



Estimation of Correlation between Quetelet's Index and Nottingham Prognostic Index in Patients of Carcinoma Breast: A Study Protocol

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: Carcinoma breast is the most prevalent neoplasm in women with the highest death rate associated with cancer worldwide. In Indian women, breast cancer ranks first, followed by cervical cancer, with its incidence increasing day by day. Obesity is an important modifiable causative factor of carcinoma breast, associated with a greater chance of contracting breast cancer, and with worse prognosis in women of all age groups. It exhibits a state of chronic-inflammation, adipokine-imbalance, insulin-resistance and increased oestrogen-signalling. This pro-tumorigenic environment stimulates cancer development through abnormal proliferation and survival of breast tissue. Quetelet's Index is the most commonly used index to classify obesity, whereas the Nottingham Prognostic Index is the most widely used index for longevity assessment and prognosis of breast cancer patients. This study estimates the correlation between Quetelet's index with Nottingham Prognostic Index.

Methods: This prospective observational study will be to be conducted in the Department of Pathology, JNMC, Wardha and AVBRH, Sawangi (Meghe), Wardha in coordination with the Department of General Surgery. Total 35 cases of Carcinoma Breast undergoing Modified Radical Mastectomy will be included in the study. Clinicopathological and anthropometric data of patients

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will be collected. The Quetelet's Index and the Nottingham Prognostic Index will be determined for each patient and data will be analyzed with appropriate statistical tests to estimate the correlation between them.

Results: Statistically significant correlation is expected between Quetelet's Index and the Nottingham Prognostic Index.

Conclusion: Conclusion will be drawn on positive/negative correlation of Quetelet's Index with different parameters of Nottingham's Prognostic Index.

Keywords: Breast cancer; causative factor; tumour.

1. INTRODUCTION

Carcinoma breast is the most prevalent neoplasm in women who have the highest death rate associated with cancer worldwide. In Indian women, breast cancer ranks first followed by cervical cancer with its incidence increasing day by day [1].

As per WHO, breast carcinoma accounts for 2.09-million cases and 6,27,000-deaths globally which is almost 15% of overall deaths occurring due to carcinomas, among women. According to Globocan-statistics 2018, almost 20.80 lakh women were diagnosed with breast carcinoma and it equated for about 24.2% of overall carcinomas in women, all over the world, making its incidence to about one in every four cancers in women [2].

In Indian women, breast cancer results in one death every 13 minutes; women in the 30-50 age group are at low risk, while women in the 50-64 age group are at high risk of developing breast carcinoma. Post-cancer survival was estimated to be 60% for Indian women with breast carcinoma, with poor survival rates mostly

attributed to late diagnosis [3]. The various etiopathological factors in breast carcinoma include age, genetic-factors, gender, endogenous and exogenous-endocrine factors, child-bearing and fertility, dietary-factors, alcohol, radiation-exposure, benign-duct-diseases, previous history of breast-carcinoma and geographical factors. Heredity plays a major role, responsible for 5-10 percent of cases of breast carcinoma found in first-degree relatives (i.e. mother, daughter, sister or grandma). It is speculated that mutations in either or both of the Breast Cancer gene 1 and Breast Cancer Gene 2 tumor suppressor genes raise the risk of carcinoma breast. Whereas factors such as breastfeeding, first pregnancy < 25 years of age, multiple pregnancy < 25 years of age, daily exercise and Asian descent are thought to decrease the risk of carcinoma breast [3].

Obesity is an important modifiable causative factor of carcinoma breast, associated with a greater chance of contracting breast cancer, as well as with worse prognosis in women of all age groups. It exhibits a state of chronic-inflammation, adipokine-imbalance, insulin-resistance and increased oestrogen-signalling.

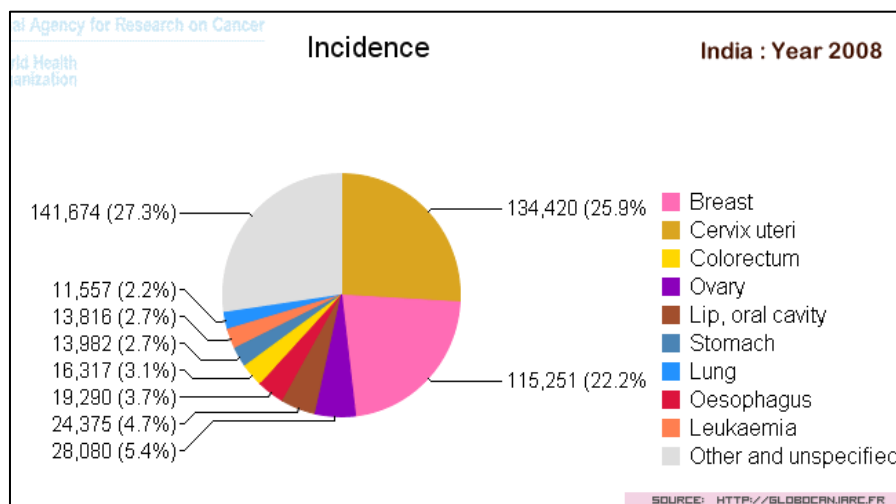


Fig. 1. Pie chart showing incidence

This pro-tumorigenic environment stimulates development of cancer through abnormal proliferation and survival of breast tissue. It is suspected that it raises the proinflammatory cytokines; both local and circulating, promotes tumour vascularization and also activates the most malignant stem cells, which causes increased tumour cell formation, invasion and metastasis [4]. In addition to this, it also accounts for increased risk of complications associated with all of the treatment modalities (surgery, chemotherapy, radiation) in carcinoma-breast.

Body mass index (Quetelet's Index) is a simple and the most commonly used index used to classify obesity, as it is the same for both genders and for any age of adults. It is defined as the weight ratio of an individual in kgs to square of height in meters. (kg/m^2). It can be measured by using the formula Quetelet's Index = $\text{Weight}(\text{kg}) / [\text{Height}(\text{m})]^2$. Studies suggest that women with higher Quetelet's Index may be associated with higher grade, increased aggressiveness of tumour, an increased risk of recurrence and mortality and those with lower BMI are relatively at a lower-risk of developing breast carcinoma and may be related with a lower grade of tumour in patients having carcinoma breast [1]. A few studies suggest that increased tumour proliferation is the trajectory which explains the cause of the worse outcome of carcinoma breast among obese ladies [5].

To estimate survival and the risk of recurrence in breast carcinoma cases, a variety of prognostic factors have been identified. Nevertheless, it cannot be speculated which aspect predominates above the others in breast cancer prognosis [3]. Therefore there has been an attempt to amalgamate each of these variables into some important indexes and grading systems.

The Nottingham Prognostic Index is the most widely used index for longevity assessment and prognosis of breast cancer patients, taking into account the following three variables –

- Size of the tumour
- Status of lymph node
- Modified Bloom Richardson's grading of the tumour [6].

In numerous studies, it has helped to discern patients on the basis of aggressiveness of the tumour and has become an important prognostic aid in determining outcome of patients with breast-carcinoma. The present study is designed

with an aim to establish a correlation between Quetelet's index and Nottingham Prognostic Index for determining the effect of obesity on aggressiveness of the tumour, predicting the survival of patients with breast-carcinoma.

2. RATIONALE

Carcinoma Breast is one of the most prevalent causes of death worldwide, with a growing prevalence every day. Obesity is a growing plight all over the world that plays a key part in the growth and propagation of the tumor. It's a modifiable risk factor. Behavioural changes (dietary and exercise) may also lead to changes in tumorigenesis, insulin-sensitivity, circulating oestrogen and oxidative stress in response to weight loss. Obesity-reduction techniques can prove to be cost-effective strategies for reducing the risk and improving outcomes in the patients with Carcinoma Breast. The Quetelet's index, which is the most widely used measure of obesity, has to be compared with the Nottingham Prognostic Index (NPI) to assess patients' outcomes; thereby being an adjunct to breast carcinoma prognosis.

3. RESEARCH GAP

The present study aims to close the gap of understanding between correlation of Quetelet's Index which is a direct measure of obesity, with Nottingham's Prognostic Index in Carcinoma Breast. It will enable to breach the gap of understanding the relationship between obesity and the tumour size, histological grade and the lymph node metastasis in Carcinoma Breast. It will help to create a frame for early, cost-effective strategies for reducing breast-cancer risk and improving breast-cancer outcome.

4. RESEARCH QUESTION

With understanding the effect of obesity on aggressiveness and proliferation of tumour cells in Carcinoma Breast, the following research question is framed –

'Does Quetelet's Index have a significant association with the size of the tumour, histological-grade and lymph node metastasis i.e. Nottingham's Prognostic Index in Carcinoma Breast.'

5. METHODOLOGY

Study Design: Observational, analytical, cross-sectional and prospective.

Place of Study: Department of Pathology, JNMC, Sawangi (Meghe), Wardha, Maharashtra.

Duration: 2020 to 2022 (2 years).

6. METHODS

- Medical records will be taken and an adequate physical examination will be carried out in all patients.
- The anthropometric data like history of built and size of their body, along with their adult weight as well as height 1 year before diagnosis, highest average weight and weight at eighteen years of age will be obtained from the respondents.
- Weight (in kgs.) and height (in meters) will be measured and Quetelet's Index will be calculated for each case.
- In addition to BMI, we will measure patients' waist and hip circumference as anthropometric indicators of obesity in relation to the likelihood of breast cancer.
- Modified Radical Mastectomy specimens of cases confirmed as Carcinoma Breast will be obtained in 10% of Formalin and the resected specimens shall be kept in 10% of formalin for 12-24 hours for fixation.
- Dissection of the received specimens and appropriate sections from the margins, tumour mass and axillary lymph nodes will be done.
- Specimens will be subjected to routine tissue processing after which routine Haematoxylin and Eosin staining will be carried out.
- The histological grade of the tumour will be determined by the Nottingham modification of Bloom-Richardson Grading System.
- Grade of the tumour will be taken as Grade I equal to one, Grade II equal to two and Grade III equal to three.
- The Nottingham Prognostic Index of each case will be calculated by evaluating the size of the tumour, status of the lymph nodes and histological grade.

Formula used will be: $NPI = [0.2 \times \text{lesion's size (in centimetres)}] + \text{status of the lymph nodes} + \text{tumour's grade}$.

- Where, 0 nodes = 1; 1-3 nodes = 2; >3 nodes = 3 and grade will be calculated as Grade I equal to one, Grade II equal to two and Grade III equal to three.
- After which, correlation of Body Mass Index of each case with its Nottingham's Prognostic Index will be done.

6.1 Sample Size

35 Patients.

The sample size was calculated by using Krejcie and Morgan formula with desired error of margin:

$$n = ((Z \alpha/2)^2 \times p \times (1-p)) / d^2$$

where,

$Z\alpha/2$ is the level of significance at 5% i.e. 95 % confidence interval = 1.96

p = Prevalence of breast carcinoma = 0.33% = 0.033 [2]

d = Desired error of margin = 6% = 0.06

n = Sample size = $((1.96)^2 \times 0.033 \times (1 - 0.033)) / (0.06)^2 = 34.05$

$n = 35$ (35 patients will be needed in the study).

6.2 Inclusion Criteria

1. All cases diagnosed as Carcinoma Breast on histopathology.
2. All cases in which Modified Radical Mastectomy has been done.
3. All female patients presenting with Carcinoma Breast.
4. Primary cases of Carcinoma Breast without any history of previous treatment.
5. All cases of Carcinoma Breast having complete height and weight data.

6.3 Exclusion Criteria

1. All cases other than carcinoma breast and cases with metastatic deposits.
2. All cases where only trucut biopsy, wedge biopsy or lobectomy has been done.
3. All cases of myoepithelial lesions, mesenchymal and fibroepithelial tumours, tumours involving nipple, metastatic tumours and adenomas.
4. All male patients presenting with Carcinoma Breast.
5. Cases with a history of neoadjuvant therapy.
6. All cases of Carcinoma Breast having incomplete height and weight data.

6.4 Statistical Analysis

Statistical research will be carried out using the 'Chi Square Test' where statistical significance will be assumed to imply a value of P less than 0.05.

6.5 Preliminary Data Recording

1. Name:
2. Age/Sex:
3. Registration Number:
4. Nature of the Specimen:
5. Local examination of breast:
6. Comorbidities:
7. Diagnosis on Histopathological Examination:
8. Height(cm.):
9. Weight(kgs.):
10. Waist circumference:

7. EXPECTED RESULTS

The study will be conducted for a period of 2 years and all the observations will be depicted in a well-tabulated master chart.

8. DISCUSSION

Breast carcinoma is a heterogeneous disorder that differs by genetic subtype, clinicopathological manifestations, prognosis and care. The features of the tumor and its response to various management plans vary depending on the level and grade of the tumor as well as the expression of the different receptors. Tumors are histologically categorized by their receptor positivity, namely estrogen, progesterone and human epidermal growth factor receptor-2 (ER, PR and HER2). A variety of causes have been found to affect an individual's risk of contracting carcinoma breast and on their overall prognosis [7].

Obesity, that is Body Mass Index more than 30 kg/m² is a significant risk factor that leads to a higher chance of contracting breast cancer. It has also been found to be correlated with a larger size of the tumor, relatively high proliferative index as well as histological score, according to some research [1].

A short review for the present work is entitled below, citing the studies from different centres establishing the correlation of Quetelet's Index with different parameters of Nottingham's Prognostic Index.

Janet R. Daling et al., conducted a study entitled "Relation of Body Mass Index with Tumour Markers and Survival among Young Women with Invasive-Ductal Breast-Carcinoma", which was population-based follow-up study of 1177 women under the age of 45 who were diagnosed with

breast carcinoma (Invasive ductal type) from 1983 to 1992. The study found that women in the maximum BMI range diagnosed with breast carcinoma at a young age had a poor survival rate and were associated with higher mortality rate. The tumours of overweight cases were considerably larger and associated with markers of elevated proliferative potential of the cells than those of smaller women [8].

Nehad M. Ayoub et al, published an article titled "Impact of Obesity on Clinicopathological Characteristics and Prognosis of disease in Pre- and Postmenopausal Breast Cancer Patients: A Retrospective Institutional Study" in which they reviewed the medical records and the electronic database of 348 patients who were diagnosed as breast carcinoma cases histologically, over a period of eleven years from 2004 to 2014. The result of the study found that obesity in contrast to non obese patients at diagnosis was correlated with advanced stage and classification of breast carcinoma as well as poor prognostic characteristics at cancer presentation [9].

Blair, Cindy K., et al., published an article titled "Obesity and survival among group of breast cancer patients is partially mediated by characteristics of the tumour" in which the role of obesity on survival was determined among 859 cases with incidence of carcinoma breast and 697 deaths from breast-cancer over a period of six years, from 1997 and 2009. The conclusion of study showed that obese and overweight cases had respectively, 1.7- and 1.8-times rise in the risk of stage third and fourth cancer and tumours of grade 3/4 [10].

Wang, Junyi, et al. published an article titled "Body Mass Index Increases the Lymph-Node Metastasis Risk of Carcinoma Breast" in which they total 20 studies with 52,904 cases until November 2019 were encompassed. A 2 stage random impact meta-analysis was conducted to check the relationship between Quetelet's Index and risk of metastasis of the lymph node. Their studies concluded that BMI greatly raises the risk of lymph node metastases in Carcinoma Breast [11].

Keskin O et al. conducted a retrospective cohort study entitled "Impact of lymph node obesity in operable breast cancer patients," involving 1,295 patients with axillary dissection and review of the association between Quetelet's Index and patient and tumour characteristics, in particular status of the lymph nodes. The study concluded that the

number of the dissection of lymph nodes was significantly higher in obese patients, but there was no connection between the proportion of lymph nodes which were positive for infiltration by malignant cells and BMI [12].

A number of related studies were reported [13-15]. Goyal et al. reported on Utility of micro vessel density and it's correlation with Nottingham prognostic index in carcinoma breast [16]. Few of the studies on different diagnostic approaches and related aspects of carcinoma breast were reviewed [17-21]. Wagh et al. reported a study on relationship between hypothyroidism and body mass index in women [22-28].

9. CONCLUSION

Conclusion will be drawn from resulted outcome.

CONSENT

Prior written consent will be received from all patients involved in the study.

ETHICAL APPROVAL

An Institutional Ethics Committee Clearance will be obtained before the start of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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