

Research Article

Statistical Comparison of Clinical and Histologic Diagnoses of Breast Tumours in Public and Private Hospitals

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Abstract

Background: Breast cancer is the leading cause of cancer deaths in Nigerian women. Most cases present in late or advanced stages with consequent poor prognosis. There are also instances of false clinical diagnoses with resultant patient adversity. Population screening based on genetics is largely unavailable to the citizens. Therefore, early diagnosis is the immediate choice available to the health system.

Methods: Retrospective data were collected including all open-breast-biopsies submitted to three histopathology laboratories. The clinical and histologic diagnoses for each sample were compared. Statistical estimate of the accuracy of clinical diagnoses of breast cancer by clinicians was calculated using histologic diagnoses as the reference standard, and by calculating the sensitivity, specificity, false rates and odds ratio. Diagnostic accuracies of clinicians working in public and private hospitals were also compared in terms of these rates.

Results: Our result showed that the diagnostic accuracy of the doctors working in public hospitals is more sensitive than that of those working in private hospitals. The overall false positive rate in both hospital groups combined is found to be high. This is probably due to unavailability of modern radiodiagnostic facilities that may otherwise enhance clinical assessment and diagnoses. The doctors in the public hospital group are generally more efficient in breast cancer diagnoses than those working in private hospitals.

Conclusion: The authors believe that better funding of the audited hospitals, regular training of the medical personnel and provision of modern radiodiagnostic facilities may probably enhance clinical accuracy of breast cancer diagnoses in these hospitals.

Keywords: breast cancer; sensitivity; specificity; false rates; odds ratio

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Introduction

Breast cancer is the leading female malignancy in the world and is believed to be the most common cancer among women in Nigeria [1-3].

Although the exact prevalence of breast cancer disease in Nigeria is not really known, the prevalence rate based on only hospital data is 116 per 100,000 population [3]. This rate is expected to be much higher in the general population. Due to the absence of systematic population-based cancer registration, most information has come from small clinical and pathology case series which suffer from serious under-reporting of cases resulting in inherent bias. These hospital-based studies have consequently affected current understanding of the pattern and characteristics of breast cancer in Africa [4]. According to International Agency for Research on Cancer (IARC) data, the 5-year incidence and mortality rates of breast cancer in Nigeria are 18,935 (30.7%) and 10,469 (22.9%) per 100,000 respectively [5].

In Nigeria patients with breast cancer disease are often associated with poor prognosis for a variety of reasons [6]. Usually, early diagnoses, properly planned and timely medical intervention coupled with follow-up as is the practice in industrialized societies is necessary to achieving a better outcome. These are in-turn dependent on education of population at risk and the general population, adequately trained health personnel, good medical facilities and a well-structured screening program, among other requirements which are still generally lacking in Nigeria.

Histopathologic assessment of breast cancer has long provided the basis for diagnosis, prediction of recurrence risk and prescription of adjuvant therapy. Biopsy techniques vary in the level of invasiveness and amount of tissue sample, which affects yield and patient experience [7]. Of all biopsy methods, open biopsy although more invasive, often allows better gross-morphological assessment, specimen sampling and also offers a better setting for more accurate histologic diagnoses. Shyyan *et al* (2006) emphasized correlation between clinical breast examination (CBE) and imaging findings with pathologic findings. They further stated the

need for a histopathologic diagnosis before initiating breast cancer treatment. Expertise in pathology therefore was reaffirmed to be a key requirement for ensuring reliable diagnostic findings [8].

Mammography is the standard of reference for the clinical detection of breast cancer and is expected to reasonably augment the clinical diagnostic accuracy. According to data from the Breast Cancer Detection Demonstration Project (1982), the false-negative rate of mammography is approximately 8%–10% [9]. Possible causes for missed breast cancers include dense parenchyma obscuring a lesion, poor positioning or technique, perception error, incorrect interpretation of a suspect finding, subtle features of malignancy, and slow growth of a lesion [10]. In another study, an assessment of the level of accuracy of clinical breast examination (CBE) for breast cancer diagnosis was carried out with a resultant false negative rate of 19% [11].

Errors related to delayed or erroneous diagnoses are frequent and is an under-reported cause of patient injury [12-15]. Apparently these errors seem to be more appreciated by malpractice lawyers particularly in the industrialized nations and more particularly in the United States of America. It is not uncommon to find these lawyers advertise their services on the internet to exploit these errors.

Erroneous diagnoses of breast cancer is often a source of psycho-social trauma to both patient and family members; in the event breast cancer is truly present, missed diagnosis increases cost of cancer management and often result to poor treatment outcome. Analysis of large cohort study, showed that patients who had recently received a cancer diagnosis had increased risks of both suicide and death from cardiovascular causes, as compared with cancer-free persons [16]. This therefore beckons the need for diagnosticians to hone their skills to avoid the unnecessary untoward effects of false diagnoses.

Published research estimating sensitivity, specificity, false rates and odds ratio of results of clinical diagnoses of breast cancer in Nigeria using histological diagnoses as the reference standard are not readily available. In this study we seek to statistically estimate the clinical diagnostic accuracy of breast cancer by clinicians using histologic diagnoses as

the reference standard by calculating the sensitivity, specificity, false rates and odds ratio. We also intend to compare the diagnostic accuracies of clinicians working in public with those working in private hospitals in terms of these rates.

Methods

Oyeka et al (2012;2013) [17,18] developed a method for assessing the strength of association of screening test results and state of nature or condition using odds ratio based on false rates, sensitivity and specificity of the test [19,20].

Oyeka et al (2013) further showed that the odds-ratio is equal to 1, ($\omega = 1$), when the screening test results and the existing condition are not in any way associated [18]. In which case the diagnostic test is unable to correctly screen a subject having the condition as actually having it, and the subject free of the condition as actually not having it. Thus the smaller the value of the odds ratio, (ω), the lower and weaker the association between the test results and state of nature; the greater or larger the value of the odds ratio (ω) the higher and stronger the association. The statistical significance of the estimated odds ratio ($\hat{\omega}$), if desired, is determined by the usual chi-square test for independence [19] using sample data.

However, as the authors noted, if sample sizes are very large as in the present data, statistical tests for significance may not be very necessary since in these cases most statistical tests tend to be significant [21,22]. In such cases, patterns and levels of results may be of greater interest and importance rather than merely statistical significance of results. This approach is adopted in this paper where emphasis is more on the interpretation of patterns and levels of differences in diagnostic results.

The methodologies developed by Oyeka and others under reference are here used with some case studies respecting breast cancer among patients in Nigeria.

Source and nature of data

Retrospective data were collected including all

open-breast-biopsies submitted to three histopathology laboratories in Anambra State, Eastern Nigeria. The three laboratories are histopathology laboratory of Nnamdi Azikiwe University Teaching Hospital, Nnewi and that of two privately owned laboratories, Pathocon Specialist Clinic and Research Institute, Nnewi and Nkeoma Specialist Hospital, Onitsha. These laboratories are accredited by Anambra State Department of Hospital Services, while the Histopathologists that work in these laboratories are certified by the National College of Pathologists, Nigeria.

The clinical diagnoses and corresponding histologic diagnoses were retrieved from pooled data from the three laboratories that were previously stored in SPSS statistical software. The clinicians using these laboratories at the time relied on clinical breast examinations (CBE) for their diagnoses, occasionally employing the use of ultra-sound scan. At the time of data collection, there was no mammography in any of the health centres studied. In this study, histopathologic diagnoses were solely based on histology and histochemical techniques. Laboratory request forms on which the clinical diagnoses were omitted by the clinicians are recorded as “no cancer” diagnoses by the authors.

Inclusion criterion

Results of all properly sampled and labelled open-breast-biopsy specimens submitted by registered physicians were included in the study.

Exclusion criteria

1. Results of breast specimens other than that acquired by open-breast-biopsy.
2. Results of non-breast biopsy specimens.
3. Breast specimens considered inadequate for histologic evaluation are excluded from the study.
4. Autolysed specimens are excluded.
5. Mislabelled specimens are also excluded.

Tables 1, 2 and 3 present clinical diagnostic data for malignant breast lesion for a sample of subjects who presented to both public and private hospitals in Anambra State Nigeria.

Table 1 Clinical Breast Cancer Screening Results for Subjects from all Hospital Combined

Clinical diagnoses	Histologic diagnoses		
	Positive for breast cancer (B)	Negative breast for cancer (\bar{B})	Total
Breast cancer present (A)	$n_{11} = 420$	$n_{12} = 135$	$n_{1.} = 555$
Breast cancer absent (\bar{A})	$n_{21} = 187$	$n_{22} = 1,438$	$n_{2.} = 1,625$
Total	$n_{.1} = 607$	$n_{.2} = 1,573$	$n_{..} = (n) 2,180$

Table 2 Clinical Breast Cancer Screening Results for Subjects from Public Hospitals

Clinical diagnoses	Histologic diagnoses		
	Positive for breast cancer (B)	Negative for breast cancer (\bar{B})	Total
Breast cancer present (A)	$n_{11} = 232$	$n_{12} = 70$	$n_{1.} = 302$
Breast cancer absent (\bar{A})	$n_{21} = 48$	$n_{22} = 419$	$n_{2.} = 467$
Total	$n_{.1} = 280$	$n_{.2} = 489$	$n_{..} = (n) 769$

Table 3 Clinical Breast Cancer Screening Results for Subjects from Private Hospitals

Clinical diagnoses	Histologic diagnoses		
	Positive for breast cancer (B)	Negative for breast cancer (\bar{B})	Total
Breast cancer present (A)	$n_{11} = 188$	$n_{12} = 65$	$n_{1.} = 253$
Breast cancer absent (\bar{A})	$n_{21} = 139$	$n_{22} = 1,019$	$n_{2.} = 1,158$
Total	$n_{.1} = 327$	$n_{.2} = 1,084$	$n_{..} = (n) 1,411$

Here the histologic diagnoses is considered the reference (gold) standard, hence it stands as the state of nature or the true state of condition; while clinical diagnoses, which accuracy is to be tested, are the provisional diagnoses as reported by various clinicians who examined the patients. The following were consequently obtained and used in the study.

Data Analysis

Applying the formulations in Oyeka et al (2013) [18] to the screening data in Tables 1, 2 and 3, we obtained the estimates of rates shown in Table 4.

Table 4 Estimated rates by type of Screening Centre

Rates	Screening Centre		
	All Hospitals	Private Hospitals	
		Public Hospitals	
Sensitivity (\hat{S}_e)	0.69193	0.82857	0.57492
Specificity (\hat{S}_p)	0.08582	0.14315	0.05996
False positive rate (\hat{F}_{+ve})	0.99075	0.99326	0.98894
False negative rate (\hat{F}_{-ve})	0.00039	0.00023	0.00052
Odds of positive response ($\hat{\Omega}_A$)	0.00934	0.00679	0.01118
Odds of negative response ($\hat{\Omega}_{\bar{A}}$)	0.00039	0.00023	0.00052
Odds ratio ($\hat{\omega} = 0$)	23.94871	29.52173	21.50000

Results

From Table 4 it is seen that the sensitivity and specificity of the screening test are respectively 82,857 and 14,315 per 100,000 for public hospitals and 57,492 and 5,996 per 100,000 patients for private hospitals. Thus the diagnostic screening test is more sensitive but less specific in public hospitals than in private hospitals.

For all hospitals combined the false positive rate is estimated as 0.99075. It is estimated to be 0.99326 in public and 0.98894 in private hospitals respectively. Thus for every 100,000 patients screened in public hospitals and found to test positive for breast cancer 99,326 are actually free of the disease compared with 98,894 for private hospital, a relative difference of 432 per 100,000 in favour of private hospitals in being better able to make more accurate diagnoses. The true positive rates for public and private hospitals are respectively 0.00674 and 0.00112, giving an overall true positive rate of 0.00925. In other words for every 100,000 patients clinically diagnosed as having breast cancer only 674 and 112 actually have the malignancy in public and private hospitals respectively, giving an overall true positive

rate of 925 per 100,000.

Similarly the estimated false negative rate for all hospitals is 0.00039. It is estimated to be 0.00023 and 0.00052 in public and private hospitals respectively. Thus for every 100,000 patients diagnosed and found to be free of breast cancer in public and private hospitals, 23 and 52 patients respectively actually have breast cancer giving an overall misdiagnoses rate of 39 per 100,000 patients that should have been so informed that they have breast cancer. The overall true negative rate for all hospitals is therefore 99,961 per 100,000 cases. The error in breast cancer diagnoses seems more attributable to private than to public hospitals.

The odds of positive response is 0.00934 for all hospitals combined; while it is 0.00679 and 0.01118 for public and private hospitals respectively. In other words among those testing positive to breast cancer, these estimated rates show that for every 100,000 patients who are diagnosed as having breast cancer 934, 679 and 1,118 patients are confirmed to actually have the disease by clinical diagnoses in all the hospitals combined, public and private hospitals respectively. Or more specifically, for every 100,000 patients who are actually free of breast cancer among those screened and found to have the disease, 934, 679 and 1,118 actually have

the disease if screened by all hospitals combined, public and private hospitals respectively. There is thus a relative difference of 439 per 100,000 in better diagnostic accuracy in favour of private hospitals over public hospitals.

Note that the estimated odds of negative response indicates that for every 100,000 cases that actually have breast cancer among those tested and found not to have the disease, about 39, 23 and 52 respectively actually have breast cancer if screened by all hospitals combined, public and private hospitals respectively.

Finally, the resulting odds ratios are found to be 23.94871, 29.52173 and 21.50000 for all hospitals combined, public and private hospitals respectively. This means that for every one patient incorrectly diagnosed as not having breast cancer there are about 30 breast cancer patients who are correctly diagnosed as having the disease if diagnoses is by public hospitals and about 22 breast cancer patients correctly diagnosed if diagnoses is by private hospitals, giving an overall rate of about 24 breast cancer patients correctly diagnosed as having the disease for every breast cancer patient incorrectly diagnosed in all hospitals.

Although there is significant positive association between clinical diagnoses and histologic diagnoses of breast lesions (the calculated chi-square values, using the usual chi-square test for independence, are 350.741 for public hospitals and 452.649 for private hospitals) in all screening centres, there is clearly stronger association in public than in private hospitals. This is because the relative sizes of the corresponding estimated odds ratios indicate that public hospitals are probably more efficient than private hospitals in being able to more accurately screen and isolate breast cancer cases.

Discussion

Our data showed that the combined breast cancer diagnostic sensitivity for all hospital groups is about 69%. This low overall sensitivity probably may be partly attributable to the rather low sensitivity in the private hospital group and partly due to the high submission of “no clinical diagnoses” by the doctors requesting histopathology investigation. We found that 459(21%) of the submitted histopathology request forms lacked provisional (clinical) diagnoses (not shown in the table). This frequency of inadequate completion of laboratory request forms has early been noted by Onyiaorah *et al* (2012) [23]. It would be instructive to further explore the

reason(s) for such omission to know which is specifically due to lack of knowledge of the diagnoses and those that are truly unwitting omissions. The clinical diagnoses of breast lesions by doctors working in public hospitals is about 26% more sensitive than that of doctors working in private hospitals, which probably explains why public hospitals are able to more accurately screen and isolate true breast cancer cases than private hospitals. This is probably due to higher number of better trained and more experienced doctors in the workforce of the public hospitals in the state than that in the private hospital group. Another probable reason for the higher sensitivity recorded by doctors in public hospitals is that these doctors are more likely to abide by established diagnostic protocol and quality management system as may be adopted by their units and/or hospitals. Moreover, the doctors in public hospitals often have the benefit of case peer review and this probably may have enhanced the sensitivity of their diagnoses of breast lesions.

The specificity seen in all hospital groups is low. This would probably have been higher if modern radiodiagnostic techniques were available and in use in these health centres. Majid *et al* (2003) demonstrated the ability of mammography to enhance the accuracy of breast cancer screening [10].

The false positive rate is found to be fairly high in both hospital groups. This may have caused some psycho-social trauma to the otherwise cancer-free patients as noted by Fang *et al* (2012) [16]. This underscores the need to have an efficient histopathology unit to quickly and more accurately disprove or confirm the diagnoses. Hence the Australian cancer network (2001) stated that treatment of cancer will depend on histologic diagnosis rather than clinical diagnosis [7]. The false negative rate are respectively 23 and 52 per 100,000 patients for public and private hospitals. These are better than the false negative rate of 190 per 100,000 recorded for screening by CBE in a case series by Day *et al* (1990) [11].

Conclusion

Our findings brought to the fore the need for more funding of our health system. Regular training and re-training of the country’s medical personnel and infrastructural development of the hospitals may probably enable better accuracy in breast cancer diagnoses.

References

- McPherson K, Steel CM and Dixon JM: ABC of breast cancer disease. Breast cancer-epidemiology, risk factors, and genetics. *BNJ*. 2000, 321:624-628
- Fisher B, Osborne KC, Bloomer WD, Margolese RG: **Neoplasms of the breast**. In *In Cancer Medicine Plus [CD-ROM]*. Edited by Holland JF, Frei III E, Bast RC, Morton DL, Kufe DW, Weichselbaum RR. Baltimore, MD: **Williams and Wilkins**; 1998
- Adebamowo CA, Ajayi OO: **Breast cancer in Nigeria**. *West Afr J Med*. 2000, 19:179-191
- Sally N Akarolo-Anthony¹, Temidayo O Ogundiran² and Clement A Adebamowo Emerging breast cancer epidemic: evidence from Africa. *Breast Cancer Research*. 2010, 12:S8
- International Agency for Research on Cancer, IARC **GLOBOCAN** 2008 <http://globocan.iarc.fr/factsheet.asp>
- Adesunikanmi ARK, Lawal OO, Adelusola KA, et al. The severity, outcome and challenges of breast cancer in Nigeria. *The Breast*. 2005, 15:399-409
- Australian Cancer Network (2001) The pathology reporting of breast cancer. A guide for pathologists, surgeons, radiologists and oncologists. Recommendations of the Australian Cancer Network Working Party
- Roman Shyyan, Shahla Masood, Rajendra A. Badwe, et al Breast Cancer in Limited-Resource Countries: Diagnosis and Pathology. *The Breast Journal*. 2006, 12:S27-S37
- Baker LH. Breast Cancer Detection Demonstration Project: five-year summary report. *CA Cancer J Clin*. 1982, 32:194-225
- Majid AS, de Paredes ES, Doherty RD, et al. Missed Breast Carcinoma: Pitfalls and Pearls. *RadioGraphics*. 2003, 23:881-895
- Day PJ, O'Rourke MG. The diagnosis of breast cancer: a clinical and mammographic comparison. *J Aust*. 1990, 18;152:635-639
- Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. *N Engl J Med*. 1991, 324:377-384
- Thomas EJ, Studdert DM, Burstin HR, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care*. 2000, 38:261-271
- Schiff GD, Kim S, Abrams R, et al. Diagnosing diagnostic errors: lessons from a multi-institutional collaborative project. In: *Advances in Patient Safety: From Research to Implementation*. Vol 2. Agency for Healthcare Research and Quality Web site. www.ahrq.gov/qual/advances. Accessed July 10, 2009.
- Graber M. Diagnostic errors in medicine: a case of neglect. *Jt Comm J Qual Patient Saf*. 2005, 31:106-113
- Fang F, Fall K, Mittleman MA, et al. Suicide and Cardiovascular Death after a Cancer Diagnosis. *N Engl J Med*. 2012, 366:1310-1318
- Oyeka ICA, Onyiaorah IV, Onyiaorah A, et al. Use of sensitivity and specificity as measure of association in screening tests. *American Journal of Research in Biology*. 2012, 1: 7-11
- Oyeka ICA and Onyiaorah IV. Estimation of False Rates-based Odds Ratios as Measure of Association in Screening Test. *Advances in Medical Sciences*. 2013, 2 : 014-024
- Fleiss JL. *Statistical Methods for Rates and Proportions*. **John Wiley and Sons**; 1973
- Kestenbaum B. Epidemiology and Biostatistics: an introduction to clinical research. **Springer Science LLC**; 2009
- Hogg RV, Craig A. Introduction to Mathematical Statistics. **Croydon Company, New York** 3rd ed. 1980
- Neter J, Wasserman W. Applied linear statistical models: regression, analysis of variance, and experimental designs. **R. D. Irwin**, 5th ed. 1974
- Onyiaorah IV, Ukah CO, Anyiam DCD et al. Effect of Remedial Measures on Inadequacies in the Completion of Laboratory Request Forms by Clinicians. *Clinical Audit*. 2012, 4:9-14