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Research Article

Genetic Determinants of Cancers in Sub-Saharan African-based Populations: A Systematic Review

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ABSTRACT

Cancer is the leading, singular cause of human deaths worldwide. It has both an inherited and a biological component and its burden is rising in Africa. The African population is grouped into North Africa (NA) and Sub-Saharan Africa (SSA) and from a genetic perspective, NA shares much of their ancestry with Eurasia. Therefore, both African population sub-types would possess distinct cancer genetic make-up based on these ancestral origins. Thus, the aim of this study was to demonstrate any distinction in the genetic variant of SSA cancer types, by reviewing all genetic studies that investigated the genetic variants of cancers in this region. A review of all molecular genetic studies that interrogated the candidate genes and susceptible variants of cancers in SSA-based populations were reviewed. Our search methodology was modelled after the Cochrane systematic review protocol, which included MeSH terms and related keywords. Some 47 articles studying 7 cancer types in 12/48 SSA countries, met the inclusion criteria. All studies screened for polymorphisms using PCR-based techniques. Despite five studies showing statistically significant genetic association to their targets, their findings were rather suggestive than empirical, as no study replicated or validated the detected variants. Accurate reporting in SSA-based population cancer study is predicated on large scale studies and confirmation of actionable genetic markers for better understanding of the genetic risk. We recommend large scale genome association studies using contemporary techniques, in a multi-country setting and Sub-Saharan Africa having less molecular genetic research, than Northern Africa should be addressed..

Keywords: *Keywords: Sub-Saharan Africa; Cancer; Genetic Variants*

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INTRODUCTION

Cancer is the leading, singular cause of human deaths worldwide and the aetiology has both a familial and a cellular-genetic component (Abnet et al., 2018, Bray et al., 2018, Coleman et al., 2018). The burden of this disease is rising, with the highest incidence and mortality recorded from Africa (Dibisa et al., 2019). Depending on the cancer type, it has varying incidence per geographical locations and this varied worldwide distribution may suggest localised genetic causality. The African population comprise of 54 countries; grouped into North Africa (NA) - 6 countries and Sub-Saharan Africa (SSA) – 48 countries. NA is surrounded by the Sahara Desert in the south, Mediterranean Sea in the north, and bounded by Asia and Europe, with the first two landmarks acting as pre-historic gene flow barriers, and the latter two heavily influenced the NA gene pool (Castaneda et al., 2009). Significantly, the Sahara Desert acts as a gene flow barrier between the NA and SSA gene pools. Thus, from a genetic perspective, NA shares a majority of their ancestry with Eurasia, compared to SSA (Schuenemann et al., 2017).

SSA is reported as the most genetically divergent population amongst humans (Henn et al., 2011). Several molecular genetic studies have provided evidence of disease-associated alleles overlap along ethnic lines, and this allele overlap is reported to improve the power of detection of newly associated disease loci and causal variant mapping (2005, Auton et al., 2015, Yoneyama et al., 2017). In this regard, it is the position of this study that both African population groups would possess a different cancer genetic causal mapping based on their distinct ancestral origin. In our group's previous unpublished study, on cancer genetic variants in African-based population, there was a suggestion of a distinct susceptible genetic variant, thus necessitating further interrogation along Africa ancestry lines.

As a step towards demonstrating distinct genetic variant to SSA cancer types, we aim to undertake a review of all genetic studies (cohort, cross-sectional and case controlled) that interrogated these variants of cancers in SSA-based populations. The objectives are to appraise the current evidence of cancer based genetic studies, catalogue the genetic

variants associated with cancers in SSA-based populations and to emphasize any knowledge gaps for future research.

MATERIALS AND METHODS

Our search methodology was modelled after the Cochrane systematic review protocol. MeSH terms and keywords comprising and related to; cancer, polymorphism, mutations, Africa, African regions and SSA countries (Table 1), were used for the initial search. Publications to be selected for this study would interrogate association of genetic variants, to cancer in (SSA) based populations.

Table 1
Search strategy to identify publications of cancers in Sub Saharan Africa

MeSH	Field; Title; Abstract
Search 1	Cancer, **or** Carcinoma **or** Neoplasm
Search 2	Africa
Search 3	Polymorphism **or** Mutation **or** Variants
Search 4	Angola **or** Benin **or** Botswana **or** Burkina Faso **or** Burundi **or** Cameroon **or** Cape Verde **or** Central African Republic **or** Chad **or** Comoros **or** Democratic Republic of Congo **or** (DRC) **or** Djibouti **or** Equatorial Guinea **or** Eritrea **or** Ethiopia **or** Gabon **or** Gambia **or** Ghana **or** Guinea **or** Guinea-Bissau **or** Ivory Coast **or** (Côte d' Ivoire) **or** Kenya **or** Lesotho **or** Liberia **or** Madagascar **or** Malawi **or** Mali **or** Mauritania **or** Mauritius **or** Mozambique **or** Namibia **or** Niger **or** Nigeria **or** Republic of Congo **or** Rwanda **or** Sao Tome & Principe **or** Senegal **or** Seychelles **or** "Sierra Leone" **or** Somalia **or** "South Africa" **or** Swaziland **or** Tanzania **or** Togo **or** Uganda **or** Zaire **or** Zambia **or** Zimbabwe **or** "Central Africa" **or** "West Africa" **or** "East Africa" **or** "Southern Africa" **or** "South Africa"

Those whose ancestral origin were from outside Africa [e.g. White Africans, African Americans, and African Europeans] were excluded. Publications were identified using the search tools; Pubmed (1809-2020), Ovid Medline (1879-2020) and Web of science (1900-2020). Additional publications were searched in the reference list of selected articles from the initial search. English language title, abstract and full text of selected publications were read to identify those suitable for this review. Genetic studies considered were:

- Genetic [candidate gene] association studies
- Sequencing studies for germline and somatic mutations.

As such, purely clinical or pathological papers were excluded. A quality assessment tool (QAT) – STrengthening the REporting of Genetic Association studies (modified-STREGA) tool (Little et al., 2009), was used to assess the selected articles. In summary, the QAT-STREGA assessed the reporting of; power calculation, case population characteristics, cancer diagnosis, case and control screening, measure of association using odds ratio, genotyping error, Hardy-Weinberg equilibrium and inclusion of National Centre for Biotechnology Information (NCBI) rs identification numbers for variants. The QAT score evaluated 9 items and each had a score of 0 – 1 which adds up to a maximum overall score of 9. A score of > 5/9 was adjudged an acceptable quality score. Data collation was undertaken using a form which documented; biodata, case and control characterisation, genotyping method, statistical analysis method and environmental association frequency

RESULTS

The study search protocol identified 376 publications from Pubmed, Ovid Medline and Web of Science (Figure 1). Based on the review of the titles and abstracts, 291 publications were removed for not being related to cancer, genetic variant, and non-African population studies. The remaining 85 publication had their full text reviewed. A total of 45 of the 85 original articles met the full text eligibility based on the above search criteria. A total of 3 additional articles were retrieved from the reference list of these 45 articles and added while 1 article that studied white South African population was removed, to make a total of 47 articles. A total of 7 cancer types in 12 SSA countries were studied in these selected articles.

Study characterization

Oesophageal Cancer: A total of 21 genetic determinant studies on oesophageal cancer were undertaken in 3/48 (6%) African countries comprising South Africa, Kenya, and Malawi, published between 1990 and 2019 (Bye et al., 2012, Bye et al., 2011, Matejcic et al., 2011, Matejcic et al., 2015, Chelule et al., 2006, Chen et al., 2019, Dandara et al., 2005, Dandara et al., 2006, Dietzsch et al., 2003, Dietzsch and Parker, 2002, Gamieldien et al., 1998, Li et al., 2005, Li et al., 2010, Li et al., 2008, Liu et al., 2016, Naidoo et al., 2005, Patel et al., 2011, Strickland et al., 2012, Victor et al., 1990, Vogelsang et al., 2012, Vos et al., 2003) (Table 2).

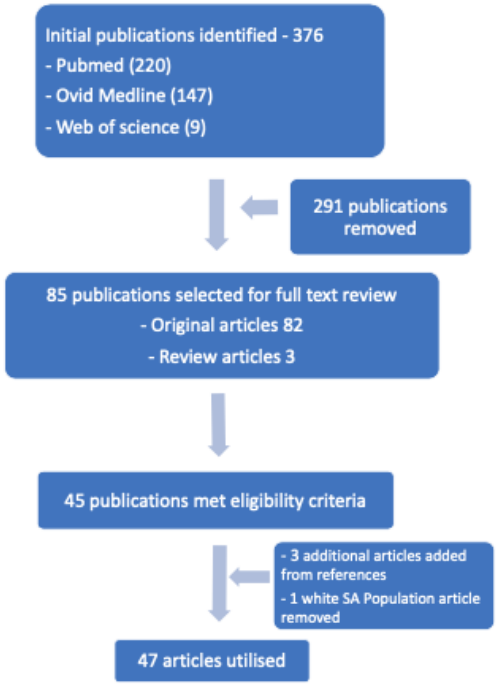

Figure 1
Search strategy flow chart

Table 2.
Studies and SSA population according to cancer types

	Cancers	Years of studies	No. of Publications (References)	Locations of studies
1.	Oesophageal	1990 - 2019	21 (Bye et al., 2012, Bye et al., 2011, Matejcic et al., 2011, Matejcic et al., 2015, Chelule et al., 2006, Chen et al., 2019, Dandara et al., 2005, Dandara et al., 2006, Dietzsch et al., 2003, Dietzsch and Parker, 2002, Gamieldien et al., 1998, Li et al., 2005, Li et al., 2010, Li et al., 2008, Liu et al., 2016, Naidoo et al., 2005, Patel et al., 2011, Strickland et al., 2012, Victor et al., 1990, Vogelsang et al., 2012, Vos et al., 2003)	South Africa, Kenya, Malawi
2.	Cervical	2001 - 2015	15 (Assoumou et al., 2015, Chambuso et al., 2019, Chatterjee et al., 2010, Chatterjee et al., 2009, Chatterjee et al., 2011, Chattopadhyay et al., 2015, Govan et al., 2003, Govan et al., 2006, Govan et al., 2007, Lin et al., 2001, Pegoraro et al., 2002, Stanczuk et al., 2001, Stanczuk et al., 2003, Stanczuk et al., 2002, Zidi et al., 2015)	Senegal, South Africa, Gabon, Zimbabwe
3.	Breast	2009 - 2019	5 (Diop et al., 2019, Habyarimana et al., 2018, Habyarimana T, 2018, Zheng et al., 2018, Zoure et al., 2018)	Senegal, Nigeria, Burkina Faso, Rwanda
4.	Colorectal	2012	1(Ogundiran et al., 2012)	Nigeria
5.	Prostate	2000 - 2018	3 (Du et al., 2018, Kittles et al., 2002, Tayeb et al., 2000)	Ghana, Nigeria, Uganda
6.	Liver	2018	1 (Marchio et al., 2018)	Cameroun
7.	Conjunctival	2005	1 (Tornesello et al., 2005)	Uganda

Table 3.
QAT-STREGA assessment according to cancer types

No.	Cancers	Screening Assays	No. of Genes Interrogated	HWE	QAT score ≥ 5 Studies	Susceptible Genes & polymorphism at <0.05
1.	Oesophageal	PCR-RFLP, PCR-SSCP, Targeted Sequencing, WES	58	7/21	19/21	25/58*
2.	Cervical	PCR-RFLP, PCR-ARMS,	9	4/15	13/15	*IL-10* (rs3024490, rs1800872, rs1800871), *CCR2-64I*, *CASP8* + *FasR* (rs3834129 + rs1800682), *TP53*, TNF-a (rs1800629, rs361525)
3.	Breast	PCR-RFLP, SNP Array	5	0/5	3/5	*BRAC1*, *BRAC2*, *TP53*, *PALB*, (*GPX1* - associated to cancer grade only)
4.	Colorectal	PCR-RFLP	1	1/1	1/1	None
5.	Prostate	PCR-RFLP, PCR-SSCP, SNP Array	3	1/4	2/4	*GSTM1*, *CYP3A4*, locus 8q24.21 (rs72725854, rs114798100, rs72725879, rs6983561, rs16901979)
6.	Liver	PCR	1	0/1	1/1	*PNPLA3* (rs738409), *IL-28B* (rs12979860)
7.	Conjunctival	PCR-RFLP	1	0/1	0/1	None

***PCR** = Polymerase Chain Reaction, **RFLP**= Restriction fragment length polymorphism; **SSCP**=Single strand conformational polymorphism; **ARMS**=Amplified refractory mutation system; **WES**=Whole exome sequencing; **SNP**=Single nucleotide polymorphism; **HWE**=Hardy Weinberg Equilibrium; ***=Excluded data on White South Africans*

A total of 18 /21 (90%) studies were case control studies on Black South African population. Sample sizes ranged from 27-880 for case and 88 – 939 for control with medians of 121 for case and 98 for control. Cancer diagnosis for all cases was by histology.

Tissues for DNA extraction were cancer tissues for case and normal tissue for control. A total of 21 studies screened for variants using PCR -based techniques and targeted sequencing by genetic analysers. One study used whole exome sequencing (WES) screening. A total of 58 genes were screened for > 100 SNPs. The Hardy Weinberg equilibrium was assessed in 7/21 (33%) studies, 5/21 studies reported power calculation. No study reported genotype error evaluation. NCBI rs numbers were reported in 6/21 (29%) of all studies. A total of 19/21 (90%) studies had a QAT-STREGA score of ≥ 5. A total of 11/21 (52%) studies showed statistically significant association to target gene polymorphisms. Additional details of these studies are shown in Table 3.

Cervical Cancer: A total of 14 genetic determinant studies on cervical cancer were undertaken in 4/48 (8%) SSA countries (Assoumou et al., 2015, Chatterjee et al., 2010, Chatterjee et al., 2009, Chatterjee et al., 2011, Chattopadhyay et al., 2015, Govan et al., 2003, Govan et al., 2006, Govan et al., 2007, Lin et al., 2001, Pegoraro et al., 2002, Stanczuk et al., 2001,

Stanczuk et al., 2003, Stanczuk et al., 2002, Zidi et al., 2015). All studies were case control and published between 2003 and 2015 (Table 2). Sample sizes ranged from 30-458 for case and 36 – 1432 for controls with medians of 103 for case and 202 for control. Cancer diagnosis for all cases was by histology. Tissues for DNA extraction were cancer tissues for case and normal tissue or blood for control. All 14 studies screened for variants using PCR – based techniques and sometimes combined with targeted sequencing. No study used SNP array or whole genome screening. 10 genes were screened comprising; *BRCA 1, 2, TP53, CASP8, CCR2, FAS, IFN-g, IL10, TNF-a* and *TGF-b*. The Hardy Weinberg equilibrium was assessed in 5/14 (36%) studies, and no study reported power calculation or reported genotype error evaluation. NCBI rs numbers were reported in 4/14 (28%) studies and 12/14 (86%) studies had a QAT-STREGA score of ≥ 5. A total of 6/10 (60%) target gene polymorphisms showed statistically significant association to cervical cancer. Additional details of this cancer type are shown in Table 3.

Breast Cancer: A total of 5 genetic determinant studies on breast cancer were conducted in 5/48 (10%) African countries (Diop et al., 2019, Habyarimana et al., 2018, Habyarimana T, 2018, Zheng et al., 2018, Zoure et al., 2018). A total of 4/5 (80%) publications were case control studies and all studies were published between 2017 - 2019 (Table 2). One study (Sluiter et al., 2009) reported on South African White population and was exclude from this study. Sample sizes ranged from 15-1136 for case and 28 – 997 for controls with medians of 116 for case and 178 for control. Cancer diagnosis for all cases was by histology. Tissues for DNA extraction were cancer tissues for case and normal tissue or blood for control. A total of 4/5 (80%) studies screened for variants using PCR-based techniques with targeted sequencing, while 1/5 (20%) undertook an expanded screening with SNP array. Five gene targets were screened comprising *BRCA 1, 2, TP53, CYP1A2,* and *GPX1*. No study assessed the Hardy Weinberg equilibrium, power calculation or genotype error evaluation. 1/5 (20%) of the studies used the NCBI rs numbers. A total of 2/5 (40%) studies had a QAT-STREGA score of ≥ 5, and 4/5 (80%) of target gene polymorphisms suggested association to breast cancer. Additional details of this cancer type are shown in Table 3.

Colorectal Cancer: One genetic determinant study on colorectal cancer was undertaken in Nigeria (Ogundiran et al., 2012). The study was a case controlled published in 2012 (Table 2). Cancer diagnosis was by histology. Tissues for DNA extraction were cancer tissues for case and normal tissue or blood for control. The study screened for variants using PCR-based techniques and targeted sequencing. The gene screened was *CASC8*. The Hardy Weinberg equilibrium was assessed and NCBI rs number was reported. The study QAT-STREGA score was > 5 however, the study reported no association to target gene polymorphism. Additional details of this study are shown in Table 3.

Prostate Cancer: Three genetic determinant studies on prostate cancer were undertaken in 3/48 (6%) of all African countries comprising Ghana, Nigeria and Uganda (Du et al., 2018, Kittles et al., 2002, Tayeb et al., 2000). All studies were published between 2000 and 2018 and a total of 1/3 (33%) studies were case control (Table 2). Cancer diagnosis for all cases was by Prostate Specific Antigen and histology. Tissues for DNA extraction were cancer tissues for case and normal tissue or blood for control. A total of 2/3 (66%) studies screened for variants using PCR -based techniques while 1 used SNP array. The genes screened were *CYP3A4* and *PCAT1*. The Hardy Weinberg equilibrium and NCBI rs number was reported in 1/3 (33%) of the studies. A total of 2/3 (66%) of all studies had a QAT-STREGA score of > 5. 2/3 (66%) studies suggested association to target gene polymorphisms. Additional details of this study are shown in Table 3.

Liver Cancer: One genetic determinant study on liver cancer was undertaken in Cameroun (Marchio et al., 2018). Study was published in between 2018 and was case control (Table 2). The sample size was 195 with 49 control. Cancer diagnosis for all cases was by histology. Tissues for DNA extraction were cancer tissues for case and normal tissue or blood for control samples. Study screened for variant using PCR – based technique. The genes screened was *TP53*. HWE and NCBI rs number for the variant was not reported. Study QAT-STREGA score was 5. The study suggested an association to *TP53* polymorphism. Additional details of this study are shown in Table 3.

Conjunctiva Cancer: One study was undertaken for the genetic determinants of conjunctival cancer in Uganda. It was a case control and was published in 2018 (Tornesello et al., 2005) (Table 2). Study screened for *TP53* polymorphism using PCR based technique and reported a risk ratio and a > 5 QAT-STREGA score

DISCUSSION

This study evaluated studies on genetic determinants associated to cancers in SSA-based populations. A total of 47 published articles studying 7 cancer types, met the inclusion criteria. This suggests a dearth of reports on genetic determinants of cancers in SSA, which is due to the absence of research infrastructure and low prioritisation due largely to the severe socio-economic burden in Africa. In my group's unpublished report, North African countries which comprise 15% of African countries, recorded 51% of cancer reports while the Sub Saharan Africa countries which constitute 85% of all African countries, recorded 49% of cancer reports, indicating that SSA is worst hit by this severe socio-economic burden.

This review reported the interrogation of variants of several gene targets using varying PCR-based molecular techniques like PCR with restriction fragment length polymorphism (RFLP) technique and amplified refractory mutation system (ARMS). PCR-RFLP locates a DNA template within a sequence, while PCR-ARMS amplifies a DNA template within a sample. Single Strand Conformational Polymorphism (SSCP) uses a conformational change that correlates to a unique single base change. Considering the strength of these techniques, RFLP and ARMS are known to be of limited utility and sensitivity while SSCP is expected to

only have a sensitivity of no more than 80% (Sluiter et al., 2009). Considering some of these techniques used may have been contemporary for their time, the modern next generation sequence technology is required to investigate the whole genome to ensure high sensitivity and inclusivity.

Furthermore, no study in this review undertook replication and validation assays for their genetic variants. This made it difficult to demonstrate any specific genetic aetiology or correlation of these variants to SSA-based population cancers. Thus, this rendered the resolution of the genetic aetiology of cancers in SSA, to be poorly defined. Therefore, it is imperative to conduct large scale studies and validation of these genetic variants to accurately assess risk across SSA populations. Few of these studies reported a power calculation and none reported a genotyping error despite the high genetic diversity associated to SSA population. This may have resulted in these studies being underpowered and possible increased genotyping error. Based on these, we submit that most of the genetic association to the polymorphisms reported should be adjudged suggestive than statistically significant. Large scale studies are reported to give higher power at identifying causal variants in cancer pathogenesis (Mahajan et al., 2014). Therefore, combining these large studies with high throughput data on the SSA populations is recommended.

In conclusion, accurate findings in SSA-based population cancer study is predicated on large scale multinational genetic studies and confirmation of actionable genetic markers that offers better understanding of the genetic risk, prognosis and therapy. In addition, attaining relevant and informed prevention and screening programs that are specific to the SSA-based populations. SSA being the worst hit in terms of lack of cancer genetic data, should be re-assessed. This is in the light of emerging routine clinical sequencing and genomic diagnosis on all incident malignancies serving as a guide for clinical and therapeutic trials.

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