



Incidence, Advances and Development of Breast Cancer in African Continent

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Abstract

Breast cancer is a type of malignant tumor that develops in the breast tissue. It mostly affects women, though men can also be diagnosed with it. Since this condition is one of the most prevalent types of cancer worldwide, knowledge and comprehension are essential for both early detection and prevention. The disease scenario in African continent is undergoing remarkable changes, with increasing morbidity and mortality due to cancer. Cancer is now the fifth leading threat of death in Africa. In spite of the advances in treatment of this devastating disease, Cancer still remains to be a challenge and its incidence rates in Africa are increasing, yet their geographic distribution and determinants are poorly characterized. The present study aims to establish the epidemiology of cancer burden in Africa and to provide a comparative perspective of the incidence, death counts, and age-standardized rates of leading cancer groups in North, Middle and Southern Africa. This study also focuses on treatment, diagnostics via machine learning and pathways targeted by breast cancer cells.

Keywords: Cancer; Machine learning; Therapeutics; Immunotherapy; Immunomodulators

Abbreviation: BC: Breast Cancer; GLOBOCAN: Global Cancer Observatory; HER2: Human Epidermal Growth Factor type-2 Receptors; DCIS: Ductal Carinoma In situ; ER or PR: Progesterone Receptors; WHO: World Health Organization; ASR: Age-Standardized Incidence; CAD: Computer-Aided Diagnosis; MRI: Magnetic Resonance Imaging; AI: Artificial Intelligence; SVM: Support Vector Machine; CNN: Convolutional Neural Network; LR: Logistic Regression; KNN: K-Nearest Neighbor; pCR: pathologic Complete Response Rates; RCT: Random Clinical Trials; PFS: Progression-Free Survival; VEGF: Vascular Endothelial Growth Factor; PARP: Poly ADP- Ribose Polymerase; FDA: Food and Drug Administration; RCC: Renal Cell Carcinoma; siRNA: small interfering RNA; ICIs: Immune Checkpoint Inhibitors; ADCs: Antibody Drug Conjugates; AR: Androgen Receptor; LAR: Luminal Androgen Receptor

Introduction

Breast Cancer (BC) is the most common Cancer occurring in Africa. However, the rising trend of Cancer is unknown, and it is the top cause of death in Africa, which needs to be investigated. Most countries in Africa are focusing on action against diseases such as Malaria, HIV and tuberculosis, while other diseases such as Cancer is their low priority. Due to lack of awareness, poor education level, their population strength and limited resources, breast cancer is a neglected healthcare issue in African countries.

In addition, lifestyle like reduced breastfeeding, diet, alcohol consumption are also the other factors for Cancer. Furthermore, one of the causes of Cancer is that African women often use other elements like more exposures to skin products, hair products and skin lightening procedures. Breast cancer mortality rates in African countries are rising compared to developed countries. Covid-19 pandemic also made the situation worse to control Cancer in Africa. However, in coming years there will be twice burden in African countries.

Presently, Cancer is one of the most important disease for the researchers [1-3] to study and cope with their causes and spread. Global Cancer Observatory (GLOBOCAN) [4] is widely used for quality and quantity data for low middle countries estimating global Cancer. However, previous studies do not provide complete knowledge of Cancer in all groups of African countries. According to the press release of world health organization [5] total of 1 154 584 cancer cases have appeared in Africa in 2022. Female breast cancer (198 553 cases) and cervical cancer (125 699 cases) diagnosed in both sexes. The most common cancer was breast cancer among women (Figure 1).

Initial screening plays a significant role in early detection of Cancer, to increase survival rate [6-10]. Screening programs could be effective for Cancer if they are implemented in an effective way. In addition, it will lead to a pathway to diagnosis and treatment and better outcomes. Mammography screening is one of the best screening methods for breast Cancer. Also, some of the initial treatments involves breast resonance imaging MRI, biopsy, and surgical resection. Further diagnosis can clarify the stages of cancer Stage I (early stage) to Stage IV (advanced). Other treatment plan involves on the basis of type and stage comprise chemotherapy, radio therapy, targeted therapy, and hormone therapy.

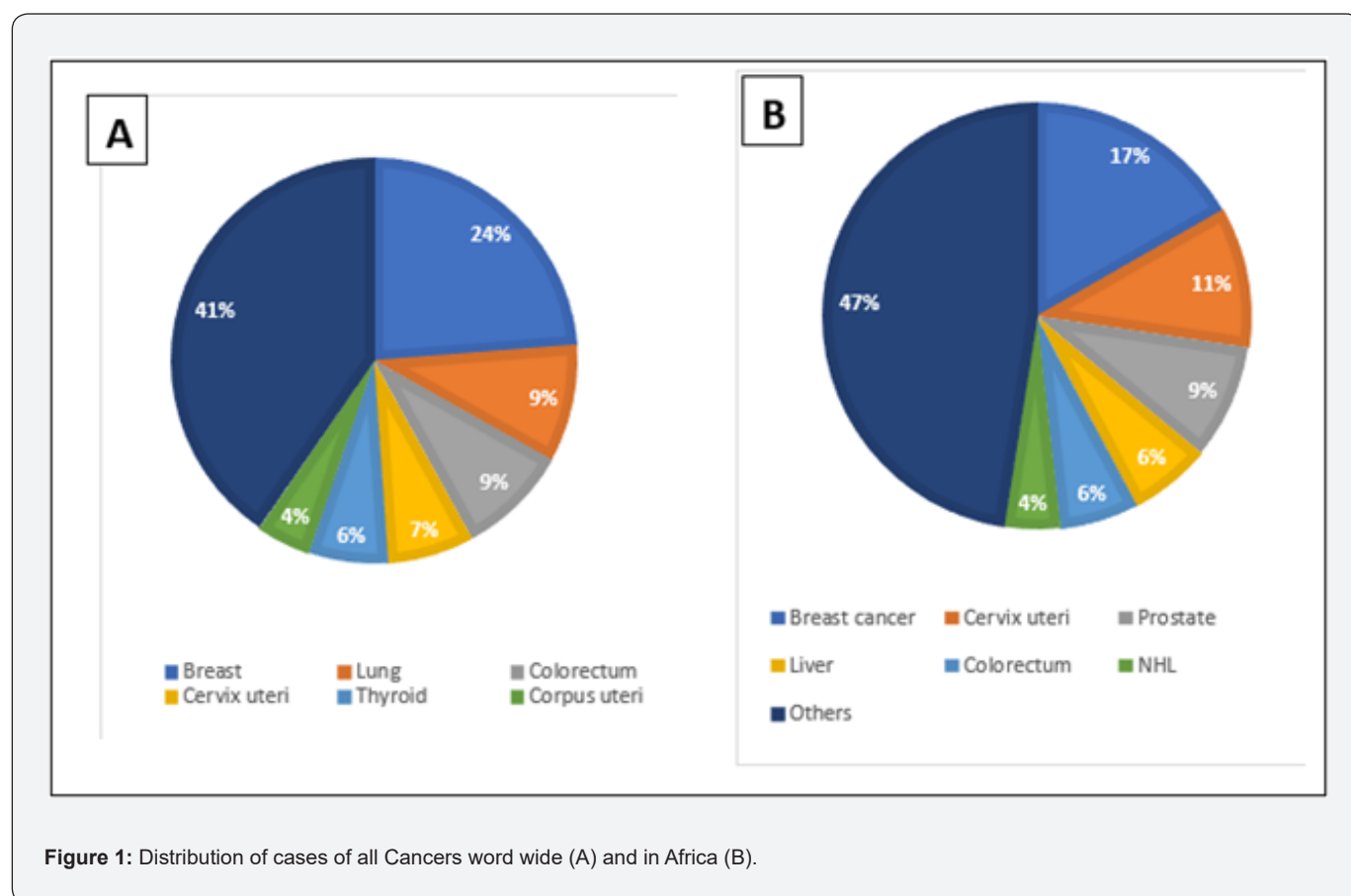


Figure 1: Distribution of cases of all Cancers world wide (A) and in Africa (B).

The complications of chemotherapy are well-known that involve risk factors like increased risk of infection, fatigue, skin reactions, blood clots, hair loss, menopause, and financial problems, all of it can cruelly affect the quality of life for the Cancer patient. Advance research in genetics have facilitated in clinical management of breast cancer. Some of the researchers proposed use of machine learning ML for classification of breast cancer. ML methods are applied for breast cancer survival prediction [11]. The application of growing technology called radiomics also improves breast cancer detection [12]. Numerous modifications in breast cancer cells change cell signaling pathways. Hence, the modifications that are studied are right away involved in the

progression and development of breast cancer pathways are those mediated by the estrogen receptor ER and human epidermal growth factor type-2 receptors (HER2/Neu or c-ErbB2). These factors accelerate breast cancer into different types based on absence or presence of estrogen, progesterone and HER2 [13].

In past few years researchers are classifying several kinds of breast cancer [14]. One of the types of breast cancer is Ductal Carinoma In situ (DCIS). It is an early cancer that has abnormal cells in milk duct and doesnot grow within further breast tissue. Invasive breast cancer which is one of the common types spread into surrounding tissues. Some other types of invasive breast cancer are Triple-negative breast cancer that refers to that cancer

in which the cancer cells don't have estrogen or progesterone receptors (ER or PR) and not have much protein called HER2 [15,16].

Inflammatory breast cancer is a type of breast cancer that block lymphatic vessels in the skin, and the breast looks swollen. The other less common cancer is Paget disease of breast which begins in ducts of breast. Angiosarcoma starts in blood or lymph vessels.

In this article the following topics have been discussed

- i. Serious issue of cancer in Africa.
- ii. Epidemiology and mortality of cancer in African countries.
- iii. Treatments and diagnostics.
- iv. Pathways targeted by Breast Cancer cells.

Epidemiology

Incidence of BC worldwide and in Africa

Breast cancer (BC) is a type of cancer that occurs in one or both breasts. The main function of the breast is to produce milk by lobules and carry it to the nipple by the ducts to feed infants. Most

types of breast cancers start in the ducts or lobules. According to World Health Organization (WHO), BC is one of the most common cancers among women representing major public health. Based on estimates of International Agency for research on cancer 2022, we have evaluated the incidence of Breast cancer and mortality rates worldwide and in Africa [15,16]. According to the International Agency for research on cancer, female breast cancer is the major type of diagnosed cancer in 2022, with an estimated 2.2 million new cases (23.8%), followed by lung (908 630 new cases)(9.4%), colorectal 856 979 new cases (8.9%), Cervix uteri (662 301 new cases) (6.9%), and Thyroid 614 729 (6.4%) word wide. The Incidence rate of Breast cancer is lower in the Africa than Asia (1026171 new cases), America and Europe (531086 new cases) where large epidemiological studies are easily conducted.

According to GLOBACAN 2022, breast Cancer remains to be the leading cause of death among African women .In 2022, the number of deaths was estimated to be 91 252 in women followed by Cervix uteri (80 614 deaths), liver (26 709 deaths) and colorectal cancers (22 668 deaths) (Table 1). The age-standardized incidence (ASR) and mortality rate of African patients with Breast cancer is estimated 40.5 and 28.2 per 100,000 people, respectively (Figure 2).

Table 1: Estimated number of incident cases and deaths Africa, females, all ages.

Cancer	Incidence	Mortality
Breast	174 957	82 368
Cervix uteri	114 376	75 908
Colorectum	31 571	21 049
Liver	25 655	24 795
Ovary	21 699	16 609
Non-Hodgkin lymphoma	16 630	10 942
Stomach	14 730	12 869
Thyroid	12 471	3 502
Corpus uteri	14 453	4 625
Leukaemia	9 526	8 430

Distribution of Cases and Deaths by Region in African countries

In North Africa (including Tunisia, Egypt, Algeria, Morocco, Libya and Sudan) the number of new cases of BC (64977) is higher than Middle (16856 new cases) and Southern Africa 15815 new cases. The Arab populations in North Africa have a higher number of new cases compared to the Middle and Southern populations. Egypt and Algeria have the highest incidence of new cases with 26845 and 14601 respectively and ASR were 55.4 and 61.9 per 100,000 respectively (Table 2).

The mortality rate in Middle and Southern African women was found to have a lower prevalence of BC compared to Northern African populations. In North of Africa, the estimated number of deaths in Egypt in 2022 is 9 596 deaths which is higher than Algeria (4 893 death cases), Morocco (4 044 deaths), Sudan (3 243 deaths), Tunisia (901 deaths) However, Libya has the lowest Incidence and death rate with 1 169 and 460 respectively. The estimated age-standardized incidence rate in Morocco (56.4 per 100.000) is higher than Algeria and Egypt with 55.8 and 48.7 per 100.000 respectively.

Table 2: Estimated number of incident cases and deaths breast cancer females in North, Middle and Southern Africa.

Population	Incidence	Mortality
Northern Africa		
Egypt	26 845	9596
Algeria	14 601	4893
Morocco	12 756	4044
Sudan	6 631	3243
Tunisia	2 820	901
Libya	1 169	460
Middle Africa		
Congo, Democratic Republic of	7 385	4254
Cameroon	4 207	2285
Angola	2 898	1333
Chad	749	446
Central African Republic	574	376
Congo, Republic of	7 385	4 254
Gabon	323	113
Equatorial Guinea	174	87
Sao Tome and Principe	16	7
Southern Africa		
South Africa	15 815	5 693
Namibia	553	227
Botswana	257	91
Lesotho	187	96
Eswatini	106	47

Compared to Middle African countries, Sao Tome and Principe has the lower number of new cases 16 with ASR 19.9 per 100,000 followed by Equatorial Guinea and Gabon with 717 and 323 new cases respectively and ASR were 16.6 and 36.4 per 100,000 respectively. In Southern Africa, the estimated number of deaths in 2022 is 5 693 and the Estimated age-standardized incidence rate (53.9 per 100.000) which is higher than South Africa with 52.6 per 100.000 (Table 2). Nigeria has the highest number of new cases in all continents with 28380 new cases followed by Egypt with 22038 new cases and Ethiopia with 16133 new cases. As per the age-standardized rates (ASR) in different types of cancers, the incidence of Breast cancer in Ethiopia (5-year prevalent cases) was estimated to be 27872 cases followed by Kenya and the united republic of Tanzania with incidence number of prevalent cases (5-year) in females is estimated 15496 and 8295 respectively (Table 3).

Diagnostics of Breast Cancer

Implementation of Machine Learning to Diagnosis of Breast Cancer

Innumerable deadly diseases for example cancer and diabetes have emerged not in the developing country like Africa

but throughout the world. Multiple attempts have been put in the diagnosis and treatment of such diseases. Medical images such as thermography, MRI (magnetic resonance imaging), mammograms, ultrasound images, histopathology are used by scientists to train the algorithm to diagnose the tumor [17]. Unfortunately, the work has fallen short because of the budget, support in terms of infrastructure, tools and experts in this area has lowered the patients to approach to the healthcare. The computer-aided diagnosis (CAD) systems have been automated, with advanced techniques to diagnose tumors [17]. Recently, artificial intelligence (AI) based approach has emerged to improve in terms of cost, diagnostic time, level of accuracy, infrastructure, resources and experts to diagnose dreadful diseases like breast cancer and diabetes.

Analysis of identification of techniques and algorithms used in AI based diagnosis for cancer

The stages and the techniques in AI-based diagnosis that can be used for breast cancer [18] are represented in (Flowchart 1). Along with the SVM (support vector machine), Naïve Bayes, CNN (Convolutional Neural Network); LR (logistic regression), KNN (K-nearest neighbor), decision tree, and random forest are used

to achieve accuracy in the breast cancer categorization [19-22]. A lot of work is done on integration of multiple techniques to create a newer hybrid version of technique to improve the accuracy.

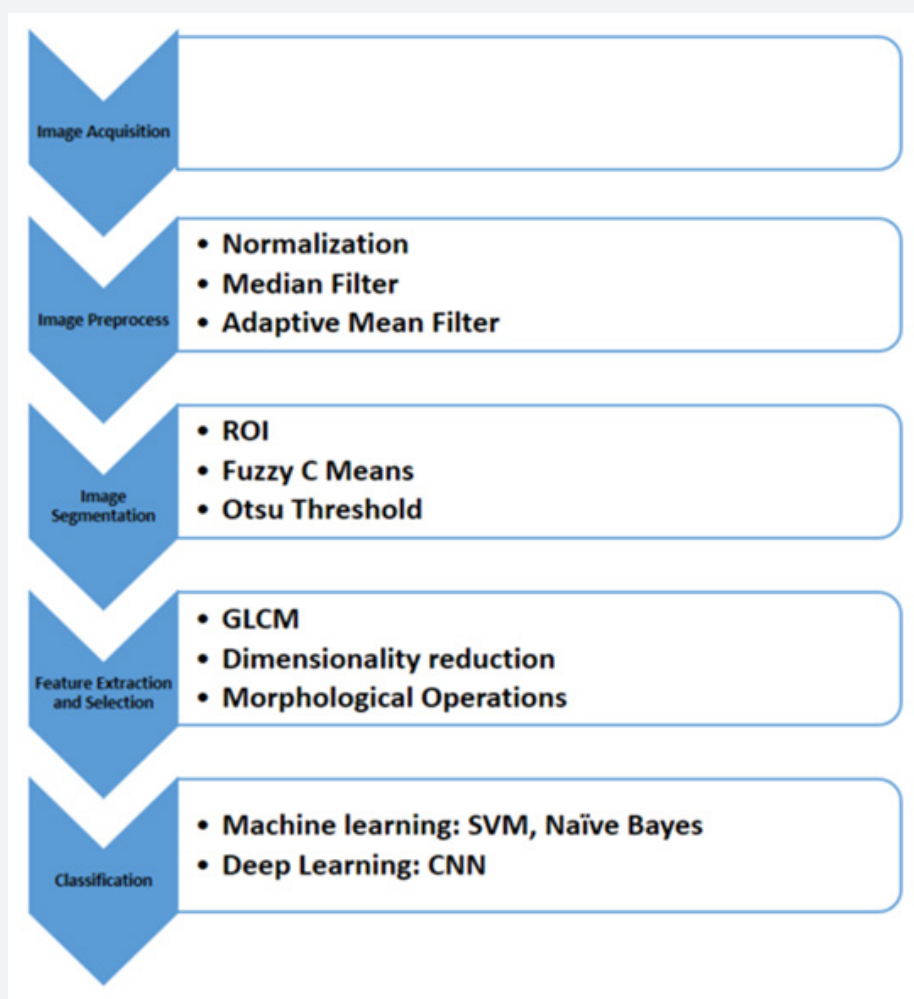
Out of these techniques, two techniques that are considered best approaches for diagnosis [17] are explained below:

Table 3: Estimated number of incident cases, deaths, ASR incidence and mortality in breast cancer females in Eastern and Western Africa.

Population	Incidence	Mortality	ASR incidence	ASR mortality
Eastern Africa				
Ethiopia	16 904	9 626	40.8	24
Kenya	7 243	3 398	40.8	19.6
Tanzania, United Republic of	4 502	2 255	25.1	12.9
Madagascar	2 875	1 498	30.3	16.4
Uganda	2999	1560	23.3	12.6
Mozambique	2 048	1 207	19.7	12
Somalia	1 811	1 165	38.6	25.7
Zimbabwe	1807	915	35.8	18.6
Malawi	1 543	872	25.2	14.8
Rwanda	799	401	16.2	8.4
Zambia	1111	507	22.3	10.8
South Sudan	1 073	657	28	17.6
Burundi	863	513	25.3	15.7
Mauritius	537	209	52.7	19
Eritrea	502	291	37.8	22.4
France, La Réunion	382	90	55.9	12.1
Djibouti	180	102	38.1	22.1
Comoros	65	34	21.5	11.8
Western Africa				
Nigeria	32 278	16 332	51.5	26.8
Ghana	5 026	2 369	40.2	19.5
Côte d'Ivoire	3 869	1785	45.4	25.4
Mali	2 278	1 348	37.7	23.3
Niger	2 145	1 354	29.6	19.5
Burkina Faso	1 372	818	21.4	13.2
Senegal	1 838	976	29.9	16.4
Benin	1 329	734	33.3	18.9
Sierra Leone	204	118	7	4.2
Togo	973	524	32.9	18.1
Guinea	717	388	16	8.9
Liberia	622	351	33.6	19.5
Mauritania	600	315	34.5	18.5
Guinea-Bissau	186	109	27.2	16.7
The Republic of the Gambia	101	50	11	5.8
Cabo Verde	67	23	23.4	7.8

K-Nearest Neighbor Model: is one of the algorithm which is used in diagnosis of disease accurately: Fine, Medium, Coarse, Cosine, and Weighted KNN models can be used in the

process. KNN technique implementation on medical data can be shown in the below (Flowchart 2):



Flowchart 1: Stages and the techniques in AI-based diagnosis.

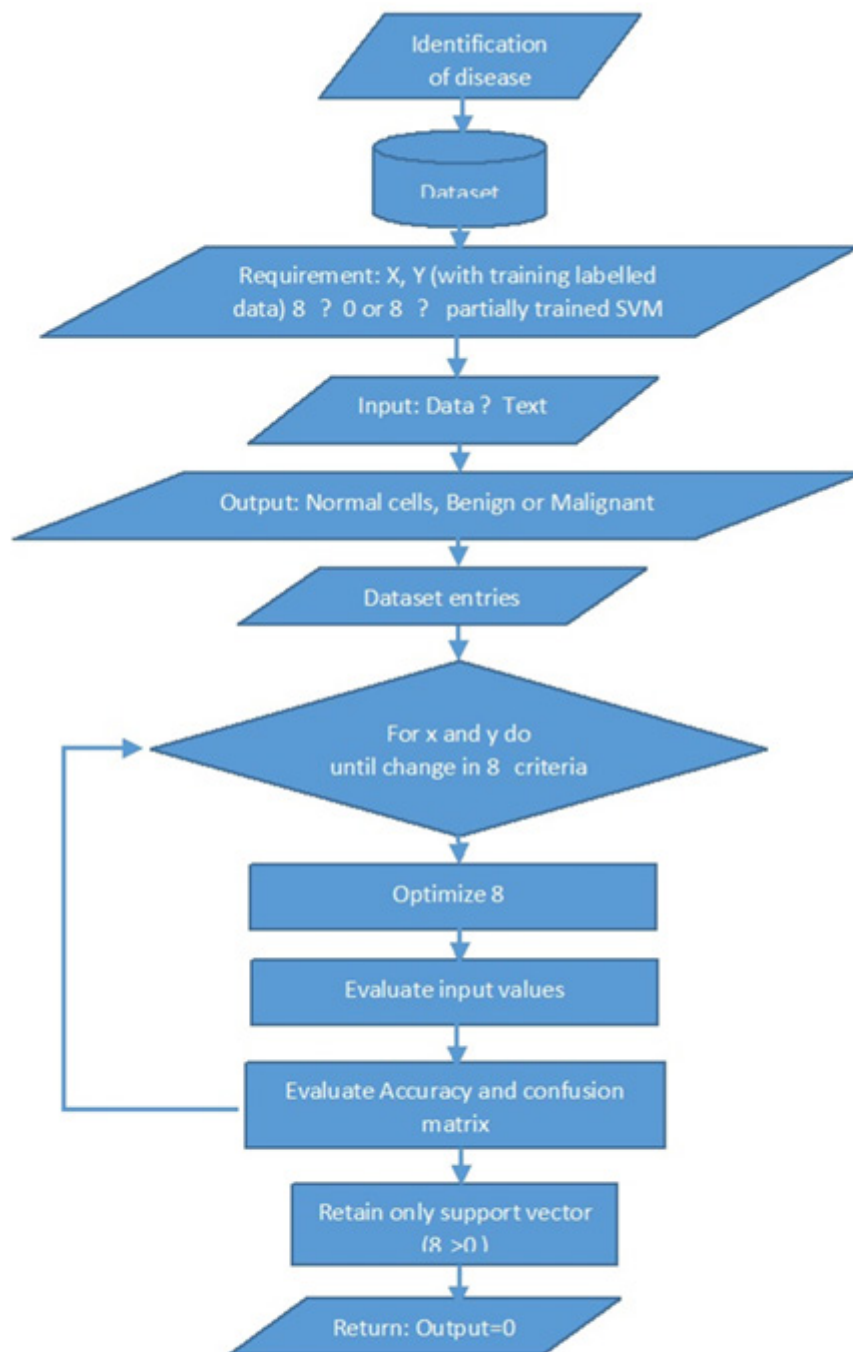
Support Vector Machine Model: To eradicate the anomalies from data, segmentation of breast cancer is done. Based on its features, the data is classified as benign or malignant. For evaluation, the SVM grabs the instances and allocate them a specific class. The ambiguity is removed, and evaluation is performed for the prediction of accurate output. By image masking, the resolution is improved and unnecessary pixels are removed. By implementing SVM, medical data undergoes through multiple steps as shown in the flowchart 2. For the categorization of the anomalies, research can be further proceeded and for features that have complexities, multilayered neural network architecture can be used [17].

Treatment of Breast Cancer

BC is usually treated with both radiation therapy, chemotherapy as well as surgery.

Chemotherapy

The mainstay treatment for both early and advanced stage of BC is cytotoxic chemotherapy. An important strategy against BC is targeting DNA repair complex like platinum compounds, P53 like (taxanes), cell proliferation like anthracycline containing regimen and targeted therapy [21]. The combination of novel chemotherapy with standard chemotherapy has proven to be an advantage according to neoadjuvant studies [23]. It has been studied that pathologic complete response rates (pCR) have been increased by 10-15% with the addition of platinum based agents in neoadjuvant chemotherapy [24]. Patients with wild-type BRCA1/2 had a higher chance of achieving pCR after neoadjuvant platinum-based chemotherapy. This indicates that platinum salts are of little value among patients having DNA repair-deficient tumors in their chemotherapy sessions including alkylating agents like cyclophosphamide [25,26].



Flowchart2: Discrimination between Benign or Malignant Tumor using Support Vector Machine Model

Flowchart 2: Discrimination between Benign or Malignant Tumor using Support Vector Machine Model.

During a PATTERN trial conducted in 2020, in comparison to standard anthracycline-taxane-based chemotherapy, carboplatin and paclitaxel regimen was linked with a higher 5-year DFS. However, the role of platinum agents was not addressed in this trial [27]. According to a study, meta-analysis was done on random clinical trials (RCT) that showed no advantage of progression-free survival (PFS) in patients who followed platinum-based regimens when compared to patients treated with other available options (HR 1.16, 95% CI 0.90–1.49; $P = 0.24$) [28]. According to another study, patients with BRCA1/2 mutations demonstrated a statistically significant PFS advantage with carboplatin vs docetaxel in the phase III study. The combination of paclitaxel and carboplatin has been linked to an unusually lengthy median PFS duration in this patient population [29,30].

Other treatments for BC at its initial stage was anthracycline-taxane-based chemotherapy along with capecitabine [31,32]. During a CREATE-X trial, a meta-analysis of individual patient data was performed by adding capecitabine in sequence or in combination and it was observed that it is related with a statistically significant DFS improvement. But this trial only included patients with residual disease after neoadjuvant chemotherapy while choosing sequential capecitabine as the standard reference treatment for these individuals [33,34]. According to another study, a meta-analysis of 26 RCTs found that dose-dense administration improved long-term results in a moderate but substantial way with a 10-year recurrence risk of 28% as compared to 31.4% of standard schedule. It is noteworthy that many trials have been done till date to compare the effects and dosages but with different drugs and different combinations of drugs and only a few comparisons have been done between same chemotherapy regimen [35,36].

Neoadjuvant Chemotherapy

Mostly BC patients are treated with a therapy called neoadjuvant chemotherapy where patients are subjected to chemotherapy before the process of surgery. This results in pathologic complete response and overall survival. During neoadjuvant treatment, the removed tissue is analyzed for the presence of any active cancer cell and when any active cancerous cell is not found, this condition is known as pathologic complete response (pCR).

Neoadjuvant therapy allows researchers to assess in vivo tumor responses to treatment. In neoadjuvant therapies, pCR plays a very important role in clinical trials due to its association with survival outcomes which in turn helps in assessing the efficacy of this therapy [37]. According to one of the study done to evaluate the response by addition of capecitabine (X) or gemcitabine (G) to docetaxel (T) followed by AC, it was observed that pCR showed no significant difference in both lymph nodes and breast of BC patients (T=AC i.e., 26 % ; TX= AC i.e., 23.3 %; TG= AC i.e., 27.3%) [38]. In the same year, when women with BC were treated with

capecitabine to docetaxel both sequentially and in combination, the results of pCR rates were found to be 8% and 11.5% for Arm A and B respectively and 19% in both arms combined after 4 cycles of docetaxel followed by 4 cycles of capecitabine or 8 cycles of concurrent docetaxel/capecitabine [39].

Neoadjuvant novel therapies have also been sought to determine the benefit of targeting vascular endothelial growth factor (VEGF) with bevacizumab. It is supposed that VEGF inhibitors might be effective against BC as BCs may require increased neoangiogenesis because of their hugely proliferative nature but no studies until now have found any BC specific effect of antiangiogenic agents [40]. Bevacizumab is being studied currently for metastatic BC. According to GeparQuinto study where bevacizumab was added to anthracycline/taxane-based preoperative chemotherapy to BC women patients, a benefit of higher likelihood of pCR was observed compared to the other subtypes of breast cancer [41].

Adjuvant Therapy

This therapy is used once the surgery is complete. But mostly it is less effective in case of BC. Patients having a large tumor or those whose lymph nodes are involved might go through this therapy. Various trials have been done but with different durations and with different drugs. Among those trials the duration of treatment and drug choice were confounded. There have been different conclusions about treatment duration among these trials.

Metronomics is also being used in adjuvant chemotherapy. A prospective randomized trial was done on 78 patients and they were either given 3 cycles of FEC100 and 3 cycles of docetaxel, carboplatin or 3 cycles of FEC100 and docetaxel alone and were followed by maintenance metronomic chemotherapy for one year. This showed improvement in the outcome parameters [42]. Many other ongoing trials are being addressed and studied like introduction of ixabepilone into the adjuvant setting or by introducing maintenance therapy. In one of the trials done in 2015 for women with BC, an extended adjuvant treatment, metronomics has been studied. However, this study, showed that extended adjuvant metronomic X was tolerated well without any serious issues [43]. Metronomic chemotherapy along with anticancer vaccines could be a promising approach in future [44].

Poly ADP- ribose polymerase (PARP) Inhibitors

PARP inhibitor makes it harder for cancer cells to fix their DNA damage as PARP inhibitors interfere with PARP enzyme that fixes DNA damage in cancerous cells also. Thus, cancer cells cannot survive in their presence. PARP enzyme fixes DNA mutation of BRCA1 or BRCA2. PARP inhibitors such as olaparib and talazoparib are used to treat the advanced stages of BC in patients with BRCA1 or BRCA2 mutation. PARP inhibition seems to be a promising approach against BC.

Immunotherapy

When immunotherapy medicines use our body's own immune system to attack the cancer cells, it is called as immunotherapy. One such medicine is pembrolizumab which is used for BC patients. This immunotherapy medicine is used to treat BC and PD-L1-positive breast cancer along with chemotherapy when surgery is unsuccessful in these cases. Pembrolizumab is also known as Keytruda. Immunotherapy is a type of biological treatment used for some types of cancers. The aim of this treatment is to boost the immune system to identify and destroy cancer cells. Recent research and clinical trials have shown that immunotherapy treatment has the potential to improve outcomes for breast cancer patients. Depending on the type and stage of cancer, antibodies and immunomodulators (Immune checkpoint inhibitors) can be used to stimulate the immune system to fight against BC cells. Various immunotherapies used are mentioned below:

Targeted Antibodies

These are also known as immune targeted therapies and are a form of immunotherapy treatment that can recognize specific markers on cancer cells then disrupt their grow and alert the immune system to target and eliminate cancer cells. Some of the drugs used are:

i. **Pertuzumab (Perjeta®):** is a humanized monoclonal antibody against extracellular domain II of the human epidermal growth factor receptor. (HER2) receptor is a novel HER2 receptor antagonist approved in 2013 by the European Medicine Agency and in 2012 by the U.S. Food and Drug Administration (FDA) as a first-line therapy to treat HER2-positive and metastatic breast cancer for patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease [45,46]. Pertuzumab is used in combination with chemotherapeutics drugs such as Herceptin, Taxotere, and docetaxel [47].

ii. **Sacituzumab govitecan (Trodelvy®):** is an antibody-drug conjugate (ADC) containing the irinotecan active metabolite, SN-38, that specifically targets human trophoblast cell surface antigen-2 (trop-2) overexpressed in many cancers [48]. ADCs are new biopharmaceutical drugs composed of monoclonal antibodies chemically linked to cytotoxic drugs used to kill cancer cells without causing any damage to healthy cells. Fistful ADCs bind to a specific target protein expressed on the tumor cell surfaces via its monoclonal antibody [49]. Then after cell internalization of ADC, the linker is cleaved, releasing the anticancer drug into the cell causing cell death. It was shown that BC cells overexpressed the trophoblast cell surface antigen 2 (Trop-2) which is a specific target of SN-38 [50-52]. This discovery makes sacituzumab govitecan a good alternative for treatment of BC patients.

iii. **Trastuzumab (Herceptin®):** A recombinant monoclonal antibody targets HER2 extracellular domain IV approved by the FDA and used for HER2 Positive Breast cancer.

iv. **Trastuzumab deruxtecan (Enhertu®):** Enhertu approved in Europe and US for the treatment of HER2-positive metastatic breast cancer [53].

v. **Trastuzumab emtansine** is a new class of chemotherapy drug called an antibody-drug conjugate, recently approved by FDA as an efficient treatment for HER2-Positive Metastatic Breast Cancer [42].

Immunomodulators

One of most important role of the immune system is its ability to make the difference between "self" cells and "non-self-cells". The body cells have specific proteins recognised by the immune system as a "self" checkpoints. Breast cancer cells use these checkpoints to avoid being identified by the immune system to escape from immune system. By targeting these checkpoint through proteins inhibitors help the immune response to fight against breast cancer cells. There are currently many FDA-approved immune checkpoint inhibitors like Pembrolizumab (Keytruda®) and it was approved by U.S. Food and Drug Administration on July 26, 2021. According to National cancer Institute, more than 1,200 trials of KEYTRUDA are being studied across different cancers such as Breast cancer, renal cell carcinoma (RCC) etc.

Tecentriq (Atezolizumab): Tecentriq is an inhibitor for PD-L1 proteins. The interaction between Tecentriq and PD-L1 led to a therapeutic blockade enhancing the tumor-specific T-cell responses resulting in improved anti-tumor activity. Tecentriq was approved by the FDA in March 2019 to be used in combination with the chemotherapy medicine Abraxane to treatment in metastatic BC and locally advanced breast cancer [54,55]. Various Nano formulations and nanomedications like liposomes, metallic nanoparticles, dendrimers, lipid based Nano medicines etc. are in use now a days around the globe for the treatment of breast cancer [15,16].

Nanoparticles

Nanoparticles are small particles, range in size from 1 to 100 nm and are utilized in medicine to treat a variety of tumors, including breast cancer [56]. These days, scientists have created a wide range of nanoparticles with unique characteristics, forms, and manufacturing processes. Liposomes, polymeric, magnetic, gold, quantum dot, and dendrimer nanoparticles are the most often utilized nanoparticles in the treatment of breast cancer patients [57-60]. Every variety of nanoparticle has a unique set of advantages and limitations, and current research aims to minimize any negative effects while maximizing effectiveness.

An overview of current studies and developments in the application of nanoparticles to the treatment of breast cancer:

a. Drug Delivery Targeted.

i. Nanoparticle-Encapsulated Chemotherapy: To

improve the targeting properties and lessen systemic toxicity of conventional chemotherapy medications like doxorubicin and paclitaxel, researchers are creating nanoparticles that encapsulate them. One significant advancement in this area is pegylated liposomal doxorubicin, or Doxil, which has already received approval for clinical use [61].

ii. Targeting Specific Receptors: More recent research focus on creating nanoparticles that specifically target receptors, such as HER2 and estrogen receptors, that are overexpressed on breast cancer cells [62]. By more accurately delivering medications to cancer cells, these tailored nanoparticles can increase therapeutic efficacy and decrease adverse effects.

b. Improved Imaging and Diagnosis.

i. Gold nanoparticles: The application of gold nanoparticles in photothermal treatment and imaging is being investigated. When exposed to laser light, their size and form can be modified to enhance contrast in imaging tests like CT and MRI. They can also be utilized in photothermal treatment to target and kill specific cancer cells [63].

ii. Quantum Dots: High-resolution imaging of cancer cells and tissues is achieved with the use of these fluorescent nanoparticles. In order to assure safe clinical applications, recent research focuses on enhancing their biocompatibility and stability [64].

c. Radiation and Thermal Therapy

i. Magnetic Nanoparticles: These particles are heated to kill cancer cells by applying an external magnetic field. This process is known as magnetic hyperthermia. Current research is enhancing these materials' magnetic characteristics and biocompatibility [65].

ii. Combination Therapies: To fight cancer, researchers are designing nanoparticles that combine medicine delivery with heat therapy [66].

d. RNA and Gene Therapy

i. RNA Nanoparticles: Small interfering RNA (siRNA) and other RNA-based treatments that can quiet genes linked to cancer are delivered using nanoparticles. The goal of recent developments is to make these RNA-loaded nanoparticles more stable and more precisely targeted [67].

ii. Gene Editing: In order to repair mutations or control the behavior of cancer cells, CRISPR/Cas9 components are also delivered by nanoparticles [68].

Ongoing Clinical Trials

The effectiveness and safety of breast cancer treatments based on nanoparticles are being studied in a number of clinical trials. In this regard, several nanoparticle formulations are being tested in clinical studies for targeted drug administration and imaging are

listed below [69].

a. NCT03903145:

i. Title: "A Study of Nanoparticle Albumin-Bound (nab) Paclitaxel and Carboplatin in Combination With Pembrolizumab in Triple-Negative Breast Cancer"

ii. Objective: Assess the safety and effectiveness of using pembrolizumab, carboplatin, and nab-paclitaxel in combination to treat triple-negative breast cancer.

iii. Status: Recruiting.

b. NCT04301284:

i. Title: "Phase I Study of Nanoparticle-Based Docetaxel and Epirubicin in HER2 Positive Breast Cancer".

ii. Objective: Examine the docetaxel and epirubicin nanoparticle formulation's safety, tolerability, and initial efficacy.

iii. Status: Recruiting.

c. NCT04409581:

i. Title: "Safety and Efficacy of Nanoparticle-Encapsulated Doxorubicin in Advanced Breast Cancer".

ii. Objective: Evaluate the efficacy and safety of a novel doxorubicin nanoparticle formulation in patients with metastatic breast cancer.

iii. status: Recruiting.

d. NCT05075419:

i. Title: "Combination Therapy With Magnetic Nanoparticles and Radiation in Breast Cancer"

ii. Objective: Investigate the use of radiation therapy and magnetic nanoparticle hyperthermia in the treatment of breast cancer.

iii. Status: Not yet recruiting.

e. NCT04768183:

i. Title: "Study of Quantum Dot Imaging for Breast Cancer Detection".

ii. Objective: Assess the application of quantum dots for enhanced imaging and breast cancer early detection.

iii. Status: Recruiting.

f. NCT04558916:

i. Title: "Targeted Delivery of siRNA Using Liposomal Nanoparticles in HER2-Positive Breast Cancer"

ii. Objective: Evaluate liposomal nanoparticles' efficacy in delivering siRNA directed against HER2-positive breast cancer.

iii. Status: Recruiting.

g. NCT04164266:

- i. Title: "Efficacy of Gold Nanoparticles in Combination with Chemotherapy for Triple-Negative Breast Cancer".
- ii. Objective: Examine if gold nanoparticles and conventional chemotherapy medications work well together to treat triple-negative breast cancer.
- iii. Status: Recruiting.

Pathways Targeted by various Therapies of Breast Cancer

Various signaling pathways are being targeted using different therapies. Some of them are listed below:

HRR Pathway

To repair DNA double strand breaks, HRR pathway is involved. HRD leads to the molecular alterations that confers to HRD in BCs with mutations of BRCA1/2 and other mutations. Germline BRCA1/2 mutations are considered as authentic biomarkers of sensitivity to DNA-targeting cytotoxic agents like platinum-based agents and PARP inhibitors [70]. HRD breast cancer cells specifically BRCA1/2 depend on PARP-mediated DNA repair for their survival and are thus very sensitive towards its inhibition. Other than BRCA1/2 other alterations are also being considered as budding biomarkers of sensitivity to PARP inhibitors.

Antibody Drug Conjugates

Antibody Drug Conjugates (ADCs) use the mechanism of cytotoxicity. ADCs only permit delivery of cytotoxic payloads to antigen-expressing cancer cells. Other than using cytotoxicity mechanism, ADCs also use other antitumor mechanisms such as inducing double-strand DNA breaks, thereby enhancing growth inhibitory effect of PARP inhibitors in BC. ADCs also modify inflammatory tumor micro environment by causing immunogenic cell death leading to the infiltration of cytotoxic T cells and antigen-presenting cells and displaying antitumor properties when combined with immune checkpoint inhibitors (ICIs) [70].

PI3K-AKT pathway inhibitors

PI3K-AKT pathway has a role in cancer. Various alterations like activating mutations in PIK3CA, AKT1 or MTOR and inactivating mutations of PTEN, PIK3R1 or INPP4B can get around to PI3K pathway activation [71].

Anti-androgen Therapy

20-40 % of BC is specified by increased expression of androgen receptor (AR). None of the AR inhibitors such as bicalutamide and enzalutamide have exhibited proper anti-tumor activity in metastatic BC patients who are androgen receptor positive till date. However, ongoing trials will clearly explain the beneficial character of AR inhibition in patients with metastatic BC

(NCT03055312) [72]. Luminal androgen receptor (LAR) subtype activates PIK3CA and AKT mutations and studies have clearly indicated the synergistic activity of contemporaneous blockage of the PI3K and AR signaling pathways in AR+ TNBC [73,74].

Conclusion

Breast cancer prevalence is alarming in African countries and it is the top cause of death in Africa. The mortality rate in Middle and Southern African women was found to have a lower prevalence of BC compared to Northern African populations. Machine learning is considered to be the most recent approach towards its diagnostics whereas conventional treatments like chemotherapy, immunotherapy, metronomic etc. are extensively used in African continent till date. Nano medications also play an important role in the treatment of breast cancer. Various signaling pathways like HRR pathway, antibody drug conjugates, anti-androgen therapy etc. are being targeted using different therapies. There is a need for better understanding and use of Nano medicines that will definitely aid in better treatment and early diagnosis of breast cancer in African continent.

Data Availability Statement

The data underlying this article are available in the article.

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Conflict of interest

Authors declare no conflict of interest.

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