Expression of aldehyde dehydrogenase 1 (ALDH1) is associated with basal-like markers and features of aggressive tumours in African breast cancer

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BACKGROUND: Putative breast cancer stem cells might express surface markers such as aldehyde dehydrogenase 1 (ALDH1) and BMI-1 proteins. The aim of this study was to explore the expression of these proteins in breast cancers from an African population and their associations with the basal-like phenotype (BLP) and other molecular characteristics.

METHODS: We analysed 192 paraffin-embedded breast carcinoma samples by tissue microarrays and immunohistochemical methods.

RESULTS: In total, 88 tumours (48%) expressed ALDH1, whereas 46 (25%) expressed BMI-1 protein. Expression of ALDH1 was associated with high histological grade (P<0.0005), high mitotic count (P<0.0005), high nuclear grade (P<0.0005), oestrogen receptor (ER) negativity (P<0.0005), progesterone receptor (PR) negativity (P=0.009), p53 expression (P=0.034), cytokeratin 5/6 positivity (P=0.008), epidermal growth factor receptor (EGFR) expression (P=0.015) and the BLP (P<0.0005), whereas it was inversely associated with BMI-1 staining (P=0.009). On the other hand, BMI-1 expression was associated with low histological grade (P=0.004) and ER positivity (P=0.001).

CONCLUSION: There was a high prevalence of ALDH1 expression among breast carcinomas and associations with basal markers and features of aggressive tumours. Studies are required to elucidate the importance of these findings for improved understanding of breast cancer biology.

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Human breast cancers have been reported to contain a sub-population of cancer cells similar to epithelial stem cells (Hamburger and Salmon, 1977; Al-Hajj et al, 2003; Abraham et al, 2005). These cells have the ability to self-renew and undergo differentiation to phenotypically diverse populations of tumour cells (Al-Hajj et al, 2003). It has been suggested that cancer stem cells drive the growth and spread of malignant tumours (Al-Hajj et al, 2003), and the stem cell hypothesis might have important implications for clinical management (Ginestier et al, 2007; Tanet et al, 2009).

The molecular diversity and subclassification of breast cancers have been reported in several studies during recent years (Perou et al, 2000; Sorlie et al, 2003; Rakha et al, 2008). Five tumour subgroups with different prognosis and response to adjuvant therapy have been identified. Of these, the basal-like and HER2 subtypes are of particular interest as both have a poor prognosis (Sorlie et al, 2001; Yang et al, 2007). The basal-like phenotype (BLP) is characterised by the expression of basal cell markers, and it overlaps with the triple-negative phenotype (TNP; ER−/PR−/HER2−) (Tischkowitz et al, 2007). It was reported that basal-like and BRCA1-associated breast carcinomas, which are also related (Foulkes et al, 2003) were both enriched with CD44+/CD24− candidate stem cells (Honeth et al, 2008), and BRCA1 has been suggested to represent a stem cell regulator (Foulkes, 2004). Previous studies indicate that stem cell-like populations in breast tissue are characterised by the expression of aldehyde dehydrogenase 1 (ALDH1), and breast cancer stem cells were isolated on the basis of increased ALDH1 expression (Ginestier et al, 2007). Thus, in the breast, expression of ALDH1 is considered to be a marker of both normal and malignant stem and progenitor cells (Ginestier et al, 2007). In established breast cancers, ALDH1 expression has been associated with poor clinical outcome (Ginestier et al, 2007) and resistance to chemotherapy (Sladek et al, 2002; Tanet et al, 2009). Furthermore, studies have indicated that human breast cancers and cell lines contain a sub-population of cells characterised by CD44+/CD24−/Lin− cell surface markers, and a partial overlap between CD44+/CD24−/Lin− and ALDH1-positive populations was reported (Al-Hajj et al, 2003; Ginestier et al, 2007; Fillmore and Kuperwasser, 2008). It is noteworthy that putative cancer stem cells expressing the combined CD44+/CD24−/ALDH1+ phenotype showed an especially high tumourigenic capacity, being able to form tumours from as few as 20 cells (Ginestier et al, 2007).

The importance of BMI-1, a transcriptional repressor of the polycomb group of transcription factors (Alkema et al, 1993) and a key regulator of self-renewal in both normal and malignant stem
cells (Liu et al, 2006), has been more controversial. Still, BMI-1 has been linked to mammary carcinogenesis in some previous studies (Dimri et al, 2002; Datta et al, 2007). Although some find BMI-1 expression to be associated with a favourable prognosis (Kim et al, 2004; Arnes et al, 2008; Choi et al, 2009), others have reported the opposite (Glinksky et al, 2005; Silva et al, 2007).

Breast cancers in African populations and among African Americans seem to be more aggressive than breast cancers in Caucasians (Ikpatt et al, 2002; Jones et al, 2004), and better insight about differences in tumour characteristics (Porter et al, 2004; Fregene and Newman, 2005; Morris et al, 2007; Bird et al, 2008) may suggest strategies to improve clinical management among Africans. In general, there is some evidence that the limitation of chemotherapy and radiation treatment may be associated with the inability to target breast cancer stem cells (Phillips et al, 2006; Fillmore and Kuperwasser, 2008; Li et al, 2008; Tanei et al, 2009), and the efficacy of HER2 inhibitors may relate to their influence on stem cell populations in HER2-positive tumours (Korkaya et al, 2008).

On this background, the purpose of our study was to examine the expression of candidate stem cell markers ALDH1 and BMI-1 in breast cancer in relation to basal-like markers, other molecular features and clinicopathological phenotype. These markers were examined in tumours from an African population in which breast cancer is assumed to be more aggressive and also associated with frequent basal-like differentiation (Nalwoga et al, 2007). In these populations, early diagnosis and effective treatment is especially challenging (Gakwaya et al, 2008).

MATERIALS AND METHODS

Patient series

Cases of primary breast carcinoma with available and technically suitable archival paraffin blocks from the period 1990 to 2002 were identified in the Kampala Cancer Registry at the Department of Pathology, Makerere University College of Health Sciences, Kampala (Uganda). The Registry serves an area of about 1914 km², which comprises of Kampala with neighbouring urban and semi-urban areas (Gondos et al, 2005) and an estimated population of 1.7 million in 2002 (Population Council, 2004). The population of females >15 years of age is about 530,000. The Baganda from the Central region is the largest ethnic group in the county, but other ethnic groups are represented. The registry methods of collecting data and results have been previously reported (Wabinga et al, 1993).

Altogether, 192 cases were included in the study, and 87 other cases with inadequate tissue available were excluded. Clinical information was obtained from the histology reports. The mean age was 46.2 years (range 18–80 years). Duration of symptoms as reported by 127 patients at the time of presentation was 17.1 months on average (median 9 months; range 0.5–108 months). The cutoff point for long duration was 9 months (median value). Stage of disease at the time of diagnosis was available in only 22 patients; the majority (n = 12) were in stage 4, 8 (36%) were in stage 3, whereas stage 1 and 2 contributed 9%. All cases were re-examined histologically (by HN and JBA) and classified according to the World Health Organisation (Tavassoli and Devilee, 2003) and histological grading was performed in accordance with the Nottingham criteria (Elston and Ellis, 1991). Nuclear grade and mitotic count was also recorded as separate variables according to the same criteria. The permission to conduct this research was obtained from the Research Ethical Committee at Makerere University College of Health Sciences.

Table 1 Immunohistochemical staining procedures

| Biomarker | Antibody | Clone | Dilution | Incubation time (min) |
|-----------|----------|-------|----------|-----------------------|
| ER        | MMA oestrogen receptor-α | IDS    | 1:50     | 30                    |
| PR        | MMA progesterone receptor | PgR 636 | 1:150    | 30                    |
| HER2      | RA c-erbB-2 oncoprotein | Polyclonal | 600     | 60                    |
| p53       | MMA p53 antigen | MB-1    | 1:50     | 60                    |
| p63       | MMA p63 protein | DO-7    | 1:1000   | 60                    |
| CK 5/6    | MMA cytokeratin 5/6 | A4A     | 1:300    | 30                    |
| P-cadherin| P-cadherin purified MA | DS1/6 B4 | 1:200    | 30                    |
| EGFR      | Mouse anti-EGFR | 56/16 G7 | 1:400    | 60                    |
| c-kit     | RA CD117,c-kit | 5 G7    | 1:30     | 30                    |
| ALDH1     | Purified M anti-ALDH | 1/200   | 1:250    | 60                    |
| BMI-1     | Anti-BMI-1 | 6C9    | 1:1      | 60                    |

Abbreviations: MMA = monoclonal mouse antihuman; MA = mouse antihuman; RA = rabbit antihuman; M = mouse; ER = oestrogen receptor; PR = progesterone receptor; EGFR = epidermal growth factor receptor; ALDH1 = aldehyde dehydrogenase 1; CK = cytokeratin.
were incubated with specific antibodies at room temperature. Regarding antibodies, P-cadherin and ALDH1 were obtained from BD Biosciences (Oxford, UK), mouse anti-EGFR was obtained from Zymed Laboratories (San Francisco, CA, USA), and BMI-1 was produced as previously described (Arnes et al., 2006; Nalwoga et al., 2008). All other antibodies were obtained from DakoCytomation A/S. All antigens were detected by the DakoCytomation EnVision + system-horseradish peroxidase for 30 min, except BMI-1 for which the CSA II kit (DakoCytomation) was used. After rinsing the sections in buffer solution, we developed the peroxidase by incubating with freshly prepared 3,3′-diaminobenzidine chromogen solution for 10 min. Sections were then rinsed in distilled water and counterstained with Meyer’s haematoxylin. Cases of breast or colonic carcinoma previously known to be positive for the markers studied were used as positive controls. For c-kit, a gastrointestinal stromal tumour (GIST) was used.

**Evaluation of staining**

Tumours without interpretable cores (2.6–4.7%) because of insufficient tumour tissue were omitted from the analysis. A total of 183–187 cases could be evaluated for the various markers. The oestrogen receptor (ER), progesterone receptor (PR), HER2, EGFR, Ki-67, p53, p63, cytokeratin (CK) 5/6, P-cadherin, c-kit and BMI-1 were evaluated as previously described (Engelsen et al., 2006; Stefansson et al., 2006; Arnes et al., 2008; Nalwoga et al., 2008). Regarding ALDH1, cytoplasmic staining was evaluated, whereas nuclear staining alone was considered nonspecific and was not included in the analysis.

For BMI-1, a staining index (values 0–9) was determined by multiplying the score for intensity of staining (none = 0, weak = 1, moderate = 2 and strong = 3) with the score for proportion of tumour cells stained (<10% = 1, 10–50% = 2, >50% = 3) (Arnes et al., 2008). The majority of cases (75%) had staining index 0, and therefore the cutoff was 0 = negative and 1–9 = positive. For ALDH1, the median staining index was 2, and the cutoff point was set at 0–2 = negative and 3–9 = positive. Ki-67 proliferative rate was determined as previously described (Nalwoga et al., 2007). The cutoff point for Ki-67 was set at 20.0% based on the median value for this series.

**Molecular subtypes**

There is no consensus on how to define different molecular subtypes of breast cancer by immunohistochemical markers, and overlapping categories exist. We used criteria on the basis of this literature (Carey et al., 2006; Yang et al., 2007; Sihto et al., 2008) for subclassification into molecular subtypes. In accordance with Carey et al. (2006), we defined the luminal A (ER + and/or PR +, HER2−), luminal B (ER + and/or PR +, HER2 +), HER2+ subtype (ER−, PR−, HER2 +) and the basal-like subtype (ER−, HER2− and CK 5/6− and/or EGFR +) subgroups. Tumours negative for all the five markers (ER, PR, HER2, CK 5/6 and EGFR) were considered as unclassified. This definition for luminal B tumours does not identify all luminal B tumours because only 30–50% are HER2+ and the rest are classified with the luminal A. Therefore, we defined BLP1 as concurrent ER−, HER2− and CK 5/6−; BLP2: concurrent ER−, HER2− and P-cadherin +; BLP3: concurrent ER−, HER2− and EGFR +; BLP4: concurrent ER−, HER2− and CK 5/6− and/or EGFR +; BLP5: concurrent ER−, HER2− and positivity for one or more basal markers (CK 5/6, P-cadherin and EGFR). BLP4 is identical to the core basal phenotype as defined by Nielsen et al. (2004) and Tischkowitz et al. (2007).

**Statistical analysis**

Statistical analysis was performed using the SPSS version 15.0 software (SPSS Inc, Chicago, IL, USA). We examined the association between ALDH1 and BMI-1 expression with other tumour characteristics using χ²-test and Fisher’s exact test. The t-test was used to detect the differences in average age between groups. A P-value of <0.05 was considered significant for any statistical test used.

**RESULTS**

In all, 88 tumours (48%) were positive for ALDH1, whereas 95 (52%) were negative for ALDH1 (Figure 1). The majority (62%) of ALDH1-positive cases were high-grade ductal carcinomas. Altogether, 40 cases (46%) showed staining in >10% of the tumour cells, whereas 16 of 88 (18%) cases had a diffuse staining in ≥50% of the tumour cells. Overall, the expression of ALDH1 seemed to be evenly distributed throughout the tumour cell population, although there were some cases with clusters of positively stained cells within the diffuse pattern. The average percentage of stained tumour cells in positive cases was 18%. Of the ALDH1-positive tumours, 31% were of the luminal subtype (27.3% luminal A, 3.4% luminal B), 31% had a basal-like subtype (core basal phenotype; BLP4), 16% were in the HER2 subtype and 23% were in the unclassified category. A majority (53%) of the ALDH1-positive cases were triple-negative tumours.

Table 2 shows ALDH1 expression and associations with clinicopathological characteristics. Patients with a shorter duration of symptoms were more likely to express ALDH1 than those with longer duration of symptoms (odds ratio 2.2; 95% confidence interval 1.05–4.5, P = 0.036). The ALDH1 expression was significantly associated with markers of poor prognosis, such as high histological grade, high mitotic counts, high nuclear grade, ER negativity, PR negativity, and p53 expression. No associations were
found between ALDH1 expression and HER2 status, p63 or c-kit positivity.

As shown in Table 3, CK5/6 was positive in 15%, P-cadherin in 27% and EGFR in 20% of all cases. One or more of these were positive in 33% of the cases (61 of 185). A total of 86 tumours (46%) were of the luminal subtypes (42%, luminal A, 4% luminal B), 22% (41 of 186) had a basal-like subtype, the HER2 subtype contributed 12% (23 of 186), and 19% (36 of 186) were in the unclassified group. Regarding the different BLP profiles, 15% (27 of 186) were BLP1, 22% (41 of 187) were BLP2, 17% (31 of 186) were BLP3, 22% (41 of 186) were BLP4 (core basal phenotype) and 26% (49 of 186) were BLP5. All tumours in the different BLP profiles were triple negative in this series. A majority of the triple-negative tumours showed basal-like differentiation; 53% (41 of 77) had a core basal profile (BLP4), whereas 64% (49 of 77) of the TNP tumours had positive expression of at least one of the three basal markers (CK5/6, P-cadherin, EGFR) combined with ER− and HER2−, corresponding to the BLP5 profile.

Table 3 also shows the relationship between ALDH1 positivity and molecular subtypes of breast cancer. The ALDH1 expression
was significantly associated with molecular subtype and BLP profiles as defined in this paper, as well as with TNP and individual basal markers CK 5/6 and EGFR. Thus, the BLP, the HER2 subgroup and the unclassified category were more likely to express ALDH1 than the luminal subtypes. In all, 46 tumours (25%) were positive for BMI-1 staining. The majority of cases (61%) were of luminal subtype (54.3% luminal A, 6.5% luminal B), whereas the basal-like category contributed 22%, 11% were in the HER2 subgroup and 7% were unclassified. In total, 13 tumours (28%) were triple negative. The BMI-1 positivity was mostly associated with features of good prognosis, such as low histological grade (P = 0.011), low mitotic counts (P = 0.010) and ER positivity (P = 0.001). Further, BMI-1 expression was inversely associated with the TNP (P = 0.037) and with ALDH1 positivity (P = 0.009). Tumours in the luminal subtype (odds ratio 5.4; 95% confidence interval 1.05–19.2, P = 0.005) were more likely to express BMI-1 than unclassified tumours. No association was found between BMI-1 expression and the other subtypes, the basal markers such as CK5/6, P-cadherin, EGFR, and the BLP profiles.

DISCUSSION
In this study, our aim was to explore the expression of candidate stem cell markers ALDH1 and BMI-1 in breast cancers from an African population and their possible associations with BLP and other molecular markers. We found that ALDH1 expression was associated with features of aggressive tumours such as high histological grade, high nuclear grade, high mitotic count, p53 expression and ER/PR negativity. In addition, ALDH1 expression was associated with a short duration of symptoms. Thus, ALDH1 status might represent an indicator of aggressive breast cancer (Ginestier et al, 2007; Morimoto et al, 2009). In support of this, others have suggested that the amount of cancer stem cells within breast tumours may correspond to the risk of distant metastases (Abraham et al, 2005; Glinsky et al, 2005).

It has been observed that basal-like breast cancers might be enriched with CD44+/CD24− cells (Honeth et al, 2008), and an overlap between CD44+/CD24− cells and ALDH1-positive cell populations were described (Ginestier et al, 2007). Moreover, the CD44+/CD24−/ALDH1− phenotype identified a highly tumourigenic cell population that was able to form tumours from as few as 20 cells. Our results showed that ALDH1 was significantly associated with the basal-like subtype and different BLP profiles, as well as with individual basal markers CK5/6 and EGFR, similar to what others have reported (Ginestier et al, 2007). To speculate, our findings might be related to the aggressive behaviour and therapy resistant features of the basal-like breast cancer subtype (Sorlie et al, 2001; Banerjee et al, 2006; Fillmore and Kuperwasser, 2008; Li et al, 2008). Moreover, we found a significant association between ALDH1 expression and the triple-negative tumours, a group whose poor prognosis has been widely reported (Dent et al, 2007).

Our findings indicate a higher frequency of ALDH1 expression (48%) in this series of breast cancer from an African population, compared with 19 and 30% in two different Caucasian populations described by Ginestier et al (2007). We also found more extensive staining in positive cases (Ginestier et al, 2007). Further, in comparison with data derived from breast tumours in Caucasian and Asian populations (Ginestier et al, 2007; Morimoto et al, 2009; Tanei et al, 2009) regarding ALDH1 positivity rate in tumours with similar characteristics (histological grade, ER, HER2, Ki-67), we observed that tumours from our present series stained in a higher percentage of cases in most poor prognosis categories (such as high histological grade, ER-negative cases, HER2-negative cases, tumours with high Ki-67 expression). Hence, apart from methodological discrepancies, biological differences might be present when comparing breast cancers from African and Caucasian populations (Elledge et al, 1994; Ikpatt et al, 2002; Jones et al, 2004; Porter et al, 2004). In line with this, a poorer outcome has been observed in African and African-American patients (Wojcik et al, 1998; Ikpatt et al, 2002) when compared with breast cancers among Caucasians, with differences in the spectrum of tumour characteristics and prognostic features such as the presence of tumour necrosis, low ER positivity rate, high HER2-positive rate, and a high frequency of basal-like features (Mbonde et al, 2001; Ikpatt et al, 2002; Carey et al, 2006; Nalwoga et al, 2006, 2007; Morris et al, 2007; Bird et al, 2008).

In contrast to our findings on ALDH1, the expression of BMI-1, another candidate stem cell marker (Arnes et al, 2008), was inversely associated with ALDH1 and related to features of good prognosis, such as low histological grade, low mitotic count, ER positivity and absence of TNP (Kim et al, 2004; Choi et al, 2009). This is in line with our recent studies of breast cancer (Arnes et al, 2008) and other tumours (Bachmann et al, 2008; Engelsen et al, 2008). The frequency of BMI-1 expression (25%) was lower than those found in other studies (43–62%) (Kim et al, 2004; Arnes et al, 2008; Choi et al, 2009). Others have found different results, BMI-1 expression being associated with more aggressive tumours (Glinsky et al, 2005; Silva et al, 2007). In addition, Glinsky et al (2005) found that expression of a BMI-1-driven 11 gene signature was associated with risk of metastases in breast carcinoma. The explanation for this inverse relationship is not known.

In conclusion, we observed a high prevalence of ALDH1 staining in this series of invasive breast carcinomas from Uganda. Expression of ALDH1 was significantly associated with a BLP and with features of aggressive tumours. Assessment of ALDH1 expression might help to identify a high-risk (Sreerama and Sladek, 1997) subgroup of breast cancers in this population. More studies are required to elucidate the possible significance of these stem cell markers in breast cancer patients.

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ALDH1 expression in African breast cancer
H Nalwoga et al
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ALDH1 expression in African breast cancer
H Nalwoga et al

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