INTRODUCTION

Cancer Stem Cell (CSC) has emerged one of the fastest growing cancer research fields. Cancer stem cells have the propensity of self-renewal, proliferation, and differentiation. Although they make up a minute subset of tumour population, the involvement of CSC in vital processes such as tumour initiation, progression, metastasis, recurrence and chemoresistance have made them worth researching into[1]. The concept of CSCs has revolutionalised cancer research. A constellation of research has identified their involvement in a great deal of hematological and non-hematological cancers including leukemia, colon cancer, brain, liver, melanoma, and breast cancer.

Putative Breast CSC have been found to include the unique combination phenotype of a high expression of the transmembrane glycoprotein CD44 and a low or no expression of the glycosylated mucin type protein CD24 ($CD44^{+}/CD24^{-/low}$). Others include a detoxifying intracellular enzyme Aldehyde dehydrogenase 1 (ALDH1), the transcriptional repressor of the Polycomb group (PcG) of transcription factors, B cell specific Moloney murine leukemia virus integration site 1 (BMI1), the cluster of differentiation 133 (CD133) also known as Prominin 1 and the sialic acid-containing glycosphingolipid, Disialoganglioside (GD2).

Varied studies have been undertaken on these breast CSC in various populations to ascertain their functional roles in contributing to tumourigenesis, progression, differentiation, survival and chemoresistance. Their relationships and associations with various clinicopathological parameters of breast cancer have also been widely studied emphasising the crucial role these stem cells play in tumour aggressiveness. Although the role of some of these stem cells remain largely consistent across studies and populations, others have still been quite controversial requiring further studies in deciphering their functionality in breast cancer. As literature on breast CSC continues to increase since the concept was first introduced about two decades ago, racial comparative studies in the field remain unremarkable. The question of whether there exist racial disparities in breast

CSC's expression pattern and their roles in contributing to the complex racial heterogeneity of breast cancer remain largely unknown. Therefore, ethnic, and racial comparative studies on breast CSC profile and functions is conceivable. In this study, a racial comparison of breast CSC and their association with various clinicopathological parameters and clinical outcomes of breast cancer is undertaken.

Methodology

English literature search in Pubmed central, Science direct, and Research gate on breast CSC between 2003 and 2020 was undertaken using keywords such as breast cancer stem cells; BMI1; Prominin1; CD133; $CD44^{+}/CD24^{-/low}$; GD2; ALDH1; and Aldehyde dehydrogenase. All research articles within the period which used Immunohistochemistry (IHC) staining technique, mRNA expression, or multiplex IHC in identifying the breast CSC were included and their association with clinicopathological features and clinical outcomes including age, tumour size, stage, grade, lymph node metastasis, mitotic count, Nottingham Prognostic Index (NPI), ER, PR, Her2, Triple negative/basal like, Disease Free Survival (DFS), and Overall Survival (OS). All papers with indication of the population/race on which the study was conducted were included in this study.

The race of the population on which the study was conducted were categorised into five races including African/Black American, Asian, Caucasian, American, Hispanic/Latino.

Results

A total of 40 research articles were included in this study comprising 4 African/Black American, 20 Asian, 10 Caucasian/White, 1 Hispanic/Latino and African/Black American, 2 American and 3 Other mixed raced studies. Table 1 shows the racial expression of breast CSC and their association with clinicopathological features.

Table 1: Racial expression of breast CSC and their association with clinicopathological features

Clinicopathological parameters	African/Black American	Asian	Caucasian	Hispanic and Latino	American	Other mixed race
Age		$CD44^{+}/CD24^{-/low2}$	$CD44^{+}/CD24^{-/low3}$ $CD133^{4}$			
Tumour Size		$ALDH1^{5-7}$	$CD44^{+}/CD24^{-/low8}$			$GD2^{9}$
Stage		$ALDH1^{5,10}$	$*CD44^{+}/CD24^{-/low11}$			
Lymph Node Metastasis		$CD44^{+}/CD24^{-/low2,12-17}$ $ALDH1^{5,10}$ $BMI1^{18}$	$CD44^{+}/CD24^{-/low3,8,13,19}$ $*CD44^{+}/CD24^{-/low11}$ $ALDH1^{20}$			$GD2^{9}$
Lymphovascular Invasion		$CD44+/CD24^{-/low\ 14}$	$CD44^{+}/CD24^{-/low3}$			
Tumour grade	$ALDH1^{21}$ $BMI1^{21}$	$ALDH1^{5-7,10,22,23}$	$ALDH1^{20}$ $*BMI1^{24}$ $CD133^{4}$			$GD2^{9}$
Mitotic count	$ALDH1^{21}$		$*BMI1^{24}$			
Nottingham Prognostic Index			$ALDH1^{20}$ $*BMI1^{24}$			
Progesterone receptor	$*ALDH1^{21,25}$	$CD44^{+}/CD24^{-/low15,16}$ $*ALDH1^{26}$	$CD44+/CD24^{-/low4}$ $*CD44^{+}/CD24^{-/low19}$			
Estrogen receptor positive		$CD44^{+}/CD24^{-/low12,16}$	$CD44^{+}/CD24^{-/low8}$			

	*ALDH1[21,25] BMI1[21]	ALDH1[26] BMI1[18]	*CD44^{+}/CD24$^{-/low19}$ ALDH1[4] BMI1[24]			
Her2 overexpression	ALDH1[25]	CD44^{+}/CD24$^{-/low12,16}$ ALDH1[7,22,27]	*BMI1[24]			CD44^{+}/CD24$^{-/low28}$
Triple Negative/Basal like tumour	CD44^{+}/CD24$^{-/low29}$ ALDH1[21,30,31]	CD44^{+}/CD24$^{-/low12,15,32}$ ALDH1[23,33,34]	CD44^{+}/CD24$^{-/low3,8\ 13,35,36}$ CD133[4]	CD44^{+}/CD24$^{-/low29}$	CD44^{+}/CD24$^{-/low37}$	CD44^{+}/CD24$^{-/low38}$
Disease Free Survival	CD44^{+}/CD24$^{-/low29}$	CD44^{+}/CD24$^{-/low12,15,16}$ ALDH1[7,23,39]	CD44^{-}/CD24^{+11}	CD44^{+}/CD24$^{-/low29}$		
Shorter Overall Survival		CD44^{+}/CD24$^{-/low12,13,15,16}$ ALDH1[5,7,22,39]	*CD44+/CD24-/low[13,40] CD44^{-}/CD24$^{+11,40}$ *BMI1[24]		ALDH1[41]	

*Breast CSC with inverse association with corresponding parameters.

CD44^{+}/CD24$^{-/low}$

A total of 13 out of 40 (32.5%) of all papers within the inclusion criteria studied the putative breast CSC CD44^{+}/CD24$^{-/low}$. It is interesting to note that all races/ethnicities had at least a paper associating this breast CSC with triple negative/basal like cancers.

Caucasian

In Caucasians, CD44+/CD24-/low was associated with poorer clinicopathological features such as age[3], tumour size[8], LN metastasis [3,8,13,19], and lymphovascular invasion[3]. Inverse associations were however found with tumour stage and lymph node metastasis by Mylona *et al*[11]. Tumour grade, mitotic count, and Nottingham Prognostic Index (NPI) were the clinicopathological parameters

that have not been associated with $CD44^{+}/CD24^{-/low}$ in Caucasians as well as in all other races. For hormone receptor status (PR and ER), although there has been associations with $CD44^{+}/CD24^{-/low}$, studies have found both positive[4,8] and inverse associations[19]. There has so far not been any association reported between Her2 expression and $CD44^{+}/CD24^{-/low}$ in this race. For clinical outcomes, there has not been any reported association between DFS and $CD44^{+}/CD24^{-/low}$ but two studies rather revealed $CD44^{-}/CD24^{+}$ phenotype have poorer outcomes (DFS and OS) [11,40].

Asian

Similar to Caucasian, studies in Asian populations have reported associations between $CD44^{+}/CD24^{-/low}$ and age[2], lymph node metastasis[2,12-17], and lymphovascular invasion[14]. Positive associations have been reported between $CD44^{+}/CD24^{-/low}$ and hormonal receptors ER[12,16], PR[15,16] and Her2 overexpression[12,16]. Contrary to the Caucasian reports, $CD44^{+}/CD24^{-/low}$ has been reported to be associated with poor clinical outcomes such as DFS[12,15,16], and OS[12,13,15,16] in quiet a significant number of studies.

African/Black American

There has not been any reported African study on $CD44^{+}/CD24^{-/low}$ yet with the exception of an unpublished data from our group which records associations between tumour grade ($p=0.018$) and higher clinical prognostic staging ($p=0.011$). However, one Black American study associated $CD44^{+}/CD24^{-/low}$ with TNBC/Basal like and shorter DFS[29].

Hispanic/Latino America

Like African/Black American, there is scarcity of studies on CD44+/CD24-/low in this race. Only a single study revealed an association with TNBC/Basal like and shorter DFS[29].

American

Only one American study had an association between CD44+/CD24-/low and TNBC/Basal like.

ALDH1

A total of 16 out of 40 (40%) studied ALDH1, making it the most well researched putative breast CSC especially in Asians. American and Hispanic/Latino recorded the least number of ALDH1 studies. Across all races, ALDH1 has so far not been reported to be associated with lymphovascular invasion.

Caucasian

Like $CD44^{+}/CD24^{-/low}$, ALDH1 is also associated with some poor clinicopathological features such as lymph node metastasis, tumour grade and Nottingham Prognostic Index (NPI)[20] in Caucasians. It is also associated with ER positivity[4]. There is however no reported association with PR, Her2 and Clinical outcomes (DFS and OS).

Asian

The Asian race had the most research data on ALDH1 (12 out of 16) [5-7,10,22,23,26,27,31,33,34,39] associated with tumour size[5-7], stage[5,10], grade[5-7,10,22,23], and lymph node metastasis[5,10]. ER positivity, Her2 overexpression[7,22,27] and TNBC/Basal like[23,33,34] have also been found to be associated with ALDH1. There was an inverse relationship with PR recorded in a study[26]. This breast CSC has also been largely associated with poor clinical outcomes in Asian populations[5,7,22,23,31,39].

African/Black American

In the African/Black American race, ALDH1 has been reported to associate with tumour grade and mitotic count[21]. Quite significantly, among Africans, this breast CSC was associated with TNBC/Basal like[21,30,31] and Her2 overexpression[25]. Inverse relationships were recorded with ER and PR[21,25]. No association with clinical outcomes (DFS and OS) has been reported in this race.

BMI1

BMI1 is one of the least researched breast CSC according to the data (3 out of 40). It has been associated with tumour grade and ER positivity in an African study[21], lymph node metastasis and ER in an Asian study[18]. Although both African and Asian studies have associated BMI1 with poor clinicopathological parameters, a Caucasian study however concluded its association with better clinicopathological features and clinical outcomes[24]. In this Caucasian study, ALDH1 was inversely associated with high tumour grade, high mitotic count, increased NPI, Her2 overexpression and Overall survival[24].

CD133

Only 1 study so far focused on with this novel breast CSC in a Caucasian population. It was however associated with age, tumour grade and triple negative/basal like breast cancer[4].

GD2

A study conducted in Iran was the only research data available on this novel breast CSC GD2. It was however associated with larger tumour size, lymph node metastasis and higher tumour grade[9]. No recorded data on Hormone receptor status, Her2 or clinical outcomes yet.

DISCUSSION

A plethora of studies have investigated racial and ethnic disparities in cancer, but similar research on breast CSC remain scanty[42]. There appears to be ill defined racial pattern breast CSC functionality from our analysis of existing data. Several factors may account for this observation. It may be as a result of the lack of existing cut off point in the scoring of IHC staining and the different scoring systems employed by various investigators[43]. Some researchers use X-tile software application in determining the cut-off point based of patient clinical outcomes[20]. The use of X-tile software in generating cut off points appears to be laudable but unfortunately not all data might include clinical outcomes. Others use the means of the individual IHC scores while others use cut off of already published data[9]. The advent of a more uniform system of scoring and cut-off point determination will be important in such racial comparison studies. The use of different antibody variants in staining breast CSC may also introduce some inconsistencies. For instance, while some researchers use the more generalised CD44 and ALDH1 antibodies, others however use the more specific CD44v6 and ALDH1A1/2 isozyme, respectively. The use of different IHC techniques such as single vs multiplex IHC staining, Immunofluorescence and confocal microscopy, mRNA expression studies etc might contribute to disparities in the role of breast CSC. Different panels of clinicopathological and clinical outcome parameters employed by investigations also poses a great challenge in such racial and ethnic comparative studies. The aforementioned factors among others may contribute to the difficulties associated with such comparative studies.

In this study, ALDH1 can be said to be associated with tumour aggressiveness since ALDH1 has significantly been associated with TNBC across races as evidenced in table 1[20,21]. It is however of no doubt that this breast CSC may contribute to tumour aggressiveness inherent in TNBC or basal like phenotype. Similarly, a high tumour grade has largely been associated with ALDH1 positivity in African, Asian and Caucasian races[10,20,23,38]. But for the paucity of data in Latino/Hispanic and American races a similar trend may have been realised. Aggressive tumours frequently disseminate haematologically rather than lymphatically, and this might explain why ALDH1 has been found not to be largely associated with axillary lymph node metastasis including an unpublished data in an African population from our group. Furthermore, ALDH1 is associated with poor clinical

outcomes such as shorter disease free survival and overall survival in a significant number of studies[5,7,22,23,39,41].

$CD44^{+}/CD24^{-/low}$ has been well researched in Asian and Caucasian populations and has largely been associated with lymph node metastasis, lymphovascular invasion, progesterone receptor positivity, and oestrogen receptor positivity. It has also been associated with poor clinical outcomes such as shorter disease-free survival and overall survival (Table 1). It can therefore be concluded that $CD44^{+}/CD24^{-/low}$ is associated with tumour metastasis in Asians and Caucasians. Quite conspicuously, $CD44^{+}/CD24^{-/low}$ has generally been associated with TNBC/basal like phenotype so far in all races. The involvement of this breast CSC in conferring tumour aggression without racial disparity can be inferred. Also, despite the general conclusion of this phenotype being associated with poor outcomes[44], two studies; Ahmed *et al* and Mylona *et al* found otherwise[11,40]. They rather found $CD44^{-}/CD24^{+}$ phenotype to be associated with favourable outcomes. It is important further studies focus on these phenotypes to better understand their involvement in breast cancer.

BMI1 is one of the least researched breast CSC. From the data gathered, the pathological features associated with BMI1 are tumour grade[21] and lymph node metastasis[18] from African and Asian populations, respectively. The involvement of BMI1 in tumour progression and metastasis could be inferred in Africans and Asians. From all 3 races that have data on BMI1, the stem cell was associated with ER expression. Despite the aforementioned role of this stem cell, a Caucasian study however associated it with better prognosis as was inversely associated with NPI, mitotic count, Her2 overexpression and shorter overall survival[24]. Due to the limited data on this putative breast cancer stem cell, a conclusive racial pattern could not be realised. Further research into this stem cell is highly recommended.

The sialic acid-containing glycosphingolipid GD2 is a novel CSC maker largely expressed in ectodermal derived tumours including breast, melanoma and neuroblastoma[45-47]. This ganglioside is also weakly expressed few normal adult tissues such as central nervous system[48]. Its high expression can be found in bone marrow derived mesenchymal stem cells[49]. It is derived from the precursor GD3 by the action of a GD3 synthase. More recently, its molecular and functional role as a breast CSC marker is currently under investigations but not as popular as the other breast CSC (Table 1). The involvement of GD2 in tumour aggression has been documented. It is known to be

associated with high tumour grade[50], larger tumour size, and lymph node involvement[9]. Its combination phenotype with the well-researched $CD44^{+}/CD24^{-/low}$ breast CSC ($GD2^{+}/CD44^{+}CD24^{-/low}$) marker has been associated with tumour invasiveness[9]. Targeting GD2 in novel cancer treatment regimen shows great promise in eliminating disseminated tumour and preventing metastasis hence more research should focus on this novel breast CSC to harness its full potential[51].

CONCLUSION

Racial disparities exist in the breast CSC pattern and functions but ill-defined due to inequalities in the volume of data across races, differences in techniques and cut off points used in their breast CSC assessment among investigators, and differences in the clinicopathological and clinical outcome parameters used in assessments. A more standardised means of assessing the role of breast cancer across investigators is warranted. A consortium is therefore necessary to develop guidelines in determining the clinicopathological significance of breast CSC in different populations. Limited data exist in African/Black American[44], Hispanic/Latinos, and American populations. Clinical outcome data also remain significantly low. Special emphasis should be placed on the analysis survival data in all populations being investigated. Further investigations are needed to better understand the role of breast CSC.

LIMITATION OF STUDY

1. Although there might be other minority racial groups within a study population, this review however, used the predominant race of the region as substantive race for comparative analysis which may introduce some bias.

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