The association between telomere length and cancer risk in population studies

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Telomeres are crucial in the maintenance of chromosome integrity and genomic stability. A series of epidemiological studies have examined the association between telomere length and the risk of cancers, but the findings remain conflicting. We performed literature review and meta-analysis to demonstrate the relationship between telomere length and cancer risk. A total of 23,379 cases and 68,792 controls from 51 publications with 62 population studies were included in this meta-analysis to assess the association between overall cancer or cancer-specific risk and telomere length. General association and dose-response relationship were evaluated based on two and three groups, respectively. The estimates of association were evaluated with odds ratios and 95% confidence intervals by the random-effects or fixed-effects model based on heterogeneity test. We observed a non-significant association between short telomeres and overall risk of cancer. Convincing evidence was observed for the association of short telomeres with an increased risk of gastrointestinal tumor and head and neck cancer. Significant dose-response associations were also observed for gastrointestinal tumor and head and neck cancer. Our findings indicate that telomeres may play diverse roles in different cancers, and short telomeres may be risk factors for the tumors of digestive system.

Telomeres consist of several thousand DNA repeats of TTAGGG in association with a protein complex at the ends of chromosomes in eukaryotic cells. Telomeres maintain chromosome integrity and genomic stability through prohibiting nucleolytic degradation, chromosomal end-to-end fusion and irregular recombination. In humans, the average telomere length ranges from 10 to 15 kb, and telomeric DNA shortens during each cell replication at a rate of 50–200 bp. In general, a critically short telomere length can trigger cell to enter replicative senescence with a result of cell death; alternatively, cells continue to divide if death does not occur, which results in genomic instability and chromosomal abnormality. Therefore, telomere length acts as a mitotic clock for eukaryotic cells, and potentially represents the number of cell replications undertaken by each cell during its lifespan.

Telomeres are strongly correlated between tissues, and the rates of telomere shortening are also similar. Telomere length in leukocytes is considered as useful surrogate for the other tissues. Numerous epidemiological studies have focused on analyzing the telomere length in peripheral blood cells in relation to various diseases, including multiple cancers. However, the reported findings are conflicting. In 2011, two meta-analysis pooling more than 20 studies reported that the short telomeres were associated with increased cancer risk. They also found particularly strong evidence for bladder, esophageal, gastric, and renal cancers, but the study numbers were limited for each cancer type. Afterwards, emerging studies with relatively large sample size investigated the association between telomere length and cancer risk. However, the findings are still conflicting other than conclusive, particularly for different cancer types. Nevertheless, more and larger studies may allow for stronger statistical power for meta-analysis, especially for single cancer type. Herein, we carried out a systematic review and meta-analysis on 56 relevant literatures to estimate the overall cancer risk or cancer-specific risk associated with telomere length and to evaluate potential between-study heterogeneity of these studies.

Materials and Methods

Search strategy and selection criteria. We conducted a literature review using PubMed to identify reports on an association between telomere length and cancer risk through May 31, 2015. The search terms

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were “telomere length”, “cancer” or “carcinoma”, and “risk”. We limited the publication language to English. The criteria included: 1) a case–control or cohort study design assessing the relationship between telomere length and cancer risk; 2) sufficient information for estimating odds ratios (ORs) and their 95% confidence intervals (CIs); 3) without overlap between studies in terms of study subjects.

Data extraction. The following data was extracted from each publication: the first author, year of publication, country, ethnicity, cancer type, the number of cases and controls grouped by median, tertiles, quartiles or quintiles of relative telomere length (T/S ratio), study design, DNA source, and method for telomere length measurement. Data was extracted separately for studies including subjects from different ethnicities, multiple cancer types or independent populations if possible. Because controls were shared for multiple cancers in two publications, each publication was divided into multiple studies in the cancer-specific analysis but treated as one study by pooling all cancer cases together as compared with shared controls. When multiple publications had the same or overlapping subjects, only the largest or latest studies were included.

Quantitative data synthesis. To simplify the analysis, we firstly collected the number of cases and controls from two groups (short and long) divided by the median telomere length for each study to evaluate the association. Because some studies reported data in three or five groups based on tertile or quintile value, we treated the groups of “Q1 and Q2” or “Q1, Q2 and Q3” as the short groups, respectively, and the other groups as the long groups. In the sensitivity analysis, we also performed analysis by dividing the subjects into three groups (short, medium and long). We combined Q2 and Q3 groups as the medium group for studies including four groups (Q1, Q2, Q3, Q4), and combined Q1 and Q2 groups as the short group, and Q4 and Q5 groups as the long group for studies including five groups (Q1, Q2, Q3, Q4, Q5). Two publications providing the numbers of two groups only were excluded in this analysis. The association between the telomere length and cancer risk was examined by ORs and 95% CIs with the group of long telomeres as the reference. We performed cancer-specific analysis by cancer type and the cancer types reported in less than 3 studies were merged into the “other types of cancer” group. Gastrointestinal tumor included those diagnosed in the stomach, esophagus, colon or rectum. Cancers arising from the bladder, kidney and prostate sites were considered tumors of the urogenital system. We also performed analysis by study type (retrospective and prospective) and ethnicity (Caucasian, Asian or African American).

We obtained the telomere length data from 51 publications consisting of 23,379 cases and 68,792 controls. When pooling all eligible studies into the meta-analysis, we found a non-significant association between short telomeres and an increased risk of overall cancer risk (OR = 1.10, 95% CI: 0.98–1.23, Table 2). The directions of association were consistent among three populations from different descents (ORs = 1.08, 1.15 and 1.22 for Caucasian, Asian and African American, respectively, Table 2). The results of analysis for subgroups of different ethnicities have been shown in Table S2. However, the association was disappeared in prospective studies (OR = 1.02, 95% CI: 0.87–1.19). Moreover, we also excluded three prospective studies recruited subjects from populations of Caucasian descent, 10 studies of Asian descent, and one study of African American descent. The quantitative PCR was used to measure the relative telomere length (T/S ratio) in 55 studies, whereas fluorescence in situ hybridization (FISH)-based assays were used in 7 studies. Additionally, blood cells were main DNA source except one study based on circulating cell-free serum DNA.

Quantitative Synthesis. The χ²-based Q test was performed to evaluate between-study heterogeneity and considered significant if P < 0.10. Heterogeneity was also quantified with the I² statistic that indicates what proportion of the total variation across studies is beyond chance. The value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity. The fixed-effects model and the random-effects model were used to pool the data from different studies based on the Mantel-Haenszel method and the DerSimonian and Laird method, respectively. When the P value of the heterogeneity test was > 0.10, the fixed-effects model was used, which assumes the homogeneity of effect size across all studies. Elsewhere the random-effects model was more appropriate, which tends to provide wider confidence intervals, when the results of the constituent studies differ among themselves. Potential publication bias was evaluated with funnel plots of effect sizes versus standard errors. Begg's test was used to examine the significance of asymmetry at a significance value of 0.10. All analysis was conducted by using Review Manage (v.5.3) and R3.0.1.

Results Characteristics of Studies. A total of 56 publications were identified with an evaluation of the association between telomere length and cancer risk (Fig. 1). Five reports were excluded because they did not provide the numbers of cases and controls grouped by the relative telomere length. The remaining 51 publications contained 62 studies (Xifeng Wu's study had datasets of four different cancers; Gabriella M. Anic's studies had three datasets of different cancers and Geyu Liang's, Beatriz Sanchez-Espiridion's, and Yang Zhang's studies had two datasets of different cancers, and Jonathan N. Hofmann had two datasets of independent populations. We summarized the general information of these 62 studies in Table 1. There were 10 studies for skin cancer, and tumors of urogenital system, 9 for gastrointestinal tumor, 8 for breast cancer, 8 for lung cancer, 4 for head and neck cancer, 3 for lymphoma, and 10 for the other types of cancer.

Of interest, in prospective studies rather than retrospective studies, short telomeres were associated with an increased risk of lung cancer in prospective studies rather than retrospective studies, short telomeres were associated with an increased risk of lung cancer.
cancer (OR = 0.78, 95% CI: 0.67–0.91). There was no obvious evidence supporting the association for the other cancer types (Table 2).

To evaluate the robustness of pooling results based on dichotomized telomere length, we further divided the cases and controls into three respective groups for each study, and tested the dose-response relationship between telomere length and cancer risk by pooling the studies together. We observed a significant increased risk of overall cancer for short telomeres with a trend OR (95% CI) of 1.09 (1.01–1.19) (Table 3). In cancer-specific analysis, dose-response effects of telomere length were also detected on gastrointestinal tumor (OR = 1.29, 95% CI: 1.08–1.54), and head and neck cancer (OR = 2.30, 95% CI: 1.74–3.02), which were consistent with the above results based on dichotomized telomere length (Table 3).

Heterogeneity analyses. Substantial heterogeneity was observed among all studies for the association between telomere length and cancer risk (P < 0.001, I² = 90%, Fig. 2). We then evaluated the potential source of heterogeneity and found significant effect difference between subgroups for cancer type (P < 0.001), study design (P = 0.008), and ethnicity (P < 0.001).

Publication bias. The shape of the funnel plot seemed symmetrical (Fig. 3), and the Begg’s test did not show a significant publication bias in the current meta-analysis (P = 0.142). These indicated that bias from publications might not have a significant influence on the results of our meta-analysis on the association between telomere length and cancer risk.

Discussion
In this study, we performed the largest and most comprehensive literature review and meta-analysis on the association of telomere length and cancer risk, including a total of 23,379 cancer cases and 68,792 controls from 51 independent publications. We did not find significant association between telomere length and overall risk of cancers, but showed a robust association with gastrointestinal tumor and head and neck cancer. In addition, we also observed promising association of short telomeres with a decreased lung cancer risk in the prospective studies. Furthermore, dose-response relationships provided further evidence for the associations with gastrointestinal tumor, and head and neck cancer.

Telomeres are specialized structures that protect chromosome ends and participate in a number of processes of a great cellular relevance, which makes the telomere crucial in cellular senescence and carcinogenesis. Progressive telomere shortening occurs with each cell division up to a point termed “replicative senescence” in most human somatic cells. Basic biology studies have established that telomere shortening is a fundamental feature of dividing cells and directly related to the age of the cell lineage, and that telomere crisis in the present of defective cell-cycle control can lead to chromosomal instability and a malignant phenotype. The dysfunctional
| Author [reference] | Country  | Year | Cancer type         | Ethnicity | No. of case/control | Study type            | Control source      | DNA source          | Measurement methods               |
|-------------------|----------|------|---------------------|-----------|---------------------|-----------------------|---------------------|---------------------|-------------------------------|
| Gabriella M. Anic et al., melonoma11,14 | USA | 2013 | melanoma            | Caucasian | 198/372             | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Gabriella M. Anic et al., BCC14 | USA | 2013 | basal cell carcinoma | Caucasian | 185/372             | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Gabriella M. Anic et al., SCC11,14 | USA | 2013 | squamous cell carcinoma | Caucasian | 136/372             | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Hongmei Nan et al.12 | USA | 2011 | cutaneous melanoma  | Caucasian | 557/579             | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Jiali Han et al., melonoma13 | USA | 2009 | melanoma            | Caucasian | 204/222             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Jiali Han et al., SCC13 | USA | 2009 | squamous cell carcinoma | Caucasian | 254/273             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Jiali Han et al., BCC13 | USA | 2009 | basal cell carcinoma | Caucasian | 282/306             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Geyu Liang et al., SCC14 | USA | 2011 | squamous cell carcinoma | Caucasian | 241/241             | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Geyu Liang et al., BCC14 | USA | 2011 | basal cell carcinoma | Caucasian | 623/1943            | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Laura S. Burke et al.15 | USA | 2013 | melanoma            | Caucasian | 119/208             | retrospective          | family-based       | whole blood or EBV-transformed lymphocytes | quantitative PCR             |
| Xiexing Wu et al., RCC16 | USA | 2003 | renal cell carcinoma | Caucasian | 32/32               | retrospective          | population-based   | leukocyte            | Q-FISH             |
| Xiexing Wu et al., BLC16 | USA | 2003 | bladder cancer      | Caucasian | 135/135             | retrospective          | population-based   | leukocyte            | Q-FISH             |
| Lisa Mirabello et al.17 | USA | 2009 | prostate cancer     | Caucasian | 612/1049            | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| B Julin et al.18 | USA | 2015 | prostate cancer     | Caucasian | 922/935             | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Lauren M. Hurwitz et al.19 | USA | 2014 | prostate cancer     | Caucasian | 112/63              | retrospective          | family-based       | leukocyte            | quantitative PCR             |
| Jonathan N. Hofmann et al.20 | USA | 2013 | renal cell carcinoma | Caucasian | 209/410             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Jonathan N. Hofmann et al., Caucasian21 | USA | 2011 | renal cell carcinoma | Caucasian | 658/550             | retrospective          | population-based   | whole blood           | quantitative PCR             |
| Jonathan N. Hofmann et al., African American21 | USA | 2011 | renal cell carcinoma | African American | 233/344             | retrospective          | population-based   | whole blood           | quantitative PCR             |
| Monica McGrath et al.22 | USA | 2007 | bladder cancer      | Caucasian | 184/192             | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Karin Broberg et al.23 | Sweden | 2005 | bladder cancer      | Caucasian | 63/93               | retrospective          | population-based   | buccal cell          | quantitative PCR             |
| Andrew J. Pellatt et al.24 | USA | 2012 | colon rectal cancer | Caucasian | 525/746             | retrospective          | population-based   | whole blood           | quantitative PCR             |
| Yong Cui et al.25 | China | 2012 | colorectal cancer   | Asian     | 512/549             | retrospective          | Population-based   | leukocyte            | quantitative PCR             |
| Qin Qin et al.26 | China | 2014 | colorectal cancer   | Asian     | 628/1256            | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Lifang Hou et al.27 | USA | 2009 | gastric cancer      | Caucasian | 300/416             | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Rosa Ana Risques et al.28 | USA | 2007 | esophageal adenocarcinoma | Caucasian | 38/300               | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Qianqian Yu et al.29 | China | 2014 | esophageal squamous cell carcinoma | Asian | 308/309             | retrospective          | hospital-based     | lymphocyte           | quantitative PCR             |
| Jiangbo Du et al.30 | China | 2015 | gastric cancer      | Asian     | 1136/1102           | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Xiaonian Liu et al.31 | China | 2009 | gastric cancer      | Asian     | 396/576             | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Jinliang Xing et al.32 | China | 2009 | esophageal cancer   | Caucasian | 94/92               | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Maria M. Gramatges et al.33 | USA | 2010 | breast cancer       | Caucasian | 102/50              | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Andrew J. Pellatt et al.34 | USA | 2013 | breast cancer       | Caucasian | 728/720             | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Jing Shen et al.35 | USA | 2009 | breast cancer       | Caucasian | 1026/1078           | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Immaculata De Vivo et al.36 | USA | 2009 | breast cancer       | Caucasian | 896/917             | retrospective          | population-based   | leukocyte            | quantitative PCR             |
| Sangmi Kim et al.37 | USA | 2011 | breast cancer       | Caucasian | 342/735             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Jing Shen et al.38 | USA | 2007 | breast cancer       | Caucasian | 283/347             | retrospective          | family-based       | leukocyte            | quantitative PCR             |
| Yun-Ling Zheng et al.39 | USA | 2010 | breast cancer       | Caucasian | 292/335             | retrospective          | population-based   | leukocyte            | Q-FISH             |
| Shimian Qu et al.40 | USA | 2012 | breast cancer       | Asian     | 601/695             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Xiexing Wu et al., LC16 | USA | 2003 | lung cancer         | Caucasian | 54/54               | retrospective          | population-based   | leukocyte            | Q-FISH             |
| Min Shen et al.41 | USA | 2011 | lung cancer         | Caucasian | 230/229             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Qing Lan et al.42 | USA | 2013 | lung cancer         | Asian     | 215/215             | prospective           | population-based   | leukocyte            | quantitative PCR             |
| Beatriz Sanchez-Espiridion et al., LAC20 | USA | 2014 | lung adenocarcinoma | Caucasian | 706/706             | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Beatriz Sanchez-Espiridion et al., LSCC24 | USA | 2014 | lung squamous cell carcinoma | Caucasian | 320/320             | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Wei Jie Seow et al.44 | USA | 2014 | lung cancer         | Caucasian | 847/847             | prospective           | Population-based   | leukocyte            | quantitative PCR             |
| Bing Sun et al.45 | USA | 2015 | lung cancer         | Caucasian | 191/207             | retrospective          | Population-based   | hospital-based     | lymphocyte            | Q-FISH             |
| Jin Sung Iang et al.46 | Korea | 2008 | lung cancer         | Asian     | 243/243             | retrospective          | hospital-based     | leukocyte            | quantitative PCR             |
| Yang Zhang et al., OCC15 | USA | 2013 | oral cavity cancer  | Caucasian | 137/335             | retrospective          | hospital-based     | lymphocyte            | quantitative PCR             |
| Yang Zhang et al., OPC24 | USA | 2013 | oropharyngeal squamous cell carcinoma | Caucasian | 188/335             | retrospective          | hospital-based     | lymphocyte            | quantitative PCR             |

Continued
Telomeres will result in chromosomal fusions, continuous “breakage-fusion-bridge” cycles, derived chromosome imbalances, gene amplifications, and ultimately the generation of complex non-reciprocal translocations, a hallmark feature of adult solid tumors and genomic instability in general \(^{24}\). At the population level, the high incidence of cancer has prompted that shortening of telomeres promotes tumor development and several studies have found that patients with shorter telomeres in peripheral blood cells have a higher risk of developing carcinomas \(^ {25}\). In this meta-analysis, although we found there is no significant association between telomere length and overall risk of cancers, but we demonstrated a significant association with gastrointestinal tumor and head and neck cancer, supporting the hypothesis that excessive telomere shortening may play an important role in accelerating tumor onset and progression. Gastrointestinal tumor and head and neck cancer is kind of epithelial malignancies in digestive system. The majority of epithelial malignancies appear to develop from morphologically defined precursor lesions termed intraepithelial neoplasia \(^ {26}\). Telomere length in more than 90% intraepithelial neoplasia is dramatically shortened \(^ {27}\). In addition, telomeres of gastrointestinal tumor may exhibit an intensified rate of shortening that is greatly accelerated as compared to the normal tissue of origin \(^ {28}\).

However, our results revealed heterogeneous association results between different cancer types. Short telomeres were convincingly associated with increased risk of gastrointestinal tumor and head and neck cancer, which, however, was not observed in other types of cancer. Of note, a significant but inverse association was shown for lung cancer in prospective studies. These inconsistent results across cancer types may reflect different carcinogenic mechanisms conferred by specific telomeres in specific cancer types. For example, several studies \(^ {29},^{30}\) found a higher risk for melanoma among individuals with longer telomeres, this may suggest that shorter telomere lengths protect against the malignant transformation of cells within melanocytic nevi by limiting proliferative capacity and triggering the entry to senescence stage. To the contrary, longer telomeres were found to be protective for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with the reason of that UV exposure may be more likely to induce genomic abnormalities in cells with shorter telomeres. In addition, Sanchez-Espiridion \( et al. \) \(^ {31}\) found that patients with lung adenocarcinoma had longer telomeres than controls, whereas patients with lung squamous cell carcinoma had shorter telomeres compared with controls. These findings suggest that telomere length may affect cancer risk in a histologic manner, further highlighting the distinct roles of telomere in cancer development.

Table 1. Information summary of 51 eligible studies included in this meta-analysis. *The controls were shared for different cancer types in the same publication.

In addition to the cancer-specific associations, telomere length may also involve in cancer risk in a complex manner rather than a simple linear relationship. Cui \( et al. \) \(^ {32}\) reported a U-shaped association between telomere length in peripheral blood cells and colorectal cancer (CRC) risk, and they found that both very short and very long telomeres are risk factors for colorectal cancer. Recently, we also reported a non-linear relationship between telomeres and gastric cancer risk \(^ {33}\). Similar results were also reported in pancreatic cancer \(^ {44}\), breast cancer \(^ {35}\) and glioma \(^ {36}\). These observations are also biologically plausible because telomeres may act as a double-edged sword in the development of cancer. Telomere shortening can generally lead to chromosomal instability and finally initiate the process of carcinogenesis \(^ {37}\). However, long telomeres may allow for more cell divisions and increase the chance of acquiring abnormalities for cancer development \(^ {38}\). However, due to lack of original data, we cannot evaluate this phenomenon in this study. Further studies are warranted to carefully test these findings.
There are some limitations in this meta-analysis. Firstly, some factors can affect the length of telomeres, such as age, gender, and tobacco smoking, and oxidative stress. The results of this meta-analysis were based on unadjusted estimates, because odds ratios (ORs) derived from different studies were not adjusted by the same potential confounders or only the number of cases and controls was provided without the detailed information of other variables. Secondly, we performed analysis by dividing the subjects into two or three groups simply due to lack of original data of relative telomere length, which may decrease the power to evaluate the relationship of telomere length and overall risk of cancers. In the main analysis of this study, we treated the groups of "Q1 and Q2" (for three groups) or "Q1, Q2 and Q3" (for five groups) as the short groups, and the other groups as the long groups. To address the stability of the results, we also treated the groups of "Q1" (for studies with three groups) or "Q1, and Q2" (for studies with five groups) as the short groups and the other groups as the long groups, and found that the results were similar (OR = 1.08, 95% CI: 0.96–1.22 for overall cancer risk).

In summary, our meta-analysis provided strong evidence for the association between short telomeres and increased risk of gastrointestinal tumor and head and neck cancer. In addition, the short telomeres also increased, although not significantly, the risk of overall cancer in the analysis of dichotomized variable, this association

| Groups                  | Numbers                  | Heterogeneity | Associations (short vs. long) |
|-------------------------|--------------------------|---------------|------------------------------|
|                         | Study Case/Control      | P             | OR(95% CI)                   | P               |
| Overall                 | 62 23379/68792           | <0.001        | 1.10(0.99–1.23)             | 0.09            |
| Populations             |                          |               |                              |                 |
| Caucasian               | 51 18727/63183           | <0.001        | 1.08(0.97–1.21)             | 0.18            |
| Asian                   | 10 4419/5265             | <0.001        | 1.15(0.78–1.68)             | 0.49            |
| African American        | 1 233/344                |               | 1.22(0.88–1.71)             | 0.23            |
| Study design            |                          |               |                              |                 |
| Prospective             | 16 7925/48662           | <0.001        | 1.02(0.87–1.19)             | 0.80            |
| Retrospective           | 46 15454/20130          | <0.001        | 1.14(0.98–1.33)             | 0.10            |
| Populations             |                          |               |                              |                 |
| Caucasian               | 51 18727/63183           | <0.001        | 1.09(0.97–1.21)             | 0.18            |
| Asian                   | 10 4419/5265             | <0.001        | 1.15(0.78–1.68)             | 0.49            |
| African American        | 1 233/344                |               | 1.22(0.88–1.71)             | 0.23            |

Table 2. Summary of meta-analysis results for associations between telomere length and cancer risk.

There are some limitations in this meta-analysis. Firstly, some factors can affect the length of telomeres, such as age, gender, and tobacco smoking, and oxidative stress. The results of this meta-analysis were based on unadjusted estimates, because odds ratios (ORs) derived from different studies were not adjusted by the same potential confounders or only the number of cases and controls was provided without the detailed information of other variables. Secondly, we performed analysis by dividing the subjects into two or three groups simply due to lack of original data of relative telomere length, which may decrease the power to evaluate the relationship of telomere length and overall risk of cancers. In the main analysis of this study, we treated the groups of "Q1 and Q2" (for three groups) or "Q1, Q2 and Q3" (for five groups) as the short groups, and the other groups as the long groups. To address the stability of the results, we also treated the groups of "Q1" (for studies with three groups) or "Q1, and Q2" (for studies with five groups) as the short groups and the other groups as the long groups, and found that the results were similar (OR = 1.08, 95% CI: 0.96–1.22 for overall cancer risk).

In summary, our meta-analysis provided strong evidence for the association between short telomeres and increased risk of gastrointestinal tumor and head and neck cancer. In addition, the short telomeres also increased, although not significantly, the risk of overall cancer in the analysis of dichotomized variable, this association...
Figure 2. ORs and 95% CIs for cancer risk associated with telomere length (short vs. long).

### Table 3. Dose-response relationship between telomere length and cancer risk by cancer type.

| Cancer type                  | Numbers | Heterogeneity | OR (95% CI) | OR (95% CI) |
|------------------------------|---------|---------------|-------------|-------------|
| **Overall**                  | 59      | <0.001        | 1.09 (1.01–1.19) | 0.037       |
| **Skin cancer**              | 10      | <0.001        | 1.11 (0.83–1.49) | 0.496       |
| **Tumors of urogenital system** | 10      | <0.001        | 1.15 (0.97–1.37) | 0.113       |
| **Gastrointestinal tumor**   | 8       | <0.001        | 1.29 (1.08–1.54) | 4.24E-03     |
| **Breast cancer**            | 8       | <0.001        | 0.96 (0.83–1.11) | 0.403       |
| **Lung cancer**              | 8       | <0.001        | 1.11 (0.86–1.42) | 0.415       |
| **Head and neck cancer**     | 2       | 0.284         | 2.30 (1.74–3.02) | 2.85E-09     |
| **Lymphoma**                 | 3       | <0.001        | 0.89 (0.53–1.38) | 0.970       |
may be influenced by the study numbers of different tumors because the effects are different between tumors. However, larger, well-designed prospective studies are needed to validate these findings, which may help to uncover the potential mechanisms of telomere dysfunction in cancer development.

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Figure 3. Funnel plot analysis to detect publication bias.
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Author Contributions
G.J. and X.Z. conceived and designed the study; X.Z., W.H. and W.X. reviewed the literature, extracted the data, and performed analysis. Y.Z., C.X. and J.D. reviewed the literature and checked the data; G.J. and X.Z. wrote and revised the manuscript. All authors reviewed and approved the manuscript prior to submission.

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