Bilateral Breast Cancer: Experience in a Poor Resource Black African Setting.

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Background: Breast cancer is the most common malignancy in women in Nigeria. Women previously treated for ipsilateral breast cancer have increased risk of developing contalateral breast cancer (CBC), the chance of which increases with longer period of survival and is associated with worse prognosis. Reports from Nigeria are few on this.The aim of this study was to assess the prevalence, predisposition, presentation, and outcome of management of bilateral breast cancer (BBC) in a population, South-western Nigeria.

Methods: A review of bio-data of all patients with BBC seen in LTH, Osogbo, Nigeria between 2001 and 2008 was done. Age, parity, age at menarche and first child birth, family history, duration of symptoms, tumour characteristics and exposure to cigarette, oral contraceptive pills (O.C Pills) and outcome of treatment were also assessed.

Results: BBC constituted 4.6% of the 256 breast cancer patients. Eight (73%) were metachronous and 91% were infiltrating ductal carcinoma. Patients' mean age, mean age at menarche and first child birth were 39, 14.5$\pm$3 and 22.5yrs respectively. Mean parity was 3.5 child birth, 91% were premenopausal and all have menstruated for 12-31yrs. None had positive family history while only 1 and 3 had insignificant exposure to cigarette and O.C pills respectively. The mean interval between the 2 onsets was 18mths (0-68mths). 91% of all tumours were advance, while 81% of the first tumours were on the right. Mean duration before presentation for the first and second tumours were 261 and 111days respectively. One patient has survived for 2 years thus far.

Conclusion: The incidence of BBC was 4.26%. Most patients were young and premenopausal with mostly infiltrating ductal carcinoma (NOS) and presenting with late stage disease, hence poor prognosis. Aggressive follow-up of patients with ipsilateral cancer will aid early detection of CBC.

Introduction

Breast cancer is the most common female malignancy in Nigeria[1]. A woman with unilateral breast cancer is known to have increased risk of developing contralateral breast cancer (CBC) [2]. This increases the agony brought about by the disease, more side effects from the ablative surgical treatment, adjuvant chemotherapy, radiotherapy all leading to poor prognosis[3].

Breast cancer incidence though known to be less in the black Africans appears to be on the increase from clinical and also laboratory experiences [4,5,6,7]. The incidence of bilateral breast cancer (BBC) has been reported to be 2.4% (Ilorin), 2% (Benin), 2.2% (Ife), 4 % (Lagos) all in Nigeria[4,8,9,10], while higher incidences of between 3.3% and 9.6% has been reported among the Caucasians [3,11-14].Breast cancer is known to occur more in younger and premenopausal women among the blacks, and usually with more aggressive lesion. A long post survival period may give a high propensity for developing metachronous CBC. This retrospective study is therefore aimed at highlighting the incidence, biodata, clinical features, histology, possible predisposing factors and outcome of treatment of patients with BBC in a Nigerian population.

Patients and Methods

The case files of all patients who have had cancer involving the two breasts during an 8 year period (2001-2008) in LAUTECH Teaching Hospital, a 300 bed hospital in Osogbo, South western Nigeria were retrieved. Bio-data, age, sex, age at menarche and first child birth, parity in addition to family history of breast or any other cancers, use of O.C pills or menopausal hormone and social habits like smoking, alcohol ingestion were extracted. The tumour locations, disease stage, histology, treatment given with outcome were also retrieved. Patients who developed primary contralateral breast cancer

(CBC) within 6 months of onset of the initial cancer were termed synchronous. The period between the onsets of the two lesions is referred to as interval. Simple analysis of results was done.

Results

Eleven (4.26%) out of 256 breast cancer patients seen during the study period had bilateral breast cancers. All were females with age ranging from 27- to 50 yrs with a mean of 39.1 years. The mean age at menarche and first child birth were 14.5 and 22.5 years respectively (Table 1). The mean parity was 3.5 child births; one was nultiparous at the age of 45yrs while 3 were grand multips having between 6-8 children. All were premenopausal except one in the peri-menopausal period. They have all menstruated for between 12-31years. None has family history of breast or any other cancer, only one patient smoked and three patients took oral contraceptive pills for period varying from 2-4 years (Table 1).

The duration before presentation of the initial tumour was between 2 months and 1 year with a mean of 261days; 45%presented within 6months as against 81% for the contalateral lesion. The mean duration of symptom for CBC was 111days. The interval between the first and second tumour onset ranged between 0 and 68 months with a mean of 18months. In only 3 patients was the interval less than 6months (synchronous) (Table 2). Tumour locations were symmetrical in 5 of the 11 cases (50% of metachronous and 33% of synchronous). Nine of the first lesions were on the right, one each of the patient with first left lesion had synchronous and metachronous contalateral lesion.

Table 1. Patients' Data and Outcome.

	Initials	Age at 1st Presentation (Yrs)	Age (Yrs) at Menarche	Age at 1st Child birth (Yrs)	Parity	Duration Before Presentation (Months) 1ST	2ND	Interval Between Presentation (Months)	Smoking	O.C. Pills Usage	Outcome
1	OB	35	13	35	2	2	1	16	-	-	LTFP
2	OS	36	14	20	8	6	6	18	-	+	LTFP
3	FF	50	18	21	6	11	3.7	24	-	-	DEAD
4	AJ*	45	18	/	0	6	2	2	-	-	DEAD
5	BO	44	13	22	6	12	8	20	-	-	LTFP
6	SA	34	13	28	2	12	1	20	+	-	DEAD
7	OA	45	14	22	4	10	1	68	-	+	DEAD
8	AO	40	15	24	4	18	6	12	-	+	DEAD
9	OO	30	15	28	2	15	9	6	-	-	DEAD
10	AK	44	12	25	3	2	1	13	-	-	ALIVE
11	UK	27	15	23	2	2	2	0	-	-	DEAD
	Mean	39.09	14.55	22.55	3.5	8.72 (261 days	3.7 (111 days)	18.09			

KEY: O.C =oral contraceptive, LTFP= Lost to follow-up. -=No, += Yes, * = Nuliparous

Table 2. Tumour Site, Stage and Histology.

Serial No.	Initials	Tumour Laterality		Tumour Location (Quadrants)		Disease Stage (Manchester Class.)		Histology	
		1ST Tumour	2ND Tumour	1ST Tumour	2ND Tumour	1ST Tumour	2ND Tumour	1ST Tumour	2ND Tumour
1	OB	R	L	UOQ	UOQ	3B	4	IDC	IDC
2	OS	R	L	CENT	CENT	3B	3B	IDC	IDC
3	FF	R	L	UIQ	CENT	4	3A	IDC	IDC
4	AJ	L	R	UOQ	CENT	4	3B	IDC	IDC
5	BO	L	R	UOQ	CENT	3B	4	IDC	IDC
6	SA	R	L	UOQ	UIQ	3B	4	IDC	IDC
7	OA	R	L	CENT	UOQ	3A	3A	IDC	IDC
8	AO	R	L	CENT	CENT	4	4	IDC	IDC
9	O	R	L	UIQ	UOQ	3B	3A	IDC	IDC
10	AK	R	L	UOQ	UOQ	2	2	IDC	IDC
11	UK	R	L	CENT	CENT	3A	3A	LYMPH	LYMPH

KEY: R=Right, L=Left, IDC=Infiltrating Ductal Carcinoma(NOS), LYNPH = lymphoma

Five and 2 of the first tumours were located in the outer and inner quadrants respectively while 4 were central. Six (55%) of the contalateral tumours were central while 4 were in the outer quadrant. Seventy-five percent of the central first lesion had centrally located contalateral lesion. (Table 2).

All except one had either Manchester stage III or IV in both breasts. All were diagnosed to be infiltrating ductal carcinoma (IDC, NOS) except the youngest (27 yr old) with generalized Burkitt lymphoma involving both breasts. (Table 2)

All patients with IDC had neo-adjuvant cytotoxic chemotherapy using cyclophosphamide and Adriamycin based regime (CAMF). The two patients with synchronous lesions were offered simultaneous bilateral mastectomy. The others had simple or modified radical or radical mastectomy at each presentation. Tamoxifen at the dose of 20mg daily was given to all while the care lasts. Three of them had radiotherapy for additional loco-regional control, two of these developed complications including pleuritis, severe pleural effusion and pulmonary fibrosis. The patient with Burkitt lymphoma was managed medically using cycles of cytotoxic drugs (CMVP) along with the clinical haematologists. Seven of the patients died and three were lost to follow-up within the first year of treatment of the contalateral breast lesion. Only one patient is still living 2 years after diagnosis of synchronous primary BBC.

Discussion

Incidences of breast cancer in women are on the increase worldwide in the recent years [4,7]. More cases of BBC should be expected, especially in areas where large percentage of breast cancer patients are found in the pre- and perimenopausal period.The younger age at presentation provide for higher risk of developing contalateral primary breast cancer (CPBC) after surviving the initial lesion. The poor survival pattern in the developing world has been attributed to various social, environmental[15], in addition to some biological factors[8].

The incidence of 4.26% found in this study is a bit higher than reported values from other centers in Nigeria but lower than reported cases among Caucasians. Poor survival rate and high rate of loss to

follow-up in addition to some social beliefs may partly explain this. Only 27% of cases were synchronous, this is in keeping with findings from other centers[11-13,16]. However the mean age of 39.1years in BBC patients is significantly lower than 47[4] and 48[16] years reported for all breast cancer patients in nearby teaching hospitals, thus supporting the fact that the former are usually younger. The mean age at menarche and the age at first child birth of these patients are all similar to that of other females with unilateral breast cancer in this environment and comparable with that of women population in the locality. Age at menarche, age at first child birth and duration of breast feeding has been implicated by some authors as possible predisposing factors to breast cancer[17]. It has also been postulated that carrying a full term pregnancy on or before 18 years is protective against breast cancer[18]. However many studies in Nigeria including that by Ihekwaba FN[19] who assessed the risk factors in 1946 breast cancer patients could not demonstrate these to be significant predisposing factors.

Parity does not appear to offer significant protection against developing first or second primary breast cancer in Nigeria, as only one of the patients in this series was nuliparous and three were grandmultips. This is in keeping with other reports from within and outside Nigeria [20-23] and in contrast to report by George GF from Baltimore (USA) [24]. I n the same vein, none of our patients with BBC had positive history as against earlier studies in Caucasians in which family history was found to be a significant predisposing factor [12,24]. Transfer genetically through the Breast cancer related antigen (BRCA) I and II as autosomal dominant trait has been proved and this may account for between 50 and 70% of highly penetrant hereditary breast cancer[2]. The strength of family history (genetic transfer) as a risk factor for unilateral and BBC still need further evaluation among indigenous black African women in view of heterogeneity of breast cancer aetiology across regions. However it will be difficult to estimate the significance of unknown family history.

The short mean duration of symptoms before the second presentation could be due to awareness from their previous experience though this appears to have no effect 0n disease stage of CBC. Mertins et.al[25] among others reported that subsequent tumours are usually of smaller size and stage, though initial tumour size and stage is strongly associated with CPBC size and stage. Aggressive follow-up care of the initial tumour including screening of contalateral breast will lead to early detection thus smaller size and stage of the subsequent cancers.

The mean interval between cancers of 18months (0-68months) is rather short compared with 117months reported by Golgas[14] or 144months by George GFet.al[24], though most are also young and premenopausal but with positive family history. Short interval, age, large second tumour size, higher number of positive lymph nodes of first and second cancers are factors that decrease the disease specific survival in patients with BBC[3,26]. Skowronek J et.al [27] reported 0 and 73.9% 5-year survival in patients with interval period < 2years and > 5years in Poland. In addition, lympho-vascular invasion, nuclear grade, histology and hormone receptor status are also related with overall survival[28]. Primary breast cancers are more common on the right[4] and 81% of first primary lesions here are found on the right. CBC lesions are noted to be commonly located centrally while upper outer quadrant lesions are commoner overall; the significance of the former is unknown.

Late presentation with breast cancer is common in the developing world [15,19,23,29], low level of awareness[30], poverty and fair of mastectomy[31] among others could account for this. Presentations of CBC at a late stage, in spite of previous experience, leave much to desire. Inadequate follow up care in addition to rapidity of growth as good number of studies have suggested a biologically aggressive form of breast cancer in Nigerians and other black women[32,33]. They are usually of poorly differentiated invasive ductal carcinoma "Not Otherwise Specified" with high proliferation ratio and poor host cellular immune reaction[22,34]-all translating to poor prognosis. Infiltrating lobular carcinoma has been described to have propensity to occur in both breasts[24] but none was found in this series, as it is uncommon in this environment[4]. The rarity of carcinoma-in-situ as histology finding in the developing world can only be accounted for by non availability of screening facility, in fact greater than 90% of most patients after self-detection[23].

Distinguishing features of primary cancer in contalateral breast has been described to include demonstration of in-situ-carcinoma in the breast tissue with invasive carcinoma, histologically dissimilar infiltration and location deep within the breast parenchyma[35].

The only case of synchronous bilateral Burkitt's lymphoma seen died within one year, this is in keeping with the experience reported by Aghadiuno et.al[36] in which 12 out of 18 patients with simultaneous bilateral breast malignancy had Burkitt lymphoma and none survived 2 years. They tend to have multi-organ involvement as depicted in a case report by Fadiora et.al.[37]

Young age, strong family history, histology confirming infiltrating lobular carcinoma, or gross multicentricity in the first primary tumour are considered as factors predisposing to developing PCBC[14,24]. Any of these should alert the surgical oncologists on the need for detail follow-up so as to be able to diagnose a CBC early enough with the hope of better prognosis. Outcome of treatment for patients with breast cancer in the developing world is generally poor.

Follow-up of patients with unilateral disease should include frequent self breast examination, 3-monthly clinical breast examination by physician, half yearly or yearly mammography or breast magnetic resonance imaging (MRI). MRI is known to detect occult malignancy missed by mammography[38].

Use of tamoxifen has been found to reduce the incidence of CPBC in women who received the drug as adjuvant therapy for the first primary breast cancer by 47% [39] and has been proved to be of value in chemoprophylaxis of breast cancer[40]. Oophorectomy brought about surgically or by irradiation and prophylactic contalateral mastectomy may be considered in those with high risk of developing CPBC[32]. In fact the concept of possible bilateralism of breast cancer should be introduced to our patients during the first visit after confirmation of a unilateral lesion and adequate education given on treatment and follow-up care plan.

Conclusion

The incidence of BBC was 4.26%, most were young with no positive family history, 90% were premenopausal and histology was IDC (NOS) in 90% of cases. The burden of BBC is enormous on both the patients and the involved treatment team. Effort should be put in to determining the risk factors to breast cancer and BBC in the black African women. Improve level of awareness of breast cancer, provision of screening facilities, coordinated multi-centered research in breast oncology and establishment of specialized oncology center will go a long way in improving the outcome of treatment of breast cancer in the poor resource African setting.

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