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ORIGINAL RESEARCH

Estimating the weighted prevalence of anxiety disorders in breast cancer patients using a Two-stage approach

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Abstract

***Background*:** A two-stage survey is useful when the actual diagnostic interview is time-consuming and expensive to administer on the general population.
Objective: To compare Schedule for Clinical Assessment in Neuropsychiatry (SCAN) with Hospital Anxiety and Depression Scale (HADS) in the determination of the prevalence of anxiety disorder in patients with breast cancer.
Methods: A cross-sectional study of 200 female patients diagnosed with breast cancer attending the Oncology Out-Patients Clinic of the Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria was done. The instruments used for the survey included a socio-demographic questionnaire, the HADS and the SCAN.
Results: The mean age of the subjects was 49.6 ± 11.2 years. Majority of the subjects (76.5%) were married. Using HADS with a threshold score of $\geq$ 8, 53 (26.5%) met the criteria for probable anxiety disorders (herein called 'cases'). Of the 68 patients (all 53 'cases' plus 15 randomly selected 10% of the non-cases) interviewed with the SCAN instrument, only 38 met the criteria for diagnosis of anxiety disorder.
Conclusions: The prevalence of anxiety disorders can be determined with greater precision using the two-stage design approach. Diagnostic tools like SCAN should therefore be incorporated in the assessment protocols for patients with breast cancer and other illnesses.

Key words: *Anxiety Disorder, Two-stage survey, Breast Cancer, Pattern.*

Introduction

Measuring the prevalence of a disease is important for reasons which include public health and policy definitions. Typically, many epidemiological surveys rely on a single phase sampling design that screens a particular population for a particular illness using one screening test or tool. [1] However, when the single screening method only evaluates symptomatology rather than diagnosis, or when the actual diagnostic interview is time-consuming and expensive to administer on the general population, a two-stage survey becomes necessary. Regardless of the area of medicine which is being studied, the use of two-stage surveys is indicated when it is clearly difficult or impossible to conduct a comprehensive evaluation of all the participants in a huge random sample of the population. [2]

Two-stage studies involve evaluating a target population for a disease using two tests. The initial screening test is designed to be relatively easy, inexpensive and non-invasive, even though it may be considered less accurate than the ideal tool for

evaluating the disease. [3] This tool is then administered to a sample of the entire target population considered for the study. Using the results of the first evaluation, the subjects are stratified, based on their initial responses or scores, into subsets which are considered for more extensive and comprehensive disease evaluations in the second phase of the study. [4] This two-stage design has been used extensively to estimate the prevalence rates of Alzheimer's disease and dementia, [5] sexually transmitted diseases, [6] and heart diseases. [7]

The advantages of two-stage surveys are numerous. Asides saving on time, costs, and other resources necessary for evaluating disease prevalence, it has been suggested that two-stage designs improve the precision of estimation as it focuses on drastically reducing the standard error for the prevalence estimate. [8] In addition, the ability to compare the sensitivity and specificity of study tools is facilitated by these two-stage studies as estimation of false and true-positive rates are usually based on data obtained from a two-stage study. [9]

Two-stage studies have been used extensively in psychiatry to ease diagnosis of relatively rare conditions.. [3, 4] First proposed as a research design by Neyman, the use of two-stage surveys in psychiatric epidemiology dates back to the 1960s. [4] Two forms of estimators are commonly used with two-stage studies in the estimation of prevalence rates from research data. The first and less commonly used method is the modeling type estimator, which is used when auxiliary information is available in addition to the main outcome variable. The second and more commonly used method is the weighting type estimator (or standardization estimator). [4] The weighted estimator, also referred to as weighted likelihood, maximizes the inverse probability of weighted sum of log-possible contributions from observations in the second phase. [9]

Anxiety is a coordinated cognitive, emotional, physiological and behavioral response pattern that aids escape from current danger and avoid future danger. It is a normal reaction to stress which may be excessive, intense, irrational and unwarranted. [10] In anxiety disorders, the frequency and intensity of anxiety responses are usually out of proportion when compared to situations that trigger them. [11] The prevalence rate of anxiety disorder in breast cancer ranges between 1% and 49%. [12] This wide variety of prevalence rates reported from studies has been linked to differences in designs, methods, sampling techniques heterogeneity of breast cancer population and more importantly, the nature of the instrument used in making the diagnosis of anxiety disorders.

Several studies have employed either the Schedule for Clinical assessment for Neuropsychiatry (SCAN) or the Hospital Anxiety and Depression Scale (HADS) tools singly or in combination to identify anxiety, depression and other neuropsychiatric disorders among diverse populations of patients with breast cancers in the United States, [13] Australia, [14,15] Thailand, [16] Japan, [17] and Germany. [18] Some of the drawbacks reported with the use of the tools were related to sample sizes, method of interviewing, selection of patients (out-patient or in-patient) stage of treatment during an interview and difficulty in the generalization of the findings. [19, 20]

There is a dearth of literature on local studies of the prevalence of anxiety disorders among patients with breast cancer. However, the clinical relevance of prevalence studies in these populations cannot be over-emphasized as the presence of anxiety disorder in breast cancer patients connotes poor prognosis since it has been shown to be negatively associated with quality of life after diagnosis, at the start of treatment and post-treatment. [21]
The aim of this study was to present a simple description of how to determine weighted prevalence of a variable using the analogy of anxiety disorders in patients with breast cancer.

Methods

Subjects

The subjects in this study were made up of female

patients diagnosed with breast cancer, and attending the Oncology Out-Patient Clinic of the Lagos State University Teaching Hospital, Ikeja, Lagos. The facility is a major cancer referral center in Lagos, southwestern Nigeria. Potential subjects were selected using a random sampling method; a clinic visit list and a random numbers table were useful in making the selections.

The eligibility criteria included (i) histological diagnosis of breast cancer, (ii) ages 18 years and above, and (iii) consent for inclusion in the study. Excluded from the study were patients with history of a chronic medical condition that has been associated with anxiety symptoms or disorder (such as thyroid disorder), those who were currently on medications known to cause anxiety symptoms such as interferon, patients attending the clinic for the first time for investigative purposes and unstable patients (critically ill or deemed unable to respond to the questionnaire).

Ethical approval for the study was obtained from the Ethical and Research Committee of the Lagos State University Teaching Hospital, Ikeja. The study was conducted in accordance with the principles of the Helsinki Declaration.

Using the Horvitz-Thompson estimator, the weighted prevalence, π, is estimated by the formula:

$$\pi = \Sigma w_i y_i / \Sigma w_i$$

Where w_i is the *ith* patient's sampling weight, y_i represented by 1 if the *ith* second-phase patient is a 'true' case, or 0 if otherwise, and Σ represents 'the sum of'. [22] Without going into too many technical details, the weighted prevalence can be simply calculated by dividing the weighted number of cases by the first-phase sample size. [3]

The prevalence rate of anxiety disorders among breast cancer patients in Nigeria was not known from the available literature reviewed. The prevalence rates have been reported to range between 1% and 49 % across several countries. [12, 14-17,19-20]

A prevalence rate of 16%, which was reported in a more recent study in Thailand was used to calculate the sample size. [16]

$$n = 206.5 \approx 207$$

Since the study population size, the total clinic enrollment was less than 10,000, the final sample size (nf) was obtained after applying the correction factor.[23]

nf = final sample size

n = Sample size in a cross-sectional study as obtained above

n = estimate of study population =530 (total number of enrolled breast cancer patients).

n = 148.92

An additional 10% was added to make room for inadequate responses, making a total of 163.9 but a total of 200 breast cancer patients were studied.

Procedure

Using a descriptive cross-sectional study approach, 200 female patients were randomly selected following a systematic sampling method, and using the sample size formula [$n = (z^2pq)/d^2$] for calculating sample size in cross sectional studies [24]; where z = 1.96, d = 0.05, p = 0.16, and q = 0.84. A correction factor was applied considering that the total clinic enrollment was less than 10,000. [23]

The patients were recruited every clinic day by recruiting every third patient on the clinic list for the day that met the inclusion criteria and had registered by 9.00 a.m. while waiting for the doctors. Each selected patient was requested to fill the socio-demographic questionnaire, before the HADS was administered. Those who scored 8 and above on the anxiety subscale of the HADS were selected as 'cases' and added to this were 10% randomly selected subjects who previously did not score up to 8 using HADS screening instrument for anxiety disorder. The total number of 'cases' were then interviewed with SCAN - which represented the second stage of the study. [25, 26] It took an average of 20 minutes to complete each relevant section of SCAN per participant.

Measures

Socio-demographic Questionnaire

This survey questionnaire was used to gather data concerning the age, gender, marital status, educational level, occupation, monthly income and social support. Occupation was classified based on

the International Standard Classification of Occupation. [27]

Hospital Anxiety and Depression Scale (HADS)

This is a 14-item rating scale designed to screen for anxiety and depression in the general population. [28] It is a self-administrable questionnaire containing seven anxiety- and depression-related items each. The responses are scored on a scale of 0 to 3 and the total score for each of the domains, anxiety and depression, are computed separately. Scores from 11 upwards indicate the presence of anxiety or depression, scores between 8 and 10 points are considered borderline while scores below 8 signify the absence of anxiety or depression. [29] In Nigeria the HADS was validated by Abiodun and he noted that the optimum cut-off score was 8 for the anxiety and depression sub-scales respectively. Abiodun also concluded that the HADS is useful in detecting psychiatric morbidity among physically ill patients in community settings as well as cancer population because it does not check for somatic symptoms. [30] The administration of this instrument is supposed to take about five minutes. [28]

Schedule for Clinical Assessment in Neuropsychiatry (SCAN)

The Schedule for Clinical Assessment in Neuropsychiatry (SCAN) is a set of instruments supported by manuals that aim to measure and classify the psychopathology in psychiatric disorders of adult life. It is the latest version of development in the present state examination (PSE). [31] SCAN has four components, namely: the 10th edition of the present state examination, items group of checklists, the clinical history schedule and the glossary of definitions.

The first part of PSE 10 section was used in this study.

The core principle of the PSE, which is also retained in SCAN, is the preservation of the features of clinical examination despite the structured nature of the interview. The interviewer attempts to elicit a comprehensive list of phenomena present within a designated time frame and rate the degree of severity. The examination involves comparing the described subjective experience of the respondents against glossary description of clinical phenomena. This is then used to generate a clinical diagnosis as described in the ICD-10 through the use of SCAN computer software.

Data Analysis

Data analyses were done with the Statistical Package for Social Sciences (SPSS) version 16. A precision level $\leq$ 0.05 was fixed for statistical significance. The prevalence of anxiety disorders was determined by the weighting method. [3]

Results

Patients' characteristics

In Table I, the mean age of the patients was 49.6 ± 11.2 years. The majority (76.5%) of the patients was married, came from monogamous family setting (76%) and had less than 5 children (83.0%). About 39% of the patients had tertiary education while 29% just had only primary education. The relatives were the major sources of support for 66.5% of the patients. More of the patients were employed at the time of carrying out the study (59.5%), while 21% earned less than 30,000 Naira monthly income.

Prevalence of anxiety disorder and the relationship between HADS classification and SCAN diagnosis of anxiety disorder

Using HADS with a threshold score of $\geq$ 8, 53 patients (26.5%) met the criteria for probable anxiety disorders while the remaining 73.5% had scores less than 8 (non-cases). At the second stage, 68 patients (all 53 probable cases and randomly selected 10% of the non-cases) were interviewed with the SCAN instrument and 38 subjects out of the 68 met the criteria for the diagnosis of anxiety disorder. The 38 patients comprised 37 patients from the HADS probable cases of anxiety disorder, and just one patient out of the initial HADS non-cases.

The relationship between HADS classification and SCAN diagnosis of anxiety disorder among the patients is reflected in Table II. About one-quarter of the patients (n = 53, 26.5%) had HADS scores suggestive of anxiety disorder. Out of the total 200

Table I: Socio-demographic characteristics of 200 study participants

Variables		*Frequencies (n)*	*Percentages (%)*
Age		**Mean: 49.6± 11.2 years**	
Marital status	Married	153	76.5
	Unmarried	47	23.5
Family Type	Monogamy	152	76.0
	Polygamy	48	24.0
Religion	Christianity	154	77.0
	Islam		23.0
Number of children	≤ 4	166	83.0
	>5	34	17.0
Education	Primary	58	29.0
	Secondary		32.0
	Tertiary	78	39.0
Ethnicity	Yoruba	150	75.0
	Hausa		2.0
	Igbo	24	12.0
	Others	22	11.0

patients screened using HADS, 53 were positive for anxiety disorder, while 15 out of the non- cases were added, thus making a total of 68 participants. Thereafter, the 68 participants were subjected to the SCAN instrument to confirm the presence of anxiety disorder; only 38 (19.0%) participants were found to have an anxiety disorder. The true-positives tested positive for anxiety disorder using both instruments, while true negatives tested negative using both instruments (Table II).

Distribution of anxiety disorders among the participants diagnosed with the SCAN instrument

Table III shows the distribution of anxiety disorders (detected using SCAN) among patients with breast cancer. The largest proportion of subjects with anxiety disorder had mixed anxiety and depressive disorders (44.7%), followed by social phobia (18.4%), panic disorder (13.2%), generalized anxiety disorder (10.5%), simple phobia (7.9%) and agoraphobia (5.3%) in descending order.

Table II: HADS and SCAN diagnoses of anxiety disorders among the participants

HADS Classification	*SCAN Diagnosis*		
	Anxiety disorder (%)	***No anxiety disorder (%)***	***Total***
HADS (Cases)	37 (97.4)	16 (53.3)	53 (77.9)
HADS (Non- cases)	1 (2.6)	14 (46.7)	15 (22.1)
Total	38 (100.0)	30 (100.0)	68 (100.0)

Table III: Distribution of anxiety disorders among the participants diagnosed with SCAN

Types of Anxiety Disorder	*Frequencies*	*Percentages*
Agoraphobia	2	5.3
Simple or specific phobia	3	7.9
Social phobia	7	18.4
Mixed anxiety disorder and depressive disorder	17	44.7
Panic attack	5	13.2
Generalized anxiety disorder	4	10.5
Total	33	100.0

Discussion

This study adopted a two-stage approach using HADS as a screening tool and SCAN as the diagnostic tool for anxiety disorders among women with breast cancer. The HADS questionnaire served as the initial survey tool for the first phase, which helped to differentiate the likely cases of anxiety disorder from the likely non-cases. The choice of HADS as the first stage tool was based on its ease of use, as it was a self-administrable questionnaire which took less than 15 minutes (on the average) to fill by the participant. Although, relatively inexpensive, HADS may be less accurate in the diagnosis of anxiety and depressive disorders, hence its choice as a simple screening tool. [28] On the other hand, the SCAN instrument was a formal interview required to further validate the responses derived from the HADS.

This example represents a 'two-stage' or 'double sampling' study design where the chance of selection of patients at the second stage is completely dependent on the results of the first stage, and perhaps, additional information gathered during the first stage. The estimation of prevalence in a two-stage study is not as difficult as it is commonly thought. It relies on the use of a sampling weight, which would be demonstrated using the results presented earlier. The present study collected data from two hundred patients with breast cancer, but the analysis used in demonstrating this concept was restricted only to those patients with complete data and proceeded to the second stage. The data gathered from the results of the first stage screening and used for random sampling in the second stage were provided by the allocation of sampling weights to each subject. This was given by the reciprocal of the sampling fraction in stage two.

During the process of data collection from the two hundred cases, we found 53 likely cases and 147 likely non-cases. In the second stage of the study, all of the likely cases (all 53 likely cases), and 15 (out of 147) of the likely non-cases were interviewed. Using this information, the sampling weights corresponding to the second stage patients from both strata were therefore 1 (i.e. 53/53) and 9.8 (147/15) for the likely and non-likely cases respectively. It is apparent that the sampling weight indicated how many of the first stage subjects were 'represented by' each of the second stage records. [3] Secondly, each of the patients had been assigned a sampling weight based on their HADS status (the likely case/likely non-case) which was the reciprocal of the sampling fractions. On the table, there were data for a total of 68 subjects (53 and 15), and the sum of these subjects' sampling weights was 200, meaning that 68 patients represented the 200 first stage subjects. Furthermore, each of the participants to whom we allocated a score of 1 after the SCAN interview was a 'true' case of anxiety disorder, while 0 represented otherwise. The multiplication of the total of this interview group and the total sampling weights (that is, 47) gave the estimation of the first phase 'true cases' represented by the 38 second stage cases. Therefore, the estimated prevalence will apparently be 47/200, which is 23.5%.

The present study yielded findings that supported the use of two-stage designs despite strong criticisms suggesting that such analyses are complicated, and that serious problems with the method may arise when there are non-responses in the second phase of the study. [32] However, the Horvitz-Thompson estimator of prevalence used in this study proved to be an effective, simple algebra and did not require any special techniques. In addition, there were no non-responses, further supporting the fact that it is possible to have second-stage with no non-responses. This is not to suggest that two-stage studies completely eliminate or precisely estimate standard errors, but to conclude that the precision with which the prevalence rate of a disease can be measured can be

much better. The cross-sectional approach and the exclusion of patients with co-morbid medical conditions and clinically unstable patients may have affected the prevalence of anxiety disorders obtained in the present study, thus the findings cannot be generalized.

Conclusion

The results of this study show that the prevalence of anxiety disorders can be determined with greater precision using diagnostic instruments than it is possible with the use of screening instruments. The weighted prevalence of anxiety as a psychological disorder shows that it occurs significantly frequently among breast cancer patients. It is notable that the HADS may be more focused on the symptoms of anxiety disorders, and may not be a good diagnostic tool for establishing the diagnosis of anxiety disorder requiring treatment. It is recommended that the SCAN is a better diagnostic tool which clinicians should incorporate into their routine assessment protocols for patients with breast cancer, and other forms of chronic illnesses.

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