Genetic Risk Factors of Secondary Lymphedema in African Breast Cancer Population

Jean Paul Muambangu Milambo1*, Leonidas Ndayisaba2, Jacques Lukenze Tamuzi3

1Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and NHLS, Cape Town, South Africa
2Department of Respiratory Intensive Care, Groote Schuur Hospital, Cape Town, South Africa
3Division of Health Systems and Public Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

*Corresponding author: Jean Paul Muambangu Milambo, Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and NHLS, Cape Town, 25 Norden Road, Parow 7500, South Africa. Tel: +27719953868; Email: Jeanpaulmilambo2@gmail.com


Received Date: 09 February, 2018; Accepted Date: 03 August, 2018; Published Date: 13 August, 2018

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.

Table 1:

<table>
<thead>
<tr>
<th>Gene variants</th>
<th>Description</th>
<th>References</th>
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<tbody>
<tr>
<td>FLT4 (VEGFR3) rs121909657</td>
<td>Lymphatic specific growth factor, strong regulator of lymphangiogenesis, hyperplastic lymphatic vessels, lymphedema. VEGF C binds to and activates VEGFR3 and VEGFR2 receptors on lymphatic epithelium</td>
<td>[5, 9]</td>
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<tr>
<td>GJC2 (cx47, 43) G357A SNP</td>
<td>Primary and secondary lymphangionesis</td>
<td>[2,3]</td>
</tr>
<tr>
<td>FOXC2 rs34221221</td>
<td>Primary and secondary lymphangionesis</td>
<td>[5]</td>
</tr>
<tr>
<td>SOX-17/18 Rs12541742</td>
<td>Lymphangionesis</td>
<td>[7]</td>
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Table legends: FLT4= fms-like Tyrosine Kinase 4 (encoding VEGFR2, 3, C); FOXC2= Forkhead Box C2; GJC2 = 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.

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

Acknowledgements
Dr. Landry Kabego and Andre Bulabula for generating comprehensive search strategy and revising molecular biology concepts in pathogenesis of cancer.

References


