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Molecular markers and *Schistosoma*-associated bladder carcinoma: A systematic review and meta-analysis

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ABSTRACT

Background: Molecular mechanisms and pathogenesis of schistosomal-associated bladder cancer (SABC), one of the most common malignancies in Africa and parts of the Middle East, is still unclear. Identification of host molecular markers involved in schistosomal related bladder carcinogenesis is of value in prediction of high-risk group, early detection and timely intervention.

Methods: PubMed, Scopus, Google Scholar, Cochrane Library and African Journals Online databases were systematically searched and reviewed. A total of 63 articles reporting 41 host molecular factors were included in the meta-analysis.

Results: Pooled odds ratio demonstrated associations of p53 expression, telomerase activity and sFas with SABC as compared to other schistosomal patients (p53 expression: OR = 9.46, 95%CI = 1.14–78.55, $p = 0.04$; telomerase by TERT: OR = 37.38, 95%CI = 4.17–334.85, $p = 0.001$; telomerase by TRAP: OR = 10.36, 95%CI = 6.08–17.64, $p < 0.00001$; sFas: OR = 34.37, 95%CI = 3.32–355.51, $p = 0.003$). In comparison to bladder cancers of other etiology, positive associations were found between SABC and p15 deletion, p16 deletion, telomerase activity and sFas (p15 deletion: OR = 4.20, 95%CI = 2.58–6.82, $p < 0.00001$; p16 deletion: OR = 4.93, 95%CI = 2.52–9.65, $p < 0.00001$; telomerase by TERT: OR = 3.01, 95%CI = 1.51–5.97, $p = 0.002$; telomerase by TRAP: OR = 2.66, 95%CI = 1.18–6.01, $p = 0.02$; sFas: OR = 4.50, 95%CI = 1.78–11.40, $p = 0.001$). Other identified associations were reported by few numbers of studies to enable reliable interpretation.

Conclusions: Variations in gene expression or genomic alterations of some molecular markers in SABC as compared to non-SABC or other schistosomal patients were identified. These suggest minute differences in the pathogenesis and physiological profile of SABC, in relation to non-SABC.

1. Introduction

Urogenital schistosomiasis (UGS) due to infection with *Schistosoma haematobium* is the most common form of schistosomiasis. It affects over 112 million people in Africa and the Middle East, with about 18 million (over 15%) developing major bladder pathogenesis [1]. Bladder cancer may in fact be the most common malignancy among males in Africa and some parts of the Middle East [2]. The adult worm inhabits the urinary bladder plexus where thousands of eggs are deposited, some of which are lodged in the bladder mucosa. The pathogenesis is due to the host induced granulomatous immune response, which may result in fibrosis, calcification of bladder walls and ultimately squamous cell carcinoma and bladder cancer in most severe cases [1,3]. Since

Abbreviations: SABC, schistosomiasis-asociated bladder cancer; ANG, angiogenin; APC, adenomatous polyposis coli; CK-20, cytokeratin-20; COX-2, cyclooxygenase-2; HER2, human epidermal growth factor receptor 2; HPV, human papilloma virus; HURP, hepatoma upregulated protein; GST, glutathione S-transferase; MMP-9, matrix metalloproteinase-9; NPip, N-nitrosopiperidine; NPyr, N-nitrosopyrrolidine; Oct3/4, octamer-binding transcription factor 4; RARβ2, retinoic acid receptor β2; TERT, telomerase reverse transcriptase; TRAP, telomeric repeat amplification protocol.

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only a minor fraction of those infected develop bladder cancer, identification of certain molecular markers will be of value in prediction of high-risk group and initiation of timely intervention. Accumulated data from other studies on molecular markers and prognosis showed that schistosomal bladder carcinogenesis cascades may not be very different from other urothelial cancers [4]. However, certain minute differences may exist and would be crucial as definitive risk factors for schistosomal and non-schistosomal bladder cancers.

Several studies are identifying the molecular mechanisms underlying neoplastic progression in schistosomiasis related bladder cancer. The expression of several cell cycle regulators especially the cyclin-dependent kinases (CDKs) inhibitors [5–7], the alteration of genes that regulate apoptosis [8–13], and other molecular markers of cancer including apoptotic markers [6,14–20] have been associated with cancer in urogenital schistosomiasis in several reports. To better understand the exact molecular mechanism and molecular markers involved in schistosomal related bladder pathogenesis, including the minute differences separating schistosomal and non-schistosomal bladder cancers, we systematically reviewed studies identifying host molecular markers for schistosomal bladder cancer. Identification of association between these risk factors and development of schistosomiasis-associated bladder cancer (SABC) was performed, in relation to other schistosomal patient and patients with bladder cancers of other etiology, respectively.

2. Methods

2.1. Registration of study protocol

We followed the recommendations of the PRISMA statement [21] for this study (Table S1). The protocol for this study was prepared before study was commenced and registered in PROSPERO-International prospective register of systematic reviews with identification number CRD42013005517 available from http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42013005517#.VG2l314xFlI.

Supplementary Table S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2015.06.004.

2.2. Search strategy and databases

Advanced searches were performed on PubMed and Scopus databases using the broad search term: "((cancer OR Neoplasm OR Neoplasia OR Tumor OR Tumors OR carcinoma) AND (bladder OR urogenital OR urinary OR vesical OR hematobium OR haematobium) AND (schistosom* OR bilharzi*))". For search on Advanced Google Scholar, we filled in the term "schistosoma OR schistosomiasis OR schistosome OR bilharzia OR bilharziasis OR hematobium OR haematobium" in the field "with all of the word", and the words "bladder cancer, urogenital cancer, cancer, carcinoma, neoplasia, neoplasm" in the field "with at least one of the words" to search the titles of articles in scholar database. The Cochrane Library and African Journals Online databases were searched with the broad term "schistosoma OR schistosomiasis OR bilharzia OR bilharziasis".

The initial searches were performed in August 2013 with no limit set for the dates of publications. A repeat search was performed in February 2015 just before meta-analysis, to identify newly published relevant studies. When necessary, authors were contacted for full texts, clarification on data and for supplementary data. Studies were excluded and classified as "full-text not available" when no responses was received from authors during the duration of the study and after a reminder.

2.3. Study inclusion criteria and study selection

Studies assessing association between host molecular markers of cancer and bladder cancer due to UGS were included in this review. All eligible studies irrespective of study type, study design, language and date were considered in the qualitative systematic review. Factors reported by more than at least two studies and whose data can be reliably extracted were then included in the meta-analysis. We limited the range of included studies to those performed on human subjects. Case studies, correspondence or reviews, and studies whose data could not be reliably retrieved were excluded.

Two reviewers performed study selection in a non-blinded manner. Initial preliminary assessment of the title and abstracts was performed to identify relevant articles. Full texts of eligible articles were then downloaded and reviewed for qualitative analysis and potential inclusion in the meta-analysis. Inclusion of a study by both reviewers was conclusive while discrepancies and disagreements as regards study eligibility were resolved by discussion and consensus with the third reviewer.

2.4. Data collection process and data items

Data collection was performed on The Review Manager (RevMan v5.2) from The Nordic Cochrane Centre, Cochrane Collaboration, 2012, as previously described [22]. Because the host factors were not determined at the beginning of the review, factors were added on first encounter. A study reporting several factors was included separately for each factor, while overlaps from multiple reports on a single study were identified and resolved.

2.5. Meta-analysis

Meta-analysis was performed on RevMan v5.2 to combine data from eligible studies [23], regardless any cut-off for the minimum number of studies required for valid interpretation. For each identified host factor, 2×2 contingency tables were generated and the odds ratio (OR) with the corresponding 95% confidence intervals (95%CI) were calculated for dichotomous outcome. For studies reporting continuous outcomes, the input data were mean and standard deviation (SD) with the standardized mean difference (SMD) as the effect measure. When the standard deviation was not reported, it was computed with the calculator function in RevMan v5.2 using other supplied data (e.g. mean, standard error of mean, p-value, etc.), if available. For each factor analyzed, a forest plot showing the respective OR or SMD with their corresponding 95%CI for each study and for the pooled data were generated. Z-Statistics was used to assess the test of overall effect with statistical significance set at $p < 0.05$. Subgroup analysis was not performed due to low number of included studies and because no subgroup existed except for factors analyzed using different methods.

2.6. Test of heterogeneity between studies

Heterogeneity or inconsistency among studies was evaluated using the Cochrane Q (Chi^2 test) and I^2 statistics [24]. The statistical significance for heterogeneity using the Chi^2 test was set as $p < 0.10$. Degree of heterogeneity was also assessed using I^2 test setting 25%, 50%, or 75% as cut-off for low, moderate or high heterogeneity, respectively. The fixed-effects model with weighting of the studies was used when there was a lack of significant heterogeneity ($p > 0.10$), while the random-effects model with weighting of the studies was used when there was heterogeneity among studies ($p < 0.10$) and I^2 values of over 50% [22,24].