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Editorial

Genetic Risk Factors of Secondary Lymphedema in African Breast Cancer Population

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Introduction

Breast Cancer Related Lymphedema (BCRL) is a common side effect associated with breast cancer patients following treatment strategies such as surgery, chemotherapy, or chemoradiotherapy. The potential contribution of genetic susceptibility to risk of developing secondary lymphedema following surgical trauma, radiation, and other tissue insults has not been studied in African settings. Data on preclinical risk assessment to guide clinicians on diagnosis pathways for identification of the patients at highest risk of BCRL is scanty; and it is unclear whether the evidence is sufficient to recommend genotyping in clinical practice. This paper hypothesizes that pre-surgical identification of a potential genomic risk for BCRL may facilitate risk prediction and earlier treatment for high-risk patients within African settings.

To the Editors

Breast Cancer Related Lymphedema (BCRL) is a significant long-term comorbidity associated with Breast Cancer (BC) management [1]. BCRL affects Quality of Life (QOL) of BC survivors; as a result of lymphatic system dysfunction related to mechanical injury [1,2]. Recent studies have identified modifiable and non-modifiable risk factors of BCRL at the clinical stage [1]. These results have also contributed to the understanding of genomic mechanisms of susceptibility for BCRL development [2-10]. The current evidence has advanced cure progress and knowledge on clinical diagnosis and risk reduction of BCRL [1,5,6,8]. However, most of these studies were conducted in developed countries with limited information on such predictors and successful management strategies within African population subgroups. Data on preclinical risk assessment to guide clinicians on diagnosis pathways for identification of the patients at highest risk of BCRL is scanty; and it is unclear whether the evidence is sufficient to recommend genotyping in clinical practice. This paper hypothesizes that pre-surgical identification of a potential genomic risk for BCRL may facilitate risk prediction and earlier treatment for high-risk patients within African settings.

This paper is written to inform ongoing systematic reviews and experimental studies on genetic variants associated with BCRL among African women following breast cancer management. This review uses the Populations, Interventions, Comparators and Outcomes (PICO) format. In this case, the eligible studies will include observational studies (prospective cohort studies, case control studies) and experimental studies (quasi-experimental, laboratory experimental studies and randomized controlled trials). In addition, the eligible studies will comprise diagnosis of BC related lymphoedema using bioinformatics techniques; statistical results reporting sample size, effect sizes, p-value and 95% confidence interval. All studies published into French, English and Afrikaans, without restriction on country and year of publication, will be also included. Moreover, the indicators of the review will include the studies reporting the case of BCRL patients, bioinformatics technologies (DNA sequencing, genotyping) using saliva or blood samples, and compared to breast cancer patients without BCRL as control group. Further, the outcomes of the studies will include identified inherited genes with their respective single nucleotide polymorphism variants detected by bioinformatics techniques.

The search strategy identified that different types of BC surgeries, radiation therapy, chemotherapy, hormonal therapy and

BMI (>25) or obesity (BMI >30) are the consistent acquired risk factors for BCRL. DNA sequencing revealed that FLT4, FOXC2 GJC2, and SOX-18 are the high penetrance genes for Secondary Lymphedema (SLE) to be established as a clinical risk assessment score for early diagnosis and prevention of BCRL. Furthermore, the research question was formulated as follows: "Among BCRL patients recruited for DNA sequencing for preclinical identification of inherited variants, are those diagnosed with BCRL at highest risk of presenting LE genotypes compared to those without LE, using bioinformatics technologies?" Table 1 shows the summary of the genes associated with BCRL

Gene variants	Description	References
FLT4 (VEGFR3) rs121909657	Lymphatic specific growth factor, strong regulator of lymphangiogenesis, hyperplastic lymphatic vessels, lymphedema. VEGF C binds to and activates VEGFR3 and VEFGR2 receptors on lymphatic epithelium	[5, 9]
GJC2 (cx47, 43) G357A SNP	Primary and secondary lymphangionesis	[2,3]
FOXC2 rs34221221	Primary and secondary lymphangionesis	[5]
SOX-17/18 Rs12541742	Lymphangionesis	[7]
Table legends: FLT4= fms-like Tyrosine Kinase 4 (encoding VEGFR2, 3, C); FOXC2= Forkhead Box C2; GJ2 = Gap junction gamma-2; and SOX-18 = Transcription factor SOX-18 is a protein that in humans is encoded by the SOX18 gene; C= cytosine, G= guanine, T= Thymine, A= adenosine, CX47= Connexin 47.		

Table 1: Selected high penetrance gene associated with breast cancer related lymphoedema.

Current data demonstrate that the incidence rates of BCRL following BC management (surgery, radiation therapy, chemotherapy and hormonal therapy) varies from 6% to 83% in literature depending to types of breast conservation strategy and diagnostic tool used to assess BCRL [1]. Although there is scarce of data on prevalence, incidence and management pathways of BCRL in lower and middle-income countries, such as those of Sub-Saharan Africa, the current data on burden of BC confirmed that BC is the firth cause of death worldwide with the largest ramifications to African countries [10]. Given the reported comorbidities associated with this condition, the pockets of information show that BCRL incidence should be increasing in African countries. Review by Jacques et al. (2018) on risk reduction strategies for BCRL in DRC revealed that there is a scarce of epidemiological data on BCRL risk factors and management in this country. The authors recommended studies to be conducted to extend body of knowledge, skills, and awareness of secondary lymphoedema throughout all the stakeholders [11].

BCRL is an inflammatory and chronic disease without curative therapy at clinical stages [1]. A recent genomic study conducted on precision assessment of BCRL risk prediction has identified that a number of BCRL genetic variants can be studied in population groups to establish complementary diagnosis for BC survivors at highest risk of BCRL [9]. In addition, many modifiable and non-modifiable risk factors for BCRL were identified in the literature; these have contributed to cure progress and advanced knowledge on preclinical diagnosis for BCRL [1]. However, most of these studies revealed that BCRL is mainly caused by breast injury and genetic disposition is an important predictor of its occurrence. Recognition of specific genetic predictors can be important tools to be developed in the clinical setting for early detection and intervention for BC patients at highest risk of BCRL [6]. A pilot study on assessing the efficacy of anti-angiogenesis or connexin-modified drugs demonstrated that good understanding of pathophysiological mechanisms of each genotype replication in different population subgroups might prevent patients from experiencing major trauma related to the current standard of care [2]. Further, most of these studies lack external validities and clinical implications for a number of countries. No study of this nature has yet been conducted in the African context, to extend the body of knowledge on LE genotypes and phenotypes based on African population subgroups.

Competing Interests

The author declares no competing interest.

Author's Contributions

- Designing, searching the articles, data extraction, writing, editing, proofreading and critical appraisal
- Edition, critical appraisal and quality improvement
- Search strategies, Gallery Proof sprints service and critical appraisal

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