

Incidence of Malignant Breast Tumors in Cases of Bleeding Per Nipples Thesis

Emad El-den Farid, Shabaan Mohamed Abd-Elmegeed, Ahmed Serag-Elden Hussain, Samr Foly Ahmed

Department of General Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Email: rooz88_2010@hotmail.com

Abstract: Background: Nipple discharge (ND) is an important presenting complaint in women attending breast clinics worldwide. It is the third most common breast complaint after breast pain and breast mass, with a prevalence of 4.8% to 7.4%, and accounts for 5% of all breast symptoms. At least 80% of women will experience at least 1 episode of nipple discharge during their reproductive years. **Objective:** To determine the incidence of malignant tumors among the patients presented with bleeding per nipples. **Patients and Methods:** It is Prospective study, that was carried out in the period from July 2017 to January 2019 in Ain Shams University hospitals. The patients were collected from breast clinics of Ain Shams university and El Minia University hospitals under supervision of supervisors. This study included 90 patients presented with bleeding per nipple, the research was performed according to the standards of the ethical committee of the faculty of medicine, Ain shams University and informed consent was obtained from every patient. **Results:** According to the incidence of malignancy that detected in our patients we found that 25 patients (27.7%) had a malignant lesions 10 patients in each group B & C and 5 patients in group A. **Conclusion:** Traditional treatment is surgical excision of the involved ductal system from which the discharge emanates. Ductal excision has been the only reliable procedure in establishing a certain diagnosis and in controlling the bloody discharge. The early success reported with image-guided excision of papilloma and duct endoscopy promises a significant improvement in diagnostic accuracy from minimally invasive emerging technology.

[Emad El-den Farid, Shabaan Mohamed Abd-Elmegeed, Ahmed Serag-Elden Hussain, Samr Foly Ahmed. **Incidence of Malignant Breast Tumors in Cases of Bleeding Per Nipples Thesis.** *Nat Sci* 2019;17(11):31-37]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). <http://www.sciencepub.net/nature>. 4. doi: [10.7537/marsnsj171119.04](https://doi.org/10.7537/marsnsj171119.04).

Keywords: Incidence; Malignant; Breast; Tumor; Case; Bleeding; Nipple; Thesis

1. Introduction

Nipple discharge (ND) is an important presenting complaint in women attending breast clinics worldwide. It is the third most common breast complaint after breast pain and breast mass, with a prevalence of 4.8% to 7.4%, and accounts for 5% of all breast symptoms. At least 80% of women will experience at least 1 episode of nipple discharge during their reproductive years ⁽¹⁾.

It is categorized as physiologic or pathologic. Pathologic nipple discharge tends to be unilateral, from a single duct orifice, spontaneous, and serous or bloodstained. Nipple discharge that exhibits any one of these features may be considered pathologic. Physiologic nipple discharge tends to be bilateral, from multiple duct orifices, and white, green, or yellow in color ⁽²⁾.

Predicting whether the causative lesion is malignant or benign is important because it affects the physician's choice of clinical follow-up or surgical treatment.

Until the 1950's nipple discharges especially when bloody, were regarded as definitely indicative of carcinoma of the breast. Many unnecessary mastectomies were performed without obtaining histological diagnosis ⁽³⁾.

Over the years this attitude has changed and now nipple discharges are investigated with clinical history, physical examination, occult blood studies, cytology of discharges, breast ultrasonography, mammography, ductography, and recently breast MRI scan studies when indicated ⁽⁴⁾.

The clinical examination and mammography are first line diagnostic approaches. Mammography may reveal calcifications that must be evaluated. It is associated with a 9.5% false-negative rate and a 1.6% false-positive rate in detecting breast cancer in patients with nipple discharge ⁽⁵⁾.

Breast US is a non-invasive diagnostic method that has proven to be useful in the evaluation of patients with ND. However, US has limitations with respect to depicting causative lesions of small masses and ductal carcinomas in situ (DCIS). The breast ultrasonography is complementary to mammography and will guide fine needle aspiration (FNA) and will help in obtaining cytology specimens from the abnormal area ⁽⁶⁾.

Cytological evaluation of nipple discharge can be done directly from the nipple. Lately, cytology has been improved by new techniques of duct lavage and duct endoscopy (ductoscopy) ⁽⁷⁾.

Ductography (Galactography, DG) is a diagnostic modality used for identification of the

secreting duct, It is performed by dilatation, catheterization and injection of a water-soluble contrast. Craniocaudal, lateral and compression views are obtained. The results may be characterized as Normal, Ductal dilatation, Filling defect or Cutoff sign ⁽⁸⁾.

Most commonly performed operations for bloody nipple discharge are microdochectomy with isolation and removal of the affected duct or radical subareolar duct excision otherwise known as Hadfield's procedure. These operations are both diagnostic and therapeutic. Histopathology of excised tissue is mandatory to confirm the diagnosis and to get proper management if malignancy is confirmed. Recently the development of endoscopic tools and fiber optics will allow safer diagnosis and treatment without any sacrifice in function and excellent aesthetic results. Today there are simple non-invasive or minimally invasive techniques that can be used in the evaluation and management of this condition which provide very good results in the majority of the cases ⁽⁹⁾.

Aim of the Work

The aim of our study is to determine the incidence of malignant tumors among the patients presented with bleeding per nipples.

2. Patients and Methods

It is Prospective study, that was carried out in the period from July 2017 to January 2019 in Ain Shams University hospitals.

The patients were collected from breast clinics of Ain Shams university and El Minia University hospitals under supervision of supervisors.

This study included 90 patients presented with bleeding per nipple, the research was performed according to the standards of the ethical committee of the faculty of medicine, Ain shams University and informed consent was obtained from every patient.

We maintained the privacy of patient and confidentiality of the data by: Each patient had special file with code number. All pictures taken were only of the side of surgery and it was unnamed. The participants included in the study were met the following inclusion and exclusion criteria:

Inclusion criteria:

Female patients aged between 16-55 years presented with bloody nipples discharge.

Exclusion criteria:

No exclusion criteria.

Clinical history:

Clinical history taking and examination was meticulously done for all patients concluding the following data: Personal and family history. History of hormonal treatment and/or contraceptive pills. Past medical history. Breast or ovarian disorders. The

history and optimal description of the features of the discharge, Regarding its date of onset, duration, frequency, spontaneous, or provoked.

Clinical examination:

General examination. Locoregional examination: for both breast and axilla.

Inspection:

Inspection was carried out using magnification and good illumination, and was initially designed to distinguish the true nipple discharge from its differential diagnoses of pseudo discharge Such as eczema, dermatosis, erosive adenomatosis of the nipple or discharge from the peri-areolar region and not from the nipple.

Palpation:

Palpation is performed using the usual breast examination technique with the patient seated and then lying down supine. Palpation is carried out quadrant by quadrant with centripetal expression of the gland looking for a mass or "trigger point" inducing the discharge.

Methods of diagnosis:

Benzidine test:

Benzidine test was done In all patients to ensure the presence of blood In the discharge. it is a sensitive test based on production of a blue color upon contact of blood with a solution of Benzidine, hydroge peroxide ad glacial acid.

Smear of the discharge:

Cytological evaluation of nipple discharge was be done for all patients. After smearing, the slide was fixed and stained by drying in open air and staining with Papanicolaou.

Tumor markers:

Serum tumors markers assessment was performed In all cases e (CEA and CA 15.3)

Imaging:

Ultrasound:

Ultrasound was performed for both breast and axilla.

Mammography:

Mammography was done in all patients.

Bi-RADS for sonomammography:

BI-RADS is designed to standardize breast imaging reporting and to reduce confusion in breast imaging interpretations. It also facilitates outcome monitoring and quality assessment.

Final assessment categories:

Negative. Benign. Probably benign. Suspicious. Highly suggestive of malignancy. Known biopsy-broken.

MRI:

MRI is used in cases of high risk with BI-RADS 4 or more or with clinical examinations and assessment bias to malignancy they were 25 patients in our study.

Galactography:

This was done for patients of the first group which had bleeding per one orifice of nipple with no breast lump detected by ultrasound or mammography.

Fine needle aspiration biopsy: This was done to patients they had cystic mass detected clinically or by ultrasound.

Core tissue biopsy: This was done to all patients was breast mass which felt clinically. All patients were divided according to their (BIRADS) radiological classification and clinical examination finding into three groups:

The first group: Patients with bleeding per nipples and the majority of them had a criteria of (BIRADS)1 and 2. 30 patients were in this group. 25 patients that were under 50 years of age and their tumor marker level was In normal value were kept under regular observation. While only 5 patients that were over 50 years of age and by assessment of tumor markers there was a high level of (CA 15.3 marker) and mastectomy was performed.

The second group: 50 patients were in this group had bleeding per nipple with mass detected clinically or radiologically or both and they had a criteria of (BIRADS)1 and 2. Their nipple discharge was examined histologically and measurement of tumour markers (CEA,CA 15.3) was done, fine

needle aspiration biopsy was done to 30 patients with mass detected sonomammography and core tissue biopsy was done to 20 patients with mass detected clinically. The result was benign In 40 cases, these patients were reassured and no further treatment was required beyond a careful follow up. In 10 cases the result was malignant and radical mastectomy was performed.

The third group: 10 patients with bleeding per nipple with mass detected clinically or radiologically or both which bias to malignancy, fine needle aspiration biopsy was done to 6 patients and core tissue biopsy was done to 4 patients, this group of patients had elevated tumour markers (CEA. CA 15.3). and they include (BIRADS) from 5 and 6. These patients were prepared for Radical mastectomy and further oncological treatment were achieved either by chemo therapy or hormonal therapy.

3. Results**Table (1):** Age of all patients.

Age	No patients. of	Percentage
20-35 years	20	22.2%
36-45 years	60	66.6%
46-55 years	10	11.1%

Table (2): Medical history a co-morbidities in all.

Parameter	No. of patients	Percentage
Family history	19	21.1%
Pregnancy	7	7.7%
Lactation	13	14.4%
Hormonal therapy	7	7.7%
D.M	16	17.7%
H.T.N	13	14.4%

Table (3): Presenting symptoms.

Symptoms	No. of patients	Percentage
Bleeding per nipples with mass	47	52.2%
Bleeding per nipples without mass	43	47.7%

Table (4): Methods of diagnosis in all patients.

Method of diagnosis	No. of patients	Percentage
Benzidin test	90	100%
Tumor marker	90	100%
Cytology of discharge	90	100%
Sono mamogram	90	100%
Galactography	20	22.2%
M.R.I	25	27.7%
F.N.A C	36	40%
Core tissue biopsy	29	32.2%

Table (5): BI-RADS classification.

BI-RADS	No. of patients	Percentage	Group
1	10	11.11%	A
2	20	22.2%	A
3	30	33.3%	B
4	20	22.2%	B
5	3	3.3%	C
6	7	7.7%	C

Table (6): Management.

Treatment	NO. of patients	Percentage
Wedge resection	50	55.5%
Radical mastectomy	20	22.25%
Non operative and follow up	20	22.25%

Table (7): Incidence of malignancy.

Group	No. of patients	Percentage
A	5	5.6%
B	10	11.1%
C	10	11.1%
Total	25	27.7%

4. Discussion

This study is a prospective study, that was carried out in the period from July 2017 to January 2019 in Ain Shams University hospitals.

The patients were collected from breast clinics of Ain Shams university and El Minia University hospitals under supervision of supervisors.

This study included 90 patients presented with bleeding per nipple, the research was performed according to the standards of the ethical committee of the faculty of medicine, Ain shams University and informed consent was obtained from every patient.

The aim of this study is to determine the incidence of malignant tumors among the patients presented with bleeding per nipples.

Similar study was carried out by **T Richards** to detect the incidence of breast cancer in patients presented with bloody nipples discharge ⁽¹⁰⁾.

Another study was done by E.R. Sauter in association of bloody nipples discharge and breast malignancies ⁽⁸⁾.

According to the age of the patients in this study 60 patients (66.6%) were between 36 -45 years old, and 10 patients (11.1%) were between 46-55years old **Kessler** ⁽¹¹⁾ reported that the age-incidence curve changes around the menopausal period, most likely due to hormonal changes 10 to 15 years earlier, flattens out in the 40 to 50 year old age range, and then increases as age increases.

Recent data showing decreased risk of breast cancer incidence at older ages, e.g., older than 75 years of age, relative to younger ages, are likely an

artifact of recent increases in breast cancer screening in the United States ⁽¹¹⁾.

According to medical history we found that 19 patients (21.1%) had positive family history and 7 patients (7.7%) had history of receiving hormonal therapy, 13patients (14.4%) were lactating, 16 patients were diabetic (17.7%) and 13 patients (14.4%) were hypertensive. Comorbidity is defined as "any additional clinical condition that has existed simultaneously or that may occur during the clinical course of a patient with an index disease under study.

In a study done by **Netti Sharma** during the period of January 2012 and December 2012, 156 biopsy-proven breast cancer patients with associated comorbidity were included in the study. In this study the comorbidities prevalent in female breast cancer patients was studied. and the patients were arranged according to the associated comorbid condition. Most prevalent associated comorbidities related to breast cancer are hypertension [34 (21.8%)], chronic obstructive pulmonary disease (COPD) [31 (19.9%)], rheumatologic disease [29 (18.6%)] and diabetes mellitus [26 (16.7%)], all four conditions were reported in more than 75% of the cases ⁽¹²⁾.

Using data from the Generations Study, a cohort of over 113,000 women from the general UK population, we analyzed breast cancer risk in relation to first-degree family history using a family history score (FHS) that takes account of the expected number of family cases based on the family's age-structure and national cancer incidence rates.

Breast cancer risk increased significantly (P trend < 0.0001) with greater FHS. There was a 3.5-fold (95% CI 2.56–4.79) range of risk between the lowest and highest FHS groups, whereas women who had two or more relatives with breast cancer, the strongest conventional familial risk factor, had a 2.5-fold (95% CI 1.83–3.47) increase in risk. Using likelihood ratio tests, the best model for determining breast cancer risk due to family history was that combining FHS and age of relative at diagnosis⁽¹³⁾.

Usha Salagame, found that current users of MHT (menopausal hormonal therapy) have approximately double the odds of developing ER+ breast cancer compared to women who had never used MHT. There was also a 2.3 fold increase in the odds of developing ER+PR+ and ER+/PR+/HER2-subtypes of breast cancer for current versus never users of MHT. None of the other breast cancer subtypes were found to have a significant association with current MHT use in his analysis⁽¹⁴⁾.

As regarding symptoms of the patients in this study we found that 47 patients (52.2%) presenting with bleeding per nipples with mass while 43 patients presented with bleeding per nipples without mass.

The American Cancer Society reported that the most common symptom of breast cancer is a new lump or mass. A painless, hard mass that has irregular edges is more likely to be cancer, but breast cancers can be tender, soft, or rounded. They can even be painful⁽¹⁵⁾.

According to the methods of investigations in this group, benzidine test, cytology of the discharge, tumor marker and sono-mamogrammic assessment were done In all patients, galactography was done In 20 patients (22.2%), F.N.A.C was done In 36 patients (40%) while tissue core biopsy was done In 29 patients (32.2%).

In a study done by **M.A. Chaudary**, by analysis of 270 patients underwent microdocheotomy for nipple discharge from a single identifiable duct, revealed that occult cancers were all accompanied by hemoglobin positive discharge. A simple method of detecting the presence of hemoglobin in the discharge was described. The incidence of cancer was found to be 5.9%. In order of frequency, intraduct papilloma, duct ectasia, cystic disease, and carcinoma accounted for over 90% of the cases⁽¹⁶⁾.

Isabella Castellano reported in his study on 139 patients with NDC (nipple discharge cytology) who underwent surgical breast resection at the Breast Unit of Città della Salute e della Scienza, Molinette Hospital and St. Anna Hospital, Turin, Italy from January 2010 to December 2015. that The correlation between NDC and histological diagnosis of surgical specimens confirmed that 100% of malignant NDC were related to an in-situ and/or invasive carcinoma.

Otherwise, only 28% (30/107) of benign/borderline NDC were related to malignancy. In the remaining 72% (77/107) of cases a papillary or hyperplastic intraductal proliferation was diagnosed⁽¹⁷⁾.

Early detection is an essential step in decreasing the mortality and morbidity of breast cancer. Mammography is a proven effective tool for early breast cancer detection. It has high sensitivity and specificity and remains the gold standard for breast cancer screening.

The American College of Radiologists-Breast Imaging Reporting and Data System (ACR-BIRADS) is a qualitative tool originally designed for use with Mammography. This system is established to standardize professional radiologic reporting with numerical scores (0–6) typically allows for understanding of patients records between multiple doctors and medical facilities.

In our study 30 patients had (BIRADS 3) criteria while 7 patients had (BIRADS 6) Data were collected from a questionnaire and mammographic imaging of the patients that filled the informed consent for the research at 2016. The questionnaire, apart from demographic characteristics, contained baseline biodata information such as reproductive history, menopausal status, family history in first-degree relatives, the use of exogenous hormonal supplements, symptoms, the reason of mammography (screening of diagnostic), and the history of prior breast surgery up to the time of the study mammogram.

Total of 924 out of 1015 women were enrolled in the study finally. The most common positive findings in mammogram studies were focal asymmetry, architectural distortion, intramammary lymph node, and accessory breast, respectively. Likelihood ratio, Chi-square test, has showed that there was a significant relationship between these positive findings and breast density in mammogram (P < 0.0001). There was also a significant relationship between these positive findings and BIRADS (P < 0.001).

Kruskal-Wallis test showed the highest BIRADS score in the mammography-reported Architectural distortion and the lowest BIRADS score in the accessory breasts (mean rank of 80% in comparison with 40%)⁽¹⁸⁾.

In 2010, **Akinola et al.**, carried out a study on mammograms and breast arterial calcifications (BAC) in 54 consecutive women seen at the Lagos University Teaching Hospital in Ikeja-Lagos. The study resolved that only 20% of the mammograms had BAC, which were related to increasing age⁽¹⁹⁾.

Mammographic patterns in 498 women imaged at the University College Hospital in Ibadan were assessed by In 2013, 180 mammograms of Ghanaian women were retrospectively reviewed by **Brakohiapa**

et al., and found screeners to be the majority with benign findings more frequently detected. Two review articles on the need for standardisation of breast ultrasound and mammography reports in Nigeria have also been published by **Obajimi et al.**, and **Akhigbe and Igbinedion** in Ibadan and Benin respectively ⁽²⁰⁾.

According to F.N.A.C and core tissue biopsy that used in this study as a method of investigation similar study was carried out on 11,947 women with breast lesions detected by preoperative needle biopsy between January 1995 and December 2012 were selected from the Shanghai Cancer Data base, which integrates information from approximately 50% of breast cancer patients in Shanghai.

For all the 11,947 women included in this study, image-guided needle biopsy was the initial diagnostic procedure. Approximately 81.0% of biopsied samples were histopathologically determined to be malignant lesions, 5.5% were determined to be high-risk lesions, and 13.5% were determined to be benign lesions ⁽²¹⁾.

As regard management of our patients a wedge resection of the sector of the breast containing the source of bleeding was carried out, including the corresponding main ducts up to the deep aspect of the nipple was done In 50 cases (55.5%) while radical mastectomy was done In 25 patients (27.8%) and regular follow up with medical treatment In 25 patients (27.8%).

Vargas HI reported in his study that Traditional treatment is surgical excision of the involved ductal system from which the discharge emanates. Ductal excision has been the only reliable procedure in establishing a certain diagnosis and in controlling the bloody discharge. The early success reported with image-guided excision of papilloma and duct endoscopy promises a significant improvement in diagnostic accuracy from minimally invasive emerging technology ⁽²²⁾.

Dietz JR reported that Selective duct excision involves removal of the bleeding ductal system with tributary ducts and the corresponding breast segment. It is indicated in women with BND with no suspicious findings on examination or mammography ⁽²³⁾.

A Hunt et al reported in his study on Patients who underwent operation for nipple discharge at a district general hospital (population 460,000) over a 3-year period that All patients with pathological nipple discharge were offered operation. Patients with surgically significant nipple discharge only of 40 years and above are recommended to undergo Hadfield's procedure (radical subareolar duct excision). Patients below 40 years of age, particularly if intending to breast feed, with persisting discharge are given the option of microdochectomy ⁽²⁴⁾.

According to the incidence of malignancy that detected in our patients we found that 25 patients

(27.7%) had a malignant lesions 10 patients in each group B & C and 5 patients in group A.

In similar study gone by **Cabioglu N et al** he found That the incidence of malignancy in patients presenting with abnormal ND is 7% to 15%, The possibility of cancer increases when the discharge is accompanied by a lump, and when the patient is over 50 years of age. [The proportion of breast carcinoma cases associated with ND ranges from 1.6% to 13%. Most cancer-associated discharges are the result of DCIS or papillary carcinoma and are frequently associated with a clinically palpable lesion or positive findings on mammography ⁽²⁵⁾.

A meta-analysis about the association between the color of nipple discharge and breast cancer risk was conducted. Eight studies, including 3,110 patients, were eligible for this meta-analysis. Compared with patients in non-bloody nipple discharge group (179/1,478), patients in bloody nipple discharge group (404/1,632) had a markedly higher breast cancer risk (OR: 2.27, 95% CI: 1.32-3.89, $P < 0.001$ for heterogeneity). Compared with patients in clear/serous group (71/575), patients in bloody nipple discharge group (326/1,271) also had a higher risk (OR: 2.49, 95% CI: 1.25-4.93, $P = 0.011$ for heterogeneity ⁽²⁶⁾.

Conclusion

Bloody nipple discharge causes a high degree of anxiety in women because of fear of breast cancer. Commonly, the absence of palpable or mammographic abnormalities gives a false sense of security, causing delays in diagnosis. Initial evaluation with physical examination and mammography is useful in detecting high-risk cases. Bloody nipple discharge is most frequently benign. It is caused by intraductal papilloma, duct ectasia, and less frequently by breast cancer. Several diagnostic tests have been proposed to establish the cause of bloody nipple discharge. Galactography, ultrasound, and exfoliative cytology are useful only when positive, but have a high rate of false-negative results and do not preclude histologic diagnosis. More recently, ductal lavages in combination with cytology have provided promising results, but experience and long-term follow-up are limited.

References

1. Alcock C, Layer GT. Predicting occult malignancy in nipple discharge. *ANZ J Surg.* 2010;80(9):646-649.
2. Fiorica JV. Nipple discharge. *Obstet Gynecol Clin North Am* 2004; 21:453- 460.
3. Garrido I, Gangloff D, Raffii A. A comparison of ductoscopy guided and conventional surgical

- excision in women with spontaneous nipple discharge. *Ann Surg* 2005; 241(4): 575-81.
4. Gupta RK, Gaskell D, Dowle CS, Simpson JS, King BR, Naran S, Lallu S, Fauck R. The role of nipple discharge cytology in the diagnosis of breast disease: a study of 1948 nipple discharge smears from 1530 patients. *Cytopathology*. 2003; 15(6):326-330.
 5. Ito Y, Tamaki Y, Nakano Y, et al. Non-palpable breast cancer with nipple discharge: how should it be treated? *Anticancer Res* 1997;17:791-4.
 6. Lamont JP, Dultz RP, Kuhn JA, Grant MD, Jones RC. Galactography in patients with nipple discharge. In *Baylor University Medical Center Proceedings*. Taylor & Francis. 2009; 13(3): 214-216.
 7. Onstad M, Stuckey A. Benign breast disorders *Obstet Gynecol Clin North Am*, 40 (3) (2013), pp. 459-473.
 8. Sauter ER, Schlatter L, Lininger J, Hewett JE. et al. The association of bloody nipple discharge with breast pathology. *Surgery*. 2004 Oct;136(4):780-5.
 9. ASarakbi W, Worku D, Escobar PF, Mokbel K. "Breast Papillomas: current management with a focus on a new diagnostic and therapeutic modality". *Int. Semin. Surg. Oncol*; 2006:3.1.
 10. Richards T, Hunt A, Courtney S, et al. Nipple Discharge: A Sign of Breast Cancer?, *Ann R Coll Surg Engl*. 2007 Mar; 89(2): 124–126.
 11. Kessler LG. The relationship between age and incidence of breast cancer. Population and screening program data. *Cancer*. 2007;69(7 Suppl):1896-903.
 12. Sharma N, Huston TL, Simmons RM. Intraoperative intraductal injection of methylene blue dye to assist in major duct excision. *Am J Surg*. 2006;191(4):553–4.
 13. Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, et al. Family history and risk of breast cancer: an analysis accounting for family structure. *Breast Cancer Res Treat*. 2017; 165(1): 193–200.
 14. Usha Salagame. Menopausal Hormone Therapy use and breast cancer risk by receptor subtypes: Results from the New South Wales Cancer Lifestyle and Evaluation of Risk (CLEAR) study. 2018; 13(11): e0205034.
 15. Jamie E, Rimsten A, Skoog V, Stenkvis B. On the significance of nipple discharge in the diagnosis of breast disease. *Acta Chir Scand*.2017.
 16. Chaudary MA, Millis RR, Davies GC, Hayward JL. Nipple discharge: the diagnostic value of testing for occult blood. *Ann. Surg.* 2002; 196, 651-655.
 17. Isabella C, Davide B, Nelson Rngel. The impact of malignant nipple discharge cytology (NDc) in surgical management of breast cancer patients *PLoS One*. 2017; 12(8): e0182073.
 18. Mehri S, Parisa SS, Amirmasoud S. nvestigation of Frequency Distribution of Breast Imaging Reporting and Data System (BIRADS) Classification and Epidemiological Factors Related to Breast Cancer in Iran: A 7-year Study (2010–2016). *Adv Biomed Res*. 2018; 7: 56.
 19. Akinola RA, Ogbera OA, Onakoya JA, Enabulele CE, Fadeyibi IO. Mammograms and breast arterial calcifications: looking beyond breast cancer: a preliminary report. *BMC research notes*. 2011; 4(1):207.
 20. Obajimi MO, Adeniji-Sofoluwe AT, Oluwasola AO, Adedokun BO, Mosuro OA, Adeoye AO, Ntekim NT, Soyemi TO, Osofundiya OO, Bassey OS. Screening mammography in Ibadan: Our experience. *Nigerian Journal of Basic and Clinical Sciences*. 2015; 12(2):74.
 21. Hao S, Liu ZB, Ling H, JJ, Shen JP, Yang WT, Shao ZM. Changing attitudes toward needle biopsies of breast cancer in Shanghai: experience and current status over the past 8 years. *Onco Targets Ther*. 2015 Oct 9;8:2865-71.
 22. Vargas HI, Vargas MP, Eldrageely K, Gonzalez KD, Khalkhali I. Outcomes of clinical and surgical assessment of women with pathological nipple discharge. *Am Surg*. 2006;72(2):124–8.
 23. Dietz JR, Crowe JP, Grundfest S, Arrigain S, Kim JA et al. Directed duct excision by using mammary ductoscopy in patients with pathologic nipple discharge. *Surgery*. 2012; 132(4):582-7.
 24. Richards T, Hunt A, Courtney S, et al. Nipple Discharge: A Sign of Breast Cancer?, *Ann R Coll Surg Engl*. 2007 Mar; 89(2): 124–126.
 25. Cabioglu N, Hunt KK, Singletary SE, Stephens TW, et al. Surgical decision making and factors determining a diagnosis of breast carcinoma in women presenting with nipple discharge. *J Am Coll Surg*. 2003;196:354.
 26. Chen L, Zhou WB, Zhao Y, Liu XA, Ding Q, Zha XM, Wang S. Bloody nipple discharge is a predictor of breast cancer risk: a meta-analysis. *Breast cancer research and treatment*. 2012; 132(1):9-14.