The prognostic significance of hTERT overexpression in cancers
A systematic review and meta-analysis

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Abstract

Background: Human telomerase reverse transcriptase (hTERT) plays an important role in cancer progression. Recently, several clinical studies investigated how the overexpression of hTERT predicts the poor prognosis of solid tumors. However, the results were inconclusive, partly because of the small numbers of patients included.

Method: We systematically searched PubMed, Web of Science, and Embase to identify relevant studies until August 2017. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to evaluate the association of hTERT expression and survival outcomes.

Results: A total of 27 studies enrolling 2530 solid tumor patients were included in this meta-analysis. There were strong significant associations between hTERT overexpression and all endpoints: overall survival (OS) (HR = 1.50, 95% CI: 1.31–1.73, \( P < .00 \)), disease-free survival (HR = 1.84, 95% CI: 1.38–2.46; \( P = .00 \)), and recurrence-free survival (HR = 1.79, 95% CI: 1.07–2.99; \( P = .028 \)). In the subgroup analysis, it was found that the overexpression of hTERT induced poor OS in lung cancer (HR = 1.51, 95% CI: 1.21–1.89; \( P = .00 \)).

Conclusion: Our comprehensive systematic review concluded that the overexpression of hTERT was associated with poor survival in human solid tumors. hTERT may be a valuable predictive biomarker for prognosis.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = Hazard ratios, hTERT = human telomerase reverse transcriptase, IHC = immunohistochemistry, ISH = in situ hybridization, OS = overall survival, RFS = recurrence-free survival, RT-PCR = Reverse transcription-polymerase chain action.

Keywords: cancer, hTERT, prognosis

1. Introduction

Cancer is a major public health problem worldwide. In China, it was predicted that there would be 4,292,000 newly diagnosed invasive cancer cases in 2015, which was almost 12,000 new cancer cases diagnosed on average each day.\textsuperscript{[1]} It is very important to explore its pathogenesis and therapeutic methods. Increasing numbers of studies have demonstrated that the imbalance between oncogenes and tumor suppressor genes is a determinant factor that induces normal cell development into tumor tissues.\textsuperscript{[2–4]} Therefore, it is meaningful to identify and characterize these genes that promote cancer progression and recognize the potential markers and specific targets for the prevention and individualized treatment of cancer.

Telomerase is a ribonucleoprotein enzyme that can extend the telomeres, which are composed of double-stranded tandem repeats of TTAGGG at the end of a chromosome.\textsuperscript{[5]} In most somatic cells, the inactivated telomerase leads telomeres to shorten with each round of cell division, and cells lose the capacity to replicate when a critical length is reached.\textsuperscript{[6]} However, in cancer cells, activated telomerase-induced cancer cells escaped from telomere shortening and ultimately promoted unlimited cancer cell proliferation and immortalization.\textsuperscript{[7]} Telomerase consists of a catalytic protein unit, human telomerase reverse transcriptase (hTERT), and human telomerase RNA. hTERT is the rate-limiting component of telomerase, and the upregulated expression of hTERT represents a surrogate marker of increased telomerase activity in most cancers.\textsuperscript{[8–9]}

It was hypothesized that the high expression of hTERT can predict the survival of cancer. A number of studies have demonstrated that the elevated expression of hTERT was associated with a poor prognosis in solid tumors such as gastric cancer, lung cancer, cervical and head cancer, glioblastoma, breast cancer, and ovarian cancer.\textsuperscript{[10–13]} However, most studies that addressed hTERT expression were limited by small sample sizes. Furthermore, several studies failed to reveal the association between hTERT expression and cancer prognosis.\textsuperscript{[14–17]} Therefore, this systematic review and quantitative meta-analysis sought to evaluate whether hTERT acts as a survival biomarker to predict cancer prognosis.
2. Materials and methods

2.1. Search strategy

This meta-analysis was conducted following the Preferred Reporting Items for systematic Reviews and Meta-Analyses guidelines.[18] A systematic literature search was performed in the electronic databases PubMed, Web of Science, and Embase (up to August 1, 2017) with the following search terms: “hTERT,” “human telomerase reverse transcriptase,” and “cancer or tumor or carcinoma or neoplasm.” In addition, the reference lists of the original research articles and reviews were also manually searched. Two evaluators completed the comprehensive search independently, and differences were resolved through discussion.

2.2. Selection and exclusion criteria

The eligible studies met the following inclusion criteria: clinical trials exploring the association between hTERT expression and the prognosis of cancer patients; the survival endpoint index was overall survival (OS), disease-free survival (DFS), or recurrence-free survival (RFS); reverse transcription-polymerase chain action, immunohistochemistry, or in situ hybridization was used to assess hTERT mRNA or protein expression; using the hTERT cutoff value, research patients were divided into positive (+) and negative (−) groups for survival analysis; Kaplan-Meier analysis or Log-hazard ratio (HR) and its 95% confidence interval (CI) were reported or could be calculated by a survival curve.

The exclusion criteria of eligible studies were as follows: study methods for hTERT detection, survival follow-up, and statistical analysis were not mentioned or ambiguous; duplicate data or repeat analysis (if >1 study was published by the same medical center (we chose the study with sufficient data or larger sample size); non-solid cancer or non-human research; study with a total number of cases <20; insufficient data to calculate HR and its 95% CI.

Hao NB and Wang K independently performed an initial assessment by identifying the eligibility of abstracts from the identified studies according to the selection and exclusion criteria. The final selection decisions were made by reading the full text if the eligibility was unclear from the sole abstract. Disagreement was resolved by discussing quality assessment and data collection.

2.3. Data extraction

Data were extracted according to the standardized format, which included the necessary information: author/year, study location, cancer type, sample size, hTERT test method, survival outcome measure, follow-up period, methods of HR estimation, HR, and its 95% CI. As the data included in our study were extracted from articles, ethical approval and patients’ written consent were not needed in our study. HR is the definition of both time to the event and censoring, and it is recommended in prognostic research. Although the majority of eligible studies did not directly report HR and 95% CI, I² value of 0% to 30%, 31% to 50%, 51% to 75%, and 75% to 100% represented insignificant, low, moderate, and considerable heterogeneity, respectively. A random-effect model was applied to the secondary analysis as I² > 50%; otherwise, a fixed-effect model was used. Publication bias was evaluated by Begg funnel plot and Egger test. The statistical analysis was performed by STATA 14.0 (STATA Corporation, College Station, TX). A 2-tailed P value < .05 was considered statistically significant.

2.4. Quality assessment

The quality of the included studies was independently assessed using the Newcastle-Ottawa Scale (NOS score) by Hao and Wang. It is generally considered that an article evaluated in the range of 0 to 5 points is of low quality, and the data extracted from such a study should be interpreted with caution. A score > 6 was considered to indicate high-quality articles.

2.5. Statistical analysis

The data collected from each eligible article was used to evaluate the relationships between hTERT overexpression and solid tumor prognosis by meta-analysis. Pooled HR with 95% CI was used to evaluate the outcomes. An observed HR > 1 implied a poor prognosis for the group with hTERT overexpression. Conversely, an observed HR < 1 implied a favorable prognosis for the group with hTERT overexpression. The heterogeneity between studies was evaluated using Cochran Q test and Higgins I² statistic.[19]

3. Results

3.1. Study selection and characteristics

According to the search strategy, 2966 references were identified in total. However, after screening of these titles and abstracts, only 89 studies were eligible for a full-text review. Finally, 27 studies were included in our meta-analysis, all of which were published from 2000 to 2016.[10-12,14-17,20-38] The detailed process of selection and exclusion is shown in Figure 1.

The main characteristics of the 27 included studies are shown in Table 1. Twelve different types of cancer were investigated in this meta-analysis, including 9 cases of lung cancer, and 3 cases of digestive cancer, breast cancer, and ovarian cancer. All the studies were investigated in different countries, including China, the United States, France, and Australia. The sample sizes ranged from 34 to 201, and the follow-up period ranged from 18 to 264 months. All included studies were of high quality with an NOS score ≥ 7.

3.2. The prognostic significance of hTERT overexpression in OS, DFS and RFS of human cancer

Of all 27 studies, HRs for OS were available in 23 studies with 2071 patients.[10-12,14-16,21-30,34-38] As there was no statistical homogeneity in all the 23 datasets (I² = 0.0%, P = .916), HR was calculated with the fixed-effects model. The forest plot results are shown in Figure 2, which indicated that the overexpression of hTERT induced poor OS (HR = 1.50, 95% CI: 1.31–1.73, P = .00).

HRs for DFS were available in 4 studies with 413 patients.[17,23,28,37] Homogeneity was accepted (I² = 47.6%, P = .126), thus, the fixed-effects model was chosen to calculate the HR. As shown in Figure 3, the pooled HR was 1.84 (95% CI: 1.38–2.46; P = .00), which indicated that hTERT overexpression was associated with poor DFS.

HRs for RFS were available in 4 studies with 374 patients.[20,30-31,33] Homogeneity was accepted (I² = 0.0%, P = .882), and the fixed-effects model was chosen to calculate the HR. As shown in Figure 4, the pooled HR was 1.79 (95% CI: 1.25–2.57; P = .00), which indicated that hTERT overexpression was associated with poor OS.

3.3. The prognostic significance of hTERT overexpression in RFS of breast cancer

Similarly, the pooled HR was 1.73 (95% CI: 1.38–2.17, P = .00), which indicated that hTERT overexpression was associated with poor DFS (Figure 5).
Figure 1. Flow diagram of dataset selection process.

Table 1
The basic characteristic of the included studies.

| Study                  | Year | Study Location | Cancer Types            | Sample Size | Test Method | Outcome Measure | Follow-up (Months) | HR Estimation | NOS Score |
|-----------------------|------|----------------|-------------------------|-------------|-------------|-----------------|-------------------|---------------|-----------|
| Bieche et al[20]      | 2000 | France         | Breast Cancer           | 134         | RT-PCR      | RFS             | 192               | Indirect      | 8         |
| Komiya et al[21]      | 2000 | Japan          | Lung cancer             | 68          | RT-PCR      | OS              | 96                | Indirect      | 8         |
| Gerttiere et al[22]   | 2002 | Germany        | Colorectal cancer       | 57          | RT-PCR      | OS              | 84                | Indirect      | 7         |
| Marchetti et al[13]   | 2002 | Italy          | Lung cancer             | 90          | RT-PCR      | OS              | 94                | Indirect      | 8         |
| Wang et al[23]        | 2002 | America        | Lung cancer             | 153         | ISH         | OS, DFS         | 264               | Indirect      | 8         |
| Fujita et al[24]      | 2003 | Japan          | Lung cancer             | 146         | ISH         | OS              | 85                | Indirect      | 7         |
| Wu[25]                | 2003 | Taiwan         | Lung cancer             | 56          | RT-PCR      | OS              | 67                | Indirect      | 7         |
| Chen[26]              | 2004 | America        | Lung cancer             | 94          | ISH         | OS              | 252               | Direct        | 8         |
| Marchetti et al[11]   | 2002 | Italy          | Ovarian cancer          | 40          | RT-PCR      | OS              | 168               | Indirect      | 7         |
| Widschwendter et al[14] | 2004 | Austria        | Cervical cancer         | 45          | RT-PCR      | OS              | 156               | Indirect      | 7         |
| Widschwendter et al[14] | 2004 | Austria        | Cervical cancer         | 45          | RT-PCR      | OS              | 156               | Indirect      | 7         |
| Alonso et al[24]      | 2005 | America        | Glioblastoma            | 34          | RT-PCR      | OS              | 108               | Indirect      | 7         |
| Domont et al[27]      | 2005 | France         | Hepatic colorectal      | 201         | IHC         | OS              | 85                | Indirect      | 7         |
| Boldrin et al[20]     | 2006 | Italy          | Glial tumors            | 39          | RT-PCR      | OS, DFS         | 38                | Indirect      | 7         |
| Chen et al[22]        | 2007 | Taiwan         | Oral squamous cell      | 62          | IHC         | OS              | 60                | Direct        | 8         |
| Mendrzyk et al[29]    | 2006 | Russia         | Intracranial Ependymoma | 155         | IHC         | OS              | 140               | Direct        | 8         |
| Zhu et al[23]         | 2006 | Canada         | Lung cancer             | 81          | RT-PCR      | OS, RFS         | 96                | Direct        | 8         |
| Tabori et al[24]      | 2006 | Canada         | Recurrent ependymoma    | 30          | IHC         | OS              | 168               | Indirect      | 7         |
| Alabat et al[13]      | 2008 | Taiwan         | Cervical cancer         | 45          | IHC         | OS              | 140               | Indirect      | 7         |
| Yang et al[31]        | 2008 | Taiwan         | Urothelial carcinoma    | 94          | IHC         | RFS             | 115               | Indirect      | 8         |
| Metzger et al[33]     | 2009 | Not clear      | Lung cancer             | 69          | RT-PCR      | OS              | 106               | Indirect      | 7         |
| van den Berg et al[17] | 2010 | Europe         | Lung cancer             | 166         | RT-PCR      | DFS             | 46                | Direct        | 8         |
| Brem-Enkaiden et al[13] | 2010 | Denmark        | Bladder cancer          | 65          | RT-PCR      | RFS             | 40                | Indirect      | 8         |
| Bertorella et al[34]  | 2013 | Italy          | Colorectal cancer       | 137         | RT-PCR      | OS              | 180               | Direct        | 8         |
| Lotosch et al[23]     | 2013 | Austria        | Glioblastoma            | 100         | RT-PCR      | OS              | 120               | Direct        | 8         |
| Guan et al[36]        | 2015 | China          | Esophageal cancer       | 150         | IHC         | OS              | 84                | Direct        | 8         |
| Gay-Belle et al[27]   | 2016 | France         | Breast cancer           | 55          | RT-PCR      | OS, DFS         | 204               | Indirect      | 7         |
| Yang et al[31]        | 2017 | China          | Cervical cancer         | 164         | IHC         | OS              | 123               | Direct        | 8         |

1 and 2: Widschwendter explored the role of hTERT in cervical and ovarian cancer in 1 article. DFS = disease-free survival, IHC = Immunohistochemistry, ISH = in situ hybridization, OS = overall survival, RFS = recurrence-free survival, RT-PCR = reverse transcription-polymerase chain action.
Figure 2. Forest plots for the correlation between human telomerase reverse transcriptase overexpression and overall survival in solid tumors. CI = confidence interval, HR = hazard ratio.

Figure 3. Forest plots for the correlation between human telomerase reverse transcriptase overexpression and disease-free survival in solid tumors. CI = confidence interval, HR = hazard ratio.
1.07–2.99; \( P = .028 \), which indicated that hTERT overexpression was associated with poor RFS.

3.3. The prognostic significance of hTERT overexpression in OS of lung cancer

Among all 27 studies, 9 studies discussed the association between hTERT overexpression and lung cancer prognosis. Van den Berg et al\(^{[17]} \) only reported hTERT overexpression with DFS. Finally, 8 studies with a total of 757 enrolled individuals dealt with the OS of hTERT overexpression in lung cancer.\(^{[10–11,21,23,25,30,32]} \) As there was no statistical homogeneity in all 8 datasets \((I^2 = 0.0\%, \ P = .928)\), HR was calculated with the fixed-effects model. The forest plot results are shown in Figure 5, which indicated that the overexpression of hTERT
induced poor OS in lung cancer (HR = 1.51, 95% CI: 1.21–1.89; P = .00).

3.4. Sensitivity analysis and publication bias
Sensitivity analyses were performed to assess the influence of each individual study on the pooled HR. As shown in Figure 6, it was found that there was no significant change owing to the omission of any single article, demonstrating the statistical robustness of our results. Begg funnel plot and Egger test were utilized to evaluate the publication bias of the included studies. The shape of the funnel plot did not reveal any obvious asymmetry, and Egger tests revealed no publication bias regarding OS (data not shown). These results still did not suggest any evidence of publication bias.

Kaplan-Meier survival curves were read and extracted by Engauge Digitizer software as described by Tierney et al[39] to calculate HR and 95% CI data according to Parmar method.

4. Discussion
hTERT fosters invasive cancer cell growth, which signifies the concerted activation of cell proliferation, angiogenesis, migration, and metastasis.[40–42] In recent years, research has focused on hTERT’s maintenance of stability to promote cancer cell growth. Recent studies have found that hTERT does not depend on its telomere-lengthening function or its telomerase activity to promote cancer cell growth and metastasis.[43] Liu et al[44] reported that hTERT interacts with β-catenin and promotes the epithelial–mesenchymal transition and stem cell-like traits in cancer cells. Hu et al demonstrated that the hTERT-MDM2 complex enhances ITGB1 expression and ultimately promotes cancer cell metastasis. The high expression of hTERT is associated with TNM stage, lymphatic metastasis, and poor prognosis.[45] Moreover, our results demonstrated that the overexpression of hTERT was associated with poor OS and DFS/RFS of human cancer patients. Thus, hTERT could be a potential target gene for cancer therapy.

In this study, we conducted a meta-analysis of hTERT in different types of solid tumors. The results showed that hTERT overexpression acted as an unfavorable prognostic factor for solid tumors. Poor OS (HR = 1.50, 95% CI: 1.31–1.73, P = .00) was found in human cancers with hTERT overexpression. These results were consistent with most included studies. However, Tee et al[15] found that the activation of hTERT was not found to significantly predict the OS rate (HR = 0.28, 95% CI: 0.02–3.32) in early cervical cancer, as both the positive and negative expression of hTERT had practically the same prognostic value in our patients. It seems contradictory that overexpressed hTERT destabilizes cell proliferation, which in turn checks the deregulation of cancer cell growth.[46] Furthermore, Andreas et al reported that hTERT methylation but not hTERT overexpression can be an independent prognostic factor for cervical cancer.[14] For the RFS and DFS, the included studies demonstrated that hTERT was a poor prognostic biomarker. However, only 4 studies were included in the subgroup analysis, and these results were not conclusive. Further research is needed to explore the role of hTERT as a diagnostic marker for RFS and DFS in human cancers.

Lung cancer is one of the most common malignancies in the world and is the leading cause of cancer-related deaths. In the subgroup analysis, it was found that the overexpression of hTERT leads to a poor OS (HR = 1.51, 95% CI: 1.21–1.89; P = .00) in lung cancer. Among the included studies, Metzger et al[45] found that the high expression of hTERT improved 5-year survival rates for non-small cell lung cancer, which was contradictory to the results of other studies. A possible reason was the limited number of telomerase-negative patients and total patients. Further research is still needed.
Aside from inspiring outcomes, some details need to be further refined. First, some of the included studies had a relatively small sample size, which may have caused a small-study effect. Second, the method of assessing hTERT expression was not consistent. Furthermore, the cutoff value for defining high and low hTERT expression varied in different studies, and it was difficult to obtain the same value. Finally, the follow-up period was not consistent in different studies, which may have influenced the final results, especially in the short follow-up period. Consequently, our estimation of the associations between hTERT overexpression and outcomes may have been overestimated.

In summary, our results showed that the overexpression of hTERT in solid tumor tissues was associated with poor survival (OS, DFS, and RFS). Meanwhile, subgroup analysis showed that hTERT overexpression also leads to the poor prognosis of lung cancer. Thus, hTERT might be a predictive biomarker for estimating the outcome of solid tumor patients. Furthermore, future studies related to specific tumor types and perspectives are needed to verify our results.

**Author contributions**

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