WHITEPAPER

Applying artificial intelligence for early detection of breast cancer

Clinical decision support tools from Arkangel AI

Arkangel Ai

Arkangel AI
1250 Guy St Suite #600,
Montreal, Quebec H3H 2L3
letstalk@arkangel.ai
www.arkangel.ai

Introduction

Breast cancer is a global public health dilemma and is today the most common tumor globally. Likewise, it is the leading cause of death in women worldwide due to cancer. The estimated 5-year survival rate for breast cancer worldwide is much higher in developed countries (80%) compared to developing countries (below 40%) [1]. There are significant differences in the number of resources and infrastructure managed by developed countries compared to developing countries. This limits improving results regarding timely recognition, diagnosis, and management of breast cancer [2]. According to the World Health Organization (WHO), it is essential to search for methods to improve the early detection of breast cancer and thus increase the survival rate worldwide.

Breast cancer comprises 18% of all cancers in women, with the incidence of breast cancer estimated to be 85 per 100,000 women by 2021 [3]. By 2012, 1.67 million new breast cancer cases had been diagnosed, approximately 25% of all cancers among women during that year. Of this value, 883,000 cases occurred in less developed countries, and 794,000 cases occurred in developed countries [4]. It is essential to consider a continent such as Asia, where 1 in 35 women suffers from this type of cancer, while in the United States, it occurs in 1 in 8 women [5]. In countries such as Iran, there are 10 cases in 100,000, and it is found mainly in densely populated areas of developing countries in South Asia [6].

Breast cancer presents an inter and intratumoral approach, so a personalized point of view is needed to obtain better patient responses when the treatment modalities are administered. There is a classification for breast cancers based on the estrogen receptor, the progesterone receptor, and the ERBB2 receptor, which has been very useful [7]. In general terms, this type of cancer is a prototypical tumor where molecular subclassification has led to the development of targeted therapies such as hormonal therapy and HER2 [8]. However, there is a need to continuously identify and develop targeted treatments to improve the therapies of each subtype, obtaining more personalized approaches that allow precision oncology [9].

Given the above, different drugs are currently prescribed for breast cancer treatment. Medications such as raloxifene or tamoxifen help ward off this cancer in people more likely to develop it [10]. Additionally, surgery on both breasts is another preventive measure when there is a greater probability of developing it. Once the tumor has been identified, different strategies are used to manage it, such as targeted therapy, hormonal therapy, radiation therapy, and chemotherapy. In case cancer has already metastasized, treatments aim to improve the quality of life and survival rate [11]. In any of these cases, there are unpleasant side effects after the treatment, which generates a lot of interest in the health industry in developing alternative methods.

1. Types Of Breast Cancer

Breast cancer is divided into invasive and non-invasive. Non-invasive breast cancer means that it has not spread outside the lobe or ducts where it was found [12]. Within this type is the lobular carcinoma in situ, which develops in the mammary lobes, and does not extend abroad [13]. Likewise, in situ, ductal carcinoma is limited only to the mammary duct [14]. Invasive breast cancer occurs when abnormal cells within the lobules or milk ducts break away into the vicinity of the breast tissue. These cancer cells can pass through the breast to different body parts via the immune system or systemic circulation [15]. The organs to which these cells most commonly spread are the brain, bones, lungs, and liver. There are several types of invasive breast cancer, including:

- Infiltrating lobular carcinoma: Originates in the mammary glands of the breast, often spreading to other areas of the body [16].
- Infiltrating ductal carcinoma originates in the breast's milk ducts, moving towards the wall of the chimney until it finally invades the fatty tissues of the breast and other parts of the body [17].
- Medullary carcinoma is invasive breast cancer that designs a discrete margin of normal and medullary tissue [18].
- Mucinous carcinoma: This is rare and is created by mucus-forming cancer cells. Generally, this type of cancer predicts better than others [19].
- Inflammatory breast cancer: a form of cancer where the breasts are swollen, red, hot, and with broad ridges, as cancer cells block the lymphatic vessels in the skin over the breast. It is cancer with rapid and uncommon growth, which makes treatment synchronization of several multidisciplinary strategies [20].
- Phyllodes tumors are benign or malignant; they develop in the breast's connective tissues. They can be treated with surgical removal, although they are infrequent [21].
- Triple-negative breast cancer is highly documented as a heterogeneous disorder with special subforms, distinguished by different clinical-pathological characteristics. It is characterized by the deficiency of the progesterone receptor, human epidermal growth factor receptor 2, and estrogen receptor expression. It is primarily destructive and is seen in premenopausal women [22].

2. Breast Cancer In LATAM

Breast cancer has severe clinical and economic consequences in societies such as Latin America. Among the main problems that need an urgent solution are early diagnosis and access to treatment alternatives based on multidisciplinary evidence. This type of cancer affects women in Latin America younger than in

Europe or North America. However, in most hospitals, frequent routine mammograms are not performed among the population [23]. It is essential to mention that each year in Latin America, approximately 115,000 women are diagnosed, and 37,000 die [24].

In figure 1, it can be seen that geographically the lowest incidence is grouped in countries in northern Latin America, such as Mexico, Panama, Ecuador, and Colombia. This is similar to countries in Asia and Africa. At the same time, the highest incidence is grouped in southern Latin American countries such as Uruguay, Argentina, and Chile, similar to the incidence in Europe or the USA. The incidence and mortality rate for this type of cancer has increased steadily over the last 25 to 30 years [25]. Risk factors that increase these rates include demographic, socioeconomic, genetic, and lifestyle factors. On the other hand, it is considered that the countries' population levels and fertility rates are inversely related to the incidence of breast cancer in Latin America [26].

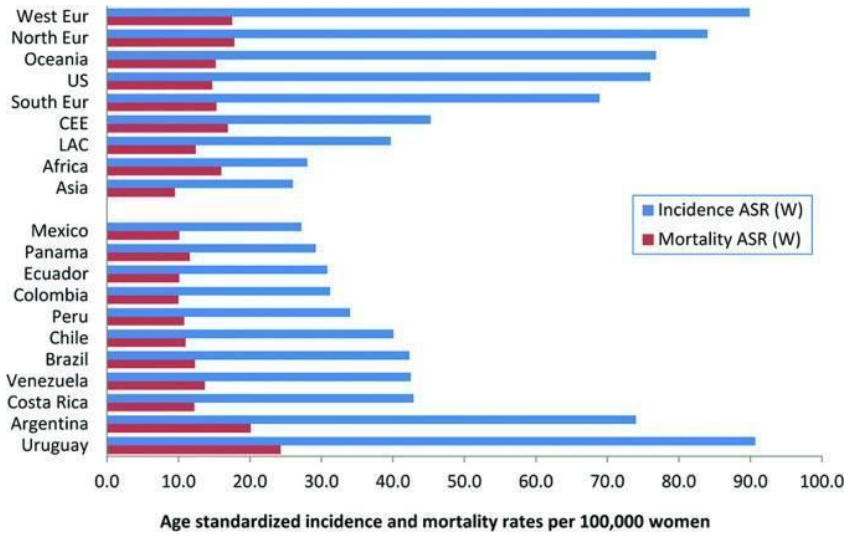

Figure 1. Breast cancer incidence and mortality in Latin America and other regions [24].

In North America and Europe, the 5-year survival rate is greater than 80%; this percentage was achieved with improved treatments and earlier diagnosis [27]. The 5-year survival rate in Latin America is considerably lower, fluctuating around 70% [28]. Even today, there is a lack of cancer registries and related data, which affects progress towards better therapies and early diagnosis. A relevant predictor of breast cancer's overall survival is the diagnosis stage. The European Union is the reference point for early diagnosis with a value of 90%. In contrast, it is estimated that the average is between 60% and 70% in Latin America. In Peru, Colombia, and Mexico, 50% of breast cancers are detected in advanced stages [28].

Now, as for the costs, they are directly related to the stage of a breast cancer diagnosis. For Latin America, the prices of a patient with stage IV breast cancer are three to four times higher than a patient with stage I [29]. In addition, the high morbidity and mortality of patients with metastases also significantly increase the general costs of health systems. In Latin American countries, some

patients are not optimally diagnosed and treated due to insufficient funding. Overall health care spending in Latin America is well below European and US standards. However, strategies are currently being carried out to expand access to health universally with the substantial participation of the private sector [29].

3. Artificial Intelligence Applied To Breast Cancer

Artificial intelligence (AI) is a broad term that encompasses various approaches to making machines mimic human decision-making. Machine learning is the most general category of AI and includes all systems that allow computers to learn from features gleaned from examples without those features being explicitly programmed. One of the first studies to explore these tools' potential in breast cancer was Kallenberg et al. [30], who implemented a sparse convolutional autoencoder that learned an increasingly abstract hierarchy of features from unlabeled data. That is a simple classifier that associates the learned characteristics with breast cancer. This method was trained and tested on mammographic images of unilateral breast cancer patients and healthy controls, demonstrating promising case classification performance .

Other studies, such as the one by Gastounioti et al. [31], perform a hybrid approach that fuses the parenchyma complexity measurements generated by radiomic analysis optimally. Using a case dataset, they demonstrated in their study that convolutional neural networks can capture disperse, subtle, and relevant interactions between parenchymal breast patterns. These patterns are present in radiomic feature maps derived from mammographic images. In the end, they improved breast cancer risk prediction from conventional parenchymal pattern analysis (AUC=0.90).

In the same way, studies such as McKinney et al. [32] focus on detecting breast cancer early, when treatment can still be successful. The main problem they identified is the high rate of false positives and negatives when interpreting a mammogram. Therefore, they propose an AI program capable of outperforming expert oncologists in predicting breast cancer. To assess the system's performance, they tested it in a clinical setting with representative data from the UK and the US. In a study of six radiologists, the raised AI system outperformed all human readers. The AUC was higher for the AI system than the radiologist, by a final margin of 11.5%. It was also found that the system reduces the workload of the people in charge of reading the mammograms by 88%.

A final study by Conan et al. in [33] uses computer-aided diagnosis (CAD), a machine learning method that analyzes patient information, and the results can be used to help clinicians in their decision-making process. In this study, the AI-based CAD system was the concurrent reader on radiologists' reading accuracy and time for breast cancer detection. Twenty-four radiologists participated in this study, reading 260 cases, where 65 were cancer, 65 were benign tumors, and 130 were expected. Mean

AUC, sensitivity, and specificity increased while reading time per case decreased. Furthermore, the use of this system was statistically significant ($p<0.01$).

3. Final thoughts and conclusions.

As discussed above, breast cancer is the leading cause of cancer death in women in Latin America. Likewise, this type of cancer's incidence and mortality rate are increasing. This generates a significant economic burden for the countries, which in most cases do not have sufficient resources to combat this disease. It is therefore urgent to find a way that allows people to have a diagnosis early enough and access optimal therapy, reducing the associated social costs. Increasing universal health coverage in most regions with efficient programs and resources is essential.

A tool that is fully prepared to improve breast cancer risk assessment and allow early diagnosis and access to timely treatment is AI. It is essential to highlight the importance of taking this step to help the region fill the gap between the 40-80% survival rate [1].. Although in regions such as LATAM, there are still many technical challenges related to mammographic imaging that must be addressed to obtain an accurate result, it is essential to start taking temporary steps toward using AI which will help leapfrog the region and impact more patients. Likewise, it is critical to improve the reproducibility, interpretability, and robustness of AI breast cancer risk models that have already been implemented using local and heterogeneous data.

SOURCES

[1] Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, E Silva GA, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL; CONCORD Working Group. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008 Aug;9(8):730-56. doi: 10.1016/S1470-2045(08)70179-7.

[2] Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, Carlson RW, Azavedo E, Harford J. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. Cancer. 2008 Oct 15;113(8 Suppl):2221-43. doi: 10.1002/cncr.23844.

[3] Han SJ, Guo QQ, Wang T, Wang YX, Zhang YX, Liu F, Luo YX, Zhang J, Wang YL, Yan YX, Peng XX, Yan YX, Ling R, He Y. Prognostic significance of interactions between ER alpha and ER beta and lymph node status in breast cancer cases. Asian Pac J Cancer Prev. 2013;14(10):6081-4. doi: 10.7314/apjcp.2013.14.10.6081.

[4] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86. doi: 10.1002/ijc.29210.

[5] Bien AM, Korzynska-Pietas M, Iwanowicz-Palus GJ. Assessment of midwifery student preparation for performing the role of breast cancer educator. Asian Pac J Cancer Prev. 2014;15(14):5633-8. doi: 10.7314/apjcp.2014.15.14.5633.

[6] Haghighat S, Akbari ME, Ghaffari S, Yavari P. Standardized breast cancer mortality rate compared to the general female population of Iran.

Asian Pac J Cancer Prev. 2012;13(11):5525-8. doi: 10.7314/apjcp.2012.13.11.5525.
[7] Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? Nat Rev Cancer. 2012 Apr 19;12(5):323-34. doi: 10.1038/nrc3261.
[8] Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. Nature. 2000 Aug 17;406(6797):747-52. doi: 10.1038/35021093.
[9] Yeo SK, Guan JL. Breast Cancer: Multiple Subtypes within a Tumor? Trends Cancer. 2017 Nov;3(11):753-760. doi: 10.1016/j.trecan.2017.09.001. Epub 2017 Oct 24. PMID: 29120751.
[10] Peng J, Sengupta S, Jordan VC. Potential of selective estrogen receptor modulators as treatments and preventives of breast cancer. Anticancer Agents Med Chem. 2009 Jun;9(5):481-99. doi: 10.2174/187152009788451833.
[11] Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017 Oct 2;50(1):33. doi: 10.1186/s40659-017-0140-9.
[12] West AV, Wullkopf L, Christensen A, Leijnse N, Tarp JM, Mathiesen J, Erler JT, Oddershede LB. Dynamics of cancerous tissue correlates with invasiveness. Sci Rep. 2017 Mar 6;7:43800. doi: 10.1038/srep43800.
[13] Clauser P, Marino MA, Baltzer PA, Bazzocchi M, Zuiani C. Management of atypical lobular hyperplasia, atypical ductal hyperplasia, and lobular carcinoma in situ. Expert Rev Anticancer Ther. 2016;16(3):335-46. doi: 10.1586/14737140.2016.1143362.
[14] Nakhlis F, Morrow M. Ductal carcinoma in situ. Surg Clin North Am. 2003 Aug;83(4):821-39. doi: 10.1016/S0039-6109(03)00072-0.
[15] Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, et al. Use of biomarkers to guide decisions about adjuvant systemic therapy for women with early-stage invasive breast cancer. J Clin Oncol. 2016; 34:1134–1150.
[16] Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 2004;6(3):R149-56. doi: 10.1186/bcr767.
[17] Somiari RI, Sullivan A, Russell S, Somiari S, Hu H, Jordan R, George A, Katenhusen R, Buchowiecka A, Arciero C, Brzeski H, Hooke J, Shriver C. High-throughput proteomic analysis of human infiltrating ductal carcinoma of the breast. Proteomics. 2003 Oct;3(10):1863-73. doi: 10.1002/pmic.200300560.
[18] Mateo AM, Pezzi TA, Sundermeyer M, Kelley CA, Klimberg VS, Pezzi CM. Chemotherapy Significantly Improves Survival for Patients with T1c-T2N0M0 Medullary Breast Cancer: 3739 Cases From the National Cancer Data Base. Ann Surg Oncol. 2017 Apr;24(4):1050-1056. doi: 10.1245/s10434-016-5649-6.
[19] Varadharajan E, Priya S, Prakash G, Mugundan A, Easwaramurthi P. Mucinous Carcinoma of the Breast with Neuroendocrine Differentiation. Iran J Pathol. 2015 Summer;10(3):231-6. PMID: 26351490
[20] Joglekar-Javadekar M, Van Laere S, Bourne M, Moalwi M, Finetti P, Vermeulen PB, Birnbaum D, Dirix LY, Ueno N, Carter M, Rains J, Ramachandran A, Bertucci F, van Golen KL. Characterization and Targeting of Platelet-Derived Growth Factor Receptor alpha (PDGFRA) in Inflammatory Breast Cancer (IBC). Neoplasia. 2017 Jul;19(7):564-573. doi: 10.1016/j.neo.2017.03.002.
[21] Strode M, Khoury T, Mangieri C, Takabe K. Update on the diagnosis and management of malignant phyllodes tumors of the breast. Breast. 2017 Jun;33:91-96. doi: 10.1016/j.breast.2017.03.001.
[22] Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010 Nov 11;363(20):1938-48. doi: 10.1056/NEJMra1001389.
[23] Justo N, Wilking N, Jönsson B, Luciani S, Cazap E. A review of breast cancer care and outcomes in Latin America. Oncologist. 2013;18(3):248-56. doi: 10.1634/theoncologist.2012-0373.

[24] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec 15;127(12):2893-917. doi: 10.1002/ijc.25516.
[25] Lozano-Ascencio R, Gómez-Dantés H, Lewis S, Torres-Sánchez L, López-Carrillo L. Tendencias del cáncer de mama en América Latina y el Caribe [Breast cancer trends in Latin America and the Caribbean]. Salud Publica Mex. 2009;51 Suppl 2:s147-56. Spanish. doi: 10.1590/s0036-36342009000800004.
[26] Robles SC, Galanis E. Breast cancer in Latin America and the Caribbean. Rev Panam Salud Publica. 2002 Mar;11(3):178-85. doi: 10.1590/s1020-49892002000300007.
[27] Allemani C, Sant M, Weir HK, Richardson LC, Baili P, Storm H, Siesling S, Torrella-Ramos A, Voogd AC, Aareleid T, Ardanaz E, Berrino F, Bielska-Lasota M, Bolick S, Cirilli C, Colonna M, Contiero P, Cress R, Crocetti E, Fulton JP, Grosclaude P, Hakulinen T, Izarzugaza MI, Malmström P, Peignaux K, Primic-Žakelj M, Rachtan J, Safaei Diba C, Sánchez MJ, Schymura MJ, Shen T, Traina A, Tryggvadottir L, Tumino R, Velten M, Vercelli M, Wolf HJ, Woronoff AS, Wu X, Coleman MP. Breast cancer survival in the US and Europe: a CONCORD high-resolution study. Int J Cancer. 2013 Mar 1;132(5):1170-81. doi: 10.1002/ijc.27725.
[28] Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, Law SC, Ahn YO, Xiang YB, Yeole BB, Shin HR, Shanta V, Woo ZH, Martin N, Sumitsawan Y, Sriplung H, Barboza AO, Eser S, Nene BM, Suwanrungruang K, Jayalekshmi P, Dikshit R, Wabinga H, Esteban DB, Laudico A, Bhurgri Y, Bah E, Al-Hamdan N. Cancer survival in Africa, Asia, and Central America: a population-based study. Lancet Oncol. 2010 Feb;11(2):165-73. doi: 10.1016/S1470-2045(09)70335-3.
[29] Eduardo Cazap. Breast Cancer in Latin America: A Map of the Disease in the Region Journal Article. 2018 American Society of Clinical Oncology Educational Book. doi: 10.1200/EDBK_201315
[30] Kallenberg M, Petersen K, Nielsen M, Ng AY, Pengfei Diao, Igel C, Vachon CM, Holland K, Winkel RR, Karssemeijer N, Lillholm M. Unsupervised Deep Learning Applied to Breast Density Segmentation and Mammographic Risk Scoring. IEEE Trans Med Imaging. 2016 May;35(5):1322-1331. doi: 10.1109/TMI.2016.2532122.
[31] Gastounioti A, Oustimov A, Hsieh MK, Pantalone L, Conant EF, Kontos D. Using Convolutional Neural Networks for Enhanced Capture of Breast Parenchymal Complexity Patterns Associated with Breast Cancer Risk. Acad Radiol. 2018 Aug;25(8):977-984. doi: 10.1016/j.acra.2017.12.025.
[32] McKinney, S.M., Sieniek, M., Godbole, V. et al. International evaluation of an AI system for breast cancer screening. Nature 577, 89–94 (2020). https://doi.org/10.1038/s41586-019-1799-6.

About Arkangel AI:

Arkangel AI is a software company based in Montreal, Canada that specializes in early disease detection using artificial intelligence. The company's mission is to enable people to live free of preventable diseases through early disease detection. Arkangel AI's products are optimized for diseases from the global south and medical equipment available in the region, translating into fewer entry barriers to urban and rural settings. Arkangel AI has operations in Canada, Colombia, Uruguay, and Mexico. For further information on this research or strategic partnerships:

Arkangel AI
1250 Guy St Suite #600, Montreal, Quebec H3H 2L3
hola@arkangel.ai
www.arkangel.ai

Contributors:

Ana Maria Hurtado
Growth Trainee
Contact: ana.hurtado@arkangel.ai

Jose Zea
CEO and Founder
Contact: jose@arkangel.ai