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Review

MiRNA-221/222 in thyroid cancer: A meta-analysis

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ABSTRACT

Objectives: A meta-analysis was performed to observe whether a difference in miRNA-221/222 expression exists in thyroid cancer with normal thyroid or BTLs (benign thyroid lesions) and, under this premise, assess its diagnostic efficacy for thyroid cancer.

Methods: Systematic electronic literature searches were conducted to include PubMed, the Cochrane Central Register of Controlled Trials, and Web of Science. The combined fold change (FC) was calculated, and pooled estimates of sensitivity, specificity, diagnostic odds ratio (DOR) and summary receiver operating characteristic (SROC) curves were calculated.

Results: Twenty-seven articles were included in this meta-analysis. The combined FC of miRNA-221/222 were 13.85 and 13.75 in thyroid cancer with normal control. For miRNA-221/222, the pooled sensitivity was 0.79 (95% CI = 0.73–0.85), specificity was 0.84 (95% CI = 0.76–0.90) and AUC (area under the curve) value was 0.88 (0.85–0.91). For miRNA-221, the pooled sensitivity was 0.82 (95% CI = 0.76–0.86) and specificity was 0.84 (95%CI = 0.74–0.91). For miRNA-222, the pooled sensitivity was 0.78 (95%CI = 0.68–0.85) and specificity was 0.83 (95% CI = 0.70–0.92).

Conclusion: Differences in expression levels of miRNA-221/222 can provide clues for exploring the etiology of thyroid cancer. In addition, miRNA-221/222 were promising molecular biomarkers that may significantly improve the diagnostic accuracy of thyroid cancer.

1. Introduction

The 2017 cancer statistics published by the American Cancer Society recorded 56,870 new cases of thyroid cancer, including 14,400 males and 42,470 females. In addition, according to statistical data, the incidence of thyroid cancer from 2004 to 2013 has increased with an annual growth rate of 5.4% for men, and 4.6% for women [1]. Thyroid cancer has become one of the fastest growing tumors in the world. The most common histological type of all thyroid cancers is papillary thyroid cancer (PTC), which is defined as a differentiated neoplasia and accounts for approximately 80%, followed by follicular thyroid cancer (FTC) [2].

The expression of microRNAs (miRNAs) is identified as one of the most promising new biological markers of thyroid cancer. MiRNAs are a class of endogenous, small non-coding, and highly conserved RNAs, which have a length of 18–25 nucleotides [3, 4]. The human genome may contain up to 1000 miRNAs that play critical roles in cell proliferation, apoptosis, and developmental timing by negatively regulating the stability or translational efficiency of their target mRNA [5, 6]. In thyroid tumors, miRNA changes have been found in papillary thyroid carcinoma [7], follicular carcinoma [8], and anaplastic carcinoma [9].

If miRNA is differentially expressed in thyroid cancer with normal thyroid or BTLs, then it could be used as a potential biomarker for

Abbreviations: miRNA, microRNA; BTL, benign thyroid lesion; FC, fold change; DOR, diagnostic odds ratio; SROC, summary receiver operating characteristic; AUC, area under the curve; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; PLR, positive likelihood ratio; NLR, negative likelihood ratio; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; HSROC, hierarchical summary receiver operating characteristic curve; FNA, fine-needle aspiration

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thyroid cancer diagnosis. Wei, et al. published a meta-analysis concerning miRNA as a potential tool in the differential diagnosis of thyroid cancer [10]. This study found that a panel of miRNA can be used as a diagnostic marker for thyroid cancer. However, if one or two miRNAs are also of high diagnostic value, then the differential diagnosis of thyroid cancer is made more convenient and effective.

Among the most intensively studied miRNAs, miRNA-221 and miRNA-222 are two highly homologous miRNAs. They are encoded in tandem on the X chromosome in humans, mice, and rats and are highly conserved in vertebrates. In addition, they share a seed sequence [11]. Blocking these miRNAs leads to a reduction in the cell growth of PTC cell lines, and their overexpression induces an increase in colony formation ability [12]. Many studies focused on the relationship between miRNA-221/222 expression and thyroid cancer as well as miRNA-221/222 as a biomarker for differential diagnosis of thyroid cancer [13, 14], but their results were usually inconsistent as different detection methods with different technological platforms and various methods for data processing and analysis were used. Every single study may be underpowered and failed to achieve comprehensive and reliable conclusion. Therefore, we carried out a meta-analysis to observe whether a difference in miRNA-221/222 expression exists in thyroid cancer with normal thyroid or BTLs and, under this premise, assess its diagnostic efficacy for thyroid cancer.

2. Materials and methods

2.1. Search strategy

A comprehensive literature search for original articles analyzing the expression and diagnostic value of miRNA-221/222 in thyroid cancer was performed by using PubMed, the Cochrane Central Register of Controlled Trials, and Web of Science. Studies were selected by using the following search terms variably combined: (“miR-221” or “microRNA-221” or “miRNA-221” or “miR-222” or “microRNA-222” or “miRNA-222”) and (“thyroid”) and (“cancer” or “carcinoma” or “tumor” or “neoplasm”). The last search was performed in September 1, 2017. Simultaneously, the reference lists of review papers and original reports were hand-searched for further relevant studies.

2.2. Inclusion and exclusion criteria

Eligible studies were included if they met the following criteria: (1) articles on the expression and diagnostic value of miRNA-221/222 for thyroid cancer, (2) diagnoses of thyroid cancer were based on standard histopathology, (3) the control groups were confirmed with benign thyroid disease or normal persons, and (4) enough data were provided in the study for further analysis. Articles were excluded based on the following criteria: (1) articles using cancer cell lines; (2) reviews, editorials, letters or meta-analyses; and (3) studies without key data.

2.3. Data extraction

Two reviewers independently read the titles and abstracts of the included articles and judged their eligibility. After excluding articles that did not meet our inclusion criteria, the full texts were read and relevant data were extracted from included studies. The following items were eligible to collect and record for each study: first author, year of publication, region of study, material, test method, ratio of males and females, histopathological typing of thyroid cancer, number of patients and controls, age, normalization control, their matching fold change, AUC, sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), DOR, and accuracy. If the FC value information was not available, original data were extracted from the article to calculate FC. The formula was $\log_2(T/N)$ for miRNA array, and $2^{-\triangle\triangle Ct}$ for RT-PCR. Two authors independently evaluated and extracted the data with the inclusion criteria. Any discrepancies were adjudicated by a third investigator.

2.4. Quality assessment

Two reviewers assessed the quality of the studies included using the revised Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) metric [15]. The QUADAS-2 comprises four domains: patient selection, index test, reference standard and flow and timing. Questions related to the specific domain were set to assess the risk of bias and applicability.

2.5. Statistical methods

The bar chart of QUADAS-2 is drawn by RevMan, version 5.3. The combined FC was calculated, expressed in mean, and divided into different groups by thyroid cancer histopathological types, controls, ethnicities, test methods, and materials. Diagnostic meta-analysis was conducted on STATA software, version 12.0 (StataCorp, College Station, TX, USA) using true positive, false positive, false negative and true negative extracted directly or through recalculation based on reported accuracy in combination with the sensitivity, specificity and sample size of a study. The random-effect model was applied to summarize the pooled estimates of diagnostic accuracy for the miRNA assay, including sensitivity, specificity, PLR, NLR, and DOR. SROC curve, hierarchical summary receiver operating characteristic curve (HSROC), and AUC were used to evaluate overall diagnostic value further. Threshold effect was assessed by SROC. If a “shoulder” shape was observed, then a threshold effect was present. Subgroup analysis of studies, which used normal persons or BTLs as control, was performed, and the diagnostic efficacy of miRNA-221 and miRNA-222 for thyroid cancer was evaluated respectively. In addition, we drew a funnel plot to investigate publication bias. The chi-square test and I^2 statistic were used to quantify the degree of between study heterogeneity. If heterogeneity among studies was recorded, the potential source of heterogeneity was investigated by sensitivity analysis and meta-regression. We investigated the influence of a single study on the overall DOR estimate by removing each study in each turn, to test the robustness of the main results (sensitivity analysis).

3. Results

3.1. Literature search

In total, 184 records for miRNA-221/222 and thyroid cancer were identified from a systematic literature search in PubMed, Cochrane, Web of Science, and the reference lists of papers. Seventy records were first screened after duplicates had been removed. After manually screening the records, 22 articles were excluded because they involved cancer lines and were review or meta-analysis, conference abstracts, or studies irrelevant to the current analysis. Of the 48 candidate articles, 9 lacked key FC data, and 12 were low-quality articles (based on QUADAS-2 metric). Therefore, a total of 27 articles were eligible for the final meta-analysis. A flow diagram of the study selection process is presented in Fig. 1.

3.2. Study characteristics and quality assessment

Finally, 27 articles were included in our meta-analysis. The articles included were published from 2005 to 2016. Twenty-four studies for miRNA-221/222 expression values were obtained, containing 1732 thyroid cancer samples, 374 BTLs samples, and 713 normal controls. All the studies were retrospective in design. Microarray assays and qRT-PCR were mostly used for comparing the expression levels of miRNA-221/222 in thyroid cancer with normal thyroid or BTLs. According to the original data and our calculations, 24 studies provided FC value information (Table 1).