Association Between CA 15-3 and ^{18}F-FDG PET/CT Findings in Recurrent Breast Cancer Patients at a Tertiary Referral Hospital in Kenya

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The tumor marker cancer antigen 15-3 (CA 15-3) is that most commonly used to monitor metastatic breast cancer during active therapy and surveillance for disease recurrence after treatment. The association of CA 15-3 and ^{18}F-FDG PET/CT findings can be considered complementary, since any significant rise may indicate the presence of disease and imaging is able to map the tumor sites. Although current guidelines do not recommend the routine performance of CA 15-3 in asymptomatic patients being followed up after definitive breast cancer treatment, most oncologists perform serial assessment of the tumor markers as part of routine follow-up of patients. The aim of this study was to evaluate the correlation between CA 15-3 levels and ^{18}F-FDG PET/CT scan findings in patients with recurrent breast cancer. **Methods:** This was a cross-sectional study with data collected retrospectively. Patients being evaluated for breast cancer recurrence with ^{18}F-FDG PET/CT imaging and CA 15-3 level were included. Evaluation of the association between CA 15-3 levels and ^{18}F-FDG PET/CT scan findings was then done. **Results:** In total, 154 cases were included in this study; 62 patients had recurrence (positive) on the ^{18}F-FDG PET/CT scans, whereas 92 patients had normal (negative) findings on follow-up ^{18}F-FDG PET/CT scans. There was an association between CA 15-3 levels and the presence or absence of recurrence on ^{18}F-FDG PET/CT scans, with 84.4% (27/32) of patients who had elevated CA 15-3 levels having disease recurrence on ^{18}F-FDG PET/CT and 84.4% (27/32) of patients who had elevated CA 15-3 levels having disease recurrence on ^{18}F-FDG PET/CT as well as a correlation with the burden of metastases. Most patients with disease recurrence on ^{18}F-FDG PET/CT, however, had normal CA 15-3 levels. **Conclusion:** Higher CA 15-3 levels correlate with breast cancer recurrence on ^{18}F-FDG PET/CT as well as with burden of metastasis. Notably, CA 15-3 levels within the reference range do not exclude breast cancer disease recurrence since more than half of patients with recurrence had normal CA 15-3 levels. ^{18}F-FDG PET/CT should therefore be considered in patients with suspected breast cancer recurrence but normal CA 15-3 levels.

Key Words: CA 15-3; ^{18}F-FDG PET/CT; breast cancer; recurrence

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Breast cancer is the most commonly diagnosed cancer type, accounting for 1 in 8 cancer diagnoses worldwide. Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer. In 2020, there were about 2.3 million new cases of breast cancer globally and about 685,000 deaths from this disease, with large geographic variations observed between countries and world regions. Breast cancer incidence rates are highest in high-income countries, but low-income countries carry a disproportionate share of breast cancer deaths (*1*).

The association of ^{18}F-FDG PET/CT and elevated tumor markers (cancer antigen 15-3 [CA 15-3]) can be considered complementary, since any significant rise in CA 15-3 levels can indicate the presence of disease and PET/CT is able to map the tumor sites (*2*). ^{18}F-FDG PET/CT is also uniquely suited to identifying heterogeneity of disease distribution such as bone-dominant disease or liver involvement, which has implications in treatment selection and prognosis. In addition, in contrast to tumor markers, which represent a sum of the tumor burden, ^{18}F-FDG PET/CT has the unique ability to demonstrate heterogeneity of disease response.

CA 15-3 levels are most commonly used to monitor metastatic breast cancer during active therapy. It can also be used to survey disease recurrence after treatment of breast cancer (*3*).

Most guidelines do not recommend routine use of CA 15-3 in the follow-up of asymptomatic patients after definitive treatment because of a lack of data that can demonstrate a survival benefit. Imaging to evaluate for metastases is also done only when indicated in clinically suspected recurrence (*4*). The European Society for Medical Oncology and the American Society of Clinical Oncology recommend a regular evaluation with history and physical examination, as well as annual mammography, in the follow-up of patients with early breast cancer. Nevertheless, many oncologists perform serial tumor marker measurement as part of routine follow-up in asymptomatic patients.

The aim of this study was to evaluate the correlation between CA 15-3 levels and ^{18}F-FDG PET/CT scan findings in patients being followed up for breast cancer.

MATERIALS AND METHODS

Study Population

This was a retrospective descriptive study conducted between February 2019 and August 2023. This study was done at the Aga Khan University Hospital, Nairobi, in the Department of Radiology and Diagnostic Imaging, Nuclear Medicine Section. The patients were being evaluated for breast cancer recurrence, had ^{18}F-FDG PET/CT performed at Aga Khan University Hospital Nairobi, and had available CA 15-3 tumor markers.

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All CA 15-3 assays were performed in the same laboratory in the institution where the study was undertaken. Laboratory services at Aga Khan University Hospital have received accreditation from the Joint Commission International and the College of American Pathologists. Ethical approval was sought from the Aga Khan University, Institutional Scientific and Ethics Review Committee, and thereafter by the National Commission for Science, Technology, and Innovation. In view of the retrospective nature of the study, with no direct impact on patient management, a waiver of informed consent was granted.

To be included, patients had to have undergone primary treatment with curative intent for breast cancer and be scheduled for follow-up ^{18}F-FDG PET/CT and, within 3 mo afterward, measurement of CA 15-3 tumor markers. The ^{18}F-FDG PET/CT scans were acquired on a Discovery MI PET/CT scanner (GE HealthCare) following a routine protocol of imaging from the vertex to the proximal femur, with a noncontrast CT scan for attenuation correction. All PET/CT studies were interpreted by 2 nuclear medicine specialists with more than 5 y of experience. Patients with incomplete data were excluded from the study.

Data Collection

A search on a PACS was done for ^{18}F-FDG PET/CT scans performed to exclude recurrence of breast cancer. For all patients with ^{18}F-FDG PET/CT performed to exclude disease recurrence, a separate search of medical records was performed to obtain tumor marker (CA 15-3) and histology results, and those patients fulfilling the inclusion criteria were then recruited into the study.

Several ^{18}F-FDG PET/CT variables were collected, including presence or absence of recurrent disease, local recurrence versus metastatic recurrence, sites of recurrence (skeletal, visceral, nodal), number of skeletal metastases (<5 or >5), nodal involvement (regional vs. nonregional), and visceral organs involved.

Data Analysis

Summary statistics are presented as mean and SD or median and interquartile range for continuous data, whereas frequencies and percentages are used for categoric data. Univariate analysis was used to compare groups, with the Student *t* test or Mann–Whitney test being used for continuous data and the Fisher exact test or χ^2 test being used for categoric data. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

In total, 154 patients being evaluated for breast cancer recurrence were enrolled from February 2019 to August 2023. All were female, with an age range of between 30 and 83 y (median age, 53 y). Sixty-two patients had recurrence (positive) on ^{18}F-FDG PET/CT, and 92 patients had normal (negative) PET/CT results. The CA 15-3 levels ranged from 0.5 to 434.2 U/mL (median, 14.2 U/mL). The demographics and clinical characteristics of patients are summarized in Table 1. The distribution of CA 15-3 and ^{18}F-FDG PET/CT findings is depicted in Figure 1.

Association Between CA 15-3 Levels and ^{18}F-FDG PET/CT Scan Findings

Of the 154 patients referred for ^{18}F-FDG PET/CT to rule out recurrence, only 32 patients had elevated CA 15-3. There was a significant association between CA 15-3 levels and the presence or absence of recurrence on ^{18}F-FDG PET/CT scans. Of patients with elevated CA 15-3 levels, 84.4% (27/32) had disease recurrence on PET/CT. Only 15.6% (5/32) patients had discordant findings of increased CA 15-3 levels with negative ^{18}F-FDG PET/CT findings. This association is depicted in Table 2.

Relationship Between CA 15-3 Levels and Patterns and Burden of Recurrent Disease

There was a statistically significant association between elevated CA 15-3 and the presence of skeletal and visceral metastases ($P = 0.002$ and 0.039, respectively). Although 24 of 27 patients with recurrence and with elevated CA 15-3 had metastatic recurrence, this was not statistically significant (Table 3). The 2 patients with local recurrence and no metastases had normal CA 15-3 levels. One patient had both local and metastatic recurrence. There was also a statistically significant association between nodal disease recurrence (regional or nonregional) and CA 15-3 levels, with most of those patients with nonregional nodal disease recurrence having elevated CA 15-3 levels. These associations are depicted in Table 3.

Histologic Subtypes and Hormonal Status

Most patients with recurrence had invasive ductal carcinoma (39 cases, 86.7%). There were 4 cases (8.9%) of invasive lobular carcinoma and 2 cases (4.4%) of ductal carcinoma in situ. Most cases of primary breast cancer had a positive hormonal status (38 cases, 73.1%). There was no association between the hormonal status in those with subsequent recurrent disease and the CA 15-3 levels. However, most triple-negative cases with recurrence had normal CA 15-3 levels. The association between hormonal status and CA 15-3 levels is summarized in Table 4

Relationship Between CA 15-3 Levels and ^{18}F-FDG PET/CT Semiquantitative Parameters, Notably SUV_{max}

The highest SUV_{max} in the ^{18}F-FDG PET/CT scans with recurrence was recorded and compared with CA 15-3 levels. The median highest SUV_{max} was 9.8 (interquartile range, 7.2–14.5). There was no relationship between CA 15-3 levels and highest SUV_{max} (correlation coefficient, 0.112; $P = 0.385$). This is depicted in Figure 2.

DISCUSSION

Follow-up of breast cancer patients to exclude recurrence can be challenging. In addition to clinical parameters, several tools have been used, including evaluation of relevant tumor markers and imaging. Despite not being recommended for routine follow-up, the use of ^{18}F-FDG PET/CT imaging in the follow-up of patients with breast cancer has been peaking worldwide (*5*).

This study found several correlations between tumor marker CA 15-3 levels and ^{18}F-FDG PET/CT findings in patients being evaluated for breast cancer recurrence. First, there was a significant association between CA 15-3 levels and the presence of recurrence on ^{18}F-FDG PET/CT, with most cases of elevated CA 15-3 tumor markers (27/32) having recurrence on PET/CT. These findings indicate that in patients with elevated CA 15-3 after treatment for breast cancer, ^{18}F-FDG PET/CT has a high diagnostic accuracy in detecting and mapping out sites of disease. A study by Reitere et al. had similar findings of a significant correlation of elevated tumor markers and positive ^{18}F-FDG PET/CT results (*6*).

A significant number of patients with normal CA 15-3 had recurrence on ^{18}F-FDG PET/CT. This suggests that ^{18}F-FDG PET/CT imaging is more sensitive in detecting recurrence than are tumor markers in patients clinically suspected to have recurrence. A study by Gallowitsch et al. found that in patients with clinical suspicion of tumor recurrence but no increase in tumor marker

TABLE 1
Demographics and Clinical Characteristics of Patients

Characteristic	Parameter	Data
Age (y)		53.0 (45.0–60.0)
Recurrence	Present	62 (40.3%)
	Absent	92 (59.7%)
Histology (n = 62)	Available	45 (72.6%)
	Not available	17 (27.4%)
Histology type (n = 45)	DCIS	2 (4.4%)
	IDC	39 (86.7%)
	ILC	4 (8.9%)
Hormonal status (n = 52)	Hormonal positive	38 (73.1%)
	Hormonal negative	14 (26.9%)
Type of recurrence (n = 62)	Both (local and metastatic)	11 (17.7%)
	Local	2 (3.2%)
	Metastatic	49 (79.0%)
Site of recurrence (n = 62)	Local	14 (22.6%)
	Nodal	40 (64.5%)
	Visceral	29 (46.8%)
	Skeletal	42 (67.7%)
	Others	3 (4.8%)
Skeletal (n = 41)	<5	14 (34.1%)
	>5	27 (65.9%)
Nodal (n = 39)	Both (regional and nonregional)	12 (30.8%)
	Nonregional	21 (53.8%)
	Regional	6 (15.4%)
Visceral (n = 29)	Lung	22 (75.9%)
	Liver	9 (31.0%)
	Pleura	5 (17.2%)
	Ovary	2 (6.9%)
	Peritoneal	1 (3.4%)
Highest SUV_{max} (n = 62)		9.80 (7.20–14.50)
CA 15-3 (U/mL)		14.6 (8.4–26.0)
CA 15-3 (U/mL)	Increased	32 (20.8%)
	Normal	122 (79.2%)

Qualitative data are number and percentage; continuous data are median and interquartile range.

levels, ^{18}F-FDG PET/CT was a reliable imaging modality for detecting recurrence (*7*). Therefore, tumor marker levels within the reference range do not exclude the possibility of a positive PET/CT result suggesting recurrence.

Five of 32 patients with elevated tumor markers did not have recurrence on ^{18}F-FDG PET/CT. These findings were similar to those of Reitere et al., who found that patients with much lower marker levels had a positive PET/CT result and that some patients with very high levels had a negative result (*6*). The patients with elevated tumor markers and negative ^{18}F-FDG PET/CT results could partly be explained by the fact that micrometastases may not be detectable on ^{18}F-FDG PET/CT. Some studies have shown that tumor marker levels can increase before clinical and radiologic findings of recurrence become apparent (*8,9*). Nonspecific elevation of CA 15-3 may also be found in patients with nonneoplastic diseases such as diverticulitis, sarcoidosis, and cirrhosis. It has also been seen in other malignancies such as lung and gastrointestinal tumors (*10,11*).

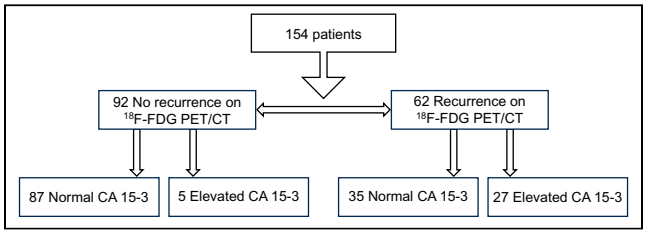

FIGURE 1. Distribution of CA 15-3 and ^{18}F-FDG PET/CT findings.

TABLE 2
Association Between CA 15-3 Levels and ^{18}F-FDG PET CT Findings

Recurrence	CA 15-3 Increased	CA 15-3 Normal	*P*
Present	27 (84.4%)	35 (28.7%)	<0.001
Absent	5 (15.6%)	87 (71.3%)	

TABLE 4
Correlation Between Hormonal Status and CA 15-3 Levels in Recurrent Disease

Hormonal status	CA 15-3 Increased	CA 15-3 Normal	*P*
Positive	18 (85.7%)	20 (64.5%)	0.118
Negative	3 (14.3%)	11 (35.5%)	

Blood tumor markers reflect the total tumor burden. Both ^{18}F-FDG PET/CT and tumor marker status are biologic tools that characterize the functional state of existing tumor tissue, with ^{18}F-FDG PET/CT providing a map of disease recurrence distribution. Tumor marker status was previously reported to be too insensitive to identify the existence of tumor tissue with a relatively smaller burden (*2*). In our study, patients with local recurrence and no metastases on ^{18}F-FDG PET/CT were found to have normal tumor marker levels. Other studies, such as that by Colomer et al. (*12*), have also reported that levels of circulating tumor markers such as CA 15-3 are related to tumor burden.

Elevated CA 15-3 levels were associated with the presence of skeletal and visceral metastases. The highest levels were seen in patients with multiple metastatic disease sites, skeletal metastases numbering more than 5, and visceral metastases. Furthermore, there was also a significant association between nodal disease recurrence (regional or nonregional) and CA 15-3 levels, with most patients who had nonregional nodal disease recurrence having elevated CA 15-3 levels. There have been conflicting results regarding the correlation of CA 15-3 and sites of recurrence. A study by Lumachi et al. found no correlation between tumor markers and type of recurrence (*13*). Fakhari et al. found a correlation between bone metastases and CA 15-3 levels (*14*).

There is no correlation between avidity based on the highest SUV_{max} and CA 15-3. This is likely due to the fact that the highest SUV_{max} does not represent overall disease burden. This finding was similar to a study by Cervino et al. (*2*), who found that SUV_{max} and CA 15-3 do not correlate. The link between CA 15-3 and glucose metabolism can be better addressed using volumetric

TABLE 3
Relationship Between CA 15-3 Levels and Patterns and Burden of Recurrent Disease

Characteristic	Parameter	CA 15-3 Increased	CA 15-3 Normal	*P*
Type of recurrence	Both (local and metastatic)	3 (11.1%)	8 (22.9%)	0.239
	Local	0 (0.0%)	2 (5.7%)	
	Metastatic	24 (88.9%)	25 (71.4%)	
Site of recurrence	Local	3 (11.1%)	11 (31.4%)	0.072
	Nodal	19 (70.4%)	21 (60.0%)	0.434
	Visceral	17 (63.0%)	12 (34.3%)	0.039
	Skeletal	24 (88.9%)	18 (51.4%)	0.002
	Others	1 (3.7%)	2 (5.7%)	1.000
Skeletal	<5 lesions	6 (25.0%)	8 (44.4%)	0.208
	>5 lesions	18 (75.0%)	10 (55.6%)	
Nodal	Both (regional and nonregional)	3 (16.7%)	9 (42.9%)	0.021
	Nonregional	14 (77.8%)	7 (33.3%)	
	Regional	1 (5.6%)	5 (23.8%)	
Visceral	Lung	12 (70.6%)	10 (83.3%)	0.665
	Liver	6 (35.3%)	3 (25.0%)	0.694
	Pleura	3 (17.6%)	2 (16.7%)	1.000
	Ovary	2 (11.8%)	0 (0.0%)	0.498
	Peritoneal	1 (5.9%)	0 (0.0%)	1.000

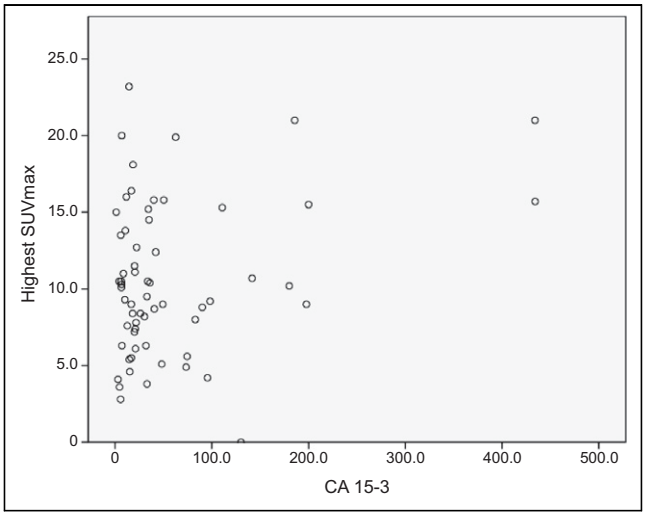

FIGURE 2. Correlation between CA 15-3 and highest SUV_{max} on ^{18}F-FDG PET/CT.

quantitative values such as metabolic tumor volume and total lesion glycolysis.

Although there was no statistically significant association between CA 15-3 and initial hormonal status, most triple-negative cases with recurrence had normal CA 15-3 levels. This is in agreement with a study by Uygur et al., who found that CA 15-3 levels were significantly higher in hormone receptor–positive patients (*15*). This can partly be explained by the fact that hormone-positive cases have higher mucin 1 glycoprotein expression (*16*).

Our study had a few limitations. First, it was retrospective, done in one institution, and entailed analysis of previous recorded data, hence restricting the ability to reduce confounding and bias. Second, most of the cases with recurrence on ^{18}F-FDG PET/CT were not confirmed on histology. Third, the fact that we had only a small proportion of patients with elevated CA 15-3 in our study may limit determining the strength of associations.

CONCLUSION

In patients being followed up after treatment of breast cancer, elevated CA 15-3 levels are associated with disease recurrence on ^{18}F-FDG PET/CT as well as with the presence of skeletal, visceral, and nonregional nodal metastases. ^{18}F-FDG PET/CT is therefore useful in mapping out sites of disease recurrence in patients with elevated CA 15-3. Notably, CA 15-3 levels within the reference range do not exclude breast cancer recurrence since more than half of patients with recurrence on ^{18}F-FDG PET/CT had normal CA 15-3 levels. ^{18}F-FDG PET/CT should therefore be considered in patients with suspected breast cancer recurrence but normal CA 15-3 levels.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is there an association between the CA 15-3 tumor marker and ^{18}F-FDG PET/CT findings in patients with breast cancer recurrence?

PERTINENT FINDINGS: Elevated CA 15-3 levels correlated with positive ^{18}F-FDG PET/CT findings in patients being evaluated for breast cancer recurrence. A statistically significant number of patients with normal CA 15-3 levels, however, had positive ^{18}F-FDG PET/CT scan findings.

IMPLICATIONS FOR PATIENT CARE: This study showed the poor predictive nature of CA 15-3 (especially normal values) in determining the presence or absence of breast cancer metastases. It also indicated that ^{18}F-FDG PET/CT has high diagnostic accuracy in detecting breast cancer recurrence and in mapping disease sites.

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