ASSOCIATION OF TELOMERE LENGTH WITH COLORECTAL CANCER RISK AND PROGNOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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BACKGROUND

- Telomeres, the ends of the eukaryotic chromosomes, maintain chromosomal stability and induce cellular senescence. (**Figure 1**)
- Telomere length has been shown to be associated with colorectal cancer (CRC) initiation and progression.

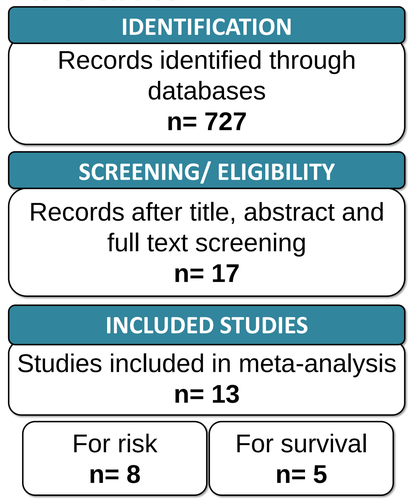
Figure 1. *Ref. Doksani, Genes (Basel), 2019*

METHODS

Study selection: Following the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines, we searched Medline, Embase and Web of Science databases through April 2020 using these Medical Subject Headings (MeSH): 'Colorectal Neoplasms' AND 'Telomere' AND ('Survival' OR 'Disease Progression' OR 'Risk'). (**Figure 2**)

Statistical analysis: We extracted odds ratios or hazard ratios (OR/ HR and 95% CI) from included studies. Because there was substantial heterogeneity in how telomeres were quantified, we converted all reported associations to a unified scale assuming a Gaussian distribution. Specifically, we compared shortest quartile (Q1) vs longest quartile (Q4) of telomere length for CRC risk, and Q1 vs Q2-Q4 for CRC survival. We performed a random effects meta-analysis, and assessed inter-study heterogeneity with Cochrane's Q, I^2 and τ^2. Funnel plots were calculated to assess potential publication bias.

Figure 2. *PRISMA flow chart of filtered studies.*



OBJECTIVE

To conduct a systematic review and meta-analysis of the association between (1) telomere length in circulating leukocytes and CRC risk; and (2) telomere length in circulating leukocytes or cancer tissue and CRC survival.

RESULTS

Table 1. *Studies included in risk and survival meta-analysis of telomere length and CRC.*

Author, Year	Specimen	TL[1] method	TL category	Reported OR/ HR (95% CI)	Calculated OR/ HR (95% CI)
Risk studies					*Quartile 4vs1*
Zee R.Y.L., 2009	PBL[2]	RTL[3]	Continuous	1.3 (0.9-1.8)	1.4 (0.8-2.2)
Lee I-M., 2010	PBL	RTL	Continuous	0.9 (0.7-1.4)	0.9 (0.5-1.8)
Pooley K.A., 2010	PBL	RTL	Quartile 4vs1	1.1 (0.5-2.4)	0.9 (0.4-1.9)
Cui Y., 2012	PBL	RTL	Quintile 1vs3	1.6 (0.9-2.6)	1.0 (0.6-1.7)
Boardman L., 2014	PBL	RTL	Percentile 10vs50	1.9 (1.1-3.4)	0.6 (0.2-1.6)
Qin Q., 2014	PBL	RTL	Shorter vs longer	1.3 (1.1-1.6)	0.7 (0.5-0.9)
Fernandez-R.C., 2018	PBL	RTL	Continuous	1.0 (0.9-1.1)	1.0 (0.9-1.1)
Luu H.N., 2019	PBL	RTL	Quartile 4vs1	1.3 (1.1-1.6)	1.3 (1.1-1.6)
Survival studies					*Quartile 1vs2-4*
Chen Y., 2014	PBL	RTL	Tertile 1-2vs3	2.4 (1.5-3.5)	2.6 (1.7-4.0)
Svenson U., 2016	PBL	RTL	Quartile 1vs2-4	0.5 (0.2-1.8)	0.5 (0.2-1.8)
Gertler R., 2004	Tissue	TRF[4]	Quartile 4vs1-3	3.3 (1.2-9.0)	0.3 (0.1-0.8)
Valls C., 2010	Tissue	TRF	Quartile 4vs1-3	2.4 (1.2-5.0)	0.4 (0.2-0.8)
Suraweera N., 2016	Tissue	RTL	Continuous	1.0 (0.8-1.3)	1.0 (0.7-1.5)

[1]TL telomere length; [2]PBL Peripheral blood leukocytes; [2]RTL Relative telomere length by quantitative PCR method; [3]TRF Telomere restriction fragment by luminescence method

Figure 3. *Forest plot of random effects model for TL and CRC risk.*

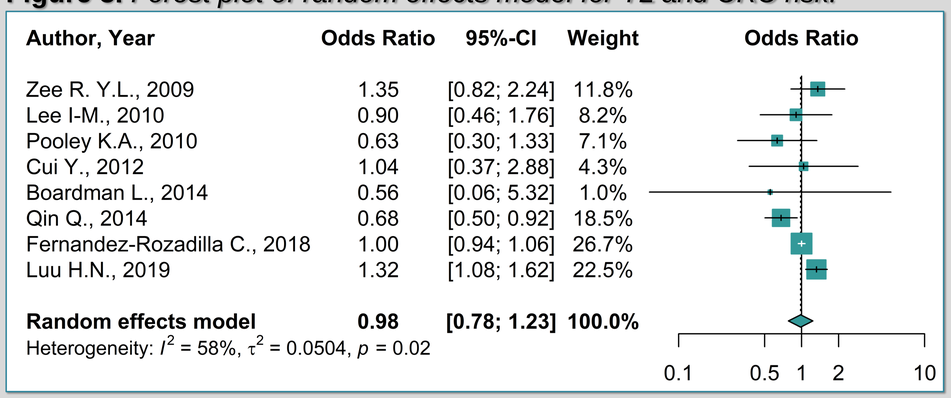


Figure 4. *Forest plot of random effects model for TL and CRC survival with subgroup analyses by specimen type (PBL Peripheral blood leukocytes and cancer tissue).*

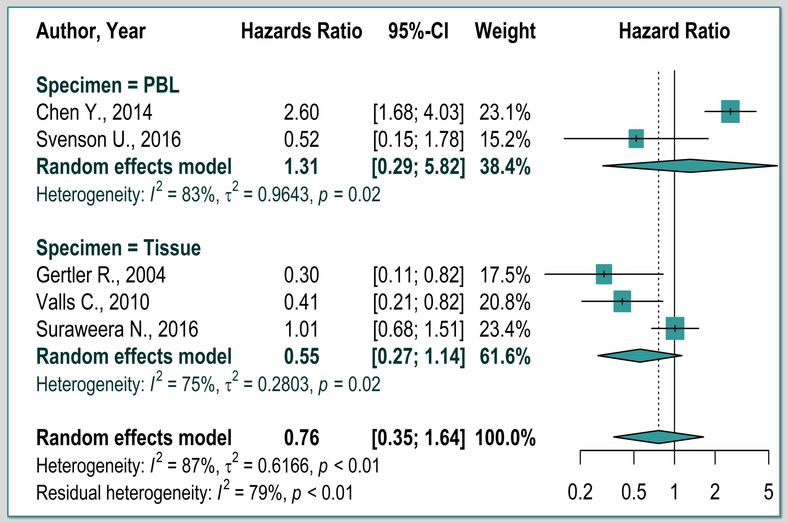
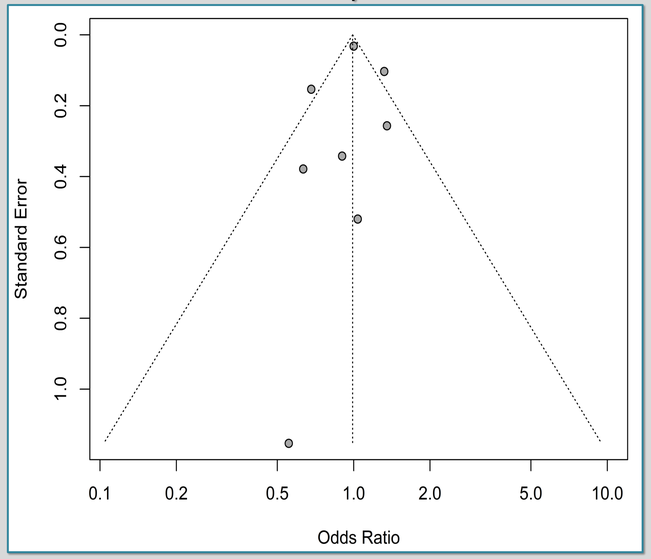


Figure 5. *Funnel plot of random effects model for TL and CRC risk to assess potential bias.*



CONCLUSIONS

- Our meta-analysis of circulating telomere length and CRC risk showed no association.
- In the meta-analysis of survival studies, shorter telomeres in circulating leukocytes and longer telomeres in tumors were associated with poorer survival, though statistically non-significant.
- Larger prospective studies evaluating telomere length in CRC survival are needed.
- Studies of telomere length would benefit from a uniform set of mandatory reporting guidelines for measurement and analysis, to decrease heterogeneity among telomere-related studies and make results easier to compare and combine.

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