Pakistan J. Zool., vol. 58(3), pp 1461-1475, 2026 **DOI**: https://dx.doi.org/10.17582/journal.pjz/20250620074102

Review Article

An Overview of Breast Cancer and the Role of ^{13}C Mass Spectrometry and Isotope-Based Imaging Methods in Early Detection

Iqra Suleman[1], Shahid Aziz[2,3]*, Shumaila Naz[1] and Faisal Rasheed[3]

[1]Department of Biosciences, Quaid Campus, University of Wah, Wah Cantt, Pakistan
[2]Institute of Allied Health Sciences, Wah Medical College, Wah Cantt and National University of Medical Sciences, Rawalpindi, Pakistan.
[3]Patients Diagnostic Lab, Isotope Application Division, Pakistan Institute of Nuclear Sciences, Islamabad, Pakistan.

Article Information
Received 20 June 2025
Revised 05 September 2025
Accepted 14 September 2025
Available online 28 January 2026 (early access)
Published 10 April 2026

Authors' Contribution
IS: Data curation, original draft writing, review, editing visualization. SA: Conceptualization, review, editing, supervision, project administration, visualization, validation. SN: Review, editing, supervision, project administration, visualization, validation. FA: Review, editing, supervision, visualization, validation.

Key words
Breast cancer, Early detection, ^{13}C isotope, Metabolic reprogramming, Diagnostic strategies

ABSTRACT

The early detection, treatment, and prevention of breast cancer are the major concerns in the realms of public health due to its persistent increase globally. Improvement in detection methods and treatment has impacted the survival rate significantly. However, despite the advances in current diagnostic techniques such as mammography, ultrasound, and MRI, challenges persist in terms of sensitivity, specificity, and early detection. To enhance diagnostic methodologies and therapeutic strategies, an advanced comprehension of the epidemiology, staging, and clinical characteristics of breast cancer is imperative. The biological diversity, associated risk factors, and trajectory of the disease profoundly impact the formulation of both therapeutic and preventive strategies. Collectively, these considerations underscore the necessity for advanced and adaptable detection methodologies. Regardless of the efficacy of current imaging techniques, there remains a need for novel methodologies that augment detection accuracy. One particularly promising approach involves the utilization of stable isotopes, particularly ^{13}C isotopes, has emerged as a promising diagnostic tool to enhance detection mechanisms. The ^{13}C isotope-based imaging methods utilize the distinct metabolic pathways of cancer cells, particularly their altered glucose metabolism. The use of ^{13}C isotope as a biomarker for breast cancer diagnosis and its role in improving current diagnostic approaches enlightens the potential of isotopes for more precise and non-invasive diagnostic advancements in breast cancer detection. These findings highlight that integrating ^{13}C isotope-based technologies could significantly enhance early detection, personalized treatment strategies, and patient outcomes.

INTRODUCTION

Breast cancer constitutes the predominant etiology of oncological mortality among the female population in 140 out of 184 nations globally and is the most frequently diagnosed malignancy, presently accounting for one in four of all cancer diagnoses in females (Angahar, 2017; Urooj *et al*., 2022). It constitutes approximately 25% of cancer cases and 16% of cancer deaths among women worldwide, with peak incidence in France, Australia, Northern America, and Northern Europe, where rates are quadruple those in South-Central Asia and Middle Africa. Women in transitioned countries exhibit significantly higher incidence rates than those in developing nations i.e., 54.1/30.8 per 100,000, yet experience lower mortality rates i.e., 11.3/15.3 per 100,000 (Bray *et al*., 2024). According to the study conducted in 2020, the incidence of breast cancer is increasing worldwide, with 2.3 million new cases and 685,000 mortalities. The projections indicate a potential surge to 2.64 million occurrences and 1.7 million deaths by the year 2030 (Shang and Xu, 2022).

Breast cancer prevalence varies significantly across different countries and regions, influenced by socioeconomic factors and healthcare access. In Europe, the burden of breast cancer was reported at 463.2 cases

* Corresponding author: saziz@bs.qau.edu.pk, sazizgc@gmail.com
0030-9923/2026/0003-1461 $ 9.00/0

per 100,000 people in 2019, which is 1.7 times the global average, with Monaco, Serbia, and Montenegro showing the highest rates (Yu *et al.*, 2024). Each year, the American Cancer Society estimates new cancer cases and deaths in the U.S. using recent population-based data from cancer registries and mortality statistics. In 2025, projections indicate 2,041,910 new cancer cases and 618,120 cancer deaths in the United States (Siegel *et al.*, 2025). Noteworthy geographic and temporal disparities in breast cancer mortality persist across various regions (Sun *et al.*, 2023; Torres-Román *et al.*, 2023), which appear to be significantly correlated with the extent of access to essential health services (Duggan *et al.*, 2021). A considerable number of sub-Saharan African nations rank among those exhibiting the highest breast cancer mortality rates globally, indicative of inadequate healthcare infrastructure and, consequently, suboptimal survival outcomes attributable to late-stage presentations of the disease (Soerjomataram *et al.*, 2023). In China, breast cancer was the most common female cancer in urban areas (Ong *et al.*, 2024). While in India, 19 per 100,000 women have breast cancer, and the prevalence of incidence has escalated over the past 40 years (Rai *et al.*, 2022). Among all the Asian nations, Pakistan has the highest risk of breast cancer development (Mubarik *et al.*, 2019). The rate of incidence is 2.5 times higher in Pakistan than in neighboring countries such as India or Iran (Majeed *et al.*, 2022). The number of cases in Pakistan is increasing, with 25,928 cases in 2020, representing 14% of all cancer diagnoses (Khan *et al.*, 2024). Another study reported approximately 34,066 new cases of breast cancer with a ratio 1 in every 9 women (Iftikhar *et al.*, 2024).

In western nations, screening initiatives have proven effective in detecting the majority of breast cancers via screening protocols rather than as a result of symptomatic presentation (Shang and Xu, 2022). Even though mortality rates from breast cancer are higher in lower and middle-income nations, there is a lack of early detection techniques, and the majority of patients with late illnesses require palliative treatment with low survival rates (Mehiret *et al.*, 2022). Prior research has indicated that early detection of cancer is crucial for effective and appropriate treatment and has the potential to halt its progression and substantially lower the mortality rate. However, current breast diagnostic techniques, including mammography, ultrasound, and magnetic resonance imaging (MRI), exhibit several limitations that compromise their precision and efficacy. Mammography, recognized as the predominant screening technique, encounters challenges in patients with dense breast tissue, resulting in diminished sensitivity and specificity (Grigoryants *et al.*, 2023). Ultrasound is an operator-dependent tool that may yield false positives, especially in younger women. MRI is sensitive but costly and less accessible, limiting its use in widespread screening. Current techniques also pose a risk due to ionizing radiation, particularly for younger women and those at elevated risk (Devi and Anandhamala, 2018; Abdul-Halim *et al.*, 2021). Furthermore, the discomfort linked to mammography, particularly from breast compression, can discourage regular screening among women (Abeelh and AbuAbeileh, 2024).

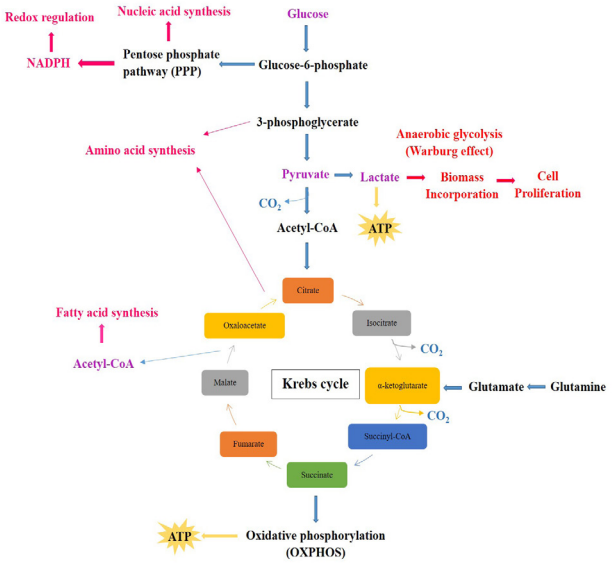

Fig. 1. Metabolic reprogramming in cancer cells: Unlike the normal cells which mainly utilize oxidative phosphorylation for energy production, cancer cells often switch towards the aerobic glycolysis or the Warburg effect, that allows cancer cells to rapidly synthesize essential biomolecules needed for growth and proliferation. The reprogrammed Krebs cycle and gluconeogenesis pathways facilitate anabolic processes, while increased lactate production marked the unique metabolic landscape supporting tumor survival and progression.

Carbon metabolism is a key aspect of reprogramming tumor metabolism (Fig. 1), as it provides energy and building blocks for tumor growth and survival (Lane *et al.*, 2020). Normal cells predominantly utilize oxidative phosphorylation (OXPHOS) to generate 36 ATP molecules per glucose. This mechanism entails the thorough oxidation of glucose to carbon dioxide and water, thereby optimizing energy yield (Kubicka *et al.*, 2021). Carbon dioxide (CO_2) is a byproduct of the citric acid cycle, which is essential for OXPHOS (Liao, 2017). On the other hand, cancerous cells demonstrate the Warburg effect, preferentially utilizing glycolysis even when oxygen is available. This metabolic adaptation

leads to the generation of lactic acid rather than carbon dioxide, yielding merely 2 ATP molecules for each glucose molecule consumed. The transition towards glycolysis facilitates the biosynthetic pathways required for the production of nucleic acids, proteins, and lipids, which are essential for expedited cellular proliferation (Liao, 2017; Kubicka *et al*., 2021). CO_2 can enhance cancer therapies by influencing tumor microenvironment, oxygen release, and blood pH, and potentially optimizing cellular mechanisms through hypercapnia and modulating metabolic pathways (Gaspary *et al*., 2024). Stable isotopes including ^{13}C-labeled glutamine or glucose can be used to study carbon metabolism, to track the fate and flux of carbon atoms in various metabolic pathways (Dong, 2020). The alterations in different metabolic processes, such as glycolysis, krebs cycle, amino acid metabolism, pentose phosphate pathway, can be intimated by ^{13}C isotopes in the variety of tumors. The identification of metabolic biomarkers and therapeutic targets for tumor metabolism reprogramming can also be identified using ^{13}C isotopes (Han *et al*., 2021). Significance of carbon isotopes in breast cancer has garnered substantial scholarly interest, particularly in interpreting tumor metabolism and treatment efficacy. Analysis on employing naturally occurring carbon isotopes have elucidated distinctive metabolic signatures that differentiate healthy breast tissues from cancerous tissues, especially focusing lipid metabolism and urea cycle (Illa *et al*., 2016).

Data collection for this systematic review was searched through Reference Citation Analysis (RCA), ScienceDirect, Research Gate, Web of Science, and PubMed databases using keywords i.e., breast cancer, signs and symptoms, stages of breast cancer, risk factors, ^{13}C isotope and diagnostic strategies, and evaluated the content of the articles. After assessing the articles, we selected 117 publications out of 1148 (Fig. 2).

STAGING AND CLASSIFICATION OF BREAST CANCER

Breast cancer staging is a critical process that determines the extent of cancer spread, guides treatment decisions, and predicts patient outcomes. The staging and classification of breast cancer are determined based on tumor size, lymph node involvement, metastatic activity, or specific biomarkers (Jacene *et al*., 2024) (Table I). This data is crucial for determining prognosis and selecting appropriate treatment strategies to manage the breast cancer (Singh *et al*., 2024; Afzal and Vahdat, 2024). Early-stage breast cancer is often curable with localized treatments, while advanced stages require systemic therapies. The 5-year survival rate for early-stage breast cancer is significantly higher than for metastatic disease (Loibl *et al*., 2024; Trayes and Cokenakes, 2021). Advances in precision medicine have integrated molecular and genetic data into the staging process, enabling more accurate prognostication and tailored therapies (Afzal and Vahdat, 2024; Singh *et al*., 2024).

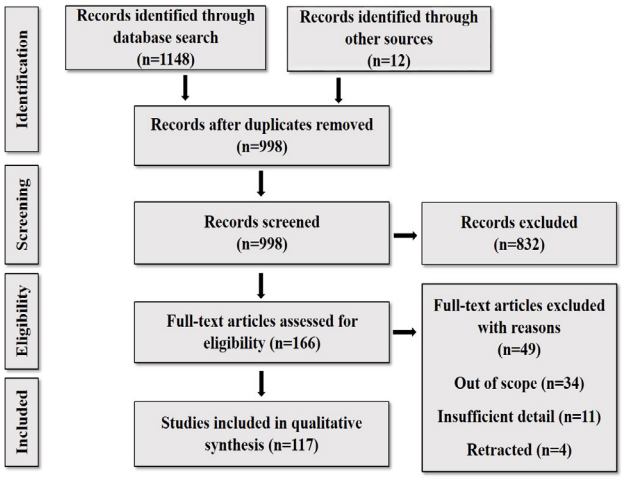

Fig. 2. PRISMA diagram with incorrect screening numbers was included inadvertently. The corrected diagram is attached for replacement.

Stage 0

Stage 0, or ductal carcinoma in situ (DCIS), is a non-invasive breast cancer that indicates that malignant cells have emerged within the breast tissue; however, they have not yet disseminated to adjacent tissues, lymph nodes, or distant organs (Trayes and Cokenakes, 2021). According to Breast Cancer Research Foundation (2024), principally, this stage is asymptomatic, while in rare cases, the patient may feel a lump or have nipple discharge (Hanna *et al*., 2019). For treating this stage, surgical choices include lumpectomy or mastectomy, and research shows that many patients with DCIS are recommended and accept surgery (Pico *et al*., 2023). Proton therapy has been investigated as a treatment option, demonstrating feasibility and low toxicity in initial trials for patients in early-stage breast cancer (Freedman *et al*., 2024). Endocrine therapy may be added for ER-positive patients (Jha and Dhale, 2024). According to the American Cancer Society (2016), the five-year survival rate for individuals diagnosed with stage 0 is nearly 100%. However, if this stage is left untreated, around 40% of cases may advance to invasive breast carcinoma (Cowell *et al*., 2013).

Table I. Stages of breast cancer: Description of symptoms, tumor size, lymph node involvement, and spreading characteristics associated with each stage of cancer, from Stage 0 (asymptomatic) to Stage IV (metastasis).

Cancer stages	Symptoms	Tumor size	Lymph nodes	Dissemination	Treatment options	Survival rate	Stage map	References
Stage 0	Asymptomatic stage, rarely shows lump or nipple discharge	Very small, Inside the glands	Not affected	Limited to the breast region	Lumpectomy, mastectomy, proton therapy, radiation therapy, endocrine therapy	100%		(Trayes and Cokenakes, 2021; Hanna *et al*., 2019; Freedman *et al*., 2024; Cowell *et al*., 2013; Jha and Dhale, 2024)
Stage I	Palpable lump, change in breast size, nipple discharge	Less than 2 cm	Not affected	Limited to the breast region	Breast-conserving surgery, mastectomy, adjuvant endocrine therapy, radiation therapy	99%		(Mitsuk, 2016; Hadar *et al*., 2024; White *et al*., 2024; Waks and Winer, 2019; Jha and Dhale, 2024)
Stage II	Pain, nausea, low appetite, diarrhea, constipation	2-5 cm	Affected by neoplasia	Limited to the breast region	Mastectomy, radiation therapy, chemotherapy	87.1%		(DePolo, 2024; Kaufmann *et al*., 2023; Perry *et al*., 2023; Saghir *et al*., 2023; Jha and Dhale, 2024; White *et al*., 2024)
Stage III	Swollen red breast, thick skin, large lump	More than 5cm	Affected by neoplasia	Limited to the breast region	Adjuvant endocrine therapy, immunotherapy, chemotherapy, lumpectomy, mastectomy, senital lymph node biopsy	68.7%		(Trayes and Cokenakes, 2021; Saghir *et al*., 2023; Maughan *et al*., 2010; Maria, 2024; Retamales *et al*., 2024)
Stage IV	Pain, Fatigue, metastasis	Any size	Affected by neoplasia	Malignancy metastasized to other organs	Endocrine therapy, chemotherapy, targeted therapy	25%		(Grobler *et al*., 2023; Gerratana *et al*., 2015; Cardoso *et al*., 2024; Jha and Dhale, 2024)

Stage I

This stage is characterized by a neoplasm that measures less than 2 cm in diameter. Furthermore, this neoplasm has not disseminated to the lymphatic nodes or to other systems (Stage 1A) or has only developed micrometastases in 1-3 lymph nodes located in the axillary region (Stage 1B), (Mitsuk, 2016). Common symptoms include a palpable lump, changes in breast shape or size, and nipple discharge. However, many patients are asymptomatic, detected through screening mammography (Hadar *et al*., 2024). Recent research has shown notable progress in treatment options and outcomes for this early stage of breast cancer. Treatment involves surgery (lumpectomy or mastectomy) with or without radiation. Moreover, depending on the tumor biology and the patient's preferences, systemic therapies (chemotherapy, hormone therapy, or targeted therapy) are suggested (Jha and Dhale, 2024; White *et al*., 2024). Survival rates for this stage differ markedly based on tumor biology. Stage I triple-negative tumors have a five-year survival rate of about 85%. Conversely, hormone receptor-positive show significantly higher survival rates, between 94% and 99% (Waks and Winer, 2019).

Stage II

Stage IIA and IIB are distinct stages of a tumor. Stage IIA refers to neoplasm with metastasis to three lymph nodes in the axillary region, minor metastatic deposits in mammary glands, or exceeds 2 cm but is less than 5 cm without metastasis. Stage IIB describes a tumor exceeding 2 cm but less than 5 cm with no metastasis, limited metastasis in three lymph nodes, or a tumor exceeding 5 cm without metastasis (DePolo, 2024). Nausea, diarrhea, low appetite,

general pain and constipation are the main symptoms in this stage (Kaufmann *et al*., 2023). At this stage, prognosis and treatment strategies are crucial to enhancing patient outcomes. According to the research patients generally opt for radiation therapy or chemotherapy. Whereas, some patients prioritise mastectomy, especially those residing farther from the hospitals (Perry *et al*., 2023). The recommendation of systemic therapies including chemotherapy, hormonal therapy, or targeted therapy is based on patient's preference and tumor biology (Jha and Dhale, 2024; White *et al*., 2024). The overall survival rates for stage II were observed to be 5 years (96%) and 10 years (87.1%), (Saghir *et al*., 2023). In comparison, the study conducted in Bangladesh reported the survival rate of 36.1% over 10 years (Nahar *et al*., 2023). The recurrence rate varies according to the lymph node involvement and treatment strategies, also impacting the patients' outcome; 2% for stage IIA and 3.5% for stage IIB. The continuous monitoring and preventive measures are important because the survivors of stage I and II breast cancer are at higher risk of second primary malignany (Schumacher *et al*., 2022).

Stage III

Locally advanced breast cancer stages (IIIA, IIIB, and IIIC) are non-metastatic (Trayes and Cokenakes, 2021). and encompasses tumors exceeding 5 cm. It has significant involvement of regional lymph node, direct invasion of the chest wall or skin, inoperable tumors without distant metastases, and inflammatory breast cancer (Maughan *et al*., 2010). According to Breast Cancer Research Foundation (2024), the symptoms include swollen red breasts with thickened skin, a large lump in the breast that feels attached to the chest wall, and a lump in the armpits and base of the neck (Maria, 2024). During the preoperative phase, adjuvant endocrine therapy (ET) or immunotherapies are used when tumors express estrogen or progesterone receptors. Preoperative chemotherapy is the only option for triple-negative tumors (Trayes and Cokenakes, 2021; Marques *et al*., 2024). The surgical phase presents two alternatives that exhibit comparable survival outcomes: a lumpectomy accompanied by radiation therapy, provided that the neoplasm can be entirely removed with favorable aesthetic results or a mastectomy. Additionally, a sentinel lymph node biopsy is conducted when there is an indication of potential nodal involvement (Trayes and Cokenakes, 2021; Retamales *et al*., 2024). The postoperative period encompasses radiotherapy, hormonal treatment, immune-modulatory therapy, and cytotoxic chemotherapy. It is imperative to provide postoperative bisphosphonates to women who have reached menopause (Trayes and Cokenakes, 2021). A study by Saghir *et al*. (2023) reported an overall survival rate of 88.3% at 5 years and 68.7% at 10 years. Recurrence rates vary significantly; overall, 30% of patients experienced recurrence within 10 years, with a notable prevalence of distant metastases (D'Oronzo *et al*., 2021).

Stage IV

Stage IV of breast cancer is marked by metastatic cancer, and the tumor can be of any size (Grobler *et al*., 2023). Metastatic breast cancer is extensively recognized for its poor prognosis in contrast to non-metastatic breast cancer. The most prevalent sites are bone, liver, lung, and brain (Gerratana *et al*., 2015). Patients commonly experience symptoms such as pain, fatigue, and complications arising from metastasis, which may require palliative care (Maughan *et al*., 2010). The therapeutic approach for metastatic breast cancer is customized, with the principal objectives being the extension of life expectancy and the alleviation of symptoms (Mitsuk, 2016). The treatment approach typically includes a combination of therapies (Schumacher *et al*., 2022). Systemic therapy constitutes the principal intervention for stage IV breast carcinoma, encompassing endocrine therapy, chemotherapy, and targeted therapy. Currently, there exists a lack of standardized guidelines for the management of stage IV breast carcinoma subsequent to multiple lines of treatment. Prospective investigations have produced incongruous findings concerning the potential survival benefits associated with the surgical intervention of the primary tumor (Zheng *et al*., 2021; Jha and Dhale, 2024). Recurrence rates can differ, with a reported 2-year recurrence rate of 11.8% following surgery. Factors like lymph node involvement and tumor characteristics significantly determine survival outcomes (Kumilau *et al*., 2022). The median overall survival (OS) is roughly 3 years, with a 5-year survival rate estimated at about 25% (Grobler *et al*., 2023).

INDICATORS TO IDENTIFY BREAST CANCER

The onset of breast cancer is characterized by the emergence of malignant cellular formations within breast tissue, frequently manifesting as palpable lumps or masses. Empirical observations indicate that breast lumps constitute the most prevalent clinical manifestation associated with breast cancer. A research investigation revealed that merely 50.5% of participants possessed knowledge that a breast lump serves as an alarming indicator, thereby highlighting a considerable deficiency in public awareness (Coleman, 2017). Such awareness is of paramount importance, as the early identification of breast

lumps can facilitate prompt diagnosis and subsequent therapeutic intervention. Other symptoms may include a change in breast size and shape due to thickening or swelling, redness or decoloration, nipple retraction, pain in the breast or nipple, dimpled skin as well as unusual warmth in one breast with the presence of discharge from the nipple (Galamba, 2024). Individuals with advanced breast cancer experience various symptoms that negatively impact their quality of life and physical capabilities. Metastatic disease primarily affects the bone, lungs, liver, and brain. Clinical manifestations of advanced breast cancer include pain, fractures, pleural effusions, and ascites. Oncological emergencies related to these metastatic sites may consist of hypercalcemia, spinal cord compression, superior vena cava obstruction, and increased intracranial pressure (Shewbridge *et al*., 2024). Previous researches underscore the significance of awareness concerning these indicators, particularly within demographic groups characterized by lower screening frequencies. Moreover, the affective and cognitive dimensions associated with the identification of symptoms have been acknowledged, as postponements in pursuing assistance frequently correspond with insufficient awareness of indicative signals (Quaife *et al*., 2014).

RISK FACTORS

Breast cancer is influenced by various factors, encompassing modifiable and non-modifiable elements. Gender, age, early onset or late cessation of menstruation, family medical history, absence of pregnancies, large breasts, and genetic susceptibility (mutations in the *BRCA* gene) are integral components of the non-modifiable risk factors (Ibarra-Cuevas *et al*., 2024; Admoun *et al*., 2022). Conversely, modifiable risk factors are associated with obesity, poor dietary habits, sedentary lifestyle, alcohol consumption, smoking, usage of birth control pills, and hormone replacement therapy (Admoun *et al*., 2022). Furthermore, environmental factors play a significant role, as exposure to endocrine-disrupting substances originating from various sources like plastics, cosmetics, detergents, and atmospheric pollutants contribute to the susceptibility to breast cancer (Akanji *et al*., 2022).

Decreased oxygen concentrations, which fall below the thresholds necessary for sustaining standard metabolic processes and physiological function within tissues (hypoxia), represent a significant oncogenic risk factor commonly observed in cases of breast carcinoma (Tutzauer *et al*., 2022). Women with a history of breast cancer are at a higher risk of developing the disease again. Either the same breast or a different breast could be the site of the second breast cancer. Moreover, women with ductal carcinoma in situ or lobular carcinoma in situ breast cancers are more likely to experience a recurrence, even though most of them do not (Buist *et al*., 2018).

DIFFERENTIAL DIAGNOSIS

Diagnostic strategies

Different diagnostic strategies, including a range of non-invasive and invasive modalities, can be used for breast cancer detection (Obeagu and Obeagu, 2024). Imaging modalities such as mammography, ultrasound, magnetic resonance imaging (MRI), positron emission tomography (PET), histopathology facilitates to acquire breast images (Chowdhury *et al*., 2024). Despite the higher specificity of traditional techniques i.e. mamography, they may have lower sensitivity in particular populations, especillay those with denser breast tissues (Abiramasundari *et al*., 2024).

Biopsy

Different types of biopsies can be used to detect breast cancer includes core biopsy (Poort *et al*., 2022), lymph node biopsy (Wang *et al*., 2019), and needle aspiration (Wang *et al*., 2020). Cells or tissue samples are taken during the biopsy procedure and analysed in the laboratory to detect the cancerous cells in the patient. The choice of biopsy technique is dependent on the lesion's palpability. Ultrasound or mammography may be utilized by the physician to locate the area for assessment (Poort *et al*., 2022). This method has a 94% accuracy rate. The cumulative probability over a ten-year period that a woman will receive at least one false-positive biopsy is estimated to be between 4.8% and 9.4% (Sandbank *et al*., 2022).

Ultrasound

An ultrasound employs high-frequency acoustic waves to visualize anatomical structures. It is essential for determining if a breast mass is a neoplasm or cyst. Additionally, ultrasound aids practitioners in accurately locating biopsy sites. Ultrasound assessments may be performed on women with advanced breast cancer to assess potential hepatic metastasis (Wang *et al*., 2019). Despite its advantages in specificity, it has a lower sensitivity (61%) and frequently underestimates tumor size (67.7%) (Alotaibi *et al*., 2024).

Mammography

Diagnostic mammography constitutes a radiographic procedure that generates an image of the breast by applying minimal radiation exposure. This modality investigates further unanticipated results from a clinical examination of breast or mammography. Additionally, mammography may be utilized concurrently with a biopsy to delineate an anomalous region (Chang *et al*., 2022). Mammography,

while the predominant screening method, has been shown to overestimate tumor sizes in 41.9% of cases and often fails to detect malignancies in dense breast tissue (Mansour *et al*., 2024).

Magnetic resonance imaging (MRI)

Breast magnetic resonance imaging is a non-invasive diagnostic technique that uses low-energy radiofrequency waves and a magnetic field to obtain detailed images of the breast's anatomical structure (Graves and Zhu, 2015). The application of MRI is particularly beneficial for quantifying the dimensions of neoplastic growths and for detecting metastatic lesions in female patients with a prior diagnosis of breast cancer. Neoplasms measuring 2 cm or less than this, have been consistently and precisely identified and quantified using MRI techniques. Conversely, larger breast tumors frequently suffer from overestimation due to the presence of aberrant breast tissue surrounding the actual lesion, which may consequently result in increased mastectomy rates (Bhushan *et al*., 2021). Although demonstrating the highest sensitivity (72.2%) and accuracy (86.9%), MRI still presents challenges, particularly its ability to reflect tumor size in all cases accurately (Alotaibi *et al*., 2024).

^{13}C mass spectrometry

The majority of cancer diagnoses rely on histological evaluations. Histopathological evaluations requires considerable expertise and knowledge of both clinical and pathological aspects. Because it is often challenging to differentiate early-stage cancers within biopsy samples using the conventional histopathological techniques (Tseng *et al*., 2023; Schlageter *et al*., 2014). Consequently, errors in diagnostic pathology can result in inappropriate patient management including treatment delays or incorrect regimens (Clary *et al*., 2002; Raab *et al*., 2005). Isotope ratio mass spectrometry (IRMS) facilitates the detection of malignancy with improved sensitivity and specificity, thus overcoming the constraints of existing detection modalities. Mass spectrometry can detect the alterations in metabolic pathways associated with cancer by examining the isotopic composition of biological samples. This nuclear methodology detetcted the increased expression of ornithine decarboxylase in cancer cell lines by measuring the amount of $^{13}CO_2$ produced because of the enzyme-mediated degradation of ^{13}C ornithine in cancerous tissues (Jaenisch *et al*., 2016).

The use of metabolic alterations as a biomarkers for disease prgression is also demonstrated by Guenther *et al*. (2015) illustrating the value of desorption ionization mass spectrometry in spatially resolved metabolic phenotyping of breast cancer. Ornithine decarboxylase may be a diagnostic or predictive biomarker for cancers and its activity has been employed to evaluate the progression of cancer (Hoshino *et al*., 2007; Geerts *et al*., 2010; Samoylenko *et al*., 2021). Furthermore, several researches have reported the elevated level of ornithine decarboxylase in cancers assessed by mRNA expression, immunohistochemistry, and radiometric liquid scintillation spectrometry at different sites such as colon (Hu *et al*., 2005), breast (Capellen *et al*., 2021), esophagus (He *et al*., 2017), and stomach (McNamara *et al*., 2021). Despite that, isotope ratio mass spectrometry has an advantage over mRNA expression, immuhistochemistry and radiometry due to the application of stable isotope, direct analysis of generated $^{13}CO_2$, and exceptionally low $^{13}CO_2$ detection limit in headspace. Isotope ratio mass spectrometry measured the $^{13}CO_2$ which is directly produced when ornithine decarboxylase reacts with stable isotope. Mass spectrometry serves as an effective adjunct to radiometry for the identifcation of resilient radionuclides (Hou and Roos, 2008). Employing the optimal counting technique for a given hazard is essential because of the possible health effects of radioactive substance releases (Gonzales *et al*., 2005).

BREAST CANCER BIOMARKERS

The role of biomarkers in breast cancer management is well-established. Biomarkers are crucial in healthcare for their ability to provide insights into disease diagnosis, prognosis, treatment response, and personalized medicine. They enable early detection, intervention, and improved patient outcomes, reducing costs and guiding treatment decisions (Das *et al*., 2023). Breast cancer biomarkers can be broadly categorized into genetic (includes mutations in genes such as *BRCA 1*, *BRCA* 2, *PIK3CA*, and *TP53*) and protein (includes HER 2, estrogen receptors (ER), progesterone receptors (PR) and Ki-67) biomarkers, each offering unique insights into the disease's biology and clinical management (Tarighati *et al*., 2023; Yang *et al*., 2023).

Moreover, studies on prognostice and predictive biomarkers suggest that a deeper understanding of metabolic substrates such as ^{13}C could significantly improve their predictive accuracy (Nicolini *et al*., 2018). Combining advanced imaging technologies with biomarker analysis is considered essential for the early detection of breast cancer (Ginsburg *et al*., 2020). Supporting this approach, Pashayan *et al*. (2020) emphasized the need for personalized early detection strategies, advocating the inclusion of metabolic biomarkers in screening programs. Their consensus highlighted that metabolic signatures, potentially measurable using ^{13}C isotopes, could be

instrumental in designing targeted prevention measures for high-risk groups. Research on serum biomarkers has highlighted their effectiveness in the early detection of malignancy. According to Kazarian *et al*. (2017), ^{13}C-based metabolic profiling may offer non-invasive biomarkers for the detection of early breast cancer. In addition, the prospective developments in blood-based biomarkers highlight their potential to support non-invasive and early detection techniques. Although many biomarkers have already been identified, incorporating metabolic profiles derived from ^{13}C isotope analysis could greatly enhance the accuracy and reliability of blood tests in diagnosing breast cancer at an early stage (Loke, 2018).

^{13}C NATURAL ABUNDANCE AS A DIAGNOSTIC BIOMARKER

^{13}C isotopic natural abundance has been investigated in biological samples as a possible diagnostic marker for breast cancer detection (Tea *et al*., 2016). This method involves analyzing the ratios of carbon isotope in tumor and contrasted with those in normal tissues. Due to changes in metabolic pathways including glycolysis, tricarboxylic acid cycle (TCA) and lipid metabolism, cancer cells tend to display unique ^{13}C/^{12}C ratios. These variations occur because enzymatic reactions often favor the lighter isotope, i.e. ^{12}C, leading to measurable differences. These isotopic changes are frequently measured using non-invasive techniques such as isotope ratio mass spectrometry (IRMS) and compound-specific isotope analysis (CSIA), offering comprehensive insights into tumor metabolism. Notably, the carbon isotope patterns in breast cancer tissues have been found to differ markedly from those in non-cancerous tissues, showing their probability as a biomarker for early diagnosis and metabolic profiling (Holland *et al*., 2021; Tea *et al*., 2021; Tea and Tcherkez, 2017).

^{13}C metabolism

The stable isotope tracing combined with metabolic profiling highlights the importance of glucose metabolism in activated CD8+ T cells. Tumor microenvironments may be reflected in metabolic alterations suggesting the potential application of ^{13}C for the detection of cancer and explaining the metaolic processes in tumor cells (Ma *et al*., 2019). A study on the oxygen-depleted cellular environment in malignancy elucidates the molecular mechanisms that govern tumor survival in low oxygen environemnts such as glycolysis, lipid metabolism, angiogenesis, immune tolerance and therapy resistance. Since it enables the development of diagnostic tools for early detection by tracking metabolic changes in hypoxic malignancies by using the ^{13}C isotopes, the afformentioned knowledge is crucial when analyzing the stable isotopes function. The improved therapeutic efficacy depends on early detection of breast cancer, while survival probabilities increases with innovative techniques such as ^{13}C signatures, labeling and imaging technologies. The need for improved patient treatment selection through biomarker identification is highlighted by the examination of the molecular classification of triple negative breast cancer (TNBC). The diversity of breast cancer, particularly in TNBC, emphasizes the significance of metabolic pathway comprehension and its impact on tumor dynamics (Garrido-Castro *et al*., 2019). Dai *et al*. (2016) further elucidated cancer hallmarks and molecular variations in breast cancer, proposing that unique metabolic reprogramming may characterize different subtypes, potentially influenced by ^{13}C substrates.

^{13}C metabolic reprogramming

Cancer cells undergo metabolic reprogramming foucsed by researchers to identify the aterations responsible for rapid growth and tumor progression (Schiliro and Firestein, 2021). Several metabolic pathways are believed to contribute in tumor spread and expansion, where ^{13}C substrate may play a major role in promoting these pathways. Research suggests that adipocyte-derived fatty acids play a significant role in stimulating breast cancer cell growth and migration, suggesting a strong link between lipid metabolism and cancer progression (Balaban *et al*., 2017). Understanding the behavior of metabolic compounds like ^{13}C within the tumor microenvironment is further aided by the investigation of circulating microRNA as non-invasive markers in breast cancer. Since microRNAs can influence metabolic activity, they might provide valuable insignts about metabolic status of tumors and their responsiveness to particular biochemical substrates (Cortez *et al*., 2012).

HYPERPOLARIZED ^{13}C MAGNETIC RESONANCE IMAGING

An increasingly crucial factor of cancer research is the metabolic profile of tumors, assessed by using carbon isotope analysis. The precision of early diagnostic techniques could be enhance by using hyperpolarized imaging techniques to detect specific metabolic alterations in breast cancer tissues. This advanced type of metabolic imaging complements the conventional imaging techniques, and provide a more comprehensive approach to understanding tumor biology (Woitek and Brindle, 2023). Unlike normal cells, cancer cells exhibit distinct metabolic behaviors, especially in the processing of glucose. Hyperpolarized ^{13}C nuclear magnetic resonance

(NMR) have shown notable shifts in glucose metabolism within the breast cancer cell cultures, shedding light on the underlying metabolic reprogramming that drives tumor development (Harris *et al*., 2013).

This method uses hyperpolarization to increase the MRI sensitivity, allowing real time observation of metabolic processes and labels naturally occurring molecules,like pyruvate, with the ^{13}C isotope (Von Morze and Merritt, 2019; Arponen *et al*., 2023). Once the hyperpolarized ^{13}C-pyruvate is introduced into the body, it is rapidly take up and metabolized by cancer cells, providing valuable insight into their metabolic behavior. The cancer cells tend to convert pyruvate into lactate at an accelerated rate because of the Warburg effect. This metabolic shift can captured by hyperpolarized ^{13}C MRI by visualizing the exchange of the ^{13}C-label between the pyruvate and lactate. The ^{13}C-label exchange is significantly higher in more aggressive breast tumors and is closely associated with the elevated levels of monocarboxylate transporter 1 (MCT1) and lactate dehydrogenase (LDH) (Arponen *et al*., 2023; Woitek and Brindle, 2023). This imaging approach has also been utilized to track early metabolic alterations in tumors undergoing neoadjuvant chemotherapy. Compared to traditional imaging modalities, hyperpolarized ^{13}C MRI offers real-time insight into tumor metabolism, enabling earlier cancer diagnosis and more precise monitoring of treatment response (Von Morze and Merritt, 2019; Arponen *et al*., 2023).

KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

Even though our understanding of breast cancer has advanced significantly, there is a crtical need for more research examining the interaction of genetic and environmental factors in various populations. Despite advancements in diagnostic methodologies and understanding breast cancer staging, knowledge gaps persist, including the need for standardized protocols and comparative effectiveness studies across diverse healthcare environments. Further research should focus on assessing the efficacy of diverse diagnostic approaches, including computer-aided detection, across diverse patient demographics. Genetic and molecular factors influence breast cancer staging and therapeutic responses. Understanding genetic susceptibilities and environmental influences could lead to tailored treatment. Liquid biopsies and minimally invasive methodologies require further scrutiny for reliability and applicability. The use of ^{13}C in breast cancer identification is promising, but longitudinal studies are needed to track metabolic changes over treatment to understand their correlation with clinical outcomes. The role of ^{13}C in distinguishing between breast cancer subtypes and its applicability in diverse populations is also under-explored. Future research should integrate ^{13}C MRI with other imaging modalities and biomarkers for a more comprehensive approach to diagnosis and treatment. Applying metabolic profiling in breast cancer diagnosis and treatment is crucial for improving patient outcomes.

CONCLUSION

In conclusion, targeted interventions, improved screening protocols and comprehensive education on risk factors are essential for reducing the burden of breast cancer and improving patient outcomes. The utilization of ^{13}C isotopes during preliminary identification of breast cancer represents a burgeoning domain. Contemporary investigations suggest that hyperpolarized ^{13}C MRI may provide valuable insights into the aggressiveness of tumors, while avant-garde detection methodologies are being formulated to augment the sensitivity associated with biomarker identification. Nonetheless, significant deficiencies exist in comprehending the fundamental mechanisms and their integration with pre-existing diagnostic paradigms. Subsequent research endeavors should focus on rectifying these deficiencies, thereby ultimately facilitating more efficacious early detection strategies in managing breast cancer.

DECLARATIONS

Generative AI and AI-assisted technology statement

The authors declare that no generative AI tools were used in this manuscript.

Statement of conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Abdul Halim, A.A., Andrew, A.M., Mohd Yasin, M.N., Abd Rahman, M.A., Jusoh, M., Veeraperumal, V., Rahim, H.A., Illahi, U., Abdul Karim, M.K. and Scavino, E., 2021. Existing and emerging breast cancer detection technologies and its challenges: A review. *Appl. Sci*., **11**: 10753. https://doi.org/10.3390/app112210753

Abeelh, E.A. and AbuAbeileh, Z., 2024. Comparative effectiveness of mammography, ultrasound, and MRI in the detection of breast carcinoma in dense breast tissue: A systematic review. *Cureus*, **16**: e59054. https://doi.org/10.7759/cureus.59054

Abiramasundari, V.K., Rajarajeswari, B. and Boban,

M.J.A., 2024. Assessing the efficacy: A comparative analysis of invasive and non-invasive diagnostic methods for early detection and screening of breast cancer. *Educ. Adm. Theory Pract*., **30**: 3610–3617.

Admoun, C. and Mayrovitz, H.N., 2022. The etiology of breast cancer. *Breast Cancer Exon. Publ*., **10**: 54. PMID: 36122154. https://doi.org/10.36255/exon-publications-breast-cancer-etiology

Afzal, M.Z. and Vahdat, L.T., 2024. Evolving management of breast cancer in the era of predictive biomarkers and precision medicine. *J. Pers. Med*., **14**: 719. https://doi.org/10.3390/jpm14070719

Akanji, M.A. and Adeyemi, O.S., 2022. Environmental and chemical risk factors for breast cancer. *Proc. Niger. Acad. Sci*., **15**: 1–5. https://doi.org/10.57046/PARF4610

Alotaibi, B.S., Alghamdi, R., Aljaman, S., Hariri, R.A., Althunayyan, L.S., AlSenan, B.F. and Alnemer, A.M., 2024. The accuracy of breast cancer diagnostic tools. *Cureus*, **16**: e51776. https://doi.org/10.7759/cureus.51776

American Cancer society, Breast Cancer, 2016. Available at: https://www.cancer.org/cancer/types/breast-cancer.html (accessed 15 Nov 2024).

Angahar, L.T., 2017. An overview of breast cancer epidemiology, risk factors, pathophysiology, and cancer risks reduction. *MOJ. Biol. Med*., **1**: 92–96. https://doi.org/10.15406/mojbm.2017.01.00019

Arponen, O., Wodtke, P., Gallagher, F.A. and Woitek, R., 2023. Hyperpolarised 13C-MRI using 13C-pyruvate in breast cancer: A review. *Eur. J. Radiol*., **167**: 111058. https://doi.org/10.1016/j.ejrad.2023.111058

Balaban, S., Shearer, R.F., Lee, L.S., Geldermalsen, M.v., Schreuder, M., Shtein, H.C., Cairns, R., Thomas, K.C., Fazakerley, D.J., Grewa, T., Holst, J., Saunders, D.N. and Hoy, A.J., 2017. Adipocyte lipolysis links obesity to breast cancer growth: Adipocyte-derived fatty acids drive breast cancer cell proliferation and migration. *Cancer Metab*., **5**: 1–14. https://doi.org/10.1186/s40170-016-0163-7

Bhushan, A., Gonsalves, A. and Menon, J.U., 2021. Current state of breast cancer diagnosis, treatment, and theranostics. *Pharmaceutics*, **13**: 723. https://doi.org/10.3390/pharmaceutics13050723

Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R.L., Soerjomataram, I. and Jemal, A., 2024. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin*., **74**: 229–263. https://doi.org/10.3322/caac.21834

Buist, D.S., Abraham, L., Lee, C.I., Lee, J.M., Lehman, C., O'Meara, E.S., Stout, N.K., Henderson, L.M., Hill, D., Wernli, K.J. and Haas, J.S., 2018. Breast biopsy intensity and findings following breast cancer screening in women with and without a personal history of breast cancer. *JAMA Intern. Med*., **178**: 458–468. https://doi.org/10.1001/jamainternmed.2017.8549

Capellen, C.C., Ortega-Rodas, J., Morwitzer, M.J., Tofilau, H.M., Dunworth, M., Casero, R.A. and Chandra, S., 2021. Hyperglycemic conditions proliferate triple negative breast cancer cells: Role of ornithine decarboxylase. *Breast Cancer Res. Treat.,* **190**: 255–264. https://doi.org/10.1007/s10549-021-06388-0

Cardoso, V.S., Boligo, A.S., Bessa, M.S., Silvestre, M., Marques, J.P., Martins, A.R., Amaral, P., Fonseca, V. and Sidiropoulou, Z., 2024. Updated evidence of primary tumor resection in stage IV breast cancer. *Eur. J. Surg. Oncol*., **50**: 107465. https://doi.org/10.1016/j.ejso.2023.107465

Chang, C.C., Ho, T.C., Lien, C.Y., Shen, D.H.Y., Chuang, K.P., Chan, H.P., Yang, M.H. and Tyan, Y.C., 2022. The effects of prior mammography screening on the performance of breast cancer detection in Taiwan. *Healthcare*, **10**: 1037. https://doi.org/10.3390/healthcare10061037

Chowdhury, N.A., Wang, L., Gu, L. and Kaya, M., 2024. Machine learning for early breast cancer detection. *J. Eng. Sci. Med. Diagn. Ther*., **8**: 1–18. https://doi.org/10.1115/1.4065756

Clary, K.M., Silverman, J.F., Liu, Y., Sturgis, C.D., Grzybicki, D.M., Mahood, L.K. and Raab, S.S., 2002. Cytohistologic discrepancies: A means to improve pathology practice and patient outcomes. *Am. J. Clin. Pathol*., **117**: 567–573. https://doi.org/10.1309/J6JM-2741-HM34-1F1E

Coleman, C., 2017. Early detection and screening for breast cancer. *Semin. Oncol. Nurs*., **33**: 141–155. https://doi.org/10.1016/j.soncn.2017.02.009

Cortez, M.A., Welsh, J.W. and Calin, G.A., 2012. Circulating microRNAs as non-invasive biomarkers in breast cancer. *Minim. Residual Dis*., **21**: 151–161. https://doi.org/10.1007/978-3-642-28160-0_13

Cowell, C.F., Weigelt, B., Sakr, R.A., Ng, C.K., Hicks, J., King, T.A. and Reis-Filho, J.S., 2013. Progression from ductal carcinoma in situ to invasive breast cancer: Revisited. *Mol. Oncol*., **7**: 859–869. https://doi.org/10.1016/j.molonc.2013.07.005

Dai, X., Xiang, L., Li, T. and Bai, Z., 2016. Cancer hallmarks, biomarkers, and breast cancer molecular subtypes. *J. Cancer*, **7**: 1281. https://doi.

org/10.7150/jca.13141

Das, S., Dey, M.K., Devireddy, R. and Gartia, M.R., 2023. Biomarkers in cancer detection, diagnosis, and prognosis. *Sensors*, **24**: 37. https://doi.org/10.3390/s24010037

DePolo, J., 2024. Breastcancer.org. 2024: Available at: https://www.breastcancer.org/research-news/metastatic-recurrence-risk-declines (accessed 18 Oct 2024).

Devi, R.R. and Anandhamala, G.S., 2018. Recent trends in medical imaging modalities and challenges for diagnosing breast cancer. *Biomed. Pharmacol. J.*, **11**: 1649–1658. https://doi.org/10.13005/bpj/1533

Dong, W., 2020. *Exploring cancer metabolism through isotopic tracing and metabolic flux analysis*. PhD thesis, Massachusetts Institute of Technology. 77 Massachusetts Avenue Cambridge, USA.

D'Oronzo, S., Gregory, W., Nicholson, S., Chong, Y.K., Brown, J. and Coleman, R., 2021. Natural history of stage II/III breast cancer, bone metastasis, and the impact of adjuvant zoledronate on the distribution of recurrences. *J. Bone Oncol.*, **28**: 100367. https://doi.org/10.1016/j.jbo.2021.100367

Duggan, C., Dario, T., Ilbawi, A.M., Fidarova, E., Laversanne, M., Curigliano, G., Bray, F. and Anderson, B.O., 2021. National health system characteristics, breast cancer stage at diagnosis, and breast cancer mortality: A population-based analysis. *Lancet Oncol.*, **22**: 1632–1642. https://doi.org/10.1016/S1470-2045(21)00462-9

Freedman, G.M., Li, T., Garver, E., Shillington, K., Shinkle, B., Tchou, J.C., Fayanju, O.M., Lin, L. and Taunk, N.K., 2024. Five-year outcomes of a phase 1/2 trial of accelerated partial breast irradiation using proton therapy for women with stage 0–IIA breast cancer. *Adv. Radiat. Oncol.*, **9**: 101334. https://doi.org/10.1016/j.adro.2023.101334

Galamba, E., 2024. Know the signs and symptoms of inflammatory breast cancer. *Oncol. Times*, **46**: 18. https://doi.org/10.1097/01.COT.0001005136.83717.c9

Garrido-Castro, A.C., Lin, N.U. and Polyak, K., 2019. Insights into molecular classifications of triple-negative breast cancer: Improving patient selection for treatment. *Cancer Discov.*, **9**: 176–198. https://doi.org/10.1158/2159-8290.CD-18-1177

Gaspary, J.F.P., Edgar, L., Lopes, L.F.D., Rosa, C.B. and Siluk, J.C.M., 2024. Translational insights into the hormetic potential of carbon dioxide: From physiological mechanisms to innovative adjunct therapeutic potential for cancer. *Front. Physiol.*, **15**: 1415037. https://doi.org/10.3389/fphys.2024.1415037

Geerts, D., Koster, J., Albert, D., Koomoa, D.L.T., Feith, D.J., Pegg, A.E., Volckmann, R., Caron, H., Versteeg, R. and Bachmann, A.S., 2010. The polyamine metabolism genes ornithine decarboxylase and antizyme 2 predict aggressive behavior in neuroblastomas with and without MYCN amplification. *Int. J. Cancer*, **126**: 2012–2024. https://doi.org/10.1002/ijc.25074

Gerratana, L., Fanotto, V., Bonotto, M., Bolzonello, S., Minisini, A.M., Fasola, G., Puglisi, F., 2015. Pattern of metastasis and outcome in patients with breast cancer. *Clin. Exp. Metastasis*, **32**: 125–133. https://doi.org/10.1007/s10585-015-9697-2

Ginsburg, O., Yip, C.-H., Brooks, A., Cabanes, A., Caleffi, M., Yataco, J.A.D., Gyawali, B., McCormack, V., Anderson, M.M.D., Mehrotra, R., Mohar, A., Murillo, R., Pace, L.E. and Paskett, E.D., 2020. Breast cancer early detection: A phased approach. *Cancer*, **126**: 2379–2393. https://doi.org/10.1002/cncr.32887

Gonzales, E.R., Garcia, S.R., Mahan, C. and Hang, W., 2005. Evaluation of mass spectrometry and radiation detection for the analysis of radionuclides. *J. Radioanal. Nucl. Chem.*, **263**: 457–465. https://doi.org/10.1007/s10967-005-0076-3

Graves, M.J. and Zhu, C., 2015. *Basic principles of magnetic resonance imaging. 3D Imaging Technol. Atheroscler.* pp. 153–169. https://doi.org/10.1007/978-1-4899-7618-5_6

Grigoryants, N.F., Sass, S. and Alexander, J., 2023. Novel technologies in breast imaging: A scoping review. *Cureus*, **15**: e44061. https://doi.org/10.7759/cureus.44061

Grobler, L., Orchard, A., Moodley, S.D., Pypers, I. and Khan, R., 2023. Recurrence rate in patients with stage IV breast cancer: A retrospective cohort study. *Eur. J. Oncol. Pharm.*, **6**: e00045. https://doi.org/10.1097/OP9.0000000000000045

Guenther, S., Muirhead, L.J., Speller, A.V., Golf, O., Strittmatter, N., Ramakrishnan, R., Goldin, R.D., Jones, E., Veselkov, K., Nicholson, J., Darzi, A. and Takats, Z., 2015. Spatially resolved metabolic phenotyping of breast cancer by desorption electrospray ionization mass spectrometry. *Cancer Res.*, **75**: 1828–1837. https://doi.org/10.1158/0008-5472.CAN-14-2258

Hadar, M., Friger, M., Ariad, S., Koretz, M., Delgado, B., Tokar, M., Bayme, M., Agassi, R., Rosenthal, M., Dyomin, V., Belochitski, O., Amir, N., Libson, S., Meirovitz, A., Lazarev, I. and Abu-Gha, S., 2024. Stage I breast cancer in the modern era:

A retrospective cohort study of 328 patients diagnosed from 2002 to 2006 with a 14-year median follow-up. *Oncology*, **102**: 663–675. https://doi.org/10.1159/000536119

Han, J., Li, Y.C.Q. and Yang, Y., 2021. Recent metabolomics analysis in tumor metabolism reprogramming. *Front. Mol. Biosci*., **8**: 763902. https://doi.org/10.3389/fmolb.2021.763902

Hanna, W.M., Parra-Herran, C., Lu, F.-I., Slodkowska, E., Rakovitch, E. and Nofech-Mozes, S., 2019. Ductal carcinoma in situ of the breast: An update for the pathologist in the era of individualized risk assessment and tailored therapies. *Mod. Pathol*., **32**: 896–915. https://doi.org/10.1038/s41379-019-0204-1

Harris, T., Degani, H. and Frydman, L., 2013. Hyperpolarized 13C NMR studies of glucose metabolism in living breast cancer cell cultures. *NMR Biomed*., **26**: 1831–1843. https://doi.org/10.1002/nbm.3024

He, W., Roh, E., Yao, K., Liu, K., Meng, X., Liu, F., Wang, P., Bode, A.M. and Dong, Z., 2017. Targeting ornithine decarboxylase (ODC) inhibits esophageal squamous cell carcinoma progression. *NP J. Precis. Oncol*., **1**: 13. https://doi.org/10.1038/s41698-017-0014-1

Holland, P., Hagopian, W.M., Jahren, A.H. and Rusten, T.E., 2021. Natural abundance isotope ratios to differentiate sources of carbon used during tumor growth *in vivo*. *BMC Biol*., **19**: 1–10. https://doi.org/10.1186/s12915-021-01012-5

Hoshino, Y., Terashima, S., Teranishi, Y., Terashima, M., Kogure, M., Saitoh, T., Osuka, F., Kashimura, S., Saze, Z. and Gotoh, M., 2007. Ornithine decarboxylase activity as a prognostic marker for colorectal cancer. *Fukushima J. med. Sci*., **53**: 1–9. https://doi.org/10.5387/fms.53.1

Hou, X. and Roos, P., 2008. Critical comparison of radiometric and mass spectrometric methods for the determination of radionuclides in environmental, biological and nuclear waste samples. *Anal. Chim. Acta*, **608**: 105–139. https://doi.org/10.1016/j.aca.2007.12.012

Hu, H.Y., Liu, X.X., Jiang, C.Y., Lu, Y., Liu, S.L., Bian, J.F., Wang, X.M., Geng, Z., Zhang, Y. and Zhang, B., 2005. Ornithine decarboxylase gene is overexpressed in colorectal carcinoma. *World J. Gastroenterol*., **11**: 2244. https://doi.org/10.3748/wjg.v11.i15.2244

Ibarra-Cuevas, Z.J., Nunez-Varela, J.I., Nunez-Varela, A., Martinez-Perez, F.E., Nava-Muñoz, S.E., Ramírez-Gámez, C.A. and Perez-Gonzalez, H.G., 2024. Determining relevant risk factors for breast cancer. *Трудыы Института Системного Программирования РАН,* **36**: 225–238. https://doi.org/10.15514/ISPRAS-2024-36(1)-14

Iftikhar, B., Zeeshan, S., Shareef, S., Naqvi, Z.H., Ali, M.A.F., Iftikhar, M., Ramzan, H.S. and Iftikhar, S., 2024. Socio-demographic, physical and clinical risk factors of breast cancer patients in Pakistan. *Hist. Med*., **10**: 177–189.

Illa, T., Martineau, E., Antheaume, I., Lalande, J., Mauve, C., Gilard, F., Barillé-Nion, S., Blackburn, A.C. and Tcherkez, G., 2016. ^{13}C and ^{15}N natural isotope abundance reflects breast cancer cell metabolism. *Sci. Rep*., **6**: 1–9. https://doi.org/10.1038/srep34251

Jacene, H., Dietsche, E. and Specht, J., 2024. The current and future roles of precision oncology in advanced breast cancer. *J. Nucl. Med*., **65**: 349–356. https://doi.org/10.2967/jnumed.122.264882

Jaenisch, S., Squire, M., Butler, R. and Yazbeck, R., 2016. *In vitro* development and validation of a non-invasive 13C-stable isotope assay for ornithine decarboxylase. *J. Breath Res*., **10**: 026009. https://doi.org/10.1088/1752-7155/10/2/026009

Jha, R.K. and Dhale, H.S., 2024. Treatment on Carcinoma of Breast. In: *Case studies on holistic medical interventions*. CRC Press, pp. 665-668. https://doi.org/10.1201/9781003596684-135

Kaufmann, T., Galaznik, A., Coombs, N. and Rocque, G.B., 2023. Abstract P5-07-12: Patient-reported symptom burden in women undergoing treatment for early stage and metastatic breast cancer. *Cancer Res*., **83**: 5–7. https://doi.org/10.1158/1538-7445.SABCS22-P5-07-12

Kazarian, A., Blyuss, O., Metodieva, G., Gentry-Maharaj, A., Ryan, A., Kiseleva, E.M., Prytomanova, O.M., Jacobs, I.J., Widschwendter, M., Menon, U. and Timms, J.F., 2017. Testing breast cancer serum biomarkers for early detection and prognosis in pre-diagnosis samples. *Br. J. Cancer*, **116**: 501–508. https://doi.org/10.1038/bjc.2016.433

Khan, N.U., Khan, B.M., Azam, I. and Hayat, A., 2024. Current situation of breast cancer in Pakistan and the dire need of early diagnosis. *Curr. Trends OMICS*, **4**: 1–17. https://doi.org/10.32350/cto.42.01

Kubicka, A., Matczak, K. and Łabieniec-Watała, M., 2021. More than meets the eye regarding cancer metabolism. *Int. J. mol. Sci*., **22**: 9507. https://doi.org/10.3390/ijms22179507

Kumilau, R., Hayati, F., Liew, J.E., Sharif, S.Z. and Lah, N.A.S.N., 2022. Short term recurrence and survival rate of breast cancer patients post surgical

treatment; North Borneo experience. *Annls Med. Surg*., **81**: 104560. https://doi.org/10.1016/j.amsu.2022.104560

Lane, A.N., Higashi, R.M. and Fan, T.W., 2020. Metabolic reprogramming in tumors: Contributions of the tumor microenvironment. *Genes Dis*., **7**: 185–198. https://doi.org/10.1016/j.gendis.2019.10.007

Liao, Y., 2017. Cancer metabolism as we know it today: A prologue to a special issue of cancer metabolism. *Genes Dis*., **4**: 4. https://doi.org/10.1016/j.gendis.2017.02.001

Loibl, S., André, F., Bachelot, T., Barrios, C.H., Bergh, J., Burstein, H.J. and Harbeck, N., 2024. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annls Oncol*., **35**: 159–182. https://doi.org/10.1016/j.annonc.2023.11.016

Loke, S.Y., 2018. The future of blood-based biomarkers for the early detection of breast cancer. *Eur. J. Cancer*,: 54–68. https://doi.org/10.1016/j.ejca.2017.12.025

Ma, E.H., **92**Verway, M.J., Johnson, R.M., Roy, D.G., Steadman, M., Hayes, S., Williams, K.S., Sheldon, R.D., Samborska, B., Kosinski, P.A., Kim, H., Griss, T., Faubert, B., Condotta, S.A. and Krawczyk, C.M., 2019. Metabolic profiling using stable isotope tracing reveals distinct patterns of glucose utilization by physiologically activated CD8+ T cells. *Immunity*, **51**: 856–870. https://doi.org/10.1016/j.immuni.2019.09.003

Majeed, A.I., Hafeez, A. and Khan, S.A., 2022. Strengthening breast cancer screening mammography services in Pakistan using Islamabad Capital Territory as a pilot public health intervention. *Healthcare*, **10**: 1106. https://doi.org/10.3390/healthcare10061106

Mansour, H., Nejjari, C., Incitti, R., Anouar, N. and Ouhajjou, A., 2024. Is the development of liquid biopsy for the early detection and the monitoring of breast cancers on its way of overtaking mammography? *Front. Med*., **11**: 1415940. https://doi.org/10.3389/fmed.2024.1415940

Maria, M., 2024. Understanding ductal carcinoma in situ (DCIS), Breast Cancer Reasearch Foundation-BCRF 2024: Available at: https://www.bcrf.org/about-breast-cancer/ (accessed 1 Nov 2024).

Marques, M., Gambaro, K., Basik, M., Saad, F., Hassan, S.N., Boudreau, D., Vincent, F., St-Hilaire, E., Mackay, H., Abdelsalam, M., Guillemette, S., Leite, R., Caron, M.-A., Patel, C. and Gerald, 2024. Evaluation of recurrence rate in Canadian patients with stage II/III HR+/HER2- early breast cancer in the real-world setting. *J. clin. Oncol*., **42**: e23303. https://doi.org/10.1200/JCO.2024.42.16_suppl.e23303

Maughan, K.L., Lutterbie, M.A. and Ham, P.S., 2010. Treatment of breast cancer. *Am. Fam. Phys*., **81**: 1339–1346.

McNamara, K.M., Gobert, A.P. and Wilson, K.T., 2021. The role of polyamines in gastric cancer. *Oncogene*, **40**: 4399–4412. https://doi.org/10.1038/s41388-021-01862-x

Mehiret, G., Molla, A. and Tesfaw, A., 2022. Knowledge on risk factors and practice of early detection methods of breast cancer among graduating students of Debre Tabor University, Northcentral Ethiopia. *BMC Women's Hlth*., **22**: 183. https://doi.org/10.1186/s12905-022-01768-0

Mitsuk, A., 2016. Breast cancer information for young women. *Turun Amk: N Opinnäytetyö*, **31**: 1–37.

Mubarik, S., Malik, S.S., Wang, Z., Li, C., Fawad, M. and Yu, C., 2019. Recent insights into breast cancer incidence trends among four Asian countries using age-period-cohort model. *Cancer Manag. Res*., **11**: 8145–8155. https://doi.org/10.2147/CMAR.S208323

Nahar, S., Uddin, J., Haque, S., Mollah, N.U., Alam, S., Bari, M.A., Ahmed, F., Akhtar, K. and Rahman, M., 2023. Ten years of survival among early-stage breast cancer patients: a hospital-based study. *Int. J. Reprod. Contracept. Obstet. Gynecol*., **12**: 544–548. https://doi.org/10.18203/2320-1770.ijrcog20230325

Nicolini, A., Ferrari, P. and Duffy, M.J., 2018. Prognostic and predictive biomarkers in breast cancer: Past, present and future. *Semin. Cancer Biol*., **52**: 56–73. https://doi.org/10.1016/j.semcancer.2017.08.010

Obeagu, E.I. and Obeagu, G.U., 2024. Breast cancer: A review of risk factors and diagnosis. *Medicine*, **103**: e36905. https://doi.org/10.1097/MD.0000000000036905

Ong, S.K., Haruyama, R., Yip, C.H., Ngan, T.T., Li, J., Lai, D., Zhang, Y., Yi, S., Shankar, A., Suzanna, E., Jung, S.-Y., Ho, P.J., Yusuf, A., Nessa, A., Jung, K.-W., Fernando, E. and Baral, S., 2024. Feasibility of monitoring global breast cancer initiative framework key performance indicators in 21 Asian National Cancer Centers Alliance member countries. *E-Clin. Med*., **67**: 1–14. https://doi.org/10.1016/j.eclinm.2023.102365

Pashayan, N., Antoniou, A.C., Ivanus, U., Esserman, L.J., Easton, D.F., French, D., Sroczynski, G., Hall, P., Cuzick, J., Evans, D.G., Simard, J., Garcia-Closas, M., Schmutzler, R., Wegwarth, O. and

Pharoah, P., 2020. Personalized early detection and prevention of breast cancer: Envision consensus statement. *Nat. Rev. Clin. Oncol*., **17**: 687–705. https://doi.org/10.1038/s41571-020-0388-9

Perry, N.J., Sharon, C.E., Tortorello, G.N., Ma, K.L., S. III, R.J., Fayanju, O.M., Tchou, J.C., Miura, J.T. and Karakousis, G.C., 2023. Impact of travel burden on the treatment of stage I and II breast cancer: A national cancer database analysis. *Surgery*, **174**: 794–800. https://doi.org/10.1016/j.surg.2023.07.004

Pico, C.X.C., Pierotti, M.L., Hasler, J.S., Williams, A.D., Handorf, E.A., Aggon, A.A., Pronovost, M., Porpiglia, A.S., Vasigh, M. and Bleicher, R.J., 2023. Disparities in the recommendation, acceptance, and performance of surgery as treatment modality for patients with stage 0–III breast cancer. *J. clin. Oncol*., **41**: 18509. https://doi.org/10.1200/JCO.2023.41.16_suppl.e18509

Poort, V.D., KJ, E., Ravesteyn, N.T.V., Broek, J.J.V.D. and Koning, H.J.D., 2022. The early detection of breast cancer using liquid biopsies: Model estimates of the benefits, harms, and costs. *Cancers*, **14**: 2951. https://doi.org/10.3390/cancers14122951

Quaife, S.L., Forbes, L.J., Ramirez, A.-J., Brain, K.E., Donnelly, C., Simon, A.E. and Wardle, J., 2014. Recognition of cancer warning signs and anticipated delay in help-seeking in a population sample of adults in the UK. *Br. J. Cancer*, **110**: 12–18. https://doi.org/10.1038/bjc.2013.684

Raab, S.S., Grzybicki, D.M., Janosky, J.E., Zarbo, R.J., Meier, F.A., Jensen, C. and Geyer, S.J., 2005. Clinical impact and frequency of anatomic pathology errors in cancer diagnoses. *Cancer-Am. Cancer Soc*., **104**: 2205–2213. https://doi.org/10.1002/cncr.21431

Rai, S., Chaitra, D., Pai, N., Divya, N., Honnalli, N. and Martin, N., 2022. Breast cancer. An overview of the disease. *Curr. Innov. Med. Med. Sci*., **8**: 118–128. https://doi.org/10.9734/bpi/cimms/v8/4241E

Retamales, J., Daneri-Navarro, A., Artagaveytia, N., Alves da Quinta, D., Abdelhay, E., Podhajcer, O.L. and Müller, B., 2024. Implementing standard diagnosis and treatment for locally advanced breast cancer through global research in Latin America: Results from a multicountry pragmatic trial. *JCO Glob. Oncol*., **10**: e2300216. https://doi.org/10.1200/GO.23.00216

Saghir, N.S.E., Khalil, L.E., Dick, J.E., Atwani, R.W., Safi, N., Charafeddine, M., Al-Masri, A., Saghir, B.N.E., Chaccour, M., Tfayli, A., Assi, H., Abbas, J., Ayoub, Z., Sbaity, E. and Moukadem, H.A., 2023. Improved survival of young patients with breast cancer 40 years and younger at diagnosis. *JCO Glob. Oncol*., **9**: e2200354, 1–7.

Samoylenko, O.A., Stakhovsky, E.O., Vitruk, Y.V. and Shlyakhovenko, V.O., 2021. Ornithine decarboxylase activity in prostate cancer. *Exp. Oncol*., **43**: 46–51. https://doi.org/10.32471/exp-oncology.2312-8852.vol-43-no-1.16011

Sandbank, J., Bataillon, G., Nudelman, A., Krasnitsky, I., Mikulinsky, R., Bien, L., Thibault, L., Shach, A.A., Sebag, G., Clark, D.P., Laifenfeld, D., Schnitt, S.J., Linhart, C., Vecsle, M. and Anne, A., 2022. Validation and real-world clinical application of an artificial intelligence algorithm for breast cancer detection in biopsies. *NPJ Breast Cancer*, **8**: 129. https://doi.org/10.1038/s41523-022-00496-w

Schiliro, C. and Firestein, B.L., 2021. Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation. *Cells*, 10: 1056. https://doi.org/10.3390/cells10051056

Schlageter, M., Terracciano, L.M., D'Angelo, S. and Sorrentino, P., 2014. Histopathology of hepatocellular carcinoma. *World J. Gastroenterol*., **20**: 15955. https://doi.org/10.3748/wjg.v20.i43.15955

Schumacher, J.R., Neuman, H.B., Yu, M., Vanness, D.J., Si, Y., Burnside, E.S., Ruddy, K.J., Partridge, A.H., Schrag, D., Edge, S.B., Zhang, Y., Jacobs, E.A., Havlena, J. and Frances, A., 2022. Surveillance imaging vs symptomatic recurrence detection and survival in stage II–III breast cancer (AFT-01). *J. Natl. Cancer Inst*., **114**: 1371–1379. https://doi.org/10.1093/jnci/djac131

Shang, C. and Xu, D., 2022. Epidemiology of breast cancer. *Oncology*, **24**: 649–663. https://doi.org/10.32604/oncologie.2022.027640

Shewbridge, A., Meade, E. and Dowling, M., 2024. Treatment and management of the clinical manifestations of advanced breast cancer. *Semin. Oncol. Nurs*., **40**: 151549. https://doi.org/10.1016/j.soncn.2023.151549

Siegel, R.L., Kratzer, T.B., Giaquinto, A.N., Sung, H. and Jemal, A., 2025. Cancer statistics, 2025. *CA Cancer J. Clin*., **75**: 10. https://doi.org/10.3322/caac.21871

Singh, H.V., Shahid, M., Jain, A. and Singhai, A.K., 2024. Breast cancer: From etiology to therapeutic interventions. *Res. J. Pharmacol. Pharmacodyn*., **16**: 199–207. https://doi.org/10.52711/2321-5836.2024.00034

Soerjomataram, I., Cabasag, C., Bardot, A., Fidler-Benaoudia, M.M., Miranda-Filho, A., Ferlay,

J. and Parkin, D.M., 2023. Cancer survival in Africa, central and south America, and Asia (SURVCAN-3): A population-based benchmarking study in 32 countries. *Lancet Oncol*., **24**: 22–32. https://doi.org/10.1016/S1470-2045(22)00704-5

Sun, K., Lei, L., Zheng, R., Zhang, S., Zeng, H., Wang, S., Li, L., Chen, R., Han, B., Peng, J., Wei, W. and He, J., 2023. Trends in incidence rates, mortality rates, and age-period-cohort effects of female breast cancer-China, 2003–2017. *China CDC Wkly*., **5**: 340. https://doi.org/10.46234/ccdcw2023.065

Tarighati, E., Keivan, H. and Mahani, H., 2023. A review of prognostic and predictive biomarkers in breast cancer. *Clin. exp. Med*., **23**: 1–16. https://doi.org/10.1007/s10238-021-00781-1

Tea, I., De Luca, A., Schiphorst, A.M., Grand, M., Barillé-Nion, S., Mirallié, E. and Tcherkez, G., 2021. Stable isotope abundance and fractionation in human diseases. *Metabolites*, **11**: 370. https://doi.org/10.3390/metabo11060370

Tea, I., Martineau, E., Antheaume, I., Lalande, J., Mauve, C., Gilard, F. and Tcherkez, G., 2016. 13C and 15N natural isotope abundance reflects breast cancer cell metabolism. *Sci. Rep*., **6**: 34251. https://doi.org/10.1038/srep34251

Tea, I., Tcherkez, G., 2017. Natural isotope abundance in metabolites: Techniques and kinetic isotope effect measurement in plant, animal, and human tissues. *Methods Enzymol*., **596**: 113–147. https://doi.org/10.1016/bs.mie.2017.07.020

Torres-Román, J.S., Ybaseta-Medina, J., Loli-Guevara, S., Bazalar-Palacios, J., Valcarce, B., Arce-Huamani, M.A., Alvarez, C.S. and Hurtado-Roca, Y., 2023. Disparities in breast cancer mortality among Latin American women: Trends and predictions for 2030. *BMC Publ. Hlth.*, **23**: 1449. https://doi.org/10.1186/s12889-023-16328-w

Trayes, K.P., Cokenakes, S.E., 2021. Breast cancer treatment. *Am. Fam. Phys*., **104**: 171–178.

Tseng, L.J., Matsuyama, A. and MacDonald-Dickinson, V., 2023. Histology: The gold standard for diagnosis? *Can. Vet. J*., **64**: 389.

Tutzauer, J., Sjöström, M., Holmberg, E., Karlsson, P., Killander, F., Leeb-Lundberg, L.M.F., Malmström, P., Niméus, E., Fernö, M. and Jögi, A., 2022. Breast cancer hypoxia in relation to prognosis and benefit from radiotherapy after breast-conserving surgery in a large, randomised trial with long-term follow-up. *Br. J. Cancer*, **126**: 1145–1156. https://doi.org/10.1038/s41416-021-01630-4

Urooj, T., Wasim, B., Mushtaq, S., Shah, S.N.N., Faisal, L., Ali, M., Rizvi, N.R. and Ali, S.F., 2022. Analysis of risk factors related to expression of basement membrane protein NID1 in females with breast cancer. *Pakistan J. Zool*., **54**: 709–719. https://doi.org/10.17582/journal.pjz/20201022151050

Von Morze, C. and Merritt, M.E., 2019. Cancer in the crosshairs: Targeting cancer metabolism with hyperpolarized carbon-13 MRI technology. *NMR Biomed*., **32**: e3937. https://doi.org/10.1002/nbm.3937

Waks, A.G. and Winer, E.P., 2019. Breast cancer treatment: A review. *J. Am. med. Assoc*., **321**: 288–300. https://doi.org/10.1001/jama.2018.19323

Wang, M., Kundu, U. and Gong, Y., 2020. Pitfalls of FNA diagnosis of thymic tumors. *Cancer Cytopathol*., **128**: 57–67 https://doi.org/10.1002/cncy.22211.

Wang, Y., Chen, H., Li, N., Ren, J., Zhang, K., Dai, M. and He, J., 2019. Ultrasound for breast cancer screening in high-risk women: Results from a population-based cancer screening program in China. *Front. Oncol*., **9**: 286. https://doi.org/10.3389/fonc.2019.00286

White, J.R., Cecchini, R.S., Harris, E.E., Mamounas, E.P., Stover, D.G., Ganz, P.A., Jagsi, R., Anderson, S.J., Bergom, C., Théberge, V., El-Tamer, M., Zellars, R.C. and Shumway, D., 2024. NRG-BR007: A phase III trial evaluating de-escalation of breast radiation (DEBRA) following breast-conserving surgery of stage 1, HR+, HER2-, RS ≤18 breast cancer. *J. clin. Oncol*., **42**: 622. https://doi.org/10.1200/JCO.2024.42.16_suppl.TPS622

Woitek, R. and Brindle, K.M., 2023. Hyperpolarized Carbon-13 MRI in breast cancer. *Diagnostics*, **13**: 2311. https://doi.org/10.3390/diagnostics13132311

Yang, T., Li, W., Huang, T. and Zhou, J., 2023. Genetic testing enhances the precision diagnosis and treatment of breast cancer. *Int. J. mol. Sci*., **24**: 16607. https://doi.org/10.3390/ijms242316607

Yu, S., Cai, X., Wang, X., Lin, X. and Chen, S.C., 2024. Disease burden of breast cancer and risk factors in 44 European countries, 1990–2019: Findings of the Global Burden of Disease Study 2019. *Front. Endocrinol*., **15**: 1405204. https://doi.org/10.3389/fendo.2024.1405204

Zheng, A., Guo, B.L., Zhang, J.G., Jin, F. and Chinese Society of Breast Surgery, 2021. Clinical information and management status of de novo stage IV breast cancer patients: A Chinese multicenter investigation (CSBrS-002). *Chin. med. J*., **134**: 1569–1575. https://doi.org/10.1097/CM9.0000000000000141