148:1895-903.
13. Donaldson ZR, Young LJ. Oxytocin, vasopressin, and the neurogenetics of sociality. Science 2008;322:900-4. doi: 10.1126/science.1158668.
14. Newcomb PA, Storer BE, Longnecker MP, Mittendorf R, Greenberg ER, Clapp RW, et al. Lactation and a reduced risk of premenopausal breast cancer.

N Engl J Med 1994;330:81-7. doi: 10.1056/NEJM199401133300201.
15. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: Collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187-95. doi: 10.1016/S0140-6736(02)09454-0.
16. Murrell TG. The potential for oxytocin (OT) to prevent breast cancer: A hypothesis. Breast Cancer Res Treat 1995;35:225-9. doi: 10.1007/BF00668213.
17. Mustacchi P. Ramazzini and Rigoni-Stern on parity and breast cancer. Clinical impression and statistical corroboration. Arch Intern Med 1961;108:639-42. doi: 10.1001/archinte.1961.03620100131018.
18. Lê MG, Bachelot A, Hill C. Characteristics of reproductive life and risk of breast cancer in a case-control study of young nulliparous women. J Clin Epidemiol 1989;42:1227-33. doi: 10.1016/0895-4356(89)90121-2.
19. Liu H, Gruber CW, Alewood PF, Möller A, Muttenthaler M. The oxytocin receptor signalling system and breast cancer: A critical review. Oncogene 2020;39:5917-32. doi: 10.1038/s41388-020-01415-8.
20. Hassiotou F, Geddes D. Anatomy of the human mammary gland: Current status of knowledge. Clin Anat 2013;26:29-48. doi: 10.1002/ca.22165.
21. Benson GK, Folley SJ. The effect of oxytocin on mammary gland involution in the rat. J Endocrinol 1957;16:189-201. doi: 10.1677/joe.0.0160189.
22. Ota K, Yokoyama A, Shinde Y. Effects of administration of oxytocin and prolactin on nucleic acids and phosphoprotein contents of mammary glands in lactating rats. Nature 1962;195:77-8. doi: 10.1038/195077b0.
23. Yokoyama A, Ota K. Effect of oxytocin replacement on lactation in rats bearing hypothalamic lesions. Endocrinol Jpn 1959;6:268-76. doi: 10.1507/endocrj1954.6.268.
24. McCann SM, Mack R, Gale C. The possible role of oxytocin in stimulating the release of prolactin. Endocrinology 1959;64:870-89. doi: 10.1210/endo-64-6-870.
25. Sapino A, Macrì L, Tonda L, Bussolati G. Oxytocin enhances myoepithelial cell differentiation and proliferation in the mouse mammary gland. Endocrinology 1993;133:838-42. doi: 10.1210/endo.133.2.8344220.
26. Wagner KU, Young WS 3rd, Liu X, Ginns EI, Li M, Furth PA, et al. Oxytocin and milk removal are required for post-partum mammary-gland development. Genes Funct 1997;1:233-44. doi: 10.1046/j.1365-4624.1997.00024.x.
27. Liu H, Muttenthaler M. High oxytocin receptor expression linked to increased cell migration and reduced survival in patients with triple-negative breast cancer. Biomedicines 2022;10:1595. doi: 10.3390/biomedicines10071595.
28. Li D, San M, Zhang J, Yang A, Xie W, Chen Y, et al. Oxytocin receptor induces mammary tumorigenesis through prolactin/p-STAT5 pathway. Cell Death Dis 2021;12:588. doi: 10.1038/s41419-021-03849-8.
29. Alizadeh AM, Heydari Z, Rahimi M, Bazgir B, Shirvani H, Alipour S, et al. Oxytocin mediates the beneficial effects of the exercise training on breast cancer. Exp Physiol 2018;103:222-35. doi: 10.1113/EP086463.
30. Cassoni P, Marrocco T, Sapino A, Allia E, Bussolati G. Oxytocin synthesis within the normal and neoplastic breast: First evidence of a local peptide source. Int J Oncol 2006;28:1263-8.
31. Cassoni P, Sapino A, Negro F, Bussolati G. Oxytocin inhibits proliferation of human breast cancer cell lines. Virchows Arch 1994;425:467-72. doi: 10.1007/BF00197549.
32. Taylor AH, Ang VT, Jenkins JS, Silverlight JJ, Coombes RC, Luqmani YA. Interaction of vasopressin and oxytocin with human breast carcinoma cells. Cancer Res 1990;50:7882-6.
33. Cassoni P, Marrocco T, Bussolati B, Allia E, Munaron L, Sapino A, et al. Oxytocin induces proliferation and migration in immortalized human dermal microvascular endothelial cells and human breast tumor-derived endothelial cells. Mol Cancer Res 2006;4:351-9. doi: 10.1158/1541-7786.MCR-06-0024.
34. Sapino A, Cassoni P, Stella A, Bussolati G. Oxytocin receptor within the breast: Biological function and distribution. Anticancer Res 1998;18:2181-6.
35. Benavente MA, Bianchi CP, Imperiale F, Aba MA. Antiproliferative effects of oxytocin and desmopressin on canine mammary cancer cells. Front Vet Sci 2016;3:119. doi: 10.3389/fvets.2016.00119.
36. Amico JA, Rauk PN, Cai HM. Estradiol and progesterone regulate oxytocin receptor binding and expression in human breast cancer cell lines. Endocrine 2002;18:79-84. doi: 10.1385/ENDO:18:1:79.
37. Copland JA, Jeng YJ, Strakova Z, Ives KL, Hellmich MR, Soloff MS. Demonstration of functional oxytocin receptors in human breast Hs578T cells and their up-regulation through a protein kinase C-dependent pathway. Endocrinology 1999;140:2258-67. doi: 10.1210/endo.140.5.6723.
38. Froes Brandao D, Strasser-Weippl K, Goss PE. Prolactin and breast cancer: The need to avoid undertreatment of serious psychiatric illnesses in breast cancer patients: A review. Cancer 2016;122:184-8. doi: 10.1002/cncr.29714.
39. Rahman T, Clevenger CV, Kaklamani V, Lauriello J, Campbell A, Malwitz K, et al. Antipsychotic treatment in breast cancer patients. Am J Psychiatry 2014;171:616-21. doi: 10.1176/appi.ajp.2013.13050650.
40. Swaminathan G, Varghese B, Fuchs SY. Regulation of prolactin receptor levels and activity in breast cancer. J Mammary Gland Biol Neoplasia 2008;13:81-91. doi: 10.1007/s10911-008-9068-6.

41. Jacobson EM, Hugo ER, Tuttle TR, Papoian R, Ben-Jonathan N. Unexploited therapies in breast and prostate cancer: Blockade of the prolactin receptor. Trends Endocrinol Metab 2010;21:691-8. doi: 10.1016/j.tem.2010.08.004.
42. Zinger M, McFarland M, Ben-Jonathan N. Prolactin expression and secretion by human breast glandular and adipose tissue explants. J Clin Endocrinol Metab 2003;88:689-96. doi: 10.1210/jc.2002-021255.
43. LaPensee EW, Schwemberger SJ, LaPensee CR, Bahassi el M, Afton SE, Ben-Jonathan N. Prolactin confers resistance against cisplatin in breast cancer cells by activating glutathione-S-transferase. Carcinogenesis 2009;30:1298-304. doi: 10.1093/carcin/bgp120.
44. da Silva PL, do Amaral VC, Gabrielli V, Montt Guevara MM, Mannella P, Baracat EC, et al. Prolactin promotes breast cancer cell migration through actin cytoskeleton remodeling. Front Endocrinol (Lausanne) 2015;6:186. doi: 10.3389/fendo.2015.00186.
45. Tworoger SS, Eliassen AH, Zhang X, Qian J, Sluss PM, Rosner BA, et al. A 20-year prospective study of plasma prolactin as a risk marker of breast cancer development. Cancer Res 2013;73:4810-9. doi: 10.1158/0008-5472.CAN-13-0665.
46. Tikk K, Sookthai D, Johnson T, Rinaldi S, Romieu I, Tjønneland A, et al. Circulating prolactin and breast cancer risk among pre- and postmenopausal women in the EPIC cohort. Ann Oncol 2014;25:1422-8. doi: 10.1093/annonc/mdu150.
47. Gabrielson M, Ubhayasekera K, Ek B, Andersson Franko M, Eriksson M, Czene K, et al. Inclusion of plasma prolactin levels in current risk prediction models of premenopausal and postmenopausal breast cancer. JNCI Cancer Spectr 2018;2:pky055. doi: 10.1093/jncics/pky055.
48. Greendale GA, Huang MH, Ursin G, Ingles S, Stanczyk F, Crandall C, et al. Serum prolactin levels are positively associated with mammographic density in postmenopausal women. Breast Cancer Res Treat 2007;105:337-46. doi: 10.1007/s10549-006-9454-y.
49. Becker S, Kaaks R. Exogenous and endogenous hormones, mammographic density and breast cancer risk: Can mammographic density be considered an intermediate marker of risk? Recent Results Cancer Res 2009;181:135-57. doi: 10.1007/978-3-540-69297-3_14.
50. Arendt LM, Rose-Hellekant TA, Sandgren EP, Schuler LA. Prolactin potentiates transforming growth factor alpha induction of mammary neoplasia in transgenic mice. Am J Pathol 2006;168:1365-74. doi: 10.2353/ajpath.2006.050861.
51. Zhou L, Wang M, Guo C, Zhu Y, Yu H, Zhang L, et al. Expression of pAkt is associated with a poor prognosis in Chinese women with invasive ductal breast cancer. Oncol Lett 2018;15:4859-66. doi: 10.3892/ol.2018.7965.
52. Olsen SN, Wronski A, Castaño Z, Dake B, Malone C, De Raedt T, et al. Loss of RasGAP tumor suppressors underlies the aggressive nature of Luminal B breast cancers. Cancer Discov 2017;7:202-17. doi: 10.1158/2159-8290.CD-16-0520.
53. Wright KL, Adams JR, Liu JC, Loch AJ, Wong RG, Jo CE, et al. Ras signaling is a key determinant for metastatic dissemination and poor survival of luminal breast cancer patients. Cancer Res 2015;75:4960-72. doi: 10.1158/0008-5472.CAN-14-2992.
54. Griffith OL, Spies NC, Anurag M, Griffith M, Luo J, Tu D, et al. The prognostic effects of somatic mutations in ER-positive breast cancer. Nat Commun 2018;9:3476. doi: 10.1038/s41467-018-05914-x.
55. Bertucci F, Ng CKY, Patsouris A, Droin N, Piscuoglio S, Carbuccia N, et al. Genomic characterization of metastatic breast cancers. Nature 2019;569:560-4. doi: 10.1038/s41586-019-1056-z.
56. Sell S. On the stem cell origin of cancer. Am J Pathol 2010;176:2584-94. doi: 10.2353/ajpath.2010.091064.
57. Agarwal N, Machiels JP, Suárez C, Lewis N, Higgins M, Wisinski K, et al. Phase I study of the prolactin receptor antagonist LFA102 in metastatic breast and castration-resistant prostate cancer. Oncologist 2016;21:535-6. doi: 10.1634/theoncologist.2015-0502.
58. Li Y, Kong X, Xuan L, Wang Z, Huang YH. Prolactin and endocrine therapy resistance in breast cancer: The next potential hope for breast cancer treatment. J Cell Mol Med 2021;25:10327-48. doi: 10.1111/jcmm.16946.
59. Wang DY, De Stavola BL, Bulbrook RD, Allen DS, Kwa HG, Fentiman IS, et al. Relationship of blood prolactin levels and the risk of subsequent breast cancer. Int J Epidemiol 1992;21:214-21. doi: 10.1093/ije/21.2.214.
60. Helzlsouer KJ, Alberg AJ, Bush TL, Longcope C, Gordon GB, Comstock GW. A prospective study of endogenous hormones and breast cancer. Cancer Detect Prev 1994;18:79-85.
61. Manjer J, Johansson R, Berglund G, Janzon L, Kaaks R, Agren A, et al. Postmenopausal breast cancer risk in relation to sex steroid hormones, prolactin and SHBG (Sweden). Cancer Causes Control 2003;14:599-607. doi: 10.1023/a:1025671317220.
62. Ho CC, Rohaizak M, Zulkifli SZ, Siti-Aishah MA, Nor-Aini U, Sharifah-Noor-Akmal SH. Serum sex hormone levels in pre- and postmenopausal breast cancer patients. Singapore Med J 2009;50:513-8.