

Original Paper

Telomere Length as a Prognostic Factor for Overall Survival in Colorectal Cancer Patients

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Key Words

Colorectal cancer • Telomere length • Prognosis

Abstract

Background/Aims: The stabilization of telomere length has important roles in the carcinogenesis of colorectal cancer. A systemic review and meta-analysis of published studies was performed to assess the prognostic role of telomere length in colorectal cancer. **Methods:** Pubmed and Embase were searched for eligible studies on the association between telomere length and overall survival in colorectal cancer patients. The pooled hazard ratio (HR) and corresponding 95% confidence intervals (95%CI) was calculated using fixed-effects or random-effects model according to the magnitude of between-study heterogeneity. **Results:** Seven individual studies with a total of 956 colorectal cancer patients were included. Long telomere length in cancer tissues was marginally associated with poorer overall survival (Random-effects HR = 1.85, 95% 0.90 to 3.83, P = 0.09). When using studies with adjusted estimates, long telomere length in cancer tissues was independently and significantly associated with poorer overall survival (Fixed-effects HR = 2.70, 95% 1.51 to 4.84, P = 0.001). However, short telomere length in peripheral blood leukocytes was independently and significantly associated with poorer overall survival (Fixed-effects HR = 2.01, 95% 1.46 to 2.77, P < 0.001). **Conclusions:** There is some evidence for telomere length as a prognostic factor for overall survival in colorectal cancer patients. More studies with large number of participants are needed to further assess the prognostic significance of telomere length in colorectal cancer patients.

© 2016 The Author(s)
Published by S. Karger AG, Basel**Introduction**

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females, which has become a major challenge for public health [1, 2]. There were over estimated 1.2 million new cases of colorectal cancer and 608,700 deaths from colorectal cancer in 2008 worldwide [3]. There are substantial progresses in the treatment of colorectal cancer in the past decade [2, 4]. Both preoperative chemo radiation and adjuvant

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chemotherapy have improved the prognosis in patients with colorectal cancer. The integration of targeted drugs with conventional treatments has also expanded the survival of colorectal cancer patients [2, 4]. However, the development of effective prognostic biomarkers is essential to aid the selection of patients likely to respond to therapy, which can further rationalize the treatment and improve the outcomes. The stabilization of telomere length has important roles in the carcinogenesis of colorectal cancer [5-7]. Previous studies have suggested that the maintenance of telomere length through the reactivation of telomerase is a prerequisite for tumors to preserve their ability to proliferate and grow [8-11]. So far, there were several studies exploring the prognostic role of telomere length in colorectal cancer, but no consistent findings were reported [12-16]. Therefore, it is necessary to assess all data and elucidate those controversial or inconclusive results. Therefore, a systemic review and meta-analysis of published studies was performed to assess the prognostic role of telomere length in colorectal cancer.

Materials and Methods

Search strategy and study selection

Pubmed and Embase were searched for eligible studies exploring the prognostic role of telomere length in colorectal cancer. The last search was updated on September 21, 2015. There was no language limitation in the search. The following search strategy was used: (telomere length) and (Colorectal cancer, colon cancer, or rectal cancer). References cited in relevant articles or reviews were also checked for additional relevant articles. Studies were considered eligible if they met the following inclusion criteria: (1) Prospective or retrospective cohort studies; (2) Patients were colorectal cancer patients; (3) Reporting data on overall mortality according to telomere length; (4) Time of follow-up was more than 12 months. Studies were excluded if any of the following existed: (1) Data could not be extracted from the published articles; (2) Outcomes were not the end points used in this meta-analysis; (3) Overlapping data. For multiple studies were reported by the same institution or authors, either the one of higher quality or the most recent publication was included in the meta-analysis. Two investigators independently reviewed and evaluated each included article. Disagreements were resolved by consensus through discussion.

Data extraction and quality assessment

Two investigators independently extracted the usable data from each included article, and disagreements were resolved by consensus through discussion. The end point used in the meta-analysis was overall mortality during follow-up. The following data were extracted from each included study: first author, publication year, country, study design, number of participants, time of follow-up, adjusted factors, and hazard ratio (HR) with corresponding 95% confidence intervals (95%CI) for overall mortality. For studies providing HRs with 95%CIs with different adjusted confounders, only the HRs with the most adjusted factors were used in the meta-analysis. In present meta-analysis, we used Newcastle-Ottawa-Scale (NOS) to evaluate the quality of included studies. We evaluated the quality of included studies by scoring on the selection of recruited participants (up to 4 scores), the comparability of contrast groups (up to 2 scores) and the assessment of outcomes (up to 3 scores). Studies with scores of no less than 6 were regarded as high quality, while those with 4 or less were regarded as low quality.

Statistical analysis

The HRs and corresponding 95%CIs were used to assess the prognostic role of telomere length in colorectal cancer. Fixed-effects or random-effects models were used to calculate the pooled HR and corresponding 95%CI according to the between-study heterogeneity. Statistical heterogeneity was assessed by performing the χ^2 based Q test and by calculating the I^2 [17, 18]. If the $P < 0.10$ and $I^2 > 50\%$, there was obvious between-study heterogeneity and a random-effects model was used to pool the HRs [19]; otherwise, the fixed-effects model was used to pool the HRs [20]. For additional sensitivity analysis, studies without adjusted HRs were excluded and those left HRs were further pooled. Funnel plot was used to detect the publication bias, and asymmetry of the funnel plot indicated risk of publication bias. The main analyses

were performed using STATA version 12.0 (StataCorp LP, College Station, Texas, USA). All P less than 0.05 were considered as significant unless otherwise specified.

Results

Study selection and characteristics

The literature search identified 136 individual and different publications (Fig. 1). After screening the titles and abstracts, 130 articles were excluded and 6 publications were further assessed by reviewing full-texts [12-16, 21]. After full-text review, one publication was excluded for containing overlapping data [21]. One publication contained three individual cohort studies, and was extracted as three different cohort studies [15]. Thus, 7 individual studies from 5 articles were included [12-16]. Those 7 studies included a total of 956

Fig. 1. Flow chart of study selection in the meta-analysis.

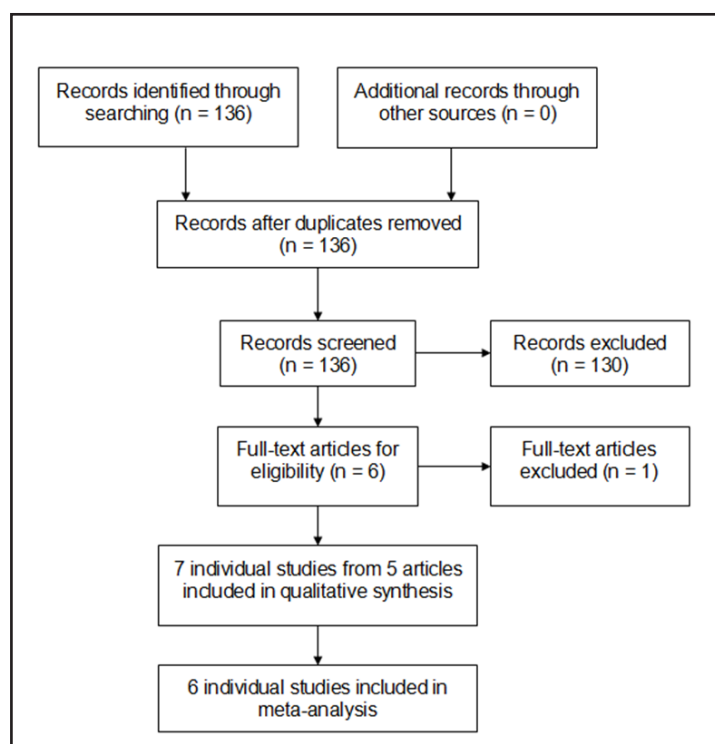


Table 1. Baseline characteristics of 5 included studies in the meta-analysis. (* The study by Chen et al. included three single and individual studies)

Study	Country	Participants (Mean age; male, %)	Follow-up	Telomere length	Adjustment	Quality scores
Gertler R 2004[12]	Germany	57 patients with R0-resected colorectal carcinoma (64.6 years; 53.6%)	76 months	Cancer tissues (Telomere length ratio >0.9)	Yes	8
Kojima K 2011[13]	Japan	106 colorectal cancer patients diagnosed between 1998 and 2002 (61 years; 56.6%)	5 years	Cancer tissues (Unclear)	No	5
Valls C 2011[14]	Spain	147 patients with sporadic colorectal cancer who had undergone surgery from February 2001 to January 2005 (70 years; 54.4%)	5 years	Cancer tissues (Terminal restriction fragment length ratio >1)	Yes	8
Chen Y 2014[15]*	China	571 CRC patients receiving surgical resection (58.9 years; 53.8%)	28 months	Peripheral blood leukocytes (Relative telomere length short vs. long)	Yes	8
Augustine TA 2015[16]	USA	75 patients who had received anti-EGFR drugs (60 years; 29.3%)	20 months	Cancer tissues (Telomere length ratio more than median)	No	6

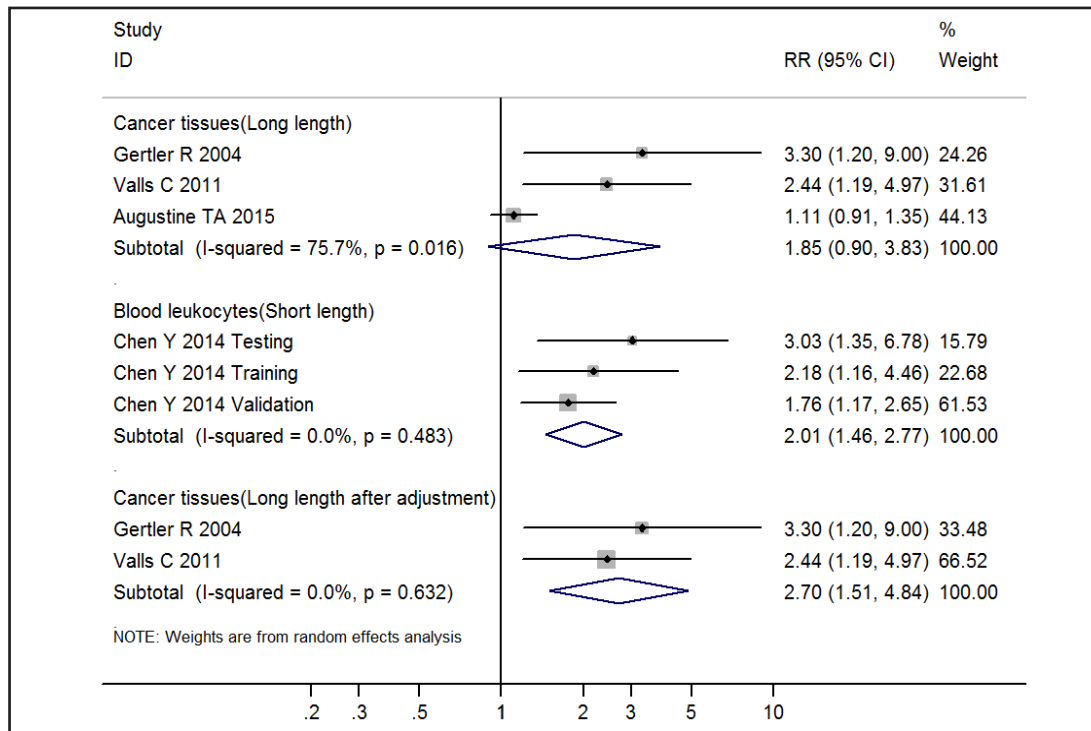


Fig. 2. Forest plot assessing the prognostic role of telomere length in colorectal cancer in the meta-analysis.

colorectal cancer patients (Table 1). Those studies were published from 2004 to 2015 (Table 1). Table 1 showed the main baseline characteristics of those included studies in the meta-analysis (Table 1). All studies were cohort studies, and the time of follow-up was more than 12 months. The number of participants with colorectal cancer ranged from 57 to 571 (Table 1). The study by Kojima et al. reported that telomere length was not associated with the survival of colorectal cancer, but didn't report the exact HR with 95%CI [13]. The outcome of quality assessment was shown in the Table 1. Most included studies had high quality (Table 1).

Telomere length and overall survival

Meta-analysis showed that long telomere length in cancer tissues was marginally associated with poorer overall survival (Random-effects HR = 1.85, 95% 0.90 to 3.83, P = 0.09) (Fig. 2). When using studies with adjusted estimates, long telomere length in cancer tissues was independently and significantly associated with poorer overall survival (Fixed-effects HR = 2.70, 95% 1.51 to 4.84, P = 0.001) (Fig. 2). However, short telomere length in peripheral blood leukocytes was independently and significantly associated with poorer overall survival (Fixed-effects HR = 2.01, 95% 1.46 to 2.77, P < 0.001) (Fig. 2).

Funnel plot was used to assess the risk of publication bias. The shape of the funnel plot didn't reveal evidence of asymmetry in the meta-analysis.

Discussion

We did a systemic review and meta-analysis of published studies to assess the prognostic role of telomere length in colorectal cancer. To the best of our knowledge, there was no meta-analysis published to evaluate the prognostic role of telomere length in colorectal cancer patients. The present study was the first meta-analysis which provided a comprehensive evaluation of the association between telomere length and overall mortality in colorectal cancer patients. The pooled results in the meta-analysis suggest that there is some evidence

for telomere length as a prognostic factor for overall survival in colorectal cancer patients.

Despite of recent findings in the researches of risk factors or novel factors involved in the carcinogenesis, the pathogenesis of colorectal cancer is still not clear [22-24]. For the treatment of colorectal cancer, there is still lack of effective method to improve patients' survival [25-27]. The identification of prognostic factors in colorectal cancer patients is essential to aid selection of patients likely to respond to therapy, which can further rationalize treatments and improve the outcomes [28]. In present meta-analysis, there is some evidence for telomere length as a prognostic factor for overall survival in colorectal cancer patients, which suggests that telomere length is a promising biomarker for rationalizing treatments and improving patients' survival.

Telomeres are the DNA sequences at the ends of linear chromosomes and it consists of a large number of TTAGGG tandem repeats in the leading strand [29]. Telomerase is an enzyme that is mainly expressed in stem cells and cancer cells, and it can compensate for telomere shortening during DNA replication and keep the telomere length. In physiological conditions, most somatic cells suffer from gradually shortening of telomere by 15–50 bp each year due to the lack of telomerase activity [30, 31]. However, abnormal alteration of telomere length can cause chromosome instability and result in subsequent carcinogenesis. The associations of telomere length with cancer development and progression have been well investigated. In addition, patients with long telomere length usually have advanced stages of cancer, which indicates that long telomere length is also a biomarker of more progression in colorectal cancer [6, 11, 32, 33]. Considering the important role of telomere length above, it has the potential to be a good biomarker in predicting patients' survival.

Previous studies have also shown that short telomere can accelerate the senescence of cells, including immune cells [34]. In addition, telomere length may serve as an indicator of immune response capacity and cell replication history, and accelerated telomere erosion is associated with telomere length may have declining immune functions, and thus have shorter survival time [34]. However, the biological mechanism underlying the effects of telomere length on the prognosis of cancer patients remains to be elucidated in future studies.

Several limitations should be considered when interpreting the findings from the meta-analysis. Firstly, there were only 7 individual studies included into the meta-analysis, which may result in high risk of bias. More prospective cohort studies are needed to provide a more precise assessment of the association between telomere length and overall mortality in colorectal cancer patients. Secondly, some studies didn't report the adjusted risk estimates in assessing the prognostic role of telomere length in colorectal cancer. Future studies need to further assess the independent prognostic role of telomere length in colorectal cancer by adjusting for known confounding factors. Finally, our meta-analysis only focused on the association between telomere length and overall mortality in colorectal cancer patients, but we didn't assess the association between telomere length and disease free survival. Currently, there were limited studies published to assess the association between telomere length and disease free survival in colorectal cancer patients. More studies are needed in the future to further assess the association between telomere length and disease free survival in colorectal cancer patients.

In summary, there is some evidence for telomere length as a prognostic factor for overall survival in colorectal cancer patients. More studies with large number of participants are needed to further assess the prognostic significance of telomere length in colorectal cancer patients.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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