Original Article

Molecular Subtyping of Carcinoma of the Female Breast in a Tertiary Teaching Hospital in Northern Nigeria

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Abstract

Background: Cancer of the breast is globally the most common female cancer including in Nigeria. Newer treatment modalities are based on tumor immunophenotyping, thus the need to characterize these tumors among women with the disease in Northern Nigeria. **Aims:** This study aims to classify carcinomas of the breast diagnosed in the pathology laboratory of a teaching hospital based on their expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2/neu (HER2/neu) overexpression. **Methodology:** The histology slides of 478 carcinomas of the breast as well as the ER, PR, and HER2 immunohistochemistry records of 118 stained cases were retrieved and reviewed. **Results:** Age range of cases was from 20 to 80 years (mean = 46.9 ± 13). The most common histomorphologic entity was invasive carcinoma (NST) which accounted for 73.2% of cases. These were followed in frequency by invasive lobular carcinoma accounting for 6.8% of cases and invasive papillary carcinoma representing 6.5% of cases. Overall, 169 cases (37.6%) were Grade III tumors while Grades II and I tumors accounted for 35.1% and 27.3% of cases, respectively. Triple-negative tumors were the most common molecular subtype and comprised 46.6% of all cases. Luminal B (LUMB) was the least common and accounted for 8% of all cases. HER2 overexpression and LUMA were seen in 17.9% and 28.8% of cases, respectively. **Conclusion:** Carcinoma of the breast in the population studied occurs at a younger age than among Caucasians. The tumors are characterized by preponderance of invasive carcinoma (NST), high histological grade, and triple-negative phenotype.

Keywords: Breast carcinoma, estrogen, human epidermal growth factor receptor 2, progesterone, receptor

Introduction

Breast cancer is the most common cancer worldwide and the second leading cause of cancer-related deaths.[1] It comprises 22.9% of invasive cancers in women and 16% of all female cancers globally.[2] Mortality rates in some African countries including Nigeria, Egypt, and Ethiopia have been found to be among the highest worldwide and has been attributed to late presentation and thus much poorer survival.[3]

Several factors have been implicated in the etiopathogenesis of breast cancer, and these include advancing age, genetics, positive family history, low residue diet, alcohol, obesity, and physical inactivity.[3] Over the last few decades, breast cancer classification has become molecular. This is in deference to its recognized heterogeneity and inadequacy of morphological features alone to completely predict tumor behavior.[4] The expression of hormone receptors including estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2/neu (HER2/neu) distinguishes classes of tumors thought to be derived from different cells of origin: HR+ (positive) and HR− (negative) tumors. Based on positivity or otherwise of these receptors, carcinomas of the breast are now classified as luminal A (LUMA), LUMB, HER2 overexpressing, and basal-like (also referred to as triple-negative breast cancers; [TNBC]). These entities have been linked to different responses to different therapeutic modalities.

This study aims to evaluate the molecular characteristics of carcinomas of the breast diagnosed in a teaching hospital in Northwestern Nigeria, hence enabling development of treatment modalities for such patients.

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Materials and Methods

All cases of carcinoma of the breast and their corresponding ER, PR, and HER2/neu status recorded in the archives of Pathology Department of Aminu Kano Teaching Hospital between January 2011 and December 2015 were retrieved.

The tumors were classified in accordance with the updated 2003 edition of the WHO histological classification of breast tumors and graded using the Scarff–Bloom–Richardson (SBR) grading system.[5] This grading system is based on three different features: tubule formation, nuclear pleomorphism, and mitotic count. Each of these features is given a Score of 1–3. The individual scores are added together to give a total score between 3 and 9 and a tumor grade is assigned based on the score: well-differentiated carcinomas (Score 3–5), moderately differentiated carcinomas (Score 6–7), and poorly differentiated carcinomas (Score 8–9).

Ensuing data was managed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp and presented with the aid of tables and charts. Statistical significance was at $P < 0.05$ at 95% confidence interval.

Results

A total of 3214 malignancies were diagnosed in the histopathology department of the teaching hospital over the 5-year period (2011–2015). Five hundred and twenty-four of these were breast cancers and comprised 14.9% of all these malignancies. Carcinomas accounted for 98.9% of the breast malignancies while the remaining 1.1% were sarcomas and lymphomas. No metastatic tumor to the breast was reported.

Of the 524 cases, only 478 cases were suitable for this study excluding noncarcinomas and those with incomplete biodata. Of the 478 cases that met the inclusion criteria, immunohistochemistry was performed on only 118 (24.7%) of them.

Table 1 depicts the age distribution of the various histomorphologic entities. Ages of affected women ranged between 20 and 80 years with mean age of 46.9 ± 13. The overall age pattern was such that from age group 20 to 29 years, the frequency rose sharply from 24 (5%) cases to 113 (23.7%) cases in the 30–39-year age range, and peaked in the 40–49-year age group which accounted for 28% of all cases [Figure 1]. From here, it dropped progressively to 7 (1.5%) cases in the 80–89 age group. With a frequency of 56.7%, women <50 years of age constituted about two-third of all cases while 5% of the women were <30 years of age.

The most common histomorphologic type, accounting for 73.2% of cases, was invasive carcinoma (NST), invasive lobular carcinoma with 6.8% of cases, invasive papillary carcinoma with 6.5% and medullary carcinoma with 3.8% of all cases. Six cases of ductal carcinoma *in situ* (DCIS) representing 1.2% of all lesions were the only noninvasive carcinomas diagnosed. The occurrence of invasive carcinoma (NST) was found to be highest in the fifth decade of life. Invasive lobular carcinoma had a wider peak age distribution of 30–49 years. Invasive papillary carcinoma and medullary carcinoma were mostly diagnosed in women aged 30–39 years. However, 67% cases of DCIS were diagnosed in women in the 30–39 age bracket [Table 1].

Histomorphologic entities were graded using the SBR grading system and the pattern is as shown in Table 2. Four hundred and fifty cases were available for grading. The largest proportions, 37.6%, were Grade III, with Grade II and I were 35.1% and 27.3%, respectively. Grade III malignancies were more frequent among invasive carcinoma (NST) and apocrine carcinoma. Other special types including invasive lobular carcinoma, invasive papillary carcinoma, adenoid cystic carcinoma, and secretory carcinoma among others, were more frequently Grade II [Table 2].

The various molecular subtypes and their percentage distribution are shown in Figure 2. In this respect, triple negative was the most frequent with 46.6% (55 of 118 cases), followed by LUMA 28.8% (34 of 118 cases), HER2 overexpressed 17.9% (21 of 118 cases), and least of all LUMB 8% (8 of 118 cases). Thus, 35.5% of the cases were ER-positive (LUMA + LUMB, Figures 3 and 4) while 64.5% were ER-negative (HER2 overexpression + triple negative, Figure 5).

Overall, triple-negative subtype was the most common molecular phenotype. Between ages 30 and 49, the

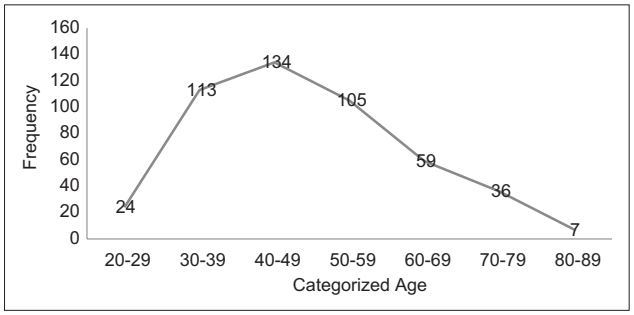

Figure 1: Line graph showing categorized-age distribution of carcinoma of the breast

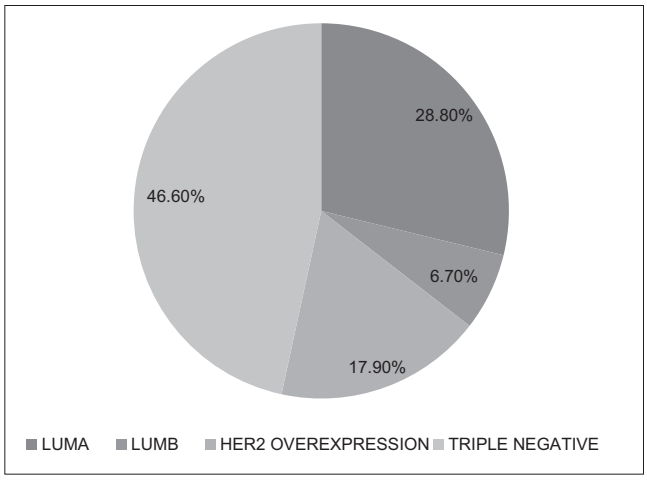

Figure 2: Pie chart showing the different molecular subtypes

Table 1: "d" Age Distribution of Histomorphologic Types (*n*=478)

Histomorphology	Categorized Age (years)							Total (%)
	20-29	30-39	40-49	50-59	60-69	70-79s	80-89	
IC (NST)	19	76	97	78	42	32	6	350 (73.2)
ILC	2	12	12	5	2	-	-	33 (6.8)
IPC	1	8	7	7	6	2	-	31 (6.5)
MDC	1	7	4	4	1	1	-	18 (3.8)
MPC	-	2	6	5	1	-	-	14 (2.9)
APC	-	3	-	3	4	1	-	11 (2.2)
DCIS	-	4	1	1	-	-	-	6 (1.2)
MC	-	-	2	-	2	-	1	5 (1.0)
ADC	-	-	2	-	-	-	-	2 (0.4)
NEC	-	-	2	-	-	-	-	2 (0.4)
OTHERS	1	1	2	1	1	-	-	6 (1.2)
Total	24	113	134	105	59	36	7	478 (100)

ADC – Adenoid cystic carcinoma, APC – Apocrine carcinoma, DCIS – Ductal carcinoma in-situ, ILC – Invasive lobular carcinoma, IC (NST) – Invasive carcinoma NST, IPC – Invasive papillary carcinoma, MDC – Medullary Carcinoma, MPC – Metaplastic carcinoma, MC – Mucinous carcinoma, NEC– Neuroendocrine carcinoma

Table 2: "d" Scarff-Bloom-Richardson grading of the histomorphologic types of carcinomas of the breast (*n*=450)

Histomorphology	SBR Grade			Total
	I	II	III	
Invasive carcinoma (NST)	69	130	151	350 (77.8%)
ILC	24	8	1	33 (7.3%)
Invasive papillary carcinoma	19	7	5	31 (7.0%)
Medullary carcinoma	7	10	1	18 (4.0%)
Apocrine carcinoma	-	1	10	11 (2.4%)
Mucinous carcinoma	2	2	1	5 (1.1%)
Secretory carcinoma	2	-	-	2 (0.4%)
Total (%)	123 (27.3%)	158 (35.1%)	169 (37.6%)	450 (100%)

n=450, *Cases of ACC, ADC, DCIS, LELC, MPC, NEC and SBC were excluded

Table 3: "d" Age Distribution of Molecular Sub-types (*n*=118)

Categorized age (years)	Immunohistochemical subtypes			Triple Negative	Total
	LUMA	LUMB	HER2 Overexpression		
	n	*n*	*n*	*n*	*n* (%)
20-29yrs	3	1	1	2	7 (5.9%)
30-39yrs	8	1	9	13	31 (26.3%)
40-49yrs	4	4	3	13	24 (20.3%)
50-59yrs	9	2	3	14	28 (23.8%)
60-69yrs	2	-	2	9	13 (11.0%)
70-79yrs	7	-	3)	4	14 (11.9%)
80-89yrs	1	-	-	-	1 (0.8%)
Total (%)	34 (28.8%)	8 (6.7%)	21 (17.9%)	55 (46.6%)	118 (100%)

Luminal A: ER+, PR+, HER2-; LUMB- Luminal B: ER+, PR+, HER2+; HER2 Overexpression- ER-, PR-, HER2+; Triple negative- ER-, PR-, HER2-

distribution of the TNBC was fairly uniform but rose to a peak in the sixth decade (50–59 years) and then progressively declined from the seventh decade. HER2 overexpression was most frequent in women 30–39 years of age, followed by women in the fifth and sixth decades (40–49 years and 50–59 years). LUMA tumors constituted 28.8% of all the molecular subtypes and women in the sixth decade accounted for one-third of all LUMA cases. The least common subtype was LUMB and accounted for 8% of all subtypes with an almost uniform distribution in women <60 years of age [Table 3].

Table 4 depicts the molecular subtyping of the various histomorphologic entities. Relative to histomorphology, triple-negative subtype was still the most common, with invasive carcinoma (NST) being the most predominant

Table 4: "d" Molecular Subtyping of Histomorphologic Entities

Histomorphology	Molecular Sub-type				Total
	LUMA	LUMB	HER2 Overexpression	Triple Negative	
IC (NST)	26	6	15	38	85 (72.1%)
IPC	3	-	1	3	7 (5.9%)
MDC	1	-	-	5	6 (5.1%)
ILC	1	1	1	2	5 (4.2%)
MPC	-	-	1	4	5 (4.2%)
AC	-	-	2	2	4 (3.4%)
DCIS	1	-	1	-	2 (1.7%)
OTHERS	2	1	-	1	4 (3.4%)
TOTAL (%)	34 (28.8)	8 (6.7%)	21 (17.9%)	55 (46.6%)	118 (100%)

AC – Apocrine carcinoma, ACC – Acinic cell carcinoma, DCIS – Ductal carcinoma in-situ, ILC – Invasive lobular carcinoma, IC (NST) – Invasive carcinoma (No Special Type), IPC – Invasive papillary carcinoma, LELC – Lymphoepithelioma like carcinoma, MDC – Medullary Carcinoma, MPC – Metaplastic carcinoma, MC – Mucinous carcinoma, NEC – Neuroendocrine carcinoma, LUMA- Luminal A, LUMB- Luminal B

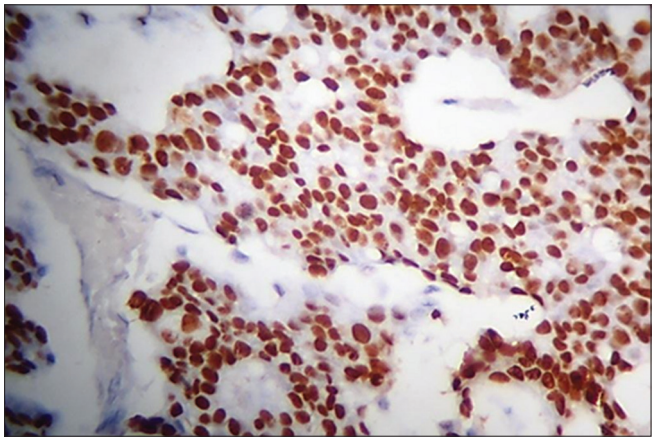

Figure 3: Photomicrograph showing strong nuclear staining in almost 100% of the invasive cells (Estrogen receptor positive; 5+3). ×10

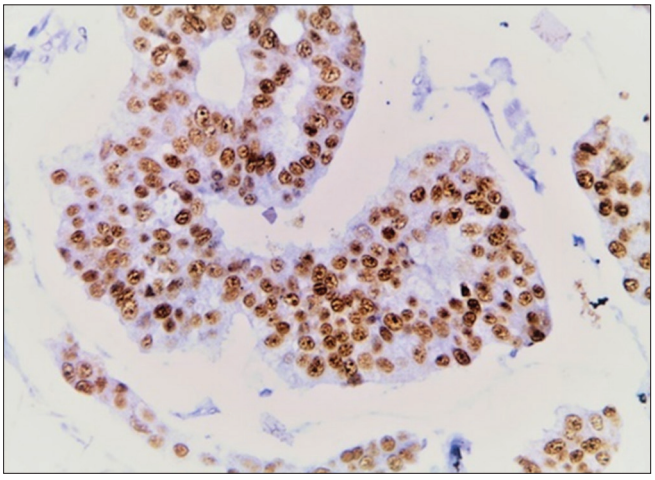

Figure 4: Photomicrograph showing strong nuclear staining in almost 100% of the cells (Progesterone receptor positive; 5+3). ×10

histomorphologic entity in all the molecular subtypes. Half of the apocrine carcinomas (2 of 4) were triple negative.

HER2 overexpression [Figure 5] was almost exclusively seen in invasive carcinoma (NST), 15 of 21, with apocrine carcinoma accounting for 2% (1 of 26).

Only a case of mucinous carcinoma was seen and it was a LUMA tumor. The other special types were quite common but invasive carcinoma (NST) was still the most common comprising 26 of 34 for LUMA and 6 of 8 for LUMB subtypes.

Discussion

Cancer of the breast comprised 14.9% of all malignancies in Kano during the 5-year study period. This is within a national range of 11.9%–31.8%[6-8] but is much higher than figures reported in Cote d'Ivoire (6.5%) and less than figures from Sudan (22.9%) and Iraqi (34%).[9-11] The predominance of carcinomas (98.9%) is comparable with findings of 92.2% in Cote d'Ivoire.[9]

The age range 20–80 years observed in this study is similar to published reports from Gombe and Ile-Ife.[12,13] The mean age of 46.9 years found in the index study is in consonance with what has been reported in other parts of Nigeria as exemplified by 42.1 years reported in Zaria, 44 years in Gombe, 45.1 years in Calabar, and 48 years in Ile-Ife.[12-15] These findings, resonating across the country, lend credence to the observation that malignant tumors in this country generally tend to occur a decade to a decade and a half earlier than what has been described among Caucasians.[16] Similar observation has been made among Africans and African-Americans living in the USA, and the cause of this has been postulated to reflect higher rates of BRCA gene mutation among non-Caucasians.[16]

In further support of this is the observation that 56.7% of the women in this study were <50 years of age in addition to approximately 1 out of every 20 being younger than 30 years of age. The peak age range of 40–49 years as found in the index study is also comparable to findings in Calabar and Maiduguri in Nigeria and Iraq in the Middle East.[11,15] In contrast, a bimodal peak age was described in Hong Kong with an initial peak age range of 40–45 probably reflecting a predominantly genetic influence and a second peak in the

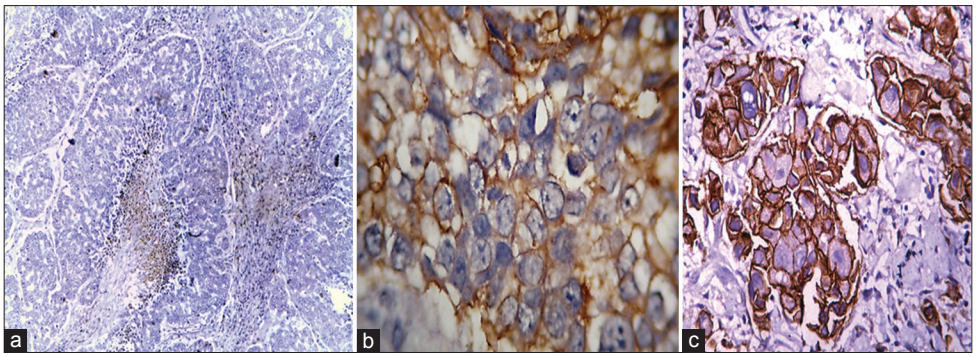

Figure 5: "d" Photomicrograph showing Invasive carcinoma (NST) demonstrating HER2 immunostaining: (a) HER2- (×10); (b) Incomplete membrane staining HER2; 2+ (×40) and (c) Complete membrane staining HER2; 3+ (×20)

75–85 year age range probably reflecting a predominance of environmental factors.[17]

Invasive carcinoma (NST), like in other studies in Nigeria, was still the most common histomorphologic entity in the index study. Yet, the percentage (73.2%) was slightly lower than what was recorded in other parts of the North, 78.8% in Gombe and 82.6% in Maiduguri, as well as in the Southern part of the country with values ranging between 75.5% and 85.2%.[6,12,18,19] Our value is also lower than what has been reported in other parts of West Africa including Ghana and Cote d'Ivoire where it ranges between 83.2% and 92.2%, as well as outside Africa where it has been between 81% and 81.8%.[13,20,21] The relatively higher occurrence of special types of the disease appears to account for this. More noteworthy, however, was the rarity of DCIS (6 of 118 cases), a finding that is in stark contrast to what is seen in the Western countries.[22] This finding perhaps shows that late presentation is the norm in Nigeria; poor uptake of breast screening strategies, especially mammography, and as described by Odusanya and Tayo[23] and by Uche,[24] inadequate awareness of breast cancer among the Nigerian populace.

Grade III tumors were more common in this series of breast cancer cases with similar predominance of Grade III tumors described by most studies in Nigeria and internationally.[6,25] The invasive non-NST tumors were mostly Grade II with the rest being Grade III. Other studies including that by Seshi *et al*. in Ghana[26] which reported the majority (60.8%) being Grade II tumor also contrasts with the other aforementioned studies. This disparity could be due to interobserver variability in grading as highlighted by Chowdhury *et al*.[27] in their study of breast cancer grading.

ER-negative cases comprising triple-negative and HER2 overexpressed tumors were the most frequent in the index study. The 46.6% frequency of triple-negative molecular subtype found in this study is lower than the 47.7% reported by Titloye *et al*.,[28] the 52.6% by Minoza *et al*.[29] in Maiduguri, and the 87% by Makanjuola *et al*.[25] in Lagos. However, these are higher than the 6% and 16% reported by El Fatemi *et al*.[30] and Adebamowo *et al*.,[31] respectively, succinctly underscoring the preponderance of this subtype in Nigeria. In comparison, the frequency of this subtype has been found to range between 14% and 29.5% in Western countries.[32,33] The implication for Nigerian women with the disease and managing oncologists is the nonsuitability of these women for neither hormonal therapy nor adjuvant therapy. Interestingly, just as observed by Tischkowitz *et al*.,[33] triple-negative tumors were also the predominant molecular subtype irrespective of age group of patients or histomorphologic entity. In addition to this, triple-negative tumors have also been associated with BRCA1 mutation.[34] This may explain the poor outcome noted by Dietze *et al.* among African women with carcinoma of the breast.[35]

HER2 overexpression was the second most common subtype of the ER-negative cases. Adebamowo *et al*.[31] in an earlier study reported HER2 overexpression as the third most common. However, studies in Sub-Saharan Africa have documented a high proportion of HER2-overexpressed cases[31,36,37] with similar studies in Asia.[38] In contrast, Huo *et al*.[39] and Seshi *et al*.[26] reported a lower frequency (15% and 25.5%, respectively). The implication for women with this molecular subtype is that their tumors may be more amenable to anti-EGFR-targeted therapy (Trastuzumab). Treatment with adjuvant trastuzumab therapy has been shown to be associated with a 52% increase in disease-free survival and a 33% reduction in risk of death.[40] While this may be a positive, Carey *et al*.[41] have. however, identified a high risk of early and frequent relapse among patients on this therapy. In Nigeria where resources are less readily available, high cost of trastuzumab may limit access to this drug, just as observed even in developed countries.[40]

The ER-positive cases are composed of LUMA and LUMB tumors. In this study, 35.5% of the cases were ER positive. Although higher than the 2.1% and 11.1% reported by Makanjuola *et al*. in Lagos[25] and Banjo *et al*.[36] in Ogun, respectively, it is close to the percentage (39.5%) reported by Minoza *et al*.[29] in Maiduguri also in Northern Nigeria but lower than the 80.2% by Adebamowo *et al*.[31] This wide variation in ER positivity rate is further highlighted by findings from outside Nigeria including Saudi Arabia (74.8%),[42] Eritrea (60%),[43] USA (58%),[41] and Egypt (55.1%).[44] LUMA tumors were common than LUMB in this study mirroring

similar report by Minoza *et al*.[29] also in Northern Nigeria as well as Seshi *et al*.[26] in Cote d'Ivoire. It however contrasts with that of El Fatemi *et al*.[30] in Morocco who described a higher frequency of LUMB. ER-positive tumors have been shown to have little response to chemotherapy with LUMB having a poorer prognosis than LUMA.[45] The implication of this in women in Northern Nigeria, though supports use of anti-estrogens (tamoxifen), is counterbalanced by relative poorer response of ER-positive tumors to chemotherapy in addition to high risk of development of resistance to anti-estrogens.[13]

Conclusion

In the population evaluated, this study has also demonstrated that similar to findings among Blacks, carcinomas of the female breast occur at a younger age than among Caucasians. This study also reaffirms that these tumors, similar to reports from other local studies, are predominantly invasive carcinoma (NST), associated with a high frequency of triple negativity and are also mostly ER negative.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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