Original Research Article

Factors Contributing to Delayed Breast Cancer presentation: A prospective study at Parirenyatwa Group of Hospitals, Harare, Zimbabwe 2010-2013.

Abstract

Background: Understanding the reasons for delay in breast cancer presentation helps in shortening the delays and reduction in morbidity and mortality.
Aim: To determine factors contributing to delayed breast cancer presentation in Central Hospitals of developing countries
Methods: A prospective observational study on patients with clinical and histological diagnosis of breast cancer attending Surgical Outpatient clinics admitted patients in general surgical wards with a diagnosis of breast cancer awaiting theatre or operated from the period 2010 to 2013. Discriminant analysis was used to model delay period with a cut of point 3 months (< 3 months / > 3 months).
Results: Age at first pregnancy, HIV status, level of education and family history are major predictors of breast cancer, respectively. Low level of education, ignorance and lack of breast cancer knowledge were among other reasons mentioned as the reason of breast cancer delay. In addition lack of knowledge of self-breast examination was associated with delay.
Conclusion: An overwhelming majority of breast cancer patients in developing countries present with advanced disease because current health education campaigns seem not be effective in improving breast cancer awareness and reducing early pregnancy. There should be a collective effort focused on social health education.

Key words: Breast Cancer, Delay, Reasons, Factor Analysis, Discriminant, Developing Countries

Introduction:
Worldwide breast cancer is the most common malignancy in females. It is the leading cause of cancer related mortality [1]. Over one to two million cases are diagnosed every year, affecting 10 to 12% of the female population and accounting for more than 500 000 deaths per year worldwide [2,3]. Zimbabwe is proud to have one of the few functional national cancer registries in Africa, which was established in 1985. The Zimbabwe National Cancer Registry 2013 Report [3] highlighted that combined cancers have the lowest survival rate. A trend analysis show an increase from 4 015 registered cases of cancer in 2005 , in 2012 was 6 107, comprising 2 621 (42,9%) males and 3 486 (57,1%) females to 6 548 in 2013 [3]. For breast cancer registered cases went up from 246 to 487 in the same period (2005 to 2013) [3]. The most recent report of the registry for the year 2013 was published in August 2015.[3] According to this report [3], 6,548 new cancer cases were diagnosed in 2013. The most commonly diagnosed cancers among all Zimbabweans were cervical cancer (18%), Kaposi sarcoma (10%), breast cancer (7%), prostate cancer (7%), non-Hodgkin lymphoma (6%),

non-melanoma skin cancer (6%), esophageal cancer (4%), colorectal cancer (4%), and squamous cell carcinoma of the conjunctiva (3%) [3].

Other studies highlighted that many Zimbabweans are dying of the disease without being diagnosed or treated due to ignorance or failure to access medication because of the high costs of cancer drugs and treatment, as the country's health system remains in a parlous state following a prolonged economic crisis. The World Health organization Zimbabwe reported that cancer accounted for 138 000 deaths in 2014 alone compared to the number of HIV related deaths in 2014 (63 853) and 2013 (61 476) , this is less than the cancer deaths even when combined. This suggests a high scaling up on research for diagnosis and treatment of the disease, evidence based medicine and early diagnosis.

In general, Breast cancer mostly affects women with a very small percentage of men being diagnosed. [2,3] Many malignancies are associated with HIV infection. In Zimbabwe younger patients who are HIV infected are found to have breast cancer. According to the national cancer registry, cancer is killing more people than malaria, tuberculosis and the HIV and Aids epidemic combined.

Factors contributing to Delayed Breast Cancer presentation studies were researched elsewhere and not in Zimbabwe, despite the huge deaths numbers due to breast cancer in Zimbabwe. Figures 1, 2 and 3, show pictures of a women with delayed breast cancer presentation.

Patients who present late as shown in figures above, have a lower survival [4], research evidence established an association between stage of diagnosis and survival [4]. Delayed patient presentation refers to a prolonged interval between the discoveries of the initial symptom to presentation to a provider and is typically defined as greater than 12 weeks [5]. The delay could be provider delay or patient delay. In provider delay patients are not referred early. This could either be due to wrong diagnoses being made or to failures encountered in the referral system especially in developing countries like Zimbabwe. In Zimbabwe family physicians refer cases of breast cancer to hospitals directly. A proportion of these patients are delayed by the general practitioners. In provider delay patients who present early are managed late thereby worsening the outcome. In patient delay patients for various reasons do not visit health providers and by the time they decide to seek medical help, the disease will be advanced.

Patient delay plays a major role in breast cancer related morbidity and mortality [5]. Patients with delays of 3 to 6 months have worse survival than those with delays of less than 3 months [6].

In the patient delay process [6], the time from the individual detecting the symptom to them recognizing that it requires medical attention is termed "appraisal delay" [7] or "passive detection"[8].

The time from the individual recognizing the symptom to seeking help is called "action appraisal [9], or behavioral delay[7]. Negative attitudes towards healthcare providers are among the determinants of behavioral delay [10, 11]. Knowledge of breast cancer symptoms and self breast examination have been associated with less appraisal and behavioral delays [8,12, 13].

Patient delay may be related to poor socioeconomic status, cultural beliefs, level of education, ignorance and access to healthcare [14], among other factors.

The Zimbabwe Ministry of Health (2014) report, show that on average 1 800 women are affected annually by either breast or cervical cancer and approximately 1 200 of the cancer affected women die from this disease annually.[2,3] In Zimbabwe, breast cancer affects one in every 10 women; one in every 100 men has to battle prostate cancer mostly affecting males above 50 years.[3] The study was carried out to cover the existing knowledge gaps on factors associated with delayed breast cancer presentation in Zimbabwe aiming to shorten the delays and reducing breast cancer mortality by targeting the risky population groups.

AIM: This studied aimed to determine the factors leading to delayed breast cancer presentation

Study design: A prospective observational study

Sampling Procedure and Sample Size

Sample Size Estimation

The minimum sample size n was obtained using the formula developed by Cochran (year 2006) was used in populations that are large:

$$n = \frac{z^2 p(1-p)}{\varepsilon^2}$$

Where,

p = Proportion of breast cancer patients in stage III & IV, p = 94%, calculated from a proportion of breast cancer patients delayed for more than three months in a study done by Muguti *et al*., (1993) in Zimbabwe

ε = margin of error set at 6 %

Z= standard normal deviate set at 1.96 for 95% confidence level

n= Population size = 61

Materials and Methods

All patients with clinical and histological diagnosis of breast cancer attending Surgical Outpatient Department clinics, admitted patients in general surgical wards with a diagnosis of breast cancer awaiting theatre or operated from the period 2010 to 2013 were included in the study. Interviews were carried out on each patient to answer specific questions on the data collection sheet. Data were collected and recorded on data collection sheets. Relevant investigations including HIV test were done and recorded. Patients were prospectively followed up from admission until they were operated upon. Final histologies were collected from Histopathology Department, analyzed and recorded.

Inclusion Criteria:

All female patients with a clinical and histological diagnosis of breast cancer with 15 years above attending clinics or admitted at Parirenyatwa University Teaching Hospital

Exclusion Criteria:
All male patients with breast cancer
Patients with breast cancer below the age of 15 years
Patients who declined operations and patients who did not have final histologies

Statistical analysis:
All data were entered in a computer and proof read before analysis. Statistical analysis was carried out by SPSS version 16 statistical package. Discriminant analysis was used to model delay period in months and clinical staging value as dependent categorical variables based on the existing relationship to breast cancer delay-predicting-factors. Descriptive statistics; means, standard deviations, canonical discriminant parameters were determined as discriminant analysis procedure. The significance levels used to indicate effect size were $p< 0.05$.

Model validation
Among other diagnostics parameters used were Wilk's lambda (preferred the smallest value), and Box's M. We used a 50% Bernoulli (0.5) random sampling of the 73 patients to create a discriminant analysis model, setting the remaining (50%) patients aside to validate the analysis. We then used the model to classify the 50% of the patients as delayed or not delayed. Checking for other assumptions see table 5

Ethics statement
Ethical approval was sought from Parirenyatwa and College of Health Sciences Joint Research (JREC). Consent to participate to in the study and to publish the inserted pictures were sought from the patients in both written and verbal form.

Conflict of Interest
The authors have none to declare. The study was self-funded.

Results:

In this study, almost 60% of the patients 43 (59%), were self-delayed out of the 73 breast cancer patients see figure 4. Out of the 73 patients in the study, rural patients were 49 (67.1%) and urban patients were 24 (32.9%). Age distribution ranged from 15 to 67, most patients, 20(27.4%) were between the age of 51-60 years (see figure 5). Out of 73 patients, 51 (69.9%) consented to HIV testing whilst 22 (30.1%) declined. Among the HIV tested patients only 7 (9.6%) were positive and 44 (60.3%) were negative. In Figure 6 show that only a small proportion of 6 (8.2%) of the participants had reached tertiary level of education and the largest proportion had reached secondary level, 38 (52.1%) followed by primary level, 23 (31.5%). In this study, almost 60% of the patients 43 (59%), were self-delayed out of the 73 breast cancer patients see figure 4.

Reasons of presentation delay and symptoms

Table 3 below shows the frequency order in which patients presented with according to the detected symptoms; mass 57 (78.1%), pain (39.7%), ulcer 13 (17.8%), Nipple discharge 12 (16.4%) and Nipple retraction 8 (11%) respectively.

Presentation delay alarming predictors (Discriminant analysis)

In table 4, the coefficients for *HIV Status* and *Reason of Delay* are higher for the Yes classification function, which means that *HIV Status* and *Reason of Delay* are alarming predictors of delay. Figure 7 show further detail by specific reasons delay. Lack of education tops other reasons given. Thus ignorance is a high risk to breast cancer presentation delay.

Checking for assumption through a correlation matrix, we observed small correlations between variables in table 5; they are not large enough to be a concern. So there is no need to look for differences between the structure matrix and discriminant function coefficients . This is a favorable condition for the assumptions of multivariate normality as also suggested by table 7 were the means standard deviations are preferably small.

The total numbers of 73 observations represents 100% of the observations have been grouped for the Discriminant Analysis. Table 6 show the distribution of observations into 2 different groups. In the present study we have categorized presentation delay into two groups viz High Delayed as '1' and Low Not delayed as '0'. Preferably for all the predictors, group means are associated with smaller group standard deviations.

In table 6 , researchers use standardized coefficients to compare variables measured on different scales. Coefficients with large absolute values correspond to variables with greater discriminating ability namely Age at first pregnancy (Coefficient; 1.061), HIV status (Coefficient; 0.89), level of education (Coefficient; 0.679), Reason of delay (Coefficient; 0.336) and family history (Coefficient; 0.221) respectively.

Discussion:

Patient data on Self delay was determined with the benchmark as presentation period (either < 3 months or ≥ 3 months) from the first symptom and was subjected to Discriminant Analysis in order to generate the Z score for developing the discriminant model towards the factors self-delay. Literature on patient-mediated and practitioner mediated delays identified in agreement with this research that; Age at first pregnancy, (Coefficient; 1.061), HIV status (Coefficient; 0.89), level of education (Coefficient; 0.679), the "patient cited" reason of delay (Coefficient; 0.336) and family history (Coefficient; 0.221) are respectively main patient-mediated factors resulting in increased time to presentation. Contrary to other studies, neither logistic regression nor chi-square tests of association show any strong evidence of an association between older age, residency and patient delay for breast cancer. The same were not among the strong discriminating factors using the discriminant model. However, other studies cited that older age is strongly associated with presentation delay.[16] In agreement with Harirchi *et al*.,2005 [17] and Montazeri *et al.*, 2003 [18], having no history of breast cancer (Coefficient; .221) was found to be moderately influencing to late presentation. Although we could not find online published Studies done in Zimbabwe on examining factors influencing late presentation for breast cancer we accessed some studies done in the Middle East, most studies show strong evidence supporting the effects of older age and lower educational level on late presentation. In agreement to our study there is also strong evidence to suggest that employment status did not influence late presentation. In this

study, we had also a similar finding with Ramirez *et al*,(1999) [18] the evidence on the effects of family history, and reason of delay other than the modeled factors were shown to be moderate. However among the specific reasons of delay lack of education was the most dominant.

Conclusion:

Not only limited to the Zimbabwean context, but in agreement with other studies done globally, Age at first pregnancy, HIV status, level of education and family history are major predictors of breast cancer, respectively. Most Breast cancer patients attending Parirenyatwa Hospital present with advanced disease. Current health education campaigns seem not be effective in improving breast cancer awareness. It is our collective responsibility to reduce this delay through various interventions focused on education and poverty alleviation. Follow-up studies regarding management of these patients need to be done so as to recommend and formulate local guidelines

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Figure 1: Patient 1 advanced breast cancer (Stage 4)

Figure 2: Patient 2 advanced ulcerated breast cancer (stage 4)

Figure 3: Patient 3 advanced ulcerated breast cancer (stage 4)

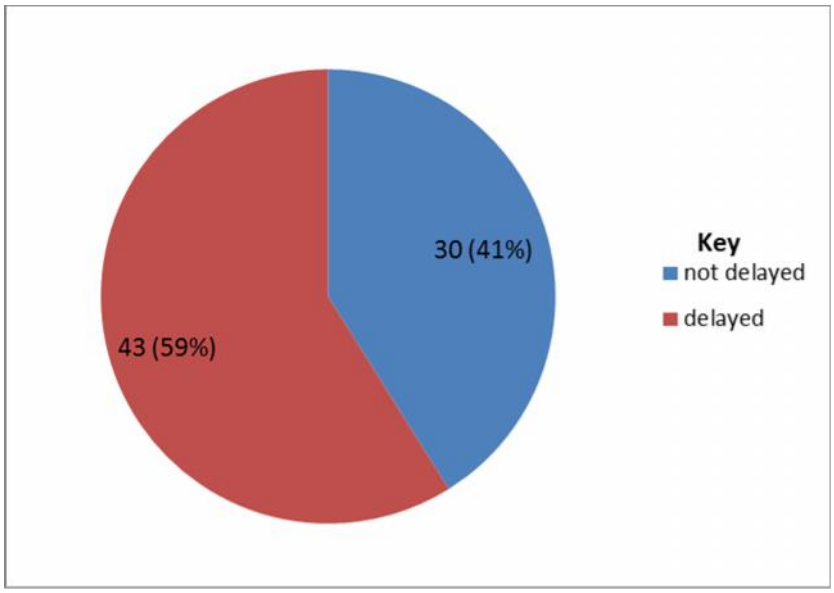

Figure 4: Prevalence of self-delay

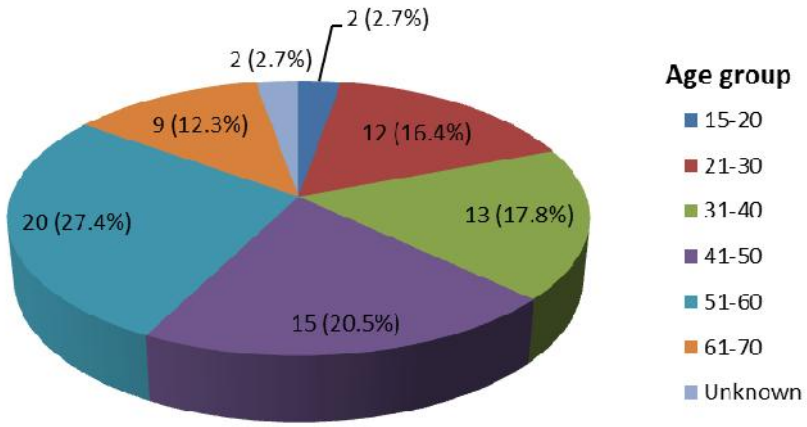

Figure 5: Breast cancer-Age Distribution

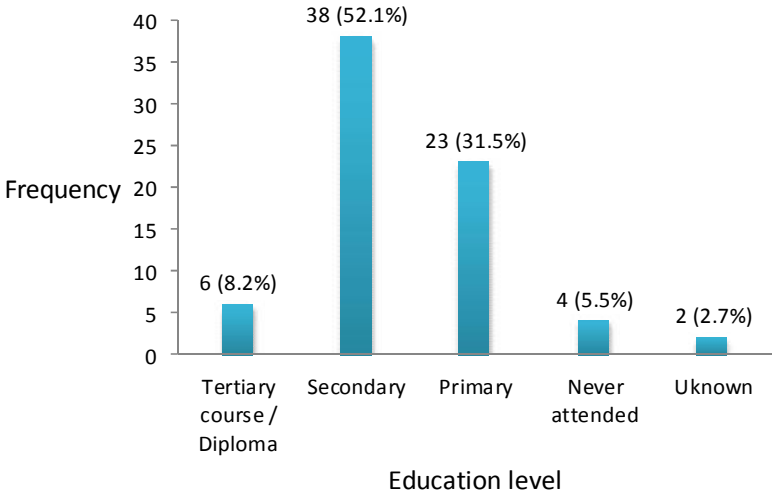

Figure 6: Highest level of education

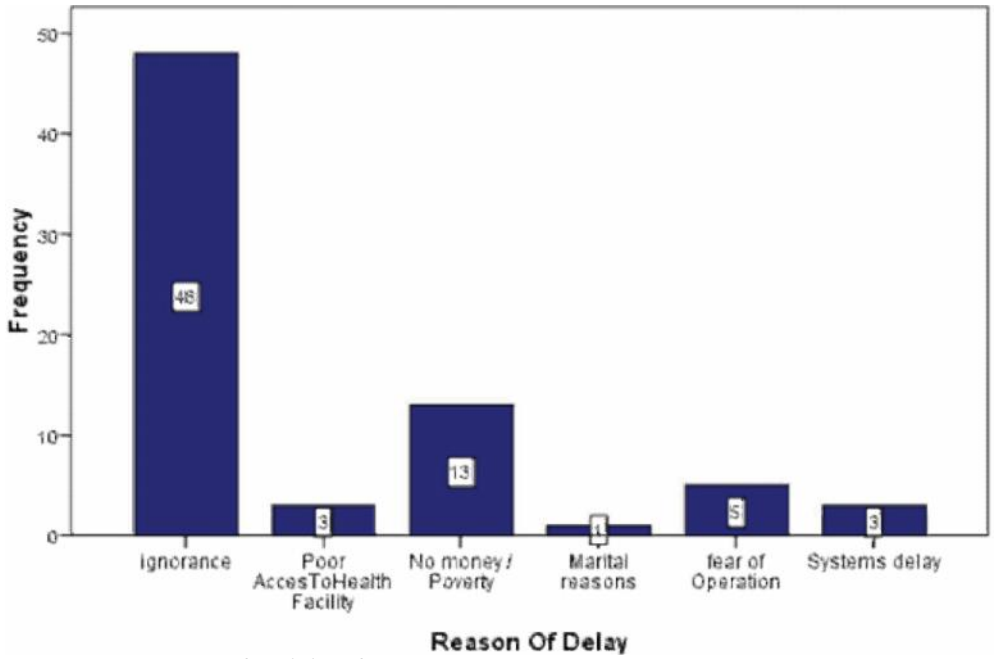

Figure 7: Reasons for delay frequency

Table 1: Knowledge of self- breast examination and Residence

Residence	Knowledge of Self Breast Examination		Total
	Yes (%)	No (%)	
Rural	12 (16.4)	37 (50.7)	49 (67.1)
Urban	7 (9.6)	17 (23.3)	24 (32.9)
Total	19 (26.0)	54 (74.0)	73 (100.0)
Note: p < 0.05 ,Statistically significant association			

Table 2: Relationship between Knowledge of self-breast examination and level of education

Knowledge of Self Breast Cancer		Level of Education				Total
		Tertiary course / Diploma	Second-ary	Primary	Never attended	
	no	0 (0%)	14 (20.9%)	10 (14.9%)	2 (3.0%)	26 (38.8%)
	yes	6 (9.0%)	22 (32.8%)	12 (17.9%)	1 (1.5%)	41 (61.2%)
Total		6 (9.0%)	36 (53.7%)	22 (32.8%)	3 (4.5%)	67 (100.0%)
***Note**: p < 0.05, Statistically significant association*						

345 **Table 3:** Symptoms

Symptom	Frequency	Percent
Mass	57	78.1
Nipple Discharge	12	16.4
Nipple Retraction	8	11
Pain	29	39.7
Ulcer	13	17.8

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348 **Table 4:** Breast Cancer delay predictors

Predictors	**Delayed presentation score**	
	No (stage 3)	**Yes** (stage 4)
HIV Status	20.240	24.526
Age at First Pregnancy	6.169	7.406
Early Menarche	-1.521	-2.525
Family History	.055	.148
Late Menopause	7.697	4.812
Level of Education	5.269	8.898
Reason of Delay	21.582	23.200
(Constant)	-91.994	-115.295
Note: *Classification Function Coefficients determined by Fisher's linear discriminant functions*		

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354 **Table 5:** The within-groups correlation matrix shows the correlations between the predictors.
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	HIVStatus	AgeAtFirstPregnancy	EarlyMenarche	FamilyHistory	LateMenopause	LevelOfEd-ucation	KnowledgeOfSelfBE	ReasonOfDe-lay	HealthWorkerOffirstContact	DurationOfSymptomsInMonths	MaritalStatus	AgeGroup	Employed
HIVStatus	1	-.24	.15	-.65	-.53	-.28	-.17	-.25	.33	-.35	-.66	.56	-.53
AgeAtFirstPregnancy	-.24	1	.3	.35	.47	.02	-.67	-.48	.18	.51	-.12	-.12	-.30
EarlyMenarche	.15	.3	1	.01	-.14	.25	.17	.3	-.03	.15	-.59	-.24	-.35
Family	-	.35	.01	1	.3	.41	-.13	.02	-.17	.18	.25	-	.3

History	.65											.08	
LateMenopause	-.53	.47	-.14	.3	1	.00	-.47	.00	-.47	.25	.00	-.66	.25
LevelOfEducation	-.28	.02	.25	.41	.00	1	.46	.28	-.65	-.42	-.18	.16	.00
KnowledgeOfSelfBE	-.17	-.67	.17	-.13	-.47	.46	1	.67	-.33	-.32	.22	-.06	.24
ReasonOfDelay	-.25	-.48	.3	.02	.00	.28	.67	1	-.33	-.44	.00	-.56	.00
HealthWorkerOffirstContact	.33	.18	-.03	-.17	-.47	-.65	-.33	-.33	1	.21	.22	.31	-.47
DurationOfSymptomsInMonths	-.35	.51	.15	.18	.25	-.42	-.32	-.44	.21	1	.29	-.31	.44
MaritalStatus	-.66	-.12	-.59	.25	.00	-.18	.22	.00	.22	.29	1	-.12	.46
AgeGroup	.56	-.12	-.24	-.08	-.66	.16	-.06	-.56	.31	-.31	-.12	1	-.26
Em-ployed	-.53	-.3	-.35	.3	.25	.00	.24	.00	-.47	.44	.46	-.26	1

Table 6: Standardized Canonical Discriminant Function Coefficients

Predictor	Function
	1
HIV Status	.890
Age at First Pregnancy	1.061
Early Menarche	-.524
Family History	.221
Late Menopause	-.424
Level of Education	.679
Reason of Delay	.336

Table 7; Group means and standard deviations

Clinical Stage		**Mean**	**Std. Deviation**	**N**	
				Unweighted	**Weighted**
Delayed (≥ 3 months)	HIV Status	1.33	0.58	3	3
	Age at First	18.67	2.52	3	3

	Pregnancy				
	Early Menarche	13.00	1.00	3	3
	Family History	1.67	0.58	3	3
	Late Menopause	2.00	0.00	3	3
	Level of Education	1.67	0.58	3	3
	Knowledge of Self Breast Examination (BE)	1.33	0.58	3	3
	Reason of Delay	1.67	1.16	3	3
	Health Worker of first Contact	2.67	1.16	3	3
	Duration of Symptoms in Months	2.67	2.08	3	3
	Marital Status	2.00	1.00	3	3
	Age Group	5.00	1.00	3	3
	Employed	1.00	0.00	3	3
Not delayed (< 3 months)	HIV Status	2.00	0.63	6	6
	Age at First Pregnancy	21.83	2.56	6	6
	Early Menarche	14.17	1.72	6	6
	Family History	5.17	8.25	6	6
	Late Menopause	1.67	0.52	6	6
	Level of Education	2.50	0.55	6	6
	Knowledge of Self (BE)	1.17	0.41	6	6
	Reason of Delay	1.00	0.00	6	6
	Health Worker of first Contact	2.33	0.82	6	6
	Duration of Symptoms in Months	2.17	1.60	6	6
	Marital Status	2.50	0.55	6	6
	Age Group	5.17	0.75	6	6
	Employed	1.67	0.52	6	6
Total	HIV Status	1.78	0.68	9	9
	Age at First Pregnancy	20.78	2.86	9	9
	Early Menarche	13.78	1.56	9	9
	Family History	4.00	6.76	9	9
	Late Menopause	1.78	0.44	9	9
	Level of Education	2.22	0.67	9	9
	Knowledge of Self (BE)	1.22	0.44	9	9
	Reason of Delay	1.22	0.67	9	9
	Health Worker of first Contact	2.44	0.88	9	9

	Duration of Symptoms in Months	2.33	1.66	9	9
	Marital Status	2.33	0.71	9	9
	Age Group	5.11	0.78	9	9
	Employed	1.44	0.53	9	9

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