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Review

Epidemiologic evidence for a role of telomere dysfunction in cancer etiology

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ABSTRACT

Telomeres, the dynamic nucleoprotein structures at the ends of linear chromosomes, maintain the genomic integrity of a cell. Telomere length shortens with age due to the incomplete replication of DNA ends with each cell division as well as damage incurred by oxidative stress. Patterns of telomere shortening, genomic instability, and telomerase expression in many cancer tissues compared to adjacent normal tissue implicate telomere crisis as a common crucial event in malignant transformation. In order to understand the role of telomere length in cancer etiology, most epidemiologic studies have measured average telomere length of peripheral blood or buccal cell DNA as a surrogate tissue biomarker of telomere dysfunction and cancer risk. In this review, we present the results from epidemiologic investigations conducted of telomere length and cancer risk. We note differences in reported associations based on study design, which may be due to biases intrinsic to retrospective studies. Finally, we conclude with study design considerations as future investigations are needed to elucidate the relationship between telomere length and a number of cancer sites.

Contents

1. Introduction

Telomeres are specialized dynamic nucleoprotein structures that maintain the structural integrity of chromosomes [1]. At birth, human telomeres are typically 10–15 kilobases (kb) in length with substantial inter-individual heterogeneity [2]. However, due to the inability of DNA polymerase to completely synthesize the daughter strand at chromosomal ends (a.k.a. the "end replication problem"), telomeric DNA is lost with each cell division [3]. On average, human telomeres lose 50–100 base pairs per mitotic division, limiting the replicative capacity of a cell [4].

The rate of telomere loss may be modified by factors other than the mitotic replication rate. Due to the high G–C content and long stretches of repetitive DNA, it is thought that telomeres suffer disproportionately higher rates of damage by oxidative stress

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compared to nontelomeric sequences. Single-stranded breaks of telomeric DNA caused either directly by reactive oxygen species or indirectly as part of the DNA repair process are not as efficiently repaired. In contrast, experimental evidence suggests antioxidants reduce telomere shortening rates *in vitro* [5,6]. Systemic exposures that contribute to oxidative stress and age-related diseases such as smoking [7–9] and obesity [9–13] have been associated with shorter telomeres in white blood cells. Whereas, healthy lifestyle choices has been hypothesized to promote a more stable telomere length [12,14,15], presumably through enhanced antioxidative capability [5]. Thus, telomere length has been proposed as an indicator of biological age (somatic fitness) rather than chronological age [16].

1.1. Tumor suppressor hypothesis

The progressive loss of telomeric DNA reduces the chromosome's ability to form functional capped telomere structures [17]. When telomeres shorten to a critical length, they become dysfunctional and trigger a DNA damage response presumably by exposing chromosome ends, which resemble double-stranded DNA breaks. Coordinated efforts between the DNA repair machinery and cell cycle checkpoint proteins decide whether to induce a state of permanent growth arrest (senescence) or programmed cell death (apoptosis) [18].

Replicative cellular senescence induced by telomere erosion has been proposed as a tumor suppressor mechanism. Placing a limit on the proliferative capacity of a cell prevents the accumulation of somatic mutations that promote carcinogenesis [19]. Oxidative stress not only increases the rate of telomere loss, it also increases the risk of acquiring oncogenic mutations. Thus, the cells most likely to undergo malignant transformation are stopped from replicating [5].

1.2. Carcinogenesis hypothesis

Cellular senescence is believed to have an antagonistic pleiotropic effect where natural selection drives a trait or process to become more common because it improves the survival or reproductive fitness of a young organism. However, as the force of natural selection declines with age, that same trait or process may have deleterious consequences in the aged organism [19]. Senescent cells no longer divide, but can remain viable and metabolically active for years [1]. Factors secreted by senescent cells such as metalloproteases, inflammatory cytokines and growth factors disrupt the function and integrity of surrounding tissue [19]. The proportion of senescent cells increases with age and contributes to the progressive decline in tissue function associated with aging. Parallel to the increase in oncogenic mutations, the probability of a senescent cell residing in close proximity to a preneoplastic cell increases with age. Whereas cellular senescence protects against cancer risk in early life, the accumulation of senescent cells may create a tumorigenic microenvironment that supports and promotes further malignant transformation of preneoplastic cells [20].

In preneoplastic cells, where senescence or apoptosis is delayed, continued proliferation results in further telomere erosion with a concurrent increase in genomic instability. Cell division continues until the cell reaches crisis, a second proliferation block characterized by gross chromosomal aberrations [20]. The vast majority of these cells undergo apoptosis. However, a rare cell may escape through the reactivation of telomerase, which at this stage is thought to facilitate tumor initiation and progression. Reactivation of telomerase is detected in >90% of human tumors, making it one of the most common abnormalities in cancer cells [1].

1.3. Pathologic evidence

Telomere shortening commonly occurs early in cancer progression as noninvasive precursor lesions from a number of different tissue types display shortened telomeres compared to adjacent normal cells [21–24]. Detailed investigations have found that shortening progresses from normal epithelium through stages of hyperplasia/metaplasia, dysplasia, and carcinoma in tissues of the breast [25] and biliary tract [26]. Additionally, chromosomal aberrations dramatically increased and telomerase was reactivated during the transition from usual ductal hyperplasia to ductal carcinoma *in situ* of the breast [25], indicating telomere crisis as a crucial tumor promoting event. Senescent cells have also been observed *in vivo* in association with early phases of tumor development [18].

2. Epidemiologic studies

2.1. Methodology

Given the proposed role of telomere shortening in early processes of carcinogenesis, telomere length has gained considerable interest as a potential biomarker of cancer risk. In an attempt to answer the question of whether telomere length is predictive of cancer risk, a number of retrospective and prospective observational studies have been conducted to estimate the strength of the hypothesized relationship in humans. For definitions of basic epidemiologic terms, see Box 1 .

Retrospective study design. In a retrospective study, patients with the particular cancer of interest are recruited as "cases" along with comparable individuals without the disease known as "controls". Being less expensive and less time-consuming than a prospective study, the retrospective design is an efficient method of investigating exploratory hypotheses particularly for rare cancers. However, these studies are highly susceptible to bias [27]. In the ideal situation, cases are selected from the same underlying population at risk as the controls. To aid in the selection of comparable groups, investigators will often match case and control participants on important confounders, i.e. factors that influence both telomere length and risk for the cancer of interest such as age, sex, and ethnicity. Without taking into account such confounding factors, systematic differences between the case and control groups may generate spurious results in the absence of a true association. In contrast, the opposite may occur in a hospital-based study where hospital patients without the cancer of interest serve as "controls". If telomere length is associated with risk of the ailments for which control patients were admitted to the hospital, and the direction of risk association is that same as that for the cancer of case patients, a true association may be masked. Furthermore, as telomere shortening has been associated with increased mortality [28], the recruitment of prevalent cases may produce invalid results due to survival bias where cancer patients that survive long enough to participate in the study may have longer telomere lengths than those who died. A final important bias to consider when assaying biologic samples is that of reverse causation. That is, rather being a causal factor in carcinogenesis, a biomarker such as short telomere length may occur as a result of the pathophysiological effects of the disease.

Prospective study design. Prospective cohort studies are conducted by enrolling a large, homogenous group of individuals that are then followed over a long period of time to ascertain the occurrence of death and/or disease. The main disadvantages of prospective studies are the cost of following a large number of participants, and the time commitment required for ascertaining an adequate number of cases, particularly for rare diseases such as cancer. However, prospective studies also offer several distinct advantages, especially when biological samples are collected and

Box 1: Basic definitions in epidemiologic research.

Adjustment: a statistical transformation to permit fair comparison between groups that may differ on important risk factors
Case: an individual with the disease or health condition of interest
Cohort: a clearly defined group of individuals followed through the same period of time together
Confidence interval: the range of plausible values for the true population value of the exposure-disease association
Confounding: when the exposure-disease relationship is distorted by the effect of a third factor
Confounding factor: a risk factor for the disease or health condition of interest that is also associated with the exposure under study
Control: an individual without the disease or health condition of interest
Covariate: risk factor included in a statistical analysis to adjust for important differences between comparison groups
Epidemiology: the study of the distribution and determinants of health-related states or events in human populations
Incident: new occurrence of a disease or health condition in the study population
Hazard rate: the rate at which individuals without the disease develop that disease for each instant of time
Hazard ratio: the ratio of the hazard rate among the exposed individuals to that of the unexposed individuals (cohort study)
Hospital-based: a study in which controls are ascertained from hospital inpatients
Matching: process of selecting controls so that they are similar to cases on potentially confounding factors
Observational: an explanatory study where the investigator examines associations without intervention
Odds Ratio: a ratio of the probability of exposure among cases to the probability of exposure among controls (case–control study)
Population-based: a study in which controls are ascertained from the general population
Prevalent: all occurrences (both new and old) of a disease or health condition in the study population
Prospective study: individuals without the disease of interest, some of whom are exposed, are followed for the subsequent onset of disease
Retrospective study: individuals with and without the disease of interest are recruited, then data are obtained on previous exposures
Reverse causation: the exposure occurs as a result of the onset of disease or health condition
Risk factor: an exposure that increases the probability of disease or health condition (e.g., age, smoking, obesity)
Selection bias: systematic error created when the control population is not representative of the population from which the cases arose
Survival bias: patients with milder, longer duration disease are over-represented than patients with aggressive disease in the case group

stored prior to disease development [29]. Such samples provide the means to establish a potential temporal relationship between a biomarker exposure such as short telomere length and subsequent cancer risk. Given the expense of biomarker assays, for such studies investigators generally create a "nested" case–control study population to reduce assay cost. Individuals are randomly selected from the cohort population and matched to cancer cases as controls. Because cancer cases arise from the same surveillance population as controls, selection bias is essentially eliminated. Another advantage of a prospective study is that multiple "nested" case–control studies can be created to examine telomere length associations with development of different cancer types, providing a broader picture for the role of telomeres in cancer risk.

Biospecimen assessment. Most epidemiologic studies have measured average telomere length of peripheral blood or buccal cell DNA as a surrogate tissue biomarker of telomere dysfunction and cancer risk. It is not certain that telomere length in blood or buccal cells accurately reflect telomere length of the target tissue of interest. However, telomere lengths are highly synchronized in fetal tissues [30] and at birth among white blood cells, umbilical artery cells, and skin cells [31]. Studies that have compared telomere length of blood DNA with that of matched skin [32,33], synovial tissue [33], or fibroblasts [34] found that significant correlations are maintained between tissues in older individuals. Inter-individual telomere length variation far exceeds the variation observed between different tissues of the same individual [30,31].

Telomere length has been measured using a variety of techniques including the terminal restriction fragment (TRF) length, quantitative fluorescence *in situ* hybridization (Q-FISH), and quantitative PCR (qPCR)-based assays. For an in depth discussion on the caveats and critical assessment of these techniques, see the accompanying review on telomere length measurement methodology (Aubert, Hills, and Landsdorp). Details of the retrospective and prospective studies on telomere length and cancer risk, including DNA source and measurement technique used, are listed in Tables 1 and 2, respectively. Unless noted otherwise, odds ratios (OR) and confidence intervals (CI) reported below compare individuals in the extreme quartiles of telomere length.

2.2. Retrospective studies of telomere length and cancer risk (Fig. 1)

Bladder cancer. Telomere length as a biomarker of bladder cancer risk has been examined in 2 retrospective case–control studies [35,36] and a case–control study nested within the Nurses' Health Study and Health Professionals Follow-up Study cohorts [37], which included cases diagnosed both before and after blood collection. Using blood or buccal cell DNA and different measurement techniques (Table 1), each study found significantly shorter telomere lengths among bladder cancer patients than controls ($P \leq 0.005$) [35–37]. For individuals with the shortest telomere lengths compared to those with the longest, the Swedish study found a significant 4.5-fold increase in bladder cancer risk [36]. The US study of male and female health professionals observed a weaker, but still statistically significant increased risk (OR = 1.88, 95% CI = 1.05–3.36; $P_{trend} = 0.006$) [37]. Wu et al. [35] combined participants from the bladder cancer case–control study with participants in the lung and renal cell cancer case–control studies. Among this combined group, short telomere length was associated with a statistically significant increased risk of developing 1 of these 3 cancers (OR = 4.41, 95% CI = 2.10–9.28; $P_{trend} = 0.001$).

Breast cancer. To date, breast cancer has had the largest number of published studies investigating telomere length associations with cancer risk. Widely inconsistent results have been reported by the 8 retrospective case–control studies [38–45]. Four studies found no statistically significant associations with overall breast cancer risk [39,40,42,43], 2 observed significant increased risk among women with short telomere lengths [38,44], whereas 2 others found a significant increased risk among women with the longest telomere lengths [41,45].

Of the studies that did not find a significant association with overall breast cancer risk, the Long Island Breast Cancer Study Project included the largest sample size with 1026 *in situ* and invasive breast cancer cases and 1070 matched population-based controls. Short telomere lengths were not associated with overall breast cancer risk. However, when stratified by menopausal status, premenopausal women with short telomere lengths were

Table 1
Details of retrospective studies on telomere length and cancer risk.

Cancer site	Sample size cases/controls	DNA source	Measurement technique[a]	Results	Matching factors	Analysis covariates	Reference
Bladder/Lung/Renal	221/164	Isolated lymphocyte culture	Q-FISH^{LSC}	Short telomeres significantly increase risk	Age, sex, ethnicity	Age, sex, smoking status	[35]
Bladder	63/158	Buccal	qPCR	Short telomeres significantly increase risk	Sex, age, year of study enrollment, residence	Age, sex, smoking status	[36]
	184/192	Buffy coat	qPCR	Short telomeres significantly increase risk	Age, sex, smoking status	Age, sex, smoking status, packyears of smoking	[37]
Breast	18/35	Buffy coat	TRF	Significant difference in peak migration	None	None	[38]
	140/108	Buffy coat	TRF	No significant association	Age, sex, ethnicity	BMI, smoking status	[39]
	287/350	Buffy coat	qPCR	No significant association	Sister controls	Age, smoking status	[40]
	265/300 0/146	Buffy coat or granulocytes	qPCR	Long telomeres significantly increase risk	None	Age	[41]
	1026/1070	Buffy coat	qPCR	No significant association	Age	Age, 15-F_{2t}-IsoP, 8-OxodG	[42]
	152/176	Buffy coat	qPCR	No significant association	Age, race	Age, smoking status, race, alcohol, education, income	[43]
	140/159	Whole blood culture	Q-FISH	No significant association	Age, race, residence		
	2243/2181	Blood (unspecified)	qPCR	Short telomeres significantly increase risk	Age, residence	Age, plate	[44]
	102/50	Whole blood	qPCR	Long telomeres significantly increase risk	Restricted to nonsmokers	Age	[45]
Colorectal	2249/2161	Blood (unspecified)	qPCR	Short telomeres significantly increase risk	Age, sex, residence	Age, sex, plate	[44]
Esophageal	94/94	Whole blood	qPCR	Short telomeres significantly increase risk	Age, sex, ethnicity	Age, sex, smoking status, drinking status, education, physical activity	[46]
Gastric	396/378	Whole blood	qPCR	Short telomeres significantly increase risk	Age, sex, residence	Age, sex, smoking status, drinking status, H. pylori infection	[48]
	300/416	Buffy coat	qPCR	Short telomeres significantly increase risk	Age, sex	Age, sex, smoking status, packyears of smoking	[47]
Head & Neck	92/92	Isolated lymphocyte culture	TRF	Short telomeres significantly increase risk	Age, sex, ethnicity	Age, sex, smoking status	[35]
	20/90	Isolated lymphocytes	TRF	No significant difference in mean length	Age	Age, sex	[49]
Lung	243/243	Buffy coat	qPCR	Short telomeres significantly increase risk	Age, sex, smoking status	Age, sex, packyears of smoking	[51]
	111/99	First morning sputum	qPCR	No significant association	Age, sex, village, cooking/heating fuel	Age, sex, smoking status, lifetime smoky coal exposure	[50]
Non-Hodgkin Lymphoma	40/40	B lymphocytes	FlowFISH	Short telomeres significantly increase risk	Age	None	[52]
Ovarian	18/35	Buffy coat	TRF	No significant difference in peak migration	None	None	[38]
	99/100	Buffy coat	MMqPCR	Short telomeres significantly increase risk	Age, study site	Age	[53]
Renal	65/65	Isolated lymphocyte culture	Q-FISH^{LSC}	Short telomeres significantly increase risk	Age, sex, ethnicity	Age, sex, smoking status, ethnicity	[55]

[a] Q-FISH, quantitative fluorescence *in situ* hybridization; LSC, laser scanning cytometry; qPCR, quantitative PCR; TRF, terminal restriction fragment length assay; MMqPCR, monochrome multiplex qPCR.

Table 2
Details of prospectives studies on telomere length and cancer risk.

Cancer site	Sample size cases/controls[a]	DNA source	Measurement technique[b]	Results	Matching factors[c]	Analysis covariates[d]	Reference
Breast	1122/1147	Buffy coat	qPCR	No significant association	Age at diagnosis, blood collection variables, ethnicity	Matching factors, smoking status, age at menarche, BMI, weight gain, age at first birth and parity, family history of breast cancer, history of benign breast disease, age at menopause, PMH duration	[56]
	199/420	Buffy coat	qPCR	No significant association	Age, sex, blood draw	Age, sex, plate	[44]
Colorectal	191/306	Whole blood	qPCR	No significant association	Age, smoking status, length of follow-up	Matching factors, randomized treatment group, BMI, alcohol use, exercise	[58]
	134/357	Whole blood	qPCR	No significant association	Age, length of follow-up	Age, smoking status, BMI, randomized treatment group, presence of colorectal polyps, alcohol use, exercise, postmenopausal status, PMH use	[57]
	185/406	Buffy coat	qPCR	No significant association	Age, sex, blood draw	Age, sex, plate	[44]
Endometrial	279/791	Buffy coat	qPCR	No significant association	Age, menopausal status, PMH use at blood draw	Matching factors, age at menarche, age at first birth and parity, smoking status, BMI, age at menopause, recent PMH use, family history of colon cancer	[10]
Esophagus	38/1741 person-years	Buffy coat	qPCR	Short telomeres significantly increase risk	N/A	Age, sex, NSAID use, smoking, waist-to-hip ratio	[59]
Non-Hodgkin Lymphoma	107/107	Whole blood	MMqPCR	Long telomeres significantly increase risk	Age	Age at randomization	[60]
Prostate	612/1049	Buffy coat	qPCR	No significant association	Age at cohort entry, ethnicity, year since initial screen, fiscal year of cohort entry	Matching factors, pack-years of smoking	[15]
Skin	218 melanoma, 285 SCC, 300 BCC/870	Buffy coat	qPCR	No significant associations	Age, ethnicity	Matching factors	[61]
General	92/787 at baseline	Whole blood	qPCR	Short telomeres significantly increase risk	N/A	Age, sex, social class, smoking, alcohol, diabetes, physical activity, BMI, HsCRP, Vitamin D, LDL	[63]

[a] SCC, squamous cell carcinoma; BCC, basal cell carcinoma.
[b] qPCR, quantitative PCR; MMqPCR, monochrome multiplex qPCR.
[c] N/A, not applicable; PMH, postmenopausal hormone.
[d] BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; HsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol.

at a significantly increased risk of breast cancer (OR = 1.61, 95% CI = 1.05–2.45; $P_{trend} = 0.01$; $P_{interaction} = 0.004$) compared to premenopausal women with the longest lengths. No association was observed among postmenopausal women [42]. Similar results were observed in another study conducted by the same group. Among high risk sister sets recruited from the Metropolitan New York Registry, a non-significant elevation in overall breast cancer risk was observed among women with the shortest telomere lengths (OR = 1.55, 95% CI = 0.88–2.73; $P_{trend} = 0.14$). The association was more pronounced among premenopausal women (OR = 2.09, 95% CI = 0.79–5.52; $P_{trend} = 0.17$) than postmenopausal women (OR = 1.34, 95% CI = 0.50–3.60), although the results did not reach significance [40]. In contrast, Zheng et al. did not observe significant associations of telomere length with either pre/perimenopausal ($OR_{below\ vs\ above\ median} = 1.26$, 95% CI = 0.74–2.12) or postmenopausal ($OR_{below\ vs\ above\ median} = 1.16$, 95% CI = 0.76–1.78) breast cancer risk in two case–control populations [43].

The largest study of telomere length on breast cancer risk included 2243 breast cancer cases and 1524 population-based matched controls from the retrospective SEARCH Breast Study and an additional 657 controls from the prospective EPIC cohort. Women with short telomeres were at a highly significant 15.5-fold increased risk of breast cancer ($P_{trend} = 2.1 \times 10^{-80}$). Estimates did not differ significantly for women diagnosed with breast cancer before 50 years of age and those 50 years and older, cut points which approximate premenopausal versus postmenopausal status [44].

Svenson et al. [41] observed quite the opposite result. Telomere lengths were measured in buffy coat samples from 265 newly diagnosed breast cancer patients and 300 population-based controls from the MONICA study in Northern Sweden. An additional 146 controls with granulocyte preparations were measured from the Malmö Diet and Cancer Cohort of Southern Sweden. Women with the longest telomere lengths had a statistically significant increased risk of breast cancer (OR = 5.17, 95% CI = 3.09–8.64; $P_{trend} < 0.001$) compared to women with the shortest telomere lengths [41]. An even stronger effect was observed in another study comparing 102 nonsmoking breast cancer patients and 50 nonsmoking employee volunteer controls without a personal or family history of cancer. Long telomere lengths were associated with a significantly increased risk of breast cancer (OR = 23.3, 95% CI = 4.4–122.3; $P_{trend} < 0.0001$) [45].

Colorectal cancer. The large retrospective SEARCH Colorectal Study found a highly statistically significant association between telomere length and colorectal cancer risk [44]. Individuals with short telomere lengths had an OR = 2.14 (95% CI = 1.77–2.59; $P_{trend} = 1.8 \times 10^{-13}$) compared to those with long telomeres.

Esophageal cancer. A US study of esophageal cancer found statistically significantly shorter telomere lengths in patients compared to controls ($P = 0.004$). Individuals in the shortest tertile had an OR of esophageal cancer risk of 2.38 (95% CI = 1.04–5.46; $P_{trend} = 0.03$) compared to individuals in the longest tertile [46].

Gastric cancer. Gastric cancer patients had significantly shorter telomeres than controls in two distinct racial populations

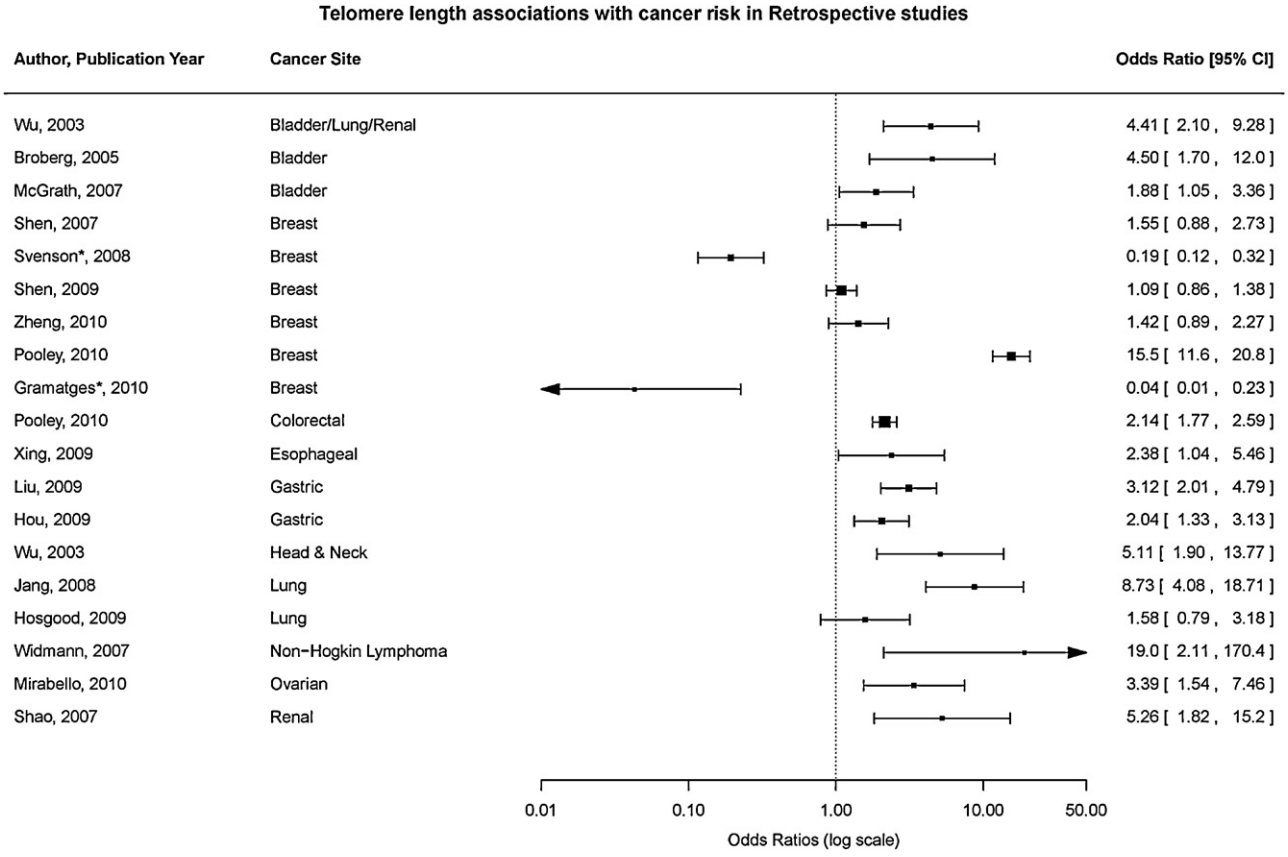

Fig. 1. Telomere length associations with cancer risk from retrospective case–control studies are presented comparing individuals in the shortest quantile to those in the longest quantile of telomere length. *R* was used to plot the study-specific, adjusted odds ratios and 95% confidence intervals. *Reported a significant association of longer telomere length with breast cancer risk; here we plot the inverse log odds ratios.

($P < 0.001$) [47,48]. In a hospital-based study of Chinese Han patients, short telomere lengths were associated with a statistically significant OR = 3.12 (95% CI = 2.01–4.79; $P_{trend} < 0.001$) of gastric cancer risk [48]. In a high-risk Polish population, a statistically significant 2-fold increase in gastric cancer risk ($P_{trend} < 0.001$) was observed among individuals with the shortest telomere lengths [47].

Head and neck cancer. Two retrospective studies conducted in North America have examined telomere length as a biomarker for risk of head and neck cancer. In the US study, average TRF length was 0.9 kb shorter among the head and neck cancer case group as compared to the control group ($P < 0.001$). Short TRF length was associated with a significantly increased risk of head and neck cancer (OR = 5.11, 95% CI = 1.90–13.77) [35]. However, among a Canadian study of squamous cell carcinoma of the head and neck TRF lengths did not differ by disease status [49].

Lung cancer. Short telomeres have been associated with lung cancer risk in 3 retrospective case–control studies [35,50,51]. Both the US study by Wu et al. [35] and Korean study by Jang et al. [51] found shorter telomere lengths among cases than controls ($P < 0.001$). In the Korean study, short telomere length was associated with a statistically significant 8.7-fold increase in lung cancer risk ($P_{trend} < 0.0001$) [51].

The third case–control study did not find an association with lung cancer risk in the general Chinese population. In contrast to the prior two studies, which evaluate blood specimens, telomere lengths were measured in DNA of morning sputum samples, which consists of a mix of cells from the lower respiratory tract potentially including malignant cells in samples from the cancer patients. Upon histological review, the authors noted a minimal number of tumor cells among patient samples. Individuals in the shortest telomere length tertile had a non-significant elevation in lung cancer risk (OR = 1.58, 95% CI = 0.85–3.27) compared to those in the longest tertile. When stratified by a single nucleotide polymorphism (SNP; rs10244817) in the *protection of telomeres 1* (*POT1*) gene, a marginally significant dose–response relationship was observed among individuals homozygous for the common allele, but not among carriers ($P_{interaction} = 0.05$). Among those with the homozygous common allele genotype, the shortest tertile of telomere length was associated with a significant 3.3-fold increased risk of lung cancer [50].

Non-Hodgkin lymphoma. A German study observed significantly shorter telomere lengths in B lymphocytes among 40 aggressive non-Hodgkin lymphoma patients as compared to age-matched controls. A statistically significant 19-fold increase in risk was observed for individuals with the shortest telomere lengths [52].

Ovarian cancer. The first study to investigate the telomere length association with ovarian cancer risk did not find a significant difference in TRF length between 18 cases and 35 healthy controls [38]. In contrast, a more recent pilot study from the Polish Ovarian Cancer Study found a significant association between telomere length and ovarian cancer risk [53]. This study used the recently developed monochrome multiplex qPCR (MMqPCR) assay, a modified version of the original qPCR assay with reduced experimental variability [54]. Cases had significantly shorter telomere lengths than controls ($P = 0.002$). Women in the shortest tertile had an OR = 3.39 (95% CI = 1.54–7.46; $P_{trend} = 0.002$) of serous ovarian cancer risk compared to women in the longest tertile. The association appeared limited to risk of developing poorly differentiated carcinoma ($OR_{below\ vs\ above\ median} = 4.89$, 95% CI = 1.93–12.34) [53].

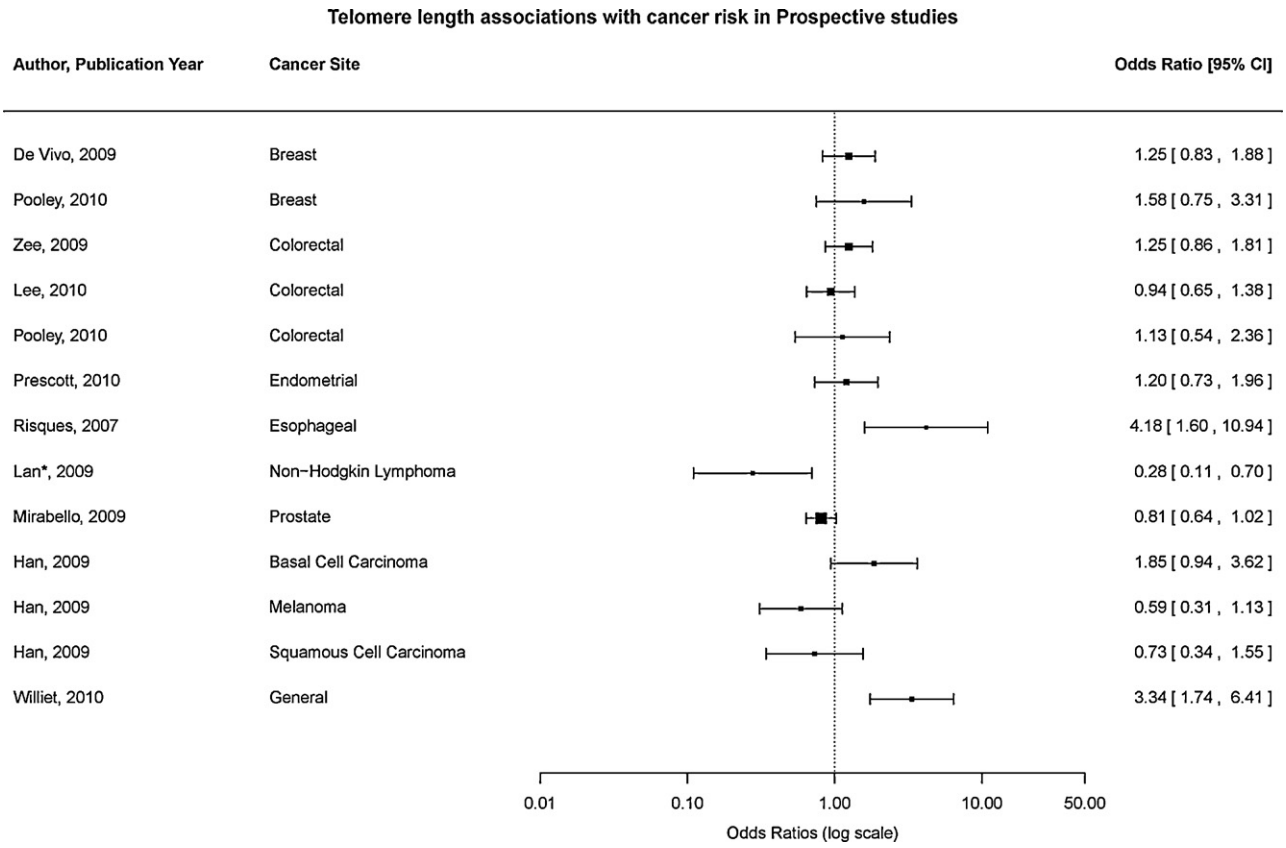

Fig. 2. Telomere length associations with cancer risk from prospective studies are presented comparing individuals in the shortest quantile to those in the longest quantile of telomere length. *R* was used to plot the study-specific, adjusted odds ratios and 95% confidence intervals. *Reported a significant association of longer telomere length with non-Hodgkin lymphoma risk; here we plot the inverse log odds ratios.

Renal cancer. Among 32 matched case–control pairs, Wu et al. found statistically significantly shorter telomere lengths among renal cell cancer cases than controls ($P = 0.019$) [35]. The result was replicated in a larger study of 65 matched case–control pairs. Individuals with the shortest telomere lengths were at a statistically significant increased risk of renal cell cancer (OR = 5.26 95% CI = 1.82–15.2; $P_{trend} = 0.001$) compared to those with the longest lengths [55].

2.3. Prospective studies of telomere length and cancer risk (Fig. 2)

Breast cancer. Two prospective studies of breast cancer risk have not found statistically significant associations with telomere length [44,56]. The case–control study of postmenopausal invasive breast cancer risk nested within the Nurses' Health Study cohort observed an OR = 1.25 (95% CI = 0.83–1.88; $P_{trend} = 0.20$) for women with the shortest telomere lengths. The association did not differ by the estrogen receptor/progesterone receptor status of tumors [56]. A similar non-significant effect estimate was found in a smaller case–control study nested within the EPIC cohort. Short telomere length was associated with a non-significant elevation in breast cancer risk (OR = 1.58, 95% CI = 0.75–3.31; $P_{trend} = 0.18$) [44].

Colorectal cancer. Three independent case–control studies nested within prospective cohorts have not found a relationship between telomere length and colorectal cancer risk [44,57,58]. Telomere length was not associated with colorectal cancer risk among men from the Physicians' Health Study (OR = 1.25, 95% CI = 0.86–1.81; $P_{trend} = 0.24$) [58], among women from the Women's Health Study (OR = 0.94, 95% CI = 0.65–1.38; $P_{trend} = 0.76$) [57], or individuals within the EPIC cohort (OR = 1.13, 95% CI = 0.54–2.36; $P_{trend} = 0.82$) [44].

Endometrial cancer. A case–control study nested within two population-based cohorts, the Nurses' Health Study and the Women's Health Study, did not find significant differences in telomere length by disease status. Women with the shortest telomere lengths had an OR = 1.20 (95% CI = 0.73–1.96; $P_{trend} = 0.37$) compared to women with the longest telomere lengths [10].

Esophageal cancer. Telomere length was a significant predictor of developing esophageal cancer in a cohort study of a high risk population of 300 patients with Barrett's esophagus. Thirty-eight participants developed esophageal adenocarcinoma over an average follow-up of 5.8 years (range 0.1–11.1 years). Patients with the shortest telomere lengths were at a statistically significantly increased risk of developing subsequent esophageal cancer (Hazard Ratio (HR) = 4.18, 95% CI = 1.60–10.94; $P_{trend} = 0.004$) [59].

Non-Hodgkin lymphoma. A statistically significant association was observed between telomere length and non-Hodgkin lymphoma risk in the prospective Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort of male smokers. Telomere length was significantly longer in cases than controls ($P = 0.0017$). Men with the longest telomere lengths had a 3.6-fold increase in overall non-Hodgkin lymphoma risk compared to men with the shortest lengths ($P_{trend} = 0.003$). Results were similar across the various subtypes of non-Hodgkin lymphoma [60].

Prostate cancer. A large study of high grade prostate cancer (Gleason score ≥ 7) nested within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort did not find a significant difference in telomere length between case and control participants. Short telomere length was associated with a non-significant OR = 0.81 (95% CI = 0.64–1.02; $P_{trend} = 0.34$) [15].

Skin cancer. A case–control study of skin cancer nested within the Nurses' Health Study found marginally significant heteroge-

neous associations with telomere length by histologic subtype. Women with the shortest telomere lengths had an elevated risk of basal cell carcinoma (BCC) (OR = 1.85, 95% CI = 0.94–3.62; P_{trend} = 0.09). In contrast, a reduced risk of melanoma was observed for women with the shortest telomere lengths (OR = 0.59, 95% CI = 0.31–1.13; P_{trend} = 0.09). No association was observed between telomere length and squamous cell carcinoma (SCC) risk [61]. Consistent with these opposing telomere length associations, the C allele of rs401681 at the TERT-CLPTM1L locus has been statistically significantly associated with increased BCC risk and decreased melanoma risk [62].

General cancer risk. A longitudinal population-based study among residents of Bruneck, Italy observed a significant increase in overall cancer risk among individuals with short telomere lengths at baseline. Among 787 healthy individuals with a baseline blood sample, 92 developed cancer over a 10 year follow-up period. After excluding 33 participants with a personal history of cancer prior to baseline, individuals in the shortest tertile had a HR = 3.34 (95% CI = 1.74–6.41) compared to those in the longest tertile. Stronger associations were observed for highly aggressive cancers such as gastric, lung, and ovarian cancer [63].

3. Future considerations

Retrospective case–control studies of telomere length generally support an increased risk of cancer associated with short telomeres as measured in blood or buccal cell DNA (Fig. 1). Cancer types strongly influenced by smoking and inflammatory processes such as bladder [35–37], renal cell [35,55], and gastric cancer [47,48] display the most consistent results, whereas inconsistent results have been observed for breast cancer. Reports on breast cancer range from a significant 96% reduction in breast cancer risk [45] to a significant 15-fold excess in breast cancer risk [44] associated with the shortest quartile of telomere length.

About half as many prospective studies have been conducted on the relationship between telomere length and cancer risk (Fig. 2). Instead of a general biomarker of cancer risk, prospective studies suggest that peripheral blood leukocyte telomere length may be associated with risk of certain cancer types. Whereas the small number of prospective studies on breast [44,56] and colorectal cancer [44,57,58] have been consistently null, statistically significant associations were observed for esophageal cancer [59] and non-Hodgkin lymphoma [60] risk. Moreover, as demonstrated by these latter studies, either the telomere hypothesis of carcinogenesis (esophageal cancer) or tumor suppressor hypothesis (non-Hodgkin lymphoma) may apply depending on the cancer of interest. Such heterogeneity is also observed between different histologic malignancies within a single organ. Within the same homogenous population, women in the shortest quartile of relative telomere length were at a marginally significant increased risk of BCC, but at a marginally significant reduced risk of melanoma [61]. The direction in risk may depend on a cell type's susceptibility to mutations. Longer telomeres in cells such as melanocytes, which commonly acquire mutations in the *BRAF* oncogene [64,65], confer a higher proliferative capacity and therefore greater opportunity to acquire additional mutations for malignant transformation.

A longitudinal study of cancer risk found a significant increase in overall cancer risk among individuals with shorter telomeres at baseline [63]. Although case numbers were small, when risk was examined by cancer type the authors noted the predictive value of telomere length appeared positively correlated with fatality rates. Statistically significant associations were observed for gastric, lung, and ovarian cancers [63], which are aggressive tumors with 5-year survival rates of less than 50% [66]. Likewise, in a longitudinal study of a high risk population of Barrett's esophagus patients, short telomere length was significantly associated with development of esophageal adenocarcinoma [59], which has an overall 5-year survival rate of 17% [66]. Given that chromosomal aberrations have been correlated with tumor aggressiveness [67], telomere shortening may be predictive of tumors displaying greater degrees of genomic instability.

The magnitude of significant associations in retrospectives studies was much greater than those reported by prospective studies. Prospective studies all measured relative telomere length using qPCR assays, whereas retrospective studies used Southern blot and Q-FISH methods in addition to the qPCR assays. The use of different methodologies is an unlikely explanation for the discrepancy between the two types of studies as data generated by the qPCR assays are strongly correlated with those from the Southern blot assay [54,68,69]. Additionally, many of the retrospective studies that used the qPCR assay found highly significant results [36,37,41,44–48,51,53]. The larger estimates are likely the result of the inherent biases of retrospective case–control studies.

The difference in retrospective versus prospective study design was probably most clearly demonstrated by Pooley et al. [44]. Using the qPCR method to assay relative telomere length in all samples, the authors observed highly statistically significant increased cancer risk associated with short telomere length in the retrospective SEARCH breast and colorectal cancer studies, but null results in the prospective EPIC breast and colorectal studies [44]. Reverse causation may have contributed to some of the associations observed in retrospective studies. DNA damage due to chemotherapy or radiotherapy may have accelerated telomere loss among cancer patients [49]. Some retrospective studies excluded cases treated with chemotherapy or radiotherapy prior to biospecimen collection [35,41,43,48,50,52,55] or conducted sensitivity analyses [39,44,53] to assess the effect of treatment. However, many studies do not provide information on chemo- or radiotherapy and surgical treatment is generally ignored. In addition to smoking and obesity, which may accelerate telomere loss by increased exposure to oxidative stress [5], psychosocial stress has also been associated with shortened telomere lengths [70–72]. The psychological impact of a cancer diagnosis and/or physical stress caused by the disease could potentially augment the rate of telomere loss. As a result, telomere length measured after cancer diagnosis may reflect the emotional and physical burden experienced rather than be a predictive biomarker for certain cancer types such as breast and colorectal cancer.

Telomere length measured in surrogate tissues, such as peripheral blood leukocytes and buccal cells, has emerged as a putative biomarker of chronic disease risk. Studies conducted using cancer somatic tissue samples implicate aberrant telomere biology in carcinogenesis. In assessing the contribution of constitutional telomere length, differences emerged between current retrospective and prospective epidemiologic studies indicating potential biases that need to be considered by future studies. Study design concerns to bear in mind are outlined in Box 2 . The risk associated with constitutional telomere length for a number of cancer types have yet to be defined. A focus on aggressive histologic subtypes or high risk populations may be particularly fruitful. Additionally, in most studies published, non-Hispanic white individuals make up the vast majority of participants. A few of the studies were conducted in Asian populations [48,50,51], but otherwise telomere length as a biomarker in non-white populations remains largely unexplored. Not only do cancer rates differ [73], but evidence suggests telomere length dynamics differ by racial and ethnic groups as well [74–76]. Thus, telomere length research in non-white populations is warranted. Carefully designed studies that collected biospecimens prior to cancer development are still needed to elucidate the relationship between telomere length and a number of cancer sites.

Box 2: Study design considerations for future assessment of telomere length in cancer risk.

Study population

- Prospective study design is optimal
- Cases and controls recruited from the same homogenous population
- Sufficient sample size of non-white individuals
- Exclusion of individuals with autoimmune or cardiovascular disease
- Careful consideration of statistical power
- Collect information on potential confounders (age, sex, BMI, smoking)

Biospecimen collection and telomere length measurement

- Prior to cancer development
- If ascertained at diagnosis, collect prior to cancer treatment or obtain detailed treatment data including chemotherapy, radiation therapy, and surgery
- Multiple biospecimens prior to cancer development
- Pre- and post-cancer diagnosis specimens
- Use of consistent tissue-type within study
- Isolate specific cell types from biospecimen
- Use of consistent storage, DNA extraction, and telomere length assay methods within study
- Cases and matched controls assayed on the same plate

Analysis

- Detailed description of and consistent analytic design
- Stratification by smoking status or other high risk exposures

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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