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Diagnostic value of fine needle aspiration cytology (FNAC) for benign and malignant breast lesions

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Author Details	Abstract
Keywords: Clinical characteristics, risk factors, cytomorphological pattern, breast cancer, and fine needle aspiration biopsy	Breast cancer (BC) is a prevalent malignancy among adult women worldwide, with the WHO's 2018 Global Burden of Cancer Study (GLOBOCAN) reporting 18.1 million new cases and 9.6 million deaths from cancer globally. BC accounts for 11.6% of overall cancer incidence in women and is the most frequently diagnosed malignancy (24.2%). In approximately 154 out of 185 countries, BC constitutes one in four newly diagnosed cancer cases in women. Post-lumbar and colorectal cancers, BC are the leading cause of cancer-related deaths in women (15%). This review aims to provide comprehensive data on the pathophysiology, risk factors, and types of breast cancers, with an emphasis on the importance of diagnostic methods, particularly fine needle aspiration (FNAC). Breast cancer is a common disorder among adult women worldwide. The WHO's GLOBOCAN study highlights the global burden of cancer, with BC being the second most common cancer type in women, following lung cancer. This review focuses on characterizing BC, its risk factors, and the significance of FNAC in diagnostic procedures. Breast cancer arises due to genetic and environmental factors. Risk factors include age, postmenopausal hormone replacement therapy, never having married, widowhood, family history of BC, late menopause or early menarche (long-term fertility), higher age at first pregnancy, alcoholism, smoking, low fruit and vegetable intake, physical inactivity, and obesity. The triple test, combining imaging diagnostics, clinical examination, and core needle biopsy or fine needle aspiration cytology (FNAC), enhances BC detection accuracy. FNAC is a rapid, cost-effective, and practical diagnostic method that provides detailed information on lesion type, aiding in early detection and treatment planning. Breast cancer remains a significant global health concern. Understanding its pathophysiology, risk factors, and diagnostic methods, particularly FNAC, is crucial for effective management and improved outcomes. Further research into FNAC's efficacy and integration into clinical practice is warranted.
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INTRODUCTION

The mammary ridge, which is located at the anterior surface of the chest wall and stretches from the groin to the axilla, is where the breast, also referred to as the mammary gland, originates on the ventral side of the trunk [1]. The breast, originating from the same embryonic tissue in both males and females, remains

relatively undeveloped in males. In contrast, it undergoes significant changes in size and shape during puberty, menstruation, pregnancy, breastfeeding, and menopause in females, influenced by various hormones, including progesterone and estrogen. [2, 3]. Mammary glands in females produce and secrete milk, which is used to nurture offspring [4].

The connective, adipose, and glandular tissues that make up the majority of the breasts have hormone receptors [5]. Adipose tissue and tubular alveolar glands make up the majority of the 15–25 glandular components known as breast lobules that make up each breast. Cooper ligaments support the lobules, which independently drain into the lactiferous duct. Consequently, each lactiferous duct opens onto the surface of the nipple. The ampulla, formed by several lactiferous ducts, traverses the nipple and opens at its tip. Lactiferous ducts are also referred to as lactiferous sinuses, which are wide dilatations located beneath the nipple surface. These sinuses function as storage for milk during lactation [6].

Breast cancer is the most common cancer type and the leading cause of cancer-related deaths among women, affecting around 2.1 million women annually. According to a WHO estimate from 2018, about 0.627 million women died from breast cancer, accounting for 15% of all female cancer fatalities. The number of cases is higher in industrialized countries and is steadily increasing worldwide. Although malignant lesions may be the main problem for patients with breast cancer, benign lesions are also among the most common and contribute significantly to morbidity in women with breast cancer. The triple assessment test, comprising clinical examination (palpation), imaging (ultrasonography or mammography), and cytological evaluation (fine-needle aspiration cytology [FNAC] or core biopsy), has gained prominence in response to the rising incidence of breast cancer. This approach facilitates the rapid and straightforward detection of cancer, enabling effective management through surgical intervention and chemotherapy. [7, 8].

Therefore, early detection of breast cancer is crucial for bettering survival and outcomes, but most women receive late-stage diagnoses because of a lack of knowledge and resources, which makes management extremely challenging. According to reports, breast cancer survival rates are often lower in developing nations, especially because of a lack of resources for early illness diagnosis, followed by a lack of knowledge and access to appropriate and efficient treatment [9].

The introduction of the triple test—comprising imaging, clinical examination, and fine-needle aspiration cytology (FNAC) or core needle biopsy—marked a significant advance in diagnostic accuracy for breast lesions.

[10]. FNAC is widely used to diagnose breast tumours since it is easy to administer, affordable, safe, and very sensitive. [11]. The Fine Needle Aspiration Cytology (FNAC) method was first published and utilized by Martin and Ellis (1930). Today, it is a highly valued and well-accepted approach used to diagnose and treat patients with breast lesions. Although some discrepancies have been noted, the great precision and accuracy of the system helped physicians create timely and accurate plans for the right medical or surgical therapy [12, 13]. The primary objectives of this review article are to provide an overview of the historical

context, pathophysiology, clinical classification, and diagnostic techniques associated with breast cancer.

Breast diseases

Breast disorders affect women of all ages and encompass both neoplastic and non-neoplastic lesions. Globally, there are variations in the prevalence of benign and malignant breast lesions. Non-cancerous lesions include fibrocystic changes, benign cysts, pyogenic abscess, subareolar abscess, granulomatous mastitis, acute and chronic mastitis, mammary duct ectasia, galactocele, and ductal epithelial hyperplasia. In contrast, fibroadenoma, lipoma, adenoma, and carcinoma are classified as breast neoplastic lesions. [14].

Benign breast diseases

Aberrations of Normal Development and Involution (ANDI) are the new term for benign breast disease (BBD) [15]. Developmental abrasions, inflammatory lesions, stromal and epithelial proliferation, and various neoplasms are only a few of the many lesions that make up benign illnesses. The majority of benign lesions are caused by fibroadenoma, breast abscesses, and fibrocystic alterations [16]. Although it is difficult to determine the precise ratio, BBD is more common than malignant ones in females. The occurrence of benign lesions starts in the second decade of life and peaks in the fourth or fifth decades, in contrast to malignant lesions, which typically appear after menopause. Furthermore, because of the public's awareness of breast cancer, benign breast tumours are thought to be very important [17].

Fibroadenoma

Fibroadenomas are the most prevalent benign breast lesions in teenagers. They are made up of stromal and epithelial proliferation. Malignant transformation of fibroadenoma can also happen in rare circumstances (0.002% to 0.125%) [18]. They manifest as a painless, solitary, firm, slowly developing, and movable lump in the breast in females of childbearing age. The age range that is typically impacted is 21–30 years old. Fibroadenomas are sometimes referred to as "breast mice" due to their distinct, firm, spherical or ovoid, smooth, and highly mobile appearance within breast tissue. The majority of fibroadenomas regresses after menopause and exhibit hormonal dependence. [19].

Additionally, fibroadenoma incidence is correlated with body mass index (BMI), with a higher prevalence observed in the 25–29.9 kg/m^2 BMI category [20]. According to Poh et al. (2010), fibroadenomas have been linked to various disorders, including Beckwith-Wiedemann syndrome, Maffucci syndrome, and Cowden syndrome [21].

Mastitis

Mastitis is an inflammatory disease that affects breast tissue and presents in both acute and chronic forms. The etiology of mastitis can be infectious, such as breast abscess, acute mastitis, and tuberculosis; localized, including duct ectasia and abscess in the subareolar area; traumatic, such as fat necrosis; idiopathic, like granulomatous mastitis; or hypersensitivity-related inflammation [22].

According to the World Health Organization (WHO), mastitis is an inflammatory illness of the breast that may occur with or without an infection. The disease is most commonly observed in the first three months of nursing, with a prevalence ranging from 75 to 95%. Its incidence varies from 6.6% to 33%, with the highest frequency reported during the lactation phase [23], particularly within the first four weeks. Patients with a history of mastitis in a prior kid are four times more likely to develop mastitis, and the risk reduces as the newborn becomes older.
Antimicrobial resistance among mastitis-causing microbes, including *Staphylococcus aureus*, *Streptococcal* species, and coagulase-negative *Staphylococci* (CNS), has increased as a result of the association between antibiotic use during nursing and mastitis (Marin et al., 2017).
Bacteria enter breast tissue through nipple epithelial cracking brought on by many conditions, including physical trauma to the breast, engorgement, clogged ducts, milk stasis, and inadequate child bonding [24]. These disorders are uncommon in non-lactating females and typically afflict girls between the ages of 18 and 50.

Tuberculosis Mastitis
Tuberculosis (TB) is one of the most prevalent infections worldwide, with Pakistan ranking fifth among nations with the highest TB burden. Approximately 21% of TB cases are extrapulmonary, affecting the lymphatic, pleural, bone or joints, meninges, peritoneum, and genitourinary systems. Although TBM is rare and primarily impacts the skin or breast, documented cases exist in regions with high prevalence of pulmonary and extrapulmonary TB. Sir Astley Cooper first described the condition in 1829 as "asscrofulous swelling of the bosom." The incidence of TBM ranges from 0.025 to 0.3% of all breast illnesses in industrialized countries to 3-5% in endemic areas. Females of childbearing age, particularly during lactation, are typically affected. Risk factors for TBM include multiparty, lactation, a history of suppurative mastitis, and acquired immune-deficiency syndrome (AIDS). TBM may present as a lump, cold abscess, discharging sinus, or non-healing ulcers mimicking cancer, with a characteristic bluish, attenuated appearance of the surrounding skin. [25].

Galactocele
A galactocele is a benign breast lesion characterized by cystic dilatation of one or more ducts due to the accumulation of milk and its by-products. It occurs predominantly in women of reproductive age, particularly during lactation or the late third trimester of pregnancy. In most cases, the cyst resolves spontaneously after delivery or cessation of breastfeeding; recurrence is uncommon and typically results from residual milk within the ductal system. [26]. although galactocele may resemble fibroadenoma or breast carcinoma, it is never associated with breast cancer and is always benign. The formation of galactocele can be attributed to prolactin stimulation, ductal blockage, and the presence of breast secretory epithelium. Other less-mentioned causes include breast surgery, oral contraceptives, and transplacental prolactin transit. Typically, galactocele manifests as hard, non-tender lumps during or shortly after lactation [27].

According to Farrokh et al. (20), FNAC typically confirms galactocele, and it can be used for both diagnostic and therapeutic purposes in these patients [28].

Lipoma

Made up of mature fat cells, lipomas are benign neoplasms that originate from mesenchymal tissues. These tumours, which are primarily encapsulated, can develop anywhere in the body, but they typically occur in areas with adipose tissue, particularly the breast. However, according to several publications, breast lipomais is quite uncommon. By analysing 1865 cases of breast biopsies, Olu-Eddo and Ugiagbe (2011) at the University of Benin Teaching Hospital reported 0.8% of cases of breast lipoma [29], while Njeze (2014) reported only one (0.6%) out of 165 patients [30]. Similarly, in an audit of 149 breast biopsies, Irabor and Okolo (2008) [31] documented 1 case of breast lipoma. In a histological analysis of 603 cases of benign breast lesions in Saudi Arabia, Albasri (2014) found only 3 occurrences of breast lipoma [32]. In India, one instance of breast lipoma was recorded out of 85 cases of benign breast tumours in a prospective study. The cause of the uncommon occurrence of lipoma in fat-rich tissue, such as the breast, was unknown. The majority of them is small and grows slowly [33]. Diagnostic ambiguity is caused by these lesions [34]. But over time, they may get larger and cause an enormous breast lipoma [35].

Phyllodes Tumor

Previously known as cystosarcomaphyllodes, these tumors represent a rare category of breast neoplasms, accounting for less than 1% of cases [36]. They are infrequently observed in adolescents or the elderly, with the highest incidence occurring in women aged 35 to 55[37].

Iginating from fibroepithelial tissue, these tumors have the potential to metastasize to other body tissues and may recur [38]. Histologically, phyllodes tumors can be categorized as benign, borderline, or malignant. While both malignant and borderline tumors have a similar likelihood of metastasis, benign phyllodes tumors may recur [39].

Breast Cancer

While there are numerous benign tumors, breast cancer remains one of the most prevalent diseases among women globally and is a source of significant concern [40]. With **2.**1 million cases annually and the highest number of cancer-related deaths among women, breast cancer is the most common cancer affecting women worldwide. In 2018, approximately 627,000 women succumbed to breast cancer, representing 15% of all cancer deaths in females. Although incidence rates are higher in more developed regions, breast cancer cases are rising in nearly every part of the globe. Geographical location significantly influences the incidence rate of breast cancer. [41]. China reports the highest number of breast cancer cases in Asia (187,213), followed by India (144,937), Japan (55,710), Indonesia (48,998), and Pakistan (34,038). Together, these five countries account for 73% of the continent's total breast cancer burden [43]. Breast cancer represents approximately 55.6% of all cancer cases and 62.1% of cancer-related deaths in Asia [44]. Globally, it remains a leading cause of morbidity and mortality

[45], ranking fifth in overall cancer mortality, with an estimated 522,000 deaths annually [42].
639,824 BC cases were reported in these countries in 2012. China tops the pack with 187,213 cases, followed by Japan (55,710), Indonesia (48,998), India (144,937 cases), and Pakistan (34,038 cases). Seventy-three percent (470,896 59) of Asia's breast cancer cases are in these five countries [43].
Breast cancer accounts for about 62.1% of deaths in underdeveloped nations and 55.6% of all cancer cases [44]. Breast cancer is one of the leading causes of disease and mortality. [45]. with 522,000 fatalities, breast cancer ranks fifth in terms of overall cancer mortality. Breast cancer ranks second in industrialized countries after lung cancer (15.4% of all deaths, or 198,000 deaths), while it is the leading cause of cancer mortality in developing countries (14.3% of all deaths, or 324,000 deaths) [46]. The highest standardized breast cancer death rate in Asia is found in Pakistan (25.2), followed by Syria (21.5), Lebanon (24) Jordan (21.8), Armenia (24.2), and Lebanon (24) as well as Pakistan. [41].

Historical Overview of Breast Cancer

The incidence and survival rates of breast cancer are rising daily. This disease has a history spanning over a thousand years. Cases of breast cancer were documented in ancient Egypt, where cautery was the standard treatment for affected areas. Surgery was occasionally employed as a drastic measure due to the limited availability of antiseptic and anesthetic agents.
The earliest known description of cancer, although not using the term itself, dates back to around 1600 B.C. in Egypt. The Edwin Smith Papyrus details eight cases of breast tumors or ulcers that were cauterized with a device known as "the fire drill." The text states, "There is no treatment" for the condition.
The term "cancer" was introduced by the Greek physician Hippocrates, often referred to as the "Father of Medicine" (460–370 B.C.). He coined the terms carcinoma and carcinos to describe tumors that cause ulcers and those that do not.
. These Greek words, which mean crab, may have been used to describe the disease since cancer has projections that resemble fingers.
Claudius Galen (130–200 AD) attributed the development of breast cancer to melancholia, recommending dietary interventions and occasional topical applications. In the 16th century, Andreas Vesalius advocated ligatures and mastectomy, rather than cautery, to control bleeding. By the 18th century, Henri Le Dran (1685–1770) recognized the association between breast cancer, poor prognosis, and regional lymph node (axillary) involvement. John Hunter (1728–1793) proposed that selected tumours could be surgically managed, advising against removal when the lesion was mobile and not adherent to underlying tissues.
In the mid-19th century, surgical records revealed that lymph node involvement correlated with high recurrence rates within eight years of mastectomy. Nevertheless, standard practice remained radical excision of the breast and associated glands to limit tumor progression. The discovery of X-rays by Wilhelm Röntgen in 1895 revolutionized cancer diagnostics. In 1913, Berlin pathologist Albert Salomon advanced breast cancer pathology by producing 3,000

radiographic images of mastectomy specimens, enabling more precise tumor mapping.

. Early mammographic studies revealed micro calcifications—appearing as radiopaque foci—within breast carcinomas. Between the 1930s and 1950s, significant progress was made in both detection and treatment. Stafford Warren (Rochester Memorial Hospital, New York) developed a stereoscopic imaging technique to improve tumor localization, while clinical staging systems for breast cancer were introduced to guide management. In 1949, Raul Leborgne (Uruguay) demonstrated that breast compression improved visualization of calcifications, and public health campaigns in the 1940s–1950s began promoting breast self-examination.

Technological advances continued through the 1960s. In 1960, Robert Egan (Houston, USA) developed a high-resolution film mammography technique, enabling reproducible images with enhanced detail. A 1963 Health Insurance Plan of New York study reported that mammography reduced five-year breast cancer mortality by 30%. Subsequent innovations—including digital imaging, computer-aided detection, and lower-dose radiation protocols—have further refined mammographic accuracy and safety

(Diamandopoulos, 1996[47, 48]).

Breast Cancer Risk Factors

Breast cancer risk can be affected by age and the use of hormone replacement therapy (HRT) after menopause. Key risk factors include having a later age at first pregnancy, lack of physical activity, being nulliparous, never having been married, being widowed, having a family history of breast cancer, consuming a diet low in fruits and vegetables, alcohol consumption, smoking, experiencing late menopause or early menarche (prolonged fertility), and being obese after menopause.[49–52]. A greater Socio-Economic Status (SES) has been associated with an increased risk of breast cancer, either at the individual or household level. Obesity and weight gain are additional high-risk factors that may impact the incidence of breast cancer. Numerous studies found a connection between breast cancer and obesity. But the results are not always the same. While some experts believe obesity may reduce the risk of breast cancer before menopause but increase it after, others argue that a BMI of more than 30 may increase the risk of breast cancer both before and after menopause. Women who menstruate late or reach menopause early are exposed to low levels of the oestrogen hormone for fewer years than those who have an early menarche or a late menopause. A relationship between the age at first full-term birth and breast cancer. Women who remain childless, have poor parity, or are older when they become pregnant for the first time are comparatively more likely to acquire breast cancer than women who have several pregnancies or have their first child relatively early in life. They also estimated that for every year of delay, the risk of breast cancer rises by 3% [53]. Breastfeeding is considered a modifiable risk factor since moms who do not nurse their infants are more vulnerable than those who do. There is a direct correlation between feeding duration and protection. However, its protective rule is unclear due to the lack of data.

Usually, genetic factors—specifically, mutations in the BRCA1 and BRCA2 genes—have an impact on the development of BC. BRCA1 mutation carriers have a 60–70%

lifetime probability of developing BC, whereas BRCA2 carriers have 45–55% likelihood. Another mutation in the TP53 gene causes aggressive breast cancer, which has a median age of 25 and starts early in the 20s or 30s. Mutations in the phosphatase and tensin homolog (PTEN) gene result in a variety of diseases. Cowden Syndrome, which has a 50–85% lifetime risk of breast cancer, is one of these. The STK11 gene mutation causes Peutz-jeghers syndrome. In their lives, up to 50% of people will get breast cancer. [54].
Germline mutations in the CDH-1 gene are linked to a 50% lifetime risk of breast cancer. Despite the low to moderate penetrance of mutations in the genes CHEK2, ATM, PALB2, and BRIP, environmental factors or lifestyle decisions may increase the risk of breast cancer. Although their incidence and penetration are still unknown, mutations in the RAD51 and related genes RAD51C and RAD51D, BARD1, XRCC2, and MRN complex (MRE11, RAD50, and NBS1) increase the risk of breast cancer. Obesity is associated with breast cancer because women produce more extra-glandular oestrogen and its metabolic products, and because hyper-insulinemia is the etiology of breast cancer [55, 56]. There is a high correlation between physical activity and breast cancer. It is considered good to engage in at least 150 minutes of physical activity every week, which lowers risk by 15% to 20% [57].

Clinical Features

On imaging studies, breast lesions typically manifested as palpable lumps, pain, nipple alterations, and discharge or abnormalities [58]. A breast lump is the most prevalent of these clinical manifestations [59].

Pathophysiology of Breast Lump

Abscess development may result from duct plugging and epidermalization of the lactiferous duct lining. Because the surgery did not address the core mechanism via which these abscesses are hypothesized to originate, patients with breast abscesses treated by incision and drainage had a significant recurrence incidence of 39–50%. It commonly occurs after the second week of delivery and may be brought on by milk stasis. There is typically a history of skin abrasion or nipple cracking. While *Streptococci* and *Staphylococcus epidermidis* are also isolated on occasion, Staphylococcus aureus is typically the causative agent. Peripheral and central (peri-areolar) breast abscesses are the hallmarks of non-lactating mastitis.
Less prevalent than peri-areolar abscesses, peripheral abscesses are often linked to an underlying condition, such as rheumatoid arthritis, diabetes mellitus, granulomatous lobular mastitis, trauma, or steroid treatment. Non-dilated, sub-areolar breast ducts are inflamed in peri-areolar lesions, often referred to as peri-ductal mastitis [60].
Cellulitis and abscesses are the most prevalent conditions affecting the skin of the lower breast, and they are more likely to recur in women who are overweight, have large breasts, and practice poor personal hygiene.
Any tissue that makes up the breast, including connective tissue, lobules, ducts, and skin, may be affected by breast lumps. Infiltrating ductal carcinoma (IDC) is the most common type of malignant breast tumor, while inflammatory carcinoma is the most aggressive and has the worst prognosis. Fibrocystic disease was the

most common breast lesion in women during routine autopsies, accounting for 60% to 90% of all cases [61].

Investigation

Since breast cancer is becoming more widely known, patients typically find breast abnormalities on their own or during a professional examination. However, more research is required to distinguish between benign and malignant tumours [62]. According to studies, the majority of cases are benign, although a sizable portion of palpable lumps are caused by cancer [59]. Because of the potential for cancer, it generates anxiety [63]. Therefore, the cornerstone of breast cancer treatment is early detection and the ability to distinguish between benign and malignant tumours [64].

Triple evaluation is being used worldwide to investigate breast masses. Clinical examinations, imaging tests (such as mammograms and breast ultrasounds), and most importantly, fine needle aspiration cytology (FNAC) are all included.

Historical background of FNAC

In 1847, Kun established the use of fine-needle aspiration as a novel diagnostic method for tumor diagnosis. Following this, a number of reports about this technique were released around the close of the 1800s. Leydon used the needle aspiration technique in 1883 to distinguish pneumonic microorganisms and, three years later, Menetrier used the same technique to identify lung cancer. Trypanosomiasis was discovered in the lymph node (LN) aspirates of individuals with sleeping sickness by Grieg and Grey in 1904. A small group of pathologists participated in this groundbreaking work, which was widely publicized by doctors who used the techniques to aid in quick diagnosis. Aspiration cytopathology received its first genuine ideological and practical boost during the interwar years. Dudgeon and Patrick from the United Kingdom (UK) proposed needle aspiration as a quick method of microscopic tumor diagnostics in 1927. Hayes E. Martin, a head and neck surgeon, and Edward B. Ellis, the chief histotechnologist at Memorial Sloan-Kettering Cancer Centre (previously New York's Memorial Hospital for Cancer and Allied Disease), embraced this concept enthusiastically in the early 1930s.

He underlined several factors that must be taken into account to achieve the best results: highlighting the aspiration technique and sample preparation; stressing the significance of the correlation between the interpretation of aspirated material and the patient's history; encouraging pathologists to compare the smear result with conventional histology; requiring that the full cytological features of an individual as well as the smear pattern be taken into consideration for accurate interpretation; and documenting the technique's utility for tumor diagnosis while taking into account its limitations.

These factors remain crucial even after more than 60 years to ensure the proper and efficient use of needle aspiration cytology.

Following a collaborative partnership spanning three decades between Martin and Stewart, fine needle aspiration cytology (FNAC) experienced significant advancement and adoption at Memorial Hospital. Concurrently, the United States Cancer Institute demonstrated limited interest in FNAC, which was initially

proposed as a safer alternative to open biopsies. At the time, concerns were raised by pathology director Ewing and other practitioners regarding potential increases in metastasis risk. Upon alleviation of these medical apprehensions in the 1960s, FNAC's reputation diminished to the extent that its utilization at Memorial Hospital was substantially reduced. However, subsequent research has demonstrated that FNAC is a minimally invasive diagnostic method characterized by high sensitivity (65-99%) and specificity (96-100%) in detecting palpable breast tumors. Additionally, FNAC is recognized for its ease of use, affordability, reliability, patient-friendly nature, and rapid result generation [65, 66].

Table 1 presents the diagnostic accuracy of fine-needle aspiration cytology (FNAC) for palpable breast lesions, as reported in multiple studies. The wide variation in specificity, sensitivity, negative predictive value (NPV), and positive predictive value (PPV) can be attributed to several factors:

1. Differences in statistical methodologies used to evaluate diagnostic accuracy.
2. Variations in study design, including the level of training and experience of the operators, as well as the type of institution in which the studies were conducted.
3. Differences in sample size, staining techniques, and access to image-guidance technologies.

Previous reports indicate that less experienced aspirators may have higher technical failure rates in achieving a positive carcinoma diagnosis, whereas more experienced pathologists demonstrate greater accuracy. Diagnostic performance is strongly influenced by specimen adequacy, which in turn affects reproducibility. Although FNAC is a relatively simple procedure, optimal sampling requires considerable technical skill to obtain sufficient material. Inadequate sampling remains a notable limitation of FNAC in some settings
[67].

Reporting categories

In June 2016, the Royal College of Pathologists released a comprehensive guideline for non-operative diagnostic techniques and reporting in breast cancer screening. The primary objective is to achieve a definitive benign or malignant diagnosis for palpable breast abnormalities. The diagnostic reports are categorized into five distinct classifications:

1. **Inadequate**: Indicates insufficient diagnostic information for a definitive diagnosis.
2. **Benign**: Confirms the presence of a benign lesion.
3. **Atypical**: Suggests a possible malignant lesion requiring further investigation.
4. **Probably Benign**: Indicates a low likelihood of malignancy, with a probable benign etiology.
5. **Suspected of Malignancy**: Points to a high likelihood of malignancy, necessitating further evaluation.
6. **Malignant**: Confirms the presence of a malignant lesion.

This classification system ensures standardized reporting and facilitates informed decision-making in the management of palpable breast abnormalities.

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Inadequate C1

The adequacy of fine needle aspiration specimens represents a multifactorial phenomenon influenced by operator expertise, technical proficiency, and lesion-specific characteristics. Pathologists conventionally define sample sufficiency by the presence of adequate epithelial cells that accurately represent the target lesion.

Sample inadequacy arises through distinct mechanistic pathways. Technical factors encompass aspiration technique deficiencies, processing errors, and staining artifacts. Biological variables include hypocellularity and hemorrhagic contamination that compromises cellular visualization.

Certain lesion types—including abscesses, cysts, fat necrosis, intramammary lymph nodes, and nipple discharge specimens—inherently lack epithelial components and should not be classified as inadequate based solely on cellular paucity. In specific diagnostic contexts, such as lipomatous lesions, adipose tissue fragments provide crucial diagnostic information and warrant detailed morphological description.

Preparation-induced artifacts significantly impact specimen interpretation. Mechanical crushing from excessive smearing pressure distorts cellular architecture. Fixation delays or improper air-drying of alcohol-fixed preparations introduce morphological distortions. Excessive specimen thickness, whether from high cellularity or proteinaceous background material, obscures diagnostic features and impedes accurate assessment.

Understanding the underlying mechanisms of specimen inadequacy facilitates appropriate clinical correlation, guides re-sampling decisions, and optimizes diagnostic accuracy in cytopathological practice.

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Benign C2

Adequate samples lacking malignant features or abnormal lesions demonstrate specific cytomorphological patterns. These specimens exhibit moderate to low cellularity, predominantly comprising ductal epithelial cells arranged in cohesive monolayers with characteristic benign features. The cellular architecture displays honeycomb configurations with well-defined cytoplasmic borders, clean background matrices, and uniform bipolar nuclei. Cystic lesions typically contain foamy macrophages and normal apocrine cells in variable proportions. Stromal components, including adipose and fibrofatty tissue fragments, are frequently observed.

Specific diagnostic entities may be definitively identified when sufficient pathognomonic features are present. Fibroadenomas, breast abscesses, lymphoid tissue, and granulomatous mastitis demonstrate characteristic cytomorphological signatures that enable confident positive diagnoses in appropriate clinical contexts.

Understanding the underlying mechanisms of specimen inadequacy facilitates appropriate clinical correlation, guides re-sampling decisions, and optimizes diagnostic accuracy in cytopathological practice.

[68].

Atypia probably benign C3

This aspirate possesses every characteristic of a benign aspirate. They do, however, possess additional characteristics that are absent from benign lesions. One or more of the following could be present: i. A little or moderate loss of cohesion ii. Pleomorphism of the nuclear iii. Modifications to the nucleus and cytoplasm that can be brought on by hormonal (HRT, pregnancy, pills) or therapeutic factors affect IV. The aforementioned characteristics are accompanied by increased cellularity.

Furthermore, certain lesions that exhibit a higher risk of cancer should be classified as C3. These include papillary lesions and probable phyllodes tumours. Even though there might not be any cytological atypia, these lesions should be reported for C3 [69] due to the possibility of malignancy.

Suspicious of malignancy C4

Category C4 comprises aspirates with atypical features that present diagnostic challenges. Three primary causes may contribute to this classification:

1. **Small, Poorly Prepared, or Inadequate Samples**: Despite limited or substandard samples, some cells may exhibit malignant characteristics.
2. **Malignant Traits Without Visible Cells**: The presence of malignant traits in the sample may suggest a malignant etiology, even in the absence of visible malignant cells. This is considered more severe than Category C3.
3. **Benign Pattern with Isolated Malignant Cells**: The overall sample may exhibit a benign pattern, such as continuous cell sheets or a high nuclear density, but with isolated cells displaying clear signs of malignancy.

These categories (C3 and C4) represent the diagnostic system's "grey area," as they can produce misleading positive or negative findings. Consequently, they pose challenges in achieving accurate and reliable diagnoses.
[68].

Malignant C5

Determinants of Cytological Sample Adequacy in Fine Needle Aspiration

The adequacy of fine needle aspiration specimens represents a multifactorial phenomenon influenced by operator expertise, technical proficiency, and lesion-specific characteristics. Pathologists conventionally define sample sufficiency by the presence of adequate epithelial cells that accurately represent the target lesion.

Sample inadequacy arises through distinct mechanistic pathways. Technical factors encompass aspiration technique deficiencies, processing errors, and staining artifacts. Biological variables include hypocellularity and hemorrhagic contamination that compromises cellular visualization.

Certain lesion types—including abscesses, cysts, fat necrosis, intramammary lymph nodes, and nipple discharge specimens—inherently lack epithelial components and should not be classified as inadequate based solely on cellular paucity. In specific diagnostic contexts, such as lipomatous lesions, adipose tissue fragments provide crucial diagnostic information and warrant detailed morphological description.

Preparation-induced artifacts significantly impact specimen interpretation. Mechanical crushing from excessive smearing pressure distorts cellular architecture. Fixation delays or improper air-drying of alcohol-fixed preparations introduce morphological distortions. Excessive specimen thickness, whether from high cellularity or proteinaceous background material, obscures diagnostic features and impedes accurate assessment.

Morphological Characteristics of Adequate Benign Specimens

Adequate samples lacking malignant features or abnormal lesions demonstrate specific cytomorphological patterns. These specimens exhibit moderate to low cellularity, predominantly comprising ductal epithelial cells arranged in cohesive monolayers with characteristic benign features. The cellular architecture displays honeycomb configurations with well-defined cytoplasmic borders, clean background matrices, and uniform bipolar nuclei. Cystic lesions typically contain foamy macrophages and normal apocrine cells in variable proportions. Stromal components, including adipose and fibrofatty tissue fragments, are frequently observed.

Specific diagnostic entities may be definitively identified when sufficient pathognomonic features are present. Fibroadenomas, breast abscesses, lymphoid tissue, and granulomatous mastitis demonstrate characteristic cytomorphological signatures that enable confident positive diagnoses in appropriate clinical contexts.

Malignant Category (C5): Cytological Features of Breast Carcinoma

The C5 category encompasses specimens with adequate cellularity exhibiting definitive cytomorphological features of malignancy. These samples demonstrate diagnostic characteristics consistent with ductal carcinoma in situ, invasive breast carcinoma, and other primary or metastatic neoplasms. The cytological architecture displays loss of cohesion, nuclear pleomorphism, increased nuclear-to-cytoplasmic ratios, and aberrant chromatin distribution patterns that collectively establish malignant transformation.

Understanding the underlying mechanisms of specimen inadequacy facilitates appropriate clinical correlation, guides re-sampling decisions, and optimizes diagnostic accuracy in cytopathological practice.

[70].

General diagnostic patterns

Differentiating benign from malignant processes is a fundamental aspect of cytological diagnosis. Benign and malignant breast lesions exhibit distinct histological and morphological patterns (Table 2). A thorough understanding of normal breast histology is therefore essential before performing fine-needle aspiration cytology (FNAC), as this knowledge improves recognition of rare lesions and reduces both false-positive and false-negative interpretations.

The present study aimed to facilitate early breast cancer detection and to characterize the morphological spectrum of breast tumours on FNAC (Table 2). Eighty-four patients aged 16–60 years presenting with palpable breast lumps were included. Following detailed history-taking and clinical examination, all patients underwent FNAC or biopsy, with ultrasonography and mammography performed when indicated. Data were recorded in a structured proforma.

All patients presented with breast lumps as the primary complaint. Of these, 58 cases (69.0%) were benign and 26 cases (30.9%) malignant. The most common benign lesion was fibroadenoma (32 cases, 38.1%), followed by fibrocystic changes (15 cases, 17.9%). Benign phyllodes tumours were rare (2 cases, 2.4%), and breast abscesses were observed in 9 patients (10.7%). Among malignant lesions, invasive ductal carcinoma (IDC) predominated (22 cases, 26.2%), followed by invasive lobular carcinoma (3 cases, 3.6%) and medullary carcinoma (1 case, 1.1%).
[71].

A comprehensive analysis involving 280 cases of palpable breast tumors was conducted by Ahmad et al. (2016). The study commenced with a thorough physical examination, followed by aspiration procedures. The resulting cytological and histological diagnoses were subsequently compared. Among the 280 breast lump aspirates, 180 cases (64.29%) were classified as benign, 32 cases (11.43%) were identified as inflammatory lesions, and 8 cases (2.86%) were deemed insufficient for evaluation. Additionally, 6 cases (2.14%) were categorized as atypical or probably benign, 8 cases (2.86%) were suggestive of malignancy, and 46 cases (16.43%) were confirmed as malignant. Histopathological examination was performed on 70 of the 280 instances. [18].

A total of 171 patients were included in the study to determine the type of lesion, age at presentation, breast side involvement, and the sensitivity and specificity of fine needle aspiration (FNAC). The study revealed that 19 (11.11%) lesions were infectious/inflammatory, 76 (44.44%) were benign, 4 (2.33%) were suspected for malignancy, 62 (36.25%) were malignant, and 9 (5.26%) were unsatisfactory cases. The left breast was more frequently affected, with a mean age of presentation at 45.5 years. Histopathological correlation was achievable in 111 cases, demonstrating the high sensitivity and specificity of FNAC.

Singh et al. (2015) evaluated cytomorphological patterns across 100 breast lesions using fine needle aspiration cytology with subsequent histological correlation where feasible. Cytological diagnoses demonstrated the following distribution: unsatisfactory (5%), inflammatory (11%), benign (10%), fibroepithelial lesions (30%), atypical probably benign (2%), suspicious probably malignant (3%), and malignant (39%). Among 30 cases with histopathological correlation, fibroadenoma represented the predominant benign entity (65% of benign lesions), while invasive ductal carcinoma constituted the majority of malignant cases (84.61%).

A comprehensive prevalence analysis of 127 female patients (age >14 years) revealed a mean presentation age of 33.41±15.86 years. Anatomical distribution favored the left breast (57.5%) and predominantly affected the upper outer quadrant (52.8%), followed by lower outer (18.9%), upper inner (13.4%), central (10.2%), and lower inner quadrants (4.7%). Diagnostic frequencies demonstrated fibroadenoma as the most common lesion (46.5%) followed by breast carcinoma (34.6%), abscesses (10.2%), fibrocystic disease (5.5%), and phyllodes tumors (3.1%).

Understanding the underlying mechanisms of specimen inadequacy facilitates appropriate clinical correlation, guides re-sampling decisions, and optimizes diagnostic accuracy in cytopathological practice.
[59].

Rahman and Islam (2013) characterized 1,778 female patients (age range: 14–86 years) presenting with palpable breast masses and axillary lymphadenopathy. The

peak incidence occurred in the 21–30 year age group (38.13%). Lesion distribution comprised fibroadenoma (28.57%), carcinoma (14.17%), fibrocystic changes (11.81%), abscess (7.93%), granulomatous lesions (6.52%), and chronic mastitis (6.3%). Age-stratified analysis revealed fibroadenoma predominance in the 21–30 year cohort (42.91%), while carcinoma peaked in the 31–40 year group (32.54%). Mean lesion diameter measured 4.3±2.0 cm with uniform anatomical site distribution. Among 116 carcinoma patients with palpable lymphadenopathy, 26 cases (10.32%) demonstrated metastatic involvement [72].

A comparative diagnostic accuracy study by Rahman et al. (2011) assessed 222 patients using both fine needle aspiration cytology and mammography. Mammographic analysis (n=112) yielded 88.39% accuracy, 82.76% sensitivity, 90.36% specificity, 75% positive predictive value, and 93.75% negative predictive value, with eight false positives and five false negatives. Conversely, FNAC demonstrated superior performance with 99.09% accuracy, 97.22% sensitivity, 97.22% specificity, 97.22% positive predictive value, and 99.46% negative predictive value, exhibiting only one false positive and one false negative result.

Understanding the underlying mechanisms of specimen inadequacy facilitates appropriate clinical correlation, guides re-sampling decisions, and optimizes diagnostic accuracy in cytopathological practice.

[73].

Study to compare the histological reports of breast lesions with those that are cytologically malignant. 524 patients who presented with a breast lump underwent FNAC. A five-tier cytological classification system encompassed malignant, benign, atypical cells, suspected malignancy, and inadequate categories. Among 524 cases analyzed, diagnostic distribution revealed benign lesions (n=431, 82.3%), malignant lesions (n=72, 13.7%), suspected malignancy (n=17, 3.2%), atypical cells (n=4, 0.8%), and inadequate specimens. Histopathological correlation was obtained in 55 of 72 cytologically malignant cases, confirming malignancy in all instances. Histological subtypes demonstrated invasive ductal carcinoma predominance (54 cases, 98.18%) with mucinous carcinoma representing 1.82% (n=1). Fine needle aspiration cytology achieved 100% accuracy and sensitivity for malignant breast lesion diagnosis, with statistical significance confirmed by Chi-square analysis (χ^2=10.83, P<0.001).

Understanding the underlying mechanisms of specimen inadequacy facilitates appropriate clinical correlation, guides re-sampling decisions, and optimizes diagnostic accuracy in cytopathological practice.

[74]. Besides the important issue is to treat with 3 R rule (Remove, Remodel, and Repair) [75] with restoring using smart materials [76].Fine-needle aspiration cytology (FNAC) and imaging remain central to the diagnosis of breast lesions. The integration of the IAC Yokohama system with ACR BI-RADS offers a streamlined yet robust framework for categorizing breast lesions, thereby facilitating patient management and enabling accurate risk stratification [77].

Conclusion

Breast diseases encompass a spectrum of neoplastic and non-neoplastic lesions, with the global incidence of benign and malignant conditions varying widely. Breast cancer remains one of the most common and life-threatening malignancies

in women worldwide. Its development is influenced by numerous risk factors, particularly genetic alterations. Early detection and accurate differentiation between benign and malignant breast lumps are critical for effective management.

The universally adopted *triple assessment*—comprising clinical examination, imaging (mammography and ultrasonography), and fine-needle aspiration cytology (FNAC)—provides a systematic approach for evaluating breast masses. FNAC offers a rapid, minimally invasive, cost-effective, and reliable preoperative diagnostic tool. Despite its high diagnostic accuracy, FNAC has limitations compared with core needle biopsy, particularly in providing architectural details.

In resource-limited settings, adherence to the *triple test* principle, combined with enhanced technical, observational, and interpretative skills, can substantially reduce the disease burden. Strengthening these competencies not only improves diagnostic precision but also facilitates early detection, informs treatment strategies, and ultimately contributes to improved breast cancer outcomes.

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REFERENCES

1. Hassiotou, F. and D. Geddes, *Anatomy of the human mammary gland: Current status of knowledge.* Clinical anatomy, 2013. **26**(1): p. 29-48.

2. Brisken, C. and B. O'Malley, *Hormone action in the mammary gland.* Cold Spring Harbor perspectives in biology, 2010: p. a003178.

3. Wood, K., M. Cameron, and K. Fitzgerald, *Breast size, bra fit and thoracic pain in young women: a correlational study.* Chiropractic & osteopathy, 2008. **16**(1): p. 1.

4. Yang, X., H. Wang, and B. Jiao, *Mammary gland stem cells and their application in breast cancer.* Oncotarget, 2017. **8**(6): p. 10675.

5. Strauss, J.F. and R.L. Barbieri, *Yen & Jaffe's Reproductive Endocrinology E-Book: Physiology, Pathophysiology, and Clinical Management*. 2013: Elsevier Health Sciences.

6. Zucca-Matthes, G., C. Urban, and A. Vallejo, *Anatomy of the nipple and breast ducts.* Gland surgery, 2016. **5**(1): p. 32.

7. Tabbara, S.O., et al., *Changing trends in breast fine-needle aspiration: results of the Papanicolaou Society of Cytopathology Survey.* Diagnostic cytopathology, 2000. **22**(2): p. 126-130.

8. Ahmed, I., et al., *Triple assessment of breast lump.* Journal of the College of Physicians and Surgeons--Pakistan: JCPSP, 2007. **17**(9): p. 535-538.

9. Jemal, A., et al., *Global cancer statistics.* CA: a cancer journal for clinicians, 2011. **61**(2): p. 69-90.

10. Bukhari, M.H. and Z.M. Akhtar, *Comparison of accuracy of diagnostic modalities for evaluation of breast cancer with review of literature.* Diagnostic cytopathology, 2009. **37**(6): p. 416-424.

11. Nasuti, J.F., P.K. Gupta, and Z.W. Baloch, *Diagnostic value and cost-effectiveness of on-site evaluation of fine-needle aspiration specimens: review of 5,688 cases.* Diagnostic cytopathology, 2002. **27**(1): p. 1-4.

12. Chaiwun, B. and P. Thorner, *Fine needle aspiration for evaluation of breast masses.* Current Opinion in Obstetrics and Gynecology, 2007. **19**(1): p. 48-55.

13. Akçil, M., E. Karaağaoğlu, and B. Demirhan, *Diagnostic accuracy of fine-needle aspiration cytology of palpable breast masses: An SROC curve with fixed and random effects linear meta-regression models.* Diagnostic cytopathology, 2008. **36**(5): p. 303-310.

14. Khatib, W.M., et al., *Cytological evaluation of breast lesions: Can it still go the long way?*

15. Ravindran, E., *Therapeutic Dilemnas of Breast Lumps.* Journal of Chalmeda Anand Rao
Institute of Medical Sciences Vol, 2012. **5**(1): p. 51.

16. Godwins, E., D. David, and J. Akeem, *Histopathologic analysis of benign breast diseases in Makurdi, North Central Nigeria.* International Journal of Medicine and Medical Sciences, 2011. **3**(5): p. 125-128.

17. Okoth, C., et al., *Benign proliferative breast diseases among female patients at a sub Saharan Africa tertiary hospital: a cross sectional study.* BMC surgery, 2013. **13**(1): p. 9.

18. Ahmad, F., et al., *Cytomorphological Study of Palpable Breast Lumps: Spectrum of Lesions and Diagnostic Utility of FNAC.*

19. Mohammed, U., M.O. Samaila, and M. Abubakar, *Pattern of adipose tissue tumors in Ahmadu Bello Universty Teaching Hospital, Zaria, Nigeria.* Annals of Nigerian Medicine, 2014. **8**(1): p. 8.

20. O'brien, S. and G.C. Kowdley, *Benign breast diseases and body mass index: is there a correlation?* The American Surgeon, 2014. **80**(5): p. 461-465.

21. Poh, M.M., T.N. Ballard, and J.J. Wendel, *Beckwith-Wiedemann syndrome and juvenile fibroadenoma: a case report.* Annals of plastic surgery, 2010. **64**(6): p. 803-806.

22. Tse, G., P.H. Tan, and F. Schmitt, *Fine needle aspiration cytology of the breast.* Verlag Berlin Heidelberg: Springer, 2013.

23. Kvist, L.J., et al., *The role of bacteria in lactational mastitis and some considerations of the use of antibiotic treatment.* International breastfeeding journal, 2008. **3**(1): p. 6.

24. Crepinsek, M.A., et al., *Interventions for preventing mastitis after childbirth.* Cochrane Database of Systematic Reviews, 2012(10): p. CD007239-1-CD007239-40.

25. Khanna, R., et al., *Mammary tuberculosis: report on 52 cases.* Postgraduate medical journal, 2002. **78**(921): p. 422-424.

26. Kim, M.J., et al., *Galactoceles mimicking suspicious solid masses on sonography.* Journal of ultrasound in medicine, 2006. **25**(2): p. 145-151.

27. Whang, I.Y., J. Lee, and K.T. Kim, *Galactocele as a changing axillary lump in a pregnant woman.* Archives of gynecology and obstetrics, 2007. **276**(4): p. 379-382.

28. Farrokh, D., et al., *Galactocele in the Axillary Accessory Breast Mimicking Suspicious Solid Mass on Ultrasound.* Case reports in obstetrics and gynecology, 2017. **2017**.

29. Olu-Eddo, A. and E.E. Ugiagbe, *Benign breast lesions in an African population: A 25-year histopathological review of 1864 cases.* Nigerian medical journal: journal of the Nigeria Medical Association, 2011. **52**(4): p. 211.

30. Njeze, G.E., *Breast lumps: A 21- year single center clinical and histological analysis.* Nigerian Journal of Surgery, 2014. **20**(1): p. 38-41.

31. Irabor, D. and C. Okolo, *An audit of 149 consecutive breast biopsies in Ibadan, Nigeria.* Pakistan Journal of Medical Sciences, 2008. **24**(2): p. 257.

32. Albasri, A.M., *Profile of benign breast diseases in western Saudi Arabia: an 8-year histopathological review of 603 cases.* Saudi medical journal, 2014. **35**(12): p. 1517.

33. Gupta, A., et al., *A study of clinical profile of benign breast diseases presenting at a tertiary care centre in central India.* Scholar J Appl Med Sci, 2015. **3**(2C): p. 695-700.

34. Nwashilli, N.J. and E.E. Ugiagbe, *Lipoma of the breast: An uncommon occurrence.* Nigerian Journal of Surgical Sciences, 2016. **26**(1): p. 12.

35. Ribeiro, R.C., R. Saltz, and L.F.E. Quintera, *Breast reconstruction with parenchymal cross after giant lipoma removal.* Aesthetic plastic surgery, 2008. **32**(4): p. 695.

36. Khosravi-Shahi, P., *Management of non metastatic phyllodes tumors of the breast: review of the literature.* Surgical oncology, 2011. **20**(4): p. e143-e148.

37. Mishra, S.P., et al., *Phyllodes tumor of breast: a review article.* ISRN surgery, 2013. **2013**.

38. Kuerer, H., *Breast surgical oncology.* Kuerer st, 2010.

39. Abe, M., et al., *Malignant transformation of breast fibroadenoma to malignant phyllodes tumor: long-term outcome of 36 malignant phyllodes tumors.* Breast Cancer, 2011. **18**(4): p. 268-272.

40. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2015.* CA: a cancer journal for clinicians, 2015. **65**(1): p. 5-29.

41. Ghoncheh, M., A. Mohammadian-Hafshejani, and H. Salehiniya, *Incidence and mortality of breast cancer and their relationship to development in Asia.* Asian Pacific Journal of Cancer Prevention, 2015. **16**(14): p. 6081-6087.

42. Keyghobadi, N., et al., *Epidemiology and trend of cancers in the province of Kerman: southeast of Iran.* Asian Pac J Cancer Prev, 2015. **16**(4): p. 1409-13.

43. Ghoncheh, M., Z. Momenimovahed, and H. Salehiniya, *Epidemiology, incidence and mortality of breast cancer in Asia.* Asian Pac J Cancer Prev, 2016. **17**(3): p. 47-52.

44. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* International journal of cancer, 2015. **136**(5): p. E359-E386.

45. Muddegowda, P.H., et al., *The value of systematic pattern analysis in FNAC of breast lesions: 225 cases with cytohistological correlation.* Journal of Cytology, 2011. **28**(1): p. 13.

46. Ferlay, J., et al., *Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012.* European journal of cancer, 2013. **49**(6): p. 1374-1403.

47. Sudhakar, A., *History of cancer, ancient and modern treatment methods.* Journal of cancer science & therapy, 2009. **1**(2): p. 1.

48. Sugimura, T., *Nutrition and dietary carcinogens.* Carcinogenesis, 2000. **21**(3): p. 387-395.

49. Chlebowski, R.T., *Nutrition and physical activity influence on breast cancer incidence and outcome.* The Breast, 2013. **22**: p. S30-S37.

50. Lacey, J.V., et al., *Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort.* BMC cancer, 2009. **9**(1): p. 84.

51. Sifuentes-Álvarez, A., et al., *Risk factors associated with breast cancer women´ s in Durango, Mexico.* Ginecologia y obstetricia de Mexico, 2015. **83**(11): p. 662-669.

52. Torre, L.A., et al., *Global cancer statistics, 2012.* CA: a cancer journal for clinicians, 2015. **65**(2): p. 87-108.

53. Lee, A., et al., *Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening.* London, UK: The Royal College of Pathologists, 2016.

54. Mehrgou, A. and M. Akouchekian, *The importance of BRCA1 and BRCA2 genes mutations in breast cancer development.* Medical journal of the Islamic Republic of Iran, 2016. **30**: p. 369.

55. Coughlin, S.S. and S.A. Smith, *The insulin-like growth factor axis, adipokines, physical activity, and obesity in relation to breast cancer incidence and recurrence.* Cancer and clinical oncology, 2015. **4**(2): p. 24.

56. Mauras, N., et al., *Estrogens and their genotoxic metabolites are increased in obese prepubertal girls.* The Journal of Clinical Endocrinology & Metabolism, 2015. **100**(6): p. 2322-2328.

57. Smith, S.G. and A.B. Chagpar, *Adherence to physical activity guidelines in breast cancer survivors.* The American Surgeon, 2010. **76**(9): p. 962-965.

58. Muddegowda, P.H., et al., *The value of systematic pattern analysis in FNAC of breast lesions: 225 cases with cytohistological correlation.* Journal of Cytology/Indian Academy of Cytologists, 2011. **28**(1): p. 13.

59. Khan, A., et al., *Correlation of fine needle aspiration cytology and histopathology diagnosis in the evaluation of breast lumps.* International Journal of Medical Students, 2014. **2**(2): p. 40-43.

60. Sheybani, F., et al., *Treatment for and clinical characteristics of granulomatous mastitis.* Obstetrics & Gynecology, 2015. **125**(4): p. 801-807.

61. Guray, M. and A.A. Sahin, *Benign breast diseases: classification, diagnosis, and management.* The oncologist, 2006. **11**(5): p. 435-449.

62. Singh, P., et al., *Cytomorphological patterns of breast lesions diagnosed on fine-needle aspiration cytology in a tertiary care hospital.* Int J Med Sci Public Health, 2015. **4**(5): p. 674-9.

63. Osime, O. and E. Ohanaka, *Analysis of five-year breast biopsies carried out in the University of Benin Teaching Hospital Benin City.* The Nigerian postgraduate medical journal, 2008. **15**(3): p. 160-163.

64. Kumar, R., *A clinicopathologic study of breast lumps in Bhairahwa, Nepal.* Asian Pac J Cancer Prev, 2010. **11**(4): p. 855-8.

65. Bukhari, M., M. Arshad, and S. Jamal, *Use of Fine Needle Aspiration in the Evaluation of Breast lumps Pathology.* Research International, 2011.

66. Gerhard, R. and F.C. Schmitt, *Liquid-based cytology in fine-needle aspiration of breast lesions: a review.* Acta cytologica, 2014. **58**(6): p. 533-542.

67. Schmidt, R.L., et al., *Methods specification for diagnostic test accuracy studies in fine-needle aspiration cytology: a survey of reporting practice.* American journal of clinical pathology, 2012. **137**(1): p. 132-141.

68. Shabb, N.S., F.I. Boulos, and F.W. Abdul-Karim, *Indeterminate and erroneous fine-needle aspirates of breast with focus on the 'true gray zone': a review.* Acta cytologica, 2013. **57**(4): p. 316-331.

69. Mendoza, P., et al., *Fine needle aspiration cytology of the breast: the nonmalignant categories.* Pathology Research International, 2011. **2011**.

70. Berner, A., et al., *Fine-needle aspiration cytology vs. core biopsy in the diagnosis of breast lesions.* Diagnostic cytopathology, 2003. **29**(6): p. 344-348.

71. Khan, A., et al., *TYPES OF BREAST LUMPS IN A TERTIARY CARE HOSPITAL.* Journal Of Medical Sciences, 2016. **24**(3): p. 133-135.

72. Rahman, M. and S. Islam, *Fine needle aspiration cytology of palpable breast lump: a study of 1778 cases.* Surgery S, 2013. **12**: p. 2161-1076.

73. Rahman, M., A. Sikder, and S. Nabi, *Diagnosis of breast lump by fine needle aspiration cytology and mammography.* Mymensingh Med J, 2011. **20**(4): p. 658-64.

74. Rupom, T.U., T. Choudhury, and S.G. Banu, *Study of fine needle aspiration cytology of breast lump: correlation of cytologically malignant cases with their histological findings.* Bangabandhu Sheikh Mujib Medical University Journal, 2011. **4**(2): p. 60-64.

75. Zhang, T., Zheng, Y., Chen, T. *et al.* Biomaterials mediated 3R (remove-remodel-repair) strategy: holistic management of *Helicobacter pylori* infection. *J Nanobiotechnol* **23**, 475 (2025). https://doi.org/10.1186/s12951-025-03455-2

76. M. Lei, B. Hou, S. Zhang, R. Chang, Y. Ji, K. Chen, J. Sun, C. Liu, G. F. Payne, X. Qu, de novo Fabrication of Dense Collagen Matrices with Patterned Hierarchical Structures for Corneal Stromal Tissue Repair. *Adv. Mater.* 2025, 2502279. **https://doi.org/10.1002/adma.202502279**

77. Munjal, P., Singh, M., Bhatt, V. R., Gautam, R., Singh, G., Khurana, N., ... & Lal, P. (2025). The Impact of International Academy of Cytology Yokohama System in Breast Fine-Needle Aspiration Biopsy Cytology and its Correlation With BI-RADS: A 6-Year Single-Institutional Experience. *Journal of Cytology*, *42*(2), 88-94.

78. Neal, L., et al. *Diagnosis and management of benign, atypical, and indeterminate breast lesions detected on core needle biopsy*. in *Mayo Clinic Proceedings*. 2014: Elsevier.

79. Kocjan, G., et al., *The role of breast FNAC in diagnosis and clinical management: a survey of current practice.* Cytopathology, 2008. **19**(5): p. 271-278.

Table 1. The accuracy values determined by various researchers independently

Researcher	Diagnostic accuracy(%)	Sensitivity(%)	Specificity (%)	PPV(%)	NPV(%)
Patel &Chauhan (2015)	**94.6**	**71.4**	**100**	**100**	**100**
Srilakshmi et al (2013)	**98.4**	**95.2**	**100**	**100**	**95.23**
Rin Yamaguchi (2012)	**88.0**	**96.7**	**84.3**	**99.5**	**98.2**
Mudde -gowda et al (2011)	**97.0**	**94.5**	**98**	**95.8**	**97.4**
Sudarat N (2009)	**91.2**	**92.5**	**90.2**	**99.4**	**85**

Table 2. General diagnostic standards for the recognition of malignant and benign breast conditions by histology [78, 79]

Criteria	Benign	Malignant
Cellularity	Usually poor or moderate	Usually high
Cell arrangement	Even, Monolayers (usually in flat sheets)	Over lapping and irregular arranged in three dimensions
Cell to cell cohesion	Good large defined clusters of cells	Poor small groups of intact cells
Types of Cell	Mixtures of myoepithelial, epithelial, and other cells Exhibited stromal fragment	Population of uniform cells
Background inflammatory cells	Clean generally Exception inflammatory conditions	Necrotic debris is present occasionally Macrophages are also present in some cases
Characteristic of Nucleus		
Elliptical (Bipolar) Nuclei bare	High in numbers Present, often in high numbers	Not present (Conspicuous)
Size about the diameter of RBC	Small in size	Variable in size , Mostly large, depend upon type of tumor
Pleomorphism	Usually Rare	Usually Common