



Association of Life-Course Educational Attainment and Breast Cancer Grade in the MEND Study

ORIGINAL RESEARCH

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ABSTRACT

Background: Nigeria reports the highest age-standardized mortality rate for breast cancer (BC) among African countries and disproportionately high rates of high-grade cancer. Histological grade is a strong predictor of mortality, and evidence suggests that educational attainment influences cancer outcomes.

Objective: We characterize the association between educational trends across the life-course and BC grade at diagnosis.

Methods: Data on 224 BC patients enrolled in the Mechanisms for Established and Novel Risk Factors for Breast Cancer in Nigerian Women (MEND) study was analyzed. Participant and parental (mother and father) education was categorized as low (primary school or less) or high (secondary school or greater). Accordingly, the educational trend across the life-course was determined for each participant relative to each parent: stable high, increasing, decreasing, or stable low. BC grade was classified as high (grade 3) or low (grades 1–2).

Findings: About 34% of participants, 71% of fathers, and 85% of mothers had low education. Approximately one-third of participants were diagnosed with high-grade BC. Participants with low-grade BC were more likely to have highly educated fathers ($p = 0.04$). After adjusting for age, comorbidities, marital status and mammogram screening, participants with highly educated fathers were 60% less likely to have high-grade BC

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TO CITE THIS ARTICLE:

Gupta A, Jones K, Deveaux A, Bevel M, Salako O, Daramola A, Hall A, Alatise O, Ogun G, Adeniyi A, Ojo A, Ayandipo O, Olajide T, Olasehinde O, Arowolo O, Adisa A, Afuwape O, Olusanya A, Adegoke A, Tollesbol TO, Arnett D, Newgard CB, Akinyemiju T. Association of Life-Course Educational Attainment and Breast Cancer Grade in the MEND Study. *Annals of Global Health*. 2021; 87(1): 59, 1–11. DOI: <https://doi.org/10.5334/aogh.3142>

(aOR 0.41; 95% CI 0.20 to 0.84) compared to those with less-educated fathers. Stable high life-course education relative to father was also associated with a significantly lower likelihood of having high-grade BC (aOR 0.36; 95% CI 0.15 to 0.87) compared to stable low life-course education. No significant associations were observed for the participant's education, mother's education, or life-course education relative to mother.

Conclusions: Early-life socioeconomic status (SES) may influence BC grade. This deserves further study to inform policies that may be useful in reducing high-grade BC in Nigeria.

INTRODUCTION

Breast cancer (BC) poses a global challenge, with an estimated 2.1 million cases diagnosed and over 0.6 million deaths in 2018 [1]. BC is the leading cause of cancer death among females [1]. According to data from 2010, women of reproductive age in developing countries are twice as likely to develop BC than their counterparts in developed countries, where cases typically occur in older women [2]. In addition, while BC incidence in Africa is lower than in all other continents except Asia, age-standardized mortality rates rank the highest globally. Nigeria, the most populous African nation, suffers from the highest mortality rate of BC among African countries [3].

Histological BC grade has significant prognostic value independent of cancer stage, with low-grade cancers associated with improved survival relative to high-grade cancers [4, 5]. Studies in Nigeria have reported a worrisome prevalence of high-grade BC, with disproportionately high numbers of aggressive cancer subtypes or clinical course when compared to White populations [6, 7]. Understanding how critical socioeconomic factors, such as education, influence BC grade is crucial to developing effective interventions and policies that can improve negative BC outcomes. In general, higher literacy is associated with improved health outcomes [8], an association that is likely driven by greater work opportunities, and access to resources useful for maintaining health [9]. There is strong evidence that educational attainment significantly influences cancer mortality [10]. It is associated with earlier BC stage at diagnosis [11–14], and increased access to BC screening [15, 16]. Research regarding the relationship between education and BC grade, specifically, is very limited and conflicting. In England, one study found that socioeconomic deprivation is associated with higher BC grade at diagnosis [17]. However, a study in a Turkish population reported no significant association between education level and BC grade [18]. Further research is needed to better characterize this relationship.

In addition to individual educational attainment, parental education level and educational trends across the life-course may also impact BC outcomes. A recent systematic review suggests that early-life socioeconomic status (SES) may be associated with increased BC mortality in the United States (US) [19]. Another US study found that higher individual, parental and life-course SES were positively associated with BC screening [20]. However, there is very limited research on the impact of parental and life-course education level on BC outcomes in developing countries, and none to our knowledge focused on cancer grade. Notably, the association of life-course SES factors such as education and BC grade is not well-defined for Nigerian patients despite disproportionately higher grade tumors observed in this population.

In this study, we will, for the first time, characterize the association between individual, parental, and life-course education and BC grade among Nigerian women. Findings will elucidate how population-level policies to address socioeconomic factors like education may be useful in improving BC prognoses in Nigeria.

MATERIALS AND METHODS

STUDY DESIGN

The Mechanisms for Established and Novel Risk Factors for Breast Cancer in Nigerian Women (MEND) study has been previously described extensively [21]. Briefly, MEND enrolled patients at five

hospital-based BC clinics in southwest Nigeria. An experienced research nurse described the study to patients visiting the clinic for a BC diagnosis. Upon presumed BC diagnosis (based on clinical evaluation, but pending pathological verification), patients were approached for participation in the study. Patients who expressed interest were then evaluated for eligibility, and the research nurse obtained written and verbal informed consent. Study participants completed a comprehensive interviewer-administered questionnaire that solicited information on sociodemographic characteristics, reproductive history, and health history, and physical measurements were taken. Routine biopsy was performed as part of the clinical standard of care, while additional research samples were obtained and sent for histopathology processing. In exchange for their participation, the participants received the supplies necessary for their clinical biopsy and a N500 telephone recharge card (approximately US \$1.50). These study procedures were approved by the Institutional Review Boards of Duke University and the participating hospitals in Nigeria.

BREAST CANCER DIAGNOSIS

BC diagnosis was verified in one of two possible ways – either a trained pathologist in Nigeria reviewed clinical biopsy samples, or research biopsy samples were shipped to the US for review by a trained US pathologist. BC grade from the Nigerian pathologists were reported on either the Nottingham or Scarff-Bloom-Richardson (SBR) scale. The Nottingham scale is a modification of the SBR grade scale, with both being similar three-level scales that are based on the tumor's architectural pattern, nuclear atypia, and mitotic rate [22]. For samples processed in the US, grade was reported on the Nottingham scale. When grade data from both sources were available, the US grade information was used in the analysis. A sensitivity analysis considering only those samples with grade reported on the Nottingham scale was performed to ensure the validity of including data from both scales. Results were similar between both sets of data, therefore we defined grade based on either of the two scales and categorized into low (grades 1–2) and high (grade 3) for analysis.

STUDY COVARIATES

Demographic characteristics and clinical history variables included: age at diagnosis, marital status, number of comorbidities (such as hypertension, high lipids, high cholesterol, and diabetes), and whether participants had received a mammogram screening in the past two years. Participants were also asked to self-report any personal history of cancer outside of their BC diagnosis. Only those with no previous history of cancer were included in the present analysis since prior cancer diagnosis might be associated with a more aggressive subsequent tumor. Participant education level and parental education level was assessed based on self-reports by the participant and categorized as the following: low (primary school or less) or high (secondary school or greater). Secondary school and college education were combined into the “high” category due to low numbers among parents. Based on this categorization, life-course education was determined relative to each participant's mother and father: stable high (if high participant education and high parental education), increasing (if high participant education and low parental education), decreasing (if low participant education and high parental education), or stable low (if low participant education and low parental education).

ANALYTICAL APPROACH

Descriptive statistics were used to characterize the study sample according to demographic and clinical characteristics and reported as frequencies and percentages. Further assessments of participant, parental, and life-course education variables were made by low/high-grade categorization. Differences in education variables (participant, parental, and life-course education) were tested using chi-square (χ^2) tests. The association between each education variable and cancer grade was tested using logistic regression models with high-grade BC as the outcome, and results were presented as odds ratios and 95% confidence intervals (CI). Each measure (participant, parental and life-course education) was considered separately in a series of models: unadjusted, adjusted for age, and adjusted for age, number of comorbidities, marital status,

and whether the participant had received a mammogram screening in the previous two years. In the models including participant and parental education, primary school or less was used as the reference group. In the models including life-course education, stable low was used as the reference group. SAS University Edition (Cary, North Carolina, United States) was used for all analyses and significance was set at $\alpha = 0.05$.

RESULTS

Most participants included in the analysis from the MEND study were between the ages of 40–49 years old (34%) and had low-grade BC (66%) ([Table 1](#)). Although about two-thirds (66%) of participants had a secondary school education or higher, most participants' mothers and fathers had a primary school education or less (85% and 71%, respectively). Concerning mother, most participants had an increasing life-course education (52%), about one-third had stable low (33%), a small proportion had stable high (14%) and no participants had a decreasing life-course education. With respect to father, most participants also had an increasing life-course education (41%), almost one-third had stable low (30%), one-quarter had stable high (25%), and a low proportion had a decreasing life-course education (4%). When stratified by age, participants who were 45 years or younger were more likely to have a stable high life-course education compared to those older than 45 years old ([Figure 1](#)). A significantly higher proportion of participants who had high-grade BC, compared to low-grade cancer, had fathers with a primary school education or less ($p = 0.04$) ([Table 2](#)).

In fully adjusted multivariable regression models predicting high-grade BC ([Table 3](#)), having a father with a high versus low education was associated with 59% lower odds of having high-grade BC (aOR 0.41; 95% CI 0.20, 0.84). Stable high versus stable low life-course education with respect to father was associated with 64% lower odds of having high-grade BC (aOR 0.36; 95% CI 0.15, 0.87). The results for increasing life-course education (aOR 0.82; 95% CI 0.40, 1.69) and decreasing life-course education (aOR 0.41; 95% CI 0.07, 2.46) with respect to father were not statistically significant. There were also no statistically significant results observed for participant education level (aOR 0.72; 95% CI 0.37, 1.36), mother education level (aOR 0.57; 95% CI 0.23, 1.38), and life-course education level with respect to mother (stable high aOR 0.51; 95% CI 0.19, 1.40, and increasing aOR 0.87; 95% CI 0.44, 1.71) across all the models.

DISCUSSION

In the present analysis of 224 female BC patients in the MEND study, we characterize the association between self-reported education (participant, parental, and life-course) and BC grade at diagnosis. We found that participants whose fathers were highly educated were more likely to have low-grade BC at diagnosis. Similarly, those with a stable high life-course education concerning father were more likely to have a low-grade cancer. Significant associations were not observed for individual participant education level, mother's education level, and life-course education regarding mother.

It is well-recognized that higher SES is associated with lower cancer stage at clinical presentation and diagnosis and lower rates of mortality [11–14]. However, the association between SES and BC grade has not been as clearly reported, especially in low- and middle-income countries like Nigeria. One study in England found that socioeconomic deprivation was associated with higher BC grade at diagnosis [17]. Focusing specifically on education, an analysis of the National Cancer Database in the US found that living in more educationally-deprived areas is associated with higher BC grade [23]. This analysis was limited by a lack of data on individual-level educational attainment. Another study reported no significant association between education level and BC grade in a Turkish population [18]. However, unlike our analysis, this study was limited by a lack of data on covariates.

To date, most studies that report the association between SES and BC outcomes have focused only on the influence of patient SES in adulthood. As Williams et al. note, inadequate attention has

| | OVERALL (%) N = 224 (100.00) |
|--|---|
| Age | |
| <40 | 41 (18.30) |
| 40–49 | 76 (33.93) |
| 50–59 | 58 (25.89) |
| 60+ | 49 (21.88) |
| Marital Status | |
| Never Married | 10 (4.46) |
| Married | 157 (70.09) |
| Separated/Divorced | 12 (5.36) |
| Widowed | 45 (20.09) |
| Mammogram Screening in Past 2 Years | |
| Yes | 26 (11.61) |
| No | 197 (87.95) |
| Comorbidities | |
| None | 17 (7.59) |
| 1–2 Conditions | 191 (85.27) |
| >2 Conditions | 16 (7.14) |
| Participant Education | |
| Primary School or Less | 76 (33.93) |
| Secondary/High School | 73 (32.59) |
| College + | 75 (33.48) |
| Mother Education | |
| Primary School or Less | 190 (84.82) |
| Secondary/High School | 18 (8.04) |
| College + | 13 (5.80) |
| Father Education | |
| Primary School or Less | 160 (71.43) |
| Secondary/High School | 40 (17.86) |
| College + | 23 (10.27) |
| Life-course Education (Mother) | |
| Stable Low | 74 (33.04) |
| Decreasing | 0 (0.00) |
| Increasing | 116 (51.79) |
| Stable High | 31 (13.84) |
| Life-course Education (Father) | |
| Stable Low | 68 (30.36) |
| Decreasing | 8 (3.57) |
| Increasing | 92 (41.07) |
| Stable High | 55 (24.55) |
| Cancer Grade | |
| 1 | 15 (6.70) |
| 2 | 132 (58.93) |
| 3 | 77 (34.38) |

Table 1 Socio-demographic and Cancer Characteristics of Breast Cancer Cases Percentages may not add up to 100% due to missing values.

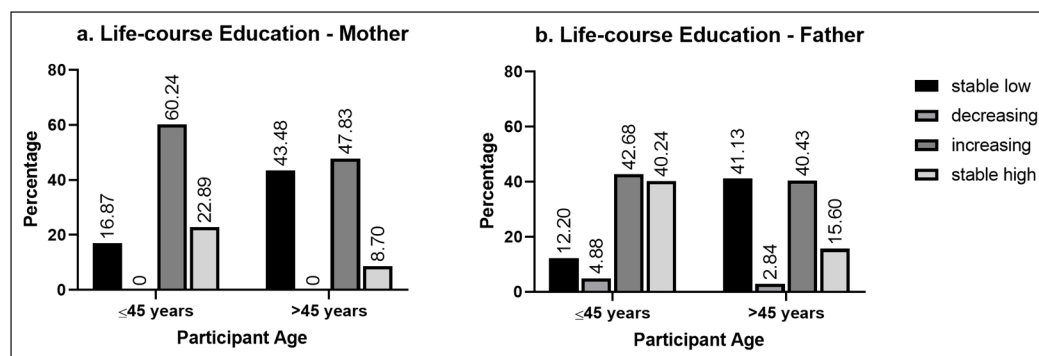


Figure 1 Distribution of life-course education by participant age. **a)** Distribution of life-course education categories relative to mother by age group. **b)** Distribution of life-course education categories relative to father by age group.

| | OVERALL | LOW-GRADE (1-2) | HIGH-GRADE (3) | P-VALUE* |
|---|------------------|-----------------|----------------|---------------|
| | N = 224 (100.00) | N = 147 (65.63) | N = 77 (34.38) | |
| Participant Education Level | | | | |
| Primary School or Less | 76 (33.93) | 48 (32.65) | 28 (36.36) | 0.5775 |
| Secondary/High School + | 148 (66.07) | 99 (67.35) | 49 (63.64) | |
| Mother Education Level | | | | |
| Primary School or Less | 190 (84.82) | 123 (83.67) | 67 (87.01) | 0.3025 |
| Secondary/High School + | 31 (13.84) | 23 (15.65) | 8 (10.39) | |
| Father Education Level | | | | |
| Primary School or Less | 160 (71.43) | 99 (67.35) | 61 (79.22) | 0.0423 |
| Secondary/High School + | 63 (28.13) | 48 (32.65) | 15 (19.48) | |
| Life-course Education Level – Mother | | | | |
| Stable Low | 74 (33.04) | 48 (32.65) | 26 (33.77) | 0.5874 |
| Decreasing | 0 (0.00) | 0 (0.00) | 0 (0.00) | |
| Increasing | 116 (51.79) | 75 (51.02) | 41 (53.25) | |
| Stable High | 31 (13.84) | 23 (15.65) | 8 (10.39) | |
| Life-course Education Level – Father | | | | |
| Stable Low | 68 (30.36) | 42 (28.57) | 26 (33.77) | 0.2478 |
| Decreasing | 8 (3.57) | 6 (4.08) | 2 (2.60) | |
| Increasing | 92 (41.07) | 57 (38.78) | 35 (45.45) | |
| Stable High | 55 (24.55) | 42 (28.57) | 13 (16.88) | |

Table 2 Education Level by Cancer Grade at Diagnosis. * Determined using Chi-Square tests Where applicable, missing values were not used to generate the p-value. Percentages may not add up to 100% due to missing values. Life-course education is defined based on participant and parent education level.

been paid to understanding the effects of SES factors over the life-course [24]. In the context of mortality, one study in the US noted that father’s education, but not mother’s, is protective against deaths due to BC [25]. This is consistent with the findings of our current study, which indicates a better prognosis (through a lower grade cancer) for participants whose fathers are more highly educated. Similarly, a recent systematic review found some evidence that lower early life SES may be associated with increased BC mortality, but most of the studies included only used occupation to determine childhood SES, ultimately providing an incomplete picture of childhood effects [19]. Our analysis addresses this gap, reporting on the effects of education as a measure of early-life SES in a highly understudied population of Nigerian women. Most research that has included parental and life-course SES was conducted in populations from more developed countries, such as the US, Britain, and Sweden [25–27]. Similar research in developing countries, such as Nigeria, is limited. This is the first study to our knowledge to characterize the association between life-course education with respect to parents and BC grade in this population.

| | UNADJUSTED | AGE | FULLY ADJUSTED |
|---|--------------------------|---------------------------|---------------------------|
| | OR (95% CI) | aOR (95% CI) ^a | aOR (95% CI) ^b |
| Participant Education Level | | | |
| Primary School or Less (Ref.) | – | – | – |
| Secondary/High School + | 0.85 (0.48, 1.51) | 0.68 (0.36, 1.29) | 0.72 (0.37, 1.36) |
| Mother Education Level | | | |
| Primary School or Less (Ref.) | – | – | – |
| Secondary/High School + | 0.64 (0.27, 1.51) | 0.57 (0.24, 1.37) | 0.57 (0.23, 1.38) |
| Father Education Level | | | |
| Primary School or Less (Ref.) | – | – | – |
| Secondary/High School + | 0.51 (0.26, 0.98) | 0.43 (0.21, 0.85) | 0.41 (0.20, 0.84) |
| Life-course Education Level – Mother | | | |
| Stable Low (Ref.) | – | – | – |
| Decreasing | # | # | # |
| Increasing | 1.01 (0.55, 1.86) | 0.83 (0.43, 1.62) | 0.87 (0.44, 1.71) |
| Stable High | 0.64 (0.25, 1.64) | 0.51 (0.19, 1.35) | 0.51 (0.19, 1.40) |
| Life-course Education Level – Father | | | |
| Stable Low (Ref.) | – | – | – |
| Decreasing | 0.54 (0.10, 2.87) | 0.40 (0.07, 2.25) | 0.41 (0.07, 2.46) |
| Increasing | 0.99 (0.52, 1.89) | 0.78 (0.39, 1.56) | 0.82 (0.40, 1.69) |
| Stable High | 0.50 (0.23, 1.10) | 0.36 (0.15, 0.84) | 0.36 (0.15, 0.87) |

Table 3 Multivariate Odds Ratios (OR) for High-Grade Diagnosis.

^aAdjusted for age.

^bAdjusted for age, mammogram screening, marital status, and comorbidities.

OR = Odds Ratio.

aOR = Adjusted Odds Ratio.

= Undefined.

Bold indicates significance p-value ≤ 0.05.

Life-course education is defined based on participant and parent education level.

The observed association between BC grade and father’s education as well as life-course education may be a consequence of stressor accumulation over the life-course. In a Dutch population, researchers found that level of education is negatively associated with financial and psychological stress, and the absence of access to resources [28]. In turn, increased stress is related to increased cancer mortality and reduced BC survival [29]. Allostatic load (AL) is a term that encapsulates the biological dysregulation that may result from excessive exposure to repeated stressors. It has often been used in the context of racial disparities but may also offer insight on differences in health outcomes by SES and speaks to the disproportionate existence of high-grade BC subtypes among Black populations in the US [30, 31]. Testing the association between education variables and BC subtype within this population may offer further insight. Furthermore, there is evidence that lower childhood socioeconomic positioning is associated with greater odds of adulthood obesity among women [32]. This may result from lower amounts of physical activity and more unhealthy food consumption due to a lack of resources [32, 33]. In turn, obesity is associated with more aggressive, and higher-grade BC, potentially due to lower levels of circulating adiponectin [34, 35]. Further research that considers the association between landmark biological features of obesity and BC grade is needed to shed light on these mechanisms. Along these lines, quality healthcare in Nigeria is costly and is often difficult for those of low SES to afford [36]. Provision of health care in early life may contribute to lower comorbidities like obesity that may increase the risk of high-grade BC.

Notably, this study found a significant association between father’s education, but not mother’s education, and BC grade at diagnosis. In the population studied, fathers had a secondary school or greater level of education at almost double the rate of mothers. This may be a consequence of a traditionally patriarchal society that valued the education of males over females, thus making father’s education a more robust predictor than mother’s and female participant’s education [37]. Interestingly, older participants were more likely to have a stable low life-course education (with

reference to both mother and father), whereas younger participants were more likely to have a stable high life-course education. Given that all participants were female, this may speak to the increasing access to education for girls in Nigeria.

There are several limitations of this study that should be discussed. Firstly, BC grade was determined at several different hospitals by different pathologists, potentially introducing unstandardized or misclassified results. However, all grade information was reported according to either the Nottingham or SBR scales, and a sensitivity analysis was conducted to ensure the compatibility of these scales for the purposes of this analysis. Secondly, participants were asked to recall the education levels of their parents, which may have introduced some recall bias into the analysis. Thirdly, the observational nature of the study design makes it difficult to draw a causal relationship. However, this study has several notable strengths, including the involvement of participants from multiple hospital sites in Nigeria, the life-course approach, and the availability of data on relevant covariates.

CONCLUSIONS

Higher father's education and life-course education were associated with a lower likelihood of high BC grade at diagnosis. Early life SES may influence BC outcomes via accumulated stressors, well-established risk factors such as obesity, and access to quality and timely care. The results of this analysis suggest the importance of adopting a life-course approach towards understanding the relationship between SES and BC outcomes. We urge further research on this topic to inform population-level policies. Addressing childhood SES may be beneficial for improving BC outcomes in Nigeria.

DATA ACCESSIBILITY STATEMENT

The data that support the findings of the study are available from the corresponding author upon reasonable request.

ETHICS AND CONSENT

This study was approved by Duke University and the participating hospitals' Institutional Review Boards (Pro00102004). All participants included provided informed consent.

ACKNOWLEDGEMENTS

We thank the many MEND investigators who contributed substantially to the inception and design of the study, and the patients and families who participated in the MEND study for their vital contribution in advancing the science of cancer in Nigeria and globally. We acknowledge the important contribution of the MEND research nurses: Cordelia Ibeneme, Peju Olabanji, Rebecca Israel, Esther Akinwale, Deborah Awodeyi, and Shukurat Oduola.

FUNDING INFORMATION

This research was specifically funded by National Institutes of Health, National Cancer Institute, Fogarty International Center (K01TW010271, T.A.). The views expressed in this paper do not represent the views of the National Institutes of Health, H3Africa Consortium or their funders.

COMPETING INTERESTS

The authors have no competing interests to declare.

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TO CITE THIS ARTICLE:

Gupta A, Jones K, Deveaux A, Bevel M, Salako O, Daramola A, Hall A, Alatise O, Ogun G, Adeniyi A, Ojo A, Ayandipo O, Olajide T, Olasehinde O, Arowolo O, Adisa A, Afuwape O, Olusanya A, Adegoke A, Tollesbol TO, Arnett D, Newgard CB, Akinyemiju T. Association of Life-Course Educational Attainment and Breast Cancer Grade in the MEND Study. *Annals of Global Health*. 2021; 87(1): 59, 1–11. DOI: <https://doi.org/10.5334/aogh.3142>

Published: 07 July 2021

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Annals of Global Health is a peer-reviewed open access journal published by Ubiquity Press.

