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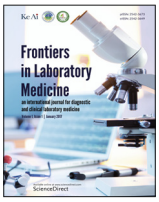

The association between long noncoding RNA H19 and pathological features in cancers: A meta-analysis

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ABSTRACT

Purpose: Long noncoding RNA (lncRNA) H19 has been reported to be up-regulated and down-regulated in numerous tumors, but the relevance of clinical pathological features is not established. So, meta-analysis was conducted to investigate the association between H19 expression and pathological features of cancers.
Method: The databases on PubMed, Web of Science, CNKI, and Wan Fang were searched for the related studies. 13 eligible studies were included with a total of 854 patients. Revman5.3 and Stata12.0 software were performed to analyze the data.
Results: The results suggested that the group of high H19 expression had a higher risk of poorly histological grade, clinical stage, deep tumor invasion (T2 stage or more), and was inclined to lymphatic metastasis, distant metastasis, and had a shorter survival time than the group of low H19 expression.
Conclusion: High expression of lncRNAH19 might act as a novel diagnostic biomarker and predict poor oncological outcomes of patients with cancers.

Contents

Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. According to the GLOBOCAN 2008 estimate, about 12.7 million cancer cases and 7.6 million cancer deaths occurred in 2008.[1] Although encouraging progress in diagnosis and cancer therapy has been achieved in the past decades, therapeutic effect and the overall survival rate are not so optimistic. Therefore, the development of a novel and effective strategy is an urgent matter for the early diagnosis and treatment of cancers.

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Noncoding RNA was once regarded as accumulated "junk sequences", with the completion of Human Genome Project, which revealed that only 1.5% of gens encode protein, while most of them do not encode protein.[2,3] Many ncRNAs play key roles in gene regulation and are important in normal cellular function as well as disease pathogenesis.[4] Among them are long noncoding RNAs (lncRNAs), which are more than 200 nt in length without protein-coding capacity and are widely involved in carcinogenesis, proliferation, invasion, metastasis.[5,6] H19 is a maternally imprinted gene, which locates in 11p15.5. It is transcribed by the RNA polymerase II and the transcript is spliced, polyadenylated, capped and exported into the cytosol. H19 is abundantly expressed in both extraembryonic and fetal tissues but decreased dramatically after birth except in a few adult organs, particularly in the mammary gland.[7,8] Emerging evidence reports that expression of H19 is up-regulated in various cancers, including breast cancer (BC),[9,10] gastric cancer (GC),[11–13] ovarian cancer (OC),[14] and non-small-cell lung cancer (NSCLC).[15] The first exon of H19 was microRNA-675 (miR-675) enhances tumorigenesis and metastasis of BC cells by down-regulating c-Cbl and Cbl-b (belong to the ubiquitin ligase E3 protein family).[10] In BC, H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1.[16] In GC, H19 can be induced by the oncogene c-Myc plasmid and plays a key role in the development and progression of GC by regulating cell proliferation.[11] H19 is also associated with tumor differentiation and TNM stage and indicates a poor prognosis of CRC and promotes tumor growth by recruiting and binding to eIF4A3.[17] All of the evidences prompt us to perform this meta-analysis to evaluate the association of high level of H19 with pathological features of tumors.

Methods

Publication search

The databases on PubMed, Web of Science, CNKI, and Wan Fang were searched from the establishment to September 2017. The association between lncRNA H19 expression and pathological features in cancers were reported in the studies. Following key words were searched in combinations: ("cancer and/or carcinoma or tumor or neoplasm", "long non-coding RNA" or "lncRNA", "H19", "pathology" and/or "clinical features"). To identify additional relevant studies, the literature references were also traced.

Inclusion and exclusion criteria

Inclusion criteria: the collected studies were considered eligibly if they met the following standards: (1) the expression of lncRNA H19 was detected in cancers; (2) the study provided at least one of the following clinicopathological features: tumor size, histological grade, tumor invasion depth, lymph node metastasis, and distant metastasis or overall survival; (3) H19 expression was divided into high and low group; (4) the data must be available to calculate odds ratios (OR) and 95% confidence interval (95% CI); (5) tissues must be tumor tissue.

Exclusion criteria were as follows: (1) reviews, case reports, meta-analysis, and duplicated publications; (2) the studies without pathological features; (3) group cannot be divided into high and low, and there was no sufficient data to calculate; (4) the studies focused on the molecular structure and function of lncRNA H19; (5) the sample size is less than 20.

Literature screening and data extraction

According to the inclusion and exclusion, two investigators (Meng Cui and Qing Luo) collected the data independently, and disagreements should be resolved by consensus or by discussion with the third investigator (Yi Zhang) before analysis started. Data extraction of literature was as follows: first author, publication year, country of origin, cancer type, number of the patients in high and low H19 expression group, detection method, and cut-off esti-

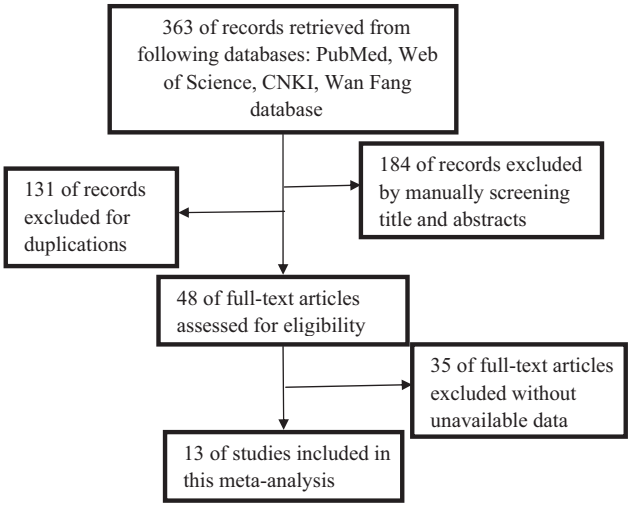

Fig. 1. Flow chart of the literature search and selection.

Table 1
Characteristic of the included studies.

Author	Year	Country	Cancer type	H19 expression		Cut-off (high/low)	Detection method	Outcome measures	NOS score
				High	Low				
Wang[18]	2016	China	GBC	13	11	Median ratio	qRT-PCR	OS	6
Ma[19]	2016	China	PDAC	17	8	Fold-change	qRT-PCR	N/A	7
Han[17]	2016	China	CRC	48	35	Fold change ≥ 3	qRT-PCR	OS .DFS	7
Huang[20]	2015	China	EC	66	67	Median	qRT-PCR	N/A	6
Zhu[14]	2015	China	OC	57	13	N/A	qRT-PCR	N/A	5
Esteves[21]	2005	China	HNSCC	11	24	N/A	qRT-PCR	N/A	5
You[22]	2014	China	GC	15	15	Median	qRT-PCR	N/A	6
Chen[13]	2016	China	GC	64	64	Fold-change ≥ 4.47	qRT-PCR	OS .DFS	7
Wang[23]	2015	China	RCC	42	50	Fold-change > 3.8	qRT-PCR	OS	7
Zhang[11]	2014	China	GC	40	40	Median	qRT-PCR	OS	6
Wang[24]	2016	China	GBC	12	8	N/A	qRT-PCR	NA	5
Zhang[15]	2015	China	NSCLC	35	35	Median	qRT-PCR	OS	6
Tan[25]	2016	China	EC	43	21	N/A	qRT-PCR	N/A	5

GC: gastric cancer; GBC: gallbladder cancer; OC: ovarian cancer; EC: esophageal cancer; RCC: renal cell carcinoma; CRC: colorectal cancer; PDAC: pancreatic ductal adenocarcinoma; HNSCC: head-and-neck squamous cell carcinomas; NSCLC: non-small-cell lung cancer; N/A: not available; NOS: Newcastle-Ottawa scale.

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