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Mini Review
Telomere Length Variation as Potential Biomarker for Diagnosing Lung, Liver, Gastric and Pancreatic Cancer

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Abstract

Telomeres present at ends of chromosomes are crucial in maintaining chromosomal integrity and genomic stability. In this review, variation in telomeric length was presented as potential biomarker in diagnosing lung, liver, gastric and pancreatic cancer types by going through available reports. A significant telomere shortening has been found to be associated with Non-small cell lung cancer (NSCLC) cases as compared to control patients ($p = 0.027$). A positive association between telomere length and survival outcome has been reported in case of squamous cell carcinomas in early stage NSCLC patients. Many studies reported the association of several single nucleotide polymorphisms and liver cirrhosis that may in turn become the main risk factor for liver cancer. Moreover, telomere shortening has been presented as a genetic risk factor for liver cirrhosis. Gastric cancer risk has been found to elevate with *Helicobacter pylori* L. infections which may involve telomere shortening mediated by over production of reactive oxygen species. Leucocyte telomere length and TERT gene variants were found to be associated with pancreatic cancer risk, but some studies found no associations between genetically predicted short telomeres and pancreatic ductal adenocarcinoma risk. Human telomerase reverse transcriptase plays an important role in telomere lengthening and has been found to be involved in different cancer propagatory mechanism. A wide group of studies revealed alteration in telomere length to be an accurate cancer biomarker though further associative studies are recommended.

Key words: Human telomerase, telomere shortening, genomic stability, cancer biomarker, non-small cell lung cancer, chromosomal integrity

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INTRODUCTION

Cancer biology has emerged as a much explored branch in recent years[1,2]. Main emphasis in these studies has been laid down on the mechanisms involved and drug delivery systems[3,4]. Besides this, accurate diagnosis of a particular cancer type is a field of extreme importance. One of the biomarkers used in case of cancer diagnosis is the alteration in telomere length. Telomeres are TTAGGG tandem repeats present at each end of chromosomes[5]. Nucleotide sequence of telomeres is repeated nearly 2000 times. Telomeres help in protecting the genome from inter-chromosomal fusions and degradation[6]. Thus, these sequences safeguard the stability of chromosomes as well as the full genome. Any kind of alteration in the length of telomere may hamper their role. Increased smoking, higher stress levels and elevated oxidative stress levels may result in decreased telomere lengths[7]. The maintenance of telomere length is attributed to telomerase activity. Any irregularity in its function may result in instability among the genome that may further lead to risk of cancer. Short as well as extremely long telomeres have been found associated with different cancer types. Telomeric shortening is also found to be associated with various disease patterns including Dyskeratosis Congenita and Parkinson's disease[8, 9]. Maintenance of a proper telomere structure, an accurate regulation of telomerase biogenesis and activity, as well as a correct telomere-telomerase interaction and a faithful telomeric DNA replication are all processes that a cell has to precisely control to safeguard its functionality[10], but a faulty telomerase action may result in genomic instability that may lead to cancer. In the present paper, an attempt had been made to compile and present the studies reporting the association of telomere length alteration with different cancer types including lung, liver, gastric and pancreatic cancer.

LUNG CANCER

Lung cancer remains the leading cause of cancer mortality worldwide[11]. Phenyl phenanthro imidazole ethylenediamine platinum (II) (PIP) has been reported to notably suppress the seeding capacity of A549 lung cancer cells[12]. It also induced telomere shortening in lung cancer, but similar results were not found in case of MRC5 cells. Similarly, in another study of Taka *et al.*[13], treatment of A549 lung cancer cells with perylene derivatives PM2 and PIPER influences the G-quadruplex by reduction in cell proliferation and tumorigenicity. Cell declining was observed when treated for longer duration. Welders (N = 101) were exposed to respirable dust at 1.2 mg m^{-3}, whereas control exposures did not exceed to 0.1 mg m^{-3} ($p<0.001$). Welders showed excessive possibility of adenomatous polyposis coli (APC) methylation in unadjusted model (odd ratio = 14, $p = 0.014$) than in adjusted model ($p = 0.052$). The TL of welders was found associated with 0.0066 units shorter telomeres ($p = 0.033$). There was no clear association between concentrations of respirable dust and the biomarkers[14]. Association between ACYP2 SNPs and lung cancer risk in the Chinese Han population were investigated and a total of 554 lung cancer patients and 603 healthy controls; 13 SNPs in ACYP2 were included[15]. To evaluate the association between SNPs and lung cancer, multivariate logistic regression analysis was used. As a result, three SNPs in ACYP2 viz. rs1682111 in the recessive model ($p = 0.029$), rs11896604 in the co-dominant model ($p = 0.045$) and over-dominant model ($p = 0.032$) and rs843720 in recessive model ($p = 0.040$) were found to be associated with increased lung cancer risk in Chinese Han population.

Non-small cell lung cancer: Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers. Potential clinical use of telomeres and telomerase activity in SCLC was investigated[16]. Telomere shortening was found more in tumours than in control tissues ($p = 0.027$). Patients whose tumours had a mean telomere length (MTL) <7.29 Kb or T/N ratio <0.97 showed a significantly poor clinical evolution ($p = 0.034$ and 0.040, respectively). Thus, telomere function may emerge as a useful molecular tool that allows selecting groups of NSCLC patients in order to establish personalized therapy protocols. Similarly, effect of short telomeres on the survival of patients with early stage of NSCLC was investigated[17]. The correlation between TL and overall survival (OS) and disease-free survival (DFS) was explored. When the patients were categorized into quartiles based on TL, those patients with the 1st quartile (shortest) of TL had a significantly worse OS and DFS than patients with the 2nd to the 4th quartiles of TL ($p = 0.001$ and 0.01, respectively). Therefore, the association between TL and survival outcome was more pronounced in squamous cell carcinomas than adenocarcinomas. Another study found that NSCLC is susceptible to increasing of DNA damage responses and prohibition of angiogenesis by telomere overhang oligonucleotides[18]. Single-nucleotide polymorphisms (SNPs) were presented to show significant correlation with NSCLC in a few sub-populations which included women, non-smokers, east Asians and subjects with adenocarcinoma[19]. The genetic alleles combined with

environmental (e.g., less-smoking) and physiological factors (gender and age) that confer longer telomeres are the strong risk factors for NSCLC. The effect of *Cynomorium songaricum* polysaccharide (CSRP) on telomere of A549 human non-small cell lung cancer cells was investigated[20]. The CSRP was found to have the anti-cancer effect. The action mechanism may be linked with preventing TERT mRNA expression, telomere shortening, preventing cell proliferation and stimulating cell apoptosis. Long telomeres have been found in correlation with recurrence in early stage NSCLC after curative resection[21]. This prospective study demonstrated that women had long telomeres as compared to men (1.12 vs. 1.06, p = 0.025) and the patients of adenocarcinoma had longer telomeres than those of other histologic types (1.11 versus 1.05, p = 0.042). Long RTL was related to increased recurrence risk in women (p = 0.044) and adenocarcinoma sub-groups (p = 0.036). Similarly, longer telomeres were found more in adenocarcinoma patients and less in Squamous Cell Carcinoma (SCC) patients as compared to controls[22]. Longer telomeres were found related with adenocarcinoma risk, with highest risk related to female sex, younger age (<60 years) and lighter smoking (<30 pack-years). Genetic variation in chromosome 5p 15.33 and TL have been reported in a systematic review to be predictive and prognostic biomarkers for lung cancer[11]. The 23 genetic variants found significant associations with overall survival (OS) and/or progression-free survival (PFS) were reported for rs401681 (CLPTM1L), rs4975616 (TERT-CLPTM1L) and rs2736109 (TERT). In tumor and blood, both shorter and longer TLs were found to be associated with OS and PFS. Correlation of telomere shortening with lung cancer risk was reported by Karimi *et al.*[23]. In 9 studies, 2925 cases of lung cancer and 2931 controls were employed. A meta-analysis revealed that lung cancer cases were expected to have shorter telomeres as compared to controls (p = 0.46) and the summary of pooled ORs of TL in adenocarcinoma lung cancer patients was 1 as compared to 1.78 for squamous cell lung cancer patients. Lung cancer risks are reported to be clearly related with short TL. In patients with breathing problems, lung cancer risk can be predicted by TL adjustment with age, sex and smoking. The TL in T-cells and its correlation with the clinical characteristics of patients with lung cancer was investigated[24]. The study included 40 patients of lung cancer and 25 controls. Telomere lengths were assessed by using quantitative real-time polymerase chain reaction methods. Hence, the results showed that telomere shortening was found more in patients as compared to controls (p<0.001) and shorter telomeres were associated with induced clinical stage (p = 0.008) and distant metastasis (p = 0.028).

Shortened telomeric length in T-cells was found in naive T-cells which might be related to lung cancer progression as naive T-cells in lung cancer patients had short telomeres than in controls (p = 0.012). It was suggested that long telomeres in peripheral white blood cells are correlated with lung cancer risk while studying the rs2736100 (CLPTM1L-TERT) polymorphism in a prospective cohort study among women in China[25]. A total of 215 female lung cancer cases and 215 controls were investigated. About 94% of recruited cases were never-smokers. A dose-response relationship between tertiles of TL and risk of lung cancer were found (p trend = 0.003). The study suggested that individuals with longer TL in peripheral white blood cells may have an increased risk of lung cancer. Correlation of seven telomere-length associated genetic variants with increased risk of lung cancer was explored in a large study of 5,457 non-smoking female Asian lung cancer cases and 4,493 non-smoking female Asian controls[26]. Genetic risk scores (GRSs) of seven TL associated variants revealed that longer telomeres were related with increased lung cancer risk for upper versus lower quartile of the weighed GRS ($p = 4.54\times10^{-14}$), even after removing rs2736100 ($p = 4.81\times10^{-3}$).

Telomere length variation (TLV) in blood lymphocytes has been reported in correlation with lung cancer risk[27]. About 191 lung cancer cases and 207 controls were undertaken in the study. The TLV across all chromosomal ends were found to be significantly related with risk of lung cancer; adjusted odds ratios 4.67 and 0.46 for younger (age</ = 60) and older (age >60) individuals. Lung cancer risk was found affected by both TLV and mean TL. When individuals with short telomeres and elevated TLV were compared with long telomeres and reduced TLV, adjusted odd ratios were found to be 8.21 and 0.33 for younger and older individuals, respectively. Another study presented 3D telomere profiles in differentiating NSCLC patients with different histologies, EGFR and smoking statuses[28]. The study investigated the 3D organization of telomeres and cytoband 17q25.3 copy number in NSCLC tissues. Cytoband 17q25.3 was examined by fluorescent *in situ* hybridization. The 3D telomeric profiling revealed that the smokers, EGFR-negative and squamous cell carcinoma sub-groups had higher numbers of low-intensity telomeres which are indicative of shorter telomeres. Profiling also showed higher numbers of telomeric aggregations compared to non-smokers, EGFR-positive and adenocarcinomas. G-quadruplex ligands were demonstrated to attenuate telomerase activity by inducing G-quadruplex formation at the 3'-overhang of telomere and at the human telomerase reverse transcriptase (hTERT) promoter[13].

Table 1: Studies reporting the association of telomere length alterations with different cancer types

Type of cancer	Inference	References
Lung cancer	PIP suppressed the seeding capacity of A549 lung cancer cells and induced telomere shortening	Mancini *et al.*[12]
Lung cancer	Telomere shortening and cell senescence induced by perylene derivatives (PM2 and PIPER) in A549 human lung cancer cells	Taka *et al.*[13]
Lung cancer	Modest signs of association between oxidative stress, telomere alterations, DNA methylation and low-to-moderate occupational exposure to particles from welding fumes	Li *et al.*[14]
Lung cancer	Positive correlation between three SNPs in telomere associated gene ACYP2 (rs1682111, rs11896604 and rs843720) with lung cancer risk	Chen *et al.*[15]
Lung cancer	TL, COPD and emphysema as risk factors for lung cancer	De-Torres *et al.*[32]
Lung cancer	Telomere shortening was found more in tumours than in control tissues (p = 0.027)	Fernandez-Marcelo *et al.*[16]
Lung cancer	Continuous long-term treatment with imetelstat resulted in sustained telomerase inhibition, progressive telomere shortening and eventual growth inhibition	Frink *et al.*[33]
Lung cancer	An association between TL and survival outcome was more pronounced in squamous cell carcinomas than adenocarcinomas	Jeon *et al.*[17]
Lung cancer	Genetic variation in chromosome 5p15.33 and TL is predictive and prognostic biomarkers for lung cancer	Kachuri *et al.*[11]
Lung cancer	Patients with lung cancer were expected to have shorter TL than the control (p = 0.46)	Karimi *et al.*[23]
Lung cancer	Longer telomeres were significantly associated with higher risk of developing recurrence in women	Kim *et al.*[21]
Lung cancer	Individuals with longer TL in peripheral white blood cells may have an increased risk of lung cancer	Lan *et al.*[25]
Lung cancer	A genetic background that favours longer TL may increase lung cancer risk	Machiela *et al.*[26]
Lung cancer	Exogenous administration of an 11-base oligonucleotide homologous to the 3'-telomere overhang sequence (T-oligo) mimics the effects of overhang exposure by inducing senescence and cell death in NSCLC cells	Puri *et al.*[18]
Lung cancer	Shortened TL in T-cells occurred in naive T-cells and might be related to lung cancer progression	Qian *et al.*[24]
Lung cancer	Long telomeres were associated with increased risk of adenocarcinoma, with the highest risk associated with female sex. In contrast, long telomeres were protective against squamous cell carcinoma	Sanchez-Espiridion *et al.*[22]
Lung cancer	Longer TL was associated with increased lung cancer risk	Seow *et al.*[34]
Lung cancer	TL variation in blood lymphocytes is significantly associated with lung cancer risk.	Sun *et al.*[27]
Lung cancer	3D telomere profiles may differentiate NSCLC patients with different histologies, EGFR, and smoking statuses.	Sunpaweravong *et al.*[28]
Lung cancer	Perylene derivatives induced telomere shortening and cell senescence in A549 human lung cancer cells	Taka *et al.*[13]
Lung cancer	Support vector machine (SVM) model and a decision tree (DT) model were developed for screening lung cancer through combined detection of FHIT, RASSF1A and p16 promoter methylation and RTL.	Wang *et al.*[35]
Lung cancer	SNP (rs2736100) showed a significant correlation with longer telomeres and NSCLC	Wei *et al.*[19]
Lung cancer	*Cynomorium songaricum* polysaccharide could significantly shorten the TL of A549 cells demonstrating its anti-cancer nature.	Yang *et al.*[20]
Liver cancer	Telomere shortening may represent a genetic risk factor for the development of cirrhosis	Carulli[29]
Liver cancer	HOTAIR is required for IKKalpha plus IKKbeta and IKKgamma to control telomerase activity and TL	An *et al.*[30]
Liver cancer	Peripheral blood samples may be utilized to assay telomere shortening as a predictor for disease persistence in HCC resulting after HBV or HCV infection	Feng *et al.*[31]
Liver cancer	HULC, MALAT1 and TRF2 are highly expressed in HCC tissues, HULC plus MALAT1 over expression drastically promotes the growth of liver cancer stem cells through telomere elongation	Wu *et al.*[36]
Liver cancer	Proposed a strategy using nuclear-shell biopolymers initiated by telomere elongation with signal molecules for selective cancer cell recognition and efficient drug delivery	Zhang *et al.*[37]
Gastric cancer	*Helicobacter pylori* infection attenuated TL and increased gastric cancer risk	Lee *et al.*[38]
Gastric cancer	Positive correlation found between *Helicobacter pylori* related PCGI methylation and telomere shortening in human gastric mucosa	Tahara *et al.*[39]
Gastric cancer	Telomere shortening in gastric mucosa was associated with increased GC but not with clinicopathological features	Tahara *et al.*[40]
Gastric cancer	Positive correlation of the rs2736100 A allele carrier with decreased hTERT mRNA expression and telomere shortening	Choi *et al.*[41]
Gastric cancer	Shorter or extreme longer telomeres may be risk factor for gastric cancer	Du *et al.*[42]
Gastric cancer	Positive correlation was found between TL and PIK3CA amplification	Heo *et al.*[43]
Gastric cancer	Associations observed between TL and mtDNA copy number in intestinal type gastric cancer samples but not in diffuse type GC	Jung *et al.*[44]
Gastric cancer	Haplotypes "TTCTAATG" and "AC" were more frequent among GC patients. Haplotype "GC" is suggestive of having a protective role	Li *et al.*[45]

Table 1: Continued

Type of cancer	Inference	References
Gastric cancer	Trastuzumab induces Oxa and DDP sensitivity in HER2-amplified GC cells and downregulate the telomere-associated gene expression	Liu *et al.*[46]
Gastric cancer	Short LTL is associated with induction of gastric or esophageal squamous cell carcinoma	Pan *et al.*[47]
Gastric cancer	Increased immunosuppressive status in response to short leukocyte RTL	Qu *et al.*[48]
Gastric cancer	Potential correlation found between telomere shortening in leukocyte DNA and clinic-pathological features and prognosis of gastric cancer	Tahara *et al.*[49]
Gastric cancer	Telomere shortening in gastric mucosa is associated with GC risk	Tahara *et al.*[40]
Gastric cancer	GKN1 increases senescence and apoptosis through regulating TL in gastric cancer	Yoon *et al.*[50]
Pancreatic cancer	Telomere shortening occurs in the early stages of pancreatic carcinogenesis and progresses with pre-cancerous development	Matsuda *et al.*[51]
Pancreatic cancer	No correlation of genetically predicted short telomeres with PDAC risk was found	Antwi *et al.*[52]
pancreatic cancer	A positive correlation was identified between the minor allele of rs401681 and telomere shortening ($p = 0.023$); shorter pre-diagnostic LTL was correlated with increased pancreatic cancer risk ($p = 0.048$)	Bao *et al.*[53]
Pancreatic cancer	A weakly positive correlation between longer LTL and pancreatic cancer risk	Campa *et al.*[54]
Pancreatic cancer	Positive correlation of longer LTL with pancreatic cancer risk was observed	Lynch *et al.*[55]
Pancreatic cancer	Short telomeres and extremely long telomeres in PBL are associated with pancreatic cancer risk.	Skinner *et al.*[56]
Pancreatic cancer	Peripheral LTL and TLV were associated with increased pancreatic cancer and CRC risks.	Zhang *et al.*[57]

ACYP2, Acylphosphatase 2; COPD: Chronic obstructive pulmonary disease, CRC: Colo-rectal cancer, DT: Decision tree, DNA: Deoxyribonucleic acid, ESCC: Esophageal squamous cell carcinoma, EGFR: Epidermal growth factor receptor, FHIT: Fragile histidine triad, GC: Gastric cancer, GKN1: Gastrokine 1, HLCC: Human lung cancer cell, HER2: Human epidermal growth factor receptor 2, HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HULC: Highly upregulated in liver cancer, hTERT: human telomerase reverse transcriptase, LTL: Leukocyte telomere length, mRNA: messenger ribonucleic acid, mtDNA: mitochondrial deoxyribonucleic acid, MALAT1: Metastasis-associated lung adenocarcinoma Transcript 1, NSCLC: Non-small cell lung cancer, PIP: Phenylphenanthroimidazole ethylenediamine platinum (II), PCGI: Promoter CpG island, PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic subunit Alpha, PDAC: Pancreatic ductal adenocarcinoma, PBL: Peripheral blood leukocyte, RTL: Relative telomere length, RASSF1A: RAS associated domain family 1, SNPs: Single nucleotide polymorphism, SCCs: Squamous cell carcinomas, SVM: Support vector machine, TL: Telomere length,TRF2: Telomere repeat-binding factor, TLV: Telomere length variation

Study showed that perylene derivatives PM2 and PIPER can induce G-quadruplex formation from both telomeric DNA and the hTERT promoter region *in vitro*. Thus, perylene derivatives are strong contenders as effective agents for cancer therapy. The data in Table 1 showed the studies reporting the association of telomere length alterations with different cancer types.

LIVER CANCER

Cirrhosis may become the main risk factor for liver cancer prolongation. Liver cirrhosis was shown to affect liver function and liver transplantation is the only possible treatment to decrease the mortality at the end stage of cirrhosis[29]. It has been seen that majority of patients who are suffering from the liver injury had some common factors including viral hepatitis, alcohol consumption and fatty liver disease. The pathogenesis of liver cirrhosis is not completely clarified. The association of telomere shortening and cirrhosis have been reported in many previous studies. Recent studies have demonstrated the relation between several single nucleotide polymorphism (SNPs) and liver cirrhosis. Recently, telomere shortening has been presented as a genetic risk factor for liver cirrhosis. Another study investigated the oncogenic action of IKKalpha, IKKbeta and IKKgamma which are components of IKK, a protein kinase[30]. It was demonstrated that IKKalpha plus IKKbeta enhanced liver cancer stem cell growth *in vitro* and *in vivo* whereas IKKgamma prevented it. HOTAIR is required for IKKalpha plus IKKbeta and IKKgamma to control telomerase activity and TL. HOTAIR handles the action of IKKalpha, IKKbeta and IKKgamma in liver cancer stem cells. A small series of highly defined patients and matched timed peripheral blood samples (PBS) as well as paired liver biopsies from patients with diagnosed hepatocellular carcinoma (HCC) were examined[31].The study reported that PBS may be utilized to assay telomere shortening as a predictor for disease persistence in HCC resulting after HBV or HCV infection, but not in non-infectious cause-stimulated HCC.

GASTRIC CANCER

Helicobacter pylori L. infection caused chronic gastritis and raises gastric cancer risk[38]. Another study demonstrated that telomere shortening may be a result of *H. pylori* infection in inflammatory gastric mucosa[38]. Gastric biopsy specimens were procured from 20 patients with chronic gastritis or peptic ulcer caused by *H. pylori* infection. Specimens showed induced NF-kappaB and superoxide dismutase activities and elevated expressions of PARP-1 and gamma-H2AX. All the parameters returned to normal levels after *H. pylori*

treatment. Telomere shortening was suggested to be caused by inflammation mediated overproduction of reactive oxygen species and PARP-1. Another study confirmed the correlation of telomere shortening in gastric mucosa with an increased GC risk[40]. A total of 217 GC patients and 102 subjects without GC were included in the study. Real-time PCR was used to measure RTL which decreased gradually in *H. pylori* negative and positive gastric mucosa of GC free subjects compared to adjacent mucosa and cancer tissue from GC patients ($p<0.0001$). Telomere shortening was found more often in non-neoplastic mucosa of GC patients as compared to GC free subjects ($p<0.0001$). Similarly, the potential link between *H. pylori* related PCGI (promoter CpG island) methylation and telomere shortening in gastric mucosa was examined[39]. About five PCGIs were identified that were closely associated with *H. pylori* infection. Multivariate analysis revealed that telomere shortening increased hyper-methylation risk ($p = 0.016$).

GENETIC VARIANTS

Various genetic polymorphisms and variants have been investigated for their possible associations with GC risk. Influence of the hTERT rs2736100 polymorphism on TL in gastric cancer has been reported[41]. The relationship between rs2736100 polymorphism and the risk of gastric cancer were examined in 243 GC patients and 246 healthy individuals. The rs2736100 A allele carrier was found to be closely associated with reduced hTERT mRNA expression and shortened TL in GC tissue and cell lines. A study reported senescence and apoptosis induced by Gastrokine 1 (GKN1) via regulating TL and telomerase activity in gastric cancer[50]. In AGSGKN1 and MKN1GKN1 cells, telomerase activity, hTERT expression and TL were found to be significantly reduced. Moreover, GKN1 caused senescence and apoptosis through up-regulation of p53, p21, p27 and p16 proteins and down-regulating SKp2. The TL in 35 gastric cancers was shortened significantly compared with the corresponding gastric mucosae. On the contrary, GKN1 expression was inversely associated with TL and c-myc and hTERT mRNA expression. A case-control study was conducted including 1136 gastric cancer cases and 1012 controls to find the link between TL, TL-related genetic variants in Caucasians and risk of gastric cancer in Chinese population[42]. A U-shaped association was observed between TL and GC risk ($p <0.001$) with odds ratios of 3.81 (2.82-5.13), 1.65 (1.21-2.26), 1.28 (0.93-1.77) and 1.78 (1.30-2.44) for individuals in the first (the shortest), second, third and fifth (the longest) quintile as compared to those in the fourth quintile as reference group. These findings suggested that either short or extreme long telomeres may be risk factor for gastric cancer.

Correlation between TL and mitochondrial DNA copy number in intestinal and diffuse type GC samples was examined[44]. Statistically significant correlation was identified in intestinal type GC samples ($r = 0.461$; $p<0.001$), but not in diffuse type GC ($r = 0.225$; $p =0.260$) which indicated that loss of the correlation of telomeres and mitochondrial function may induce the initiation or progression of gastric cancer. The association between single nucleotide polymorphisms (SNPs) in ACYP2 gene and gastric cancer risk in the northwest Chinese Han population was investigated[45]. About 302 GC cases and 300 controls were recruited from northwest China and 13 SNPs from ACYP2 gene were selected. The results revealed that the haplotypes "TTCTAATG" (rs1682111, rs843752, rs10439478, rs843645, rs11125529, rs12615793, rs843711 and rs11896604) and "AC" (rs843706 and rs17045754) were found to be more frequent among patients with GC. The haplotype "CG" has been suggested to have protective role in the GC risk ($p<0.05$). Similarly, HER2 amplification occurred in more than 20% of gastric cancer cases[46]. A study evaluated the combined antitumor efficacy of trastuzumab and various platinum agents in GC cells and the mechanisms involved. The apoptotic effect of the platinum agents on GC cells was observed by double-staining with Annexin V-fluorescein isothiocyanate and propodium iodide. Results indicated the potential role of low-dose trastuzumab administration for increasing oxaliplatin and cisplatin sensitivity in HER2-amplified GC cells[46].

Association of TL in peripheral blood leukocytes with GC risk or oesophageal squamous cell carcinoma (ESCC) in a Chinese Han population was investigated[47]. A total of 574 GC cases, 740 ESCC cases and 774 age and sex-matched healthy controls were included in the study. Shorter RTL was found more in GC or ESCC patients (GC: 1.20 ± 0.42; ESCC: 1.27 ± 0.48) as compared to controls (1.41 ± 0.58). An increasing association between short RTL and smoking in increasing GC ($p = 4.50\times10^{-9}$) or ESCC ($p = 5.93\times10^{-33}$) risks were also observed. Short TL might be a potential molecular marker to identify high-risk individuals[47]. Another study demonstrated that telomere shortening in peripheral blood leukocyte is an independent prognostic marker complementing TNM (Tumor, Nodes and Metastases) stage and correlated with an immunosuppressive phenotype in GC patients[48]. Patients with shorter RTL were found to have worse

overall survival and relapse-free survival than those with long RTL in all patient sets. Patients with short RTL also had a higher CD_{4+} T-cell percentage in PBMCs (Peripheral blood mononuclear cell), $CD^{+}_{19}IL^{-10+}$ Breg percentage in B-cells and plasma IL^{-10} concentration showing an increased immunosuppressive status with short leukocyte RTL. Similarly, the potential association between telomere shortening in the leukocyte DNA, clinic-pathological features and prognosis of gastric cancer in 207 Japanese GC patients was evaluated using quantitative real time polymerase chain reaction (PCR)[49]. Short-telomere group was significantly associated with advanced stage ($p = 0.015$) and worse overall survival (OS). Telomere shortening in leukocyte DNA was found associated with advanced stage and poor prognosis of GC which may reflect their reduced immune response.

PANCREATIC CANCER

Chromosomal instability and telomere shortening in the pancreatic duct epithelium have been reported to be associated with carcinogenesis of the pancreas[51]. The associations of TL and pancreatic cancer risk have been reported[58]. On the contrary, no correlation of genetically predicted short telomeres with pancreatic ductal adenocarcinoma risk was found[52]. Leucocyte telomere length (LTL) and genetic variants at the TERT gene region were found related to pancreatic cancer risk[53]. In this study included a total of 386 cases and 896 controls, revealing the association between short LTL and increased pancreatic cancer risk ($p = 0.048$). Three SNPs at TERT (linkage disequilibrium $r2<0.25$) including rs401681 ($p = 0.002$), rs2736100 ($p = 0.001$) and rs2736098 ($p = 0.002$) were found associated with pancreatic cancer risk. A positive correlation was identified between the minor allele of rs401681 and telomere shortening ($p = 0.023$). In a prospective study, a total of 331 cases and 331 controls were included and the results revealed that LTL was more in cases (0.59 ± 0.20) as compared to controls (0.57 ± 0.17) and a weakly positive correlation between longer LTL and pancreatic cancer risk was observed. The results of the study do not support LTL as a uniform and strong predictor of pancreatic cancer[54]. Another prospective study suggested a positive correlation of longer LTL with induced pancreatic cancer risk ($p = 0.007$)[55]. Another study by Mormile[59] also suggested the associations of TL and pancreatic cancer risk.

Telomere shortening in peripheral blood leukocytes (PBL) has been found in association with pancreatic cancer risk. Conflictingly, extreme long telomeres may also be associated with it[56]. Another study suggested that LTL and TLV have associations with increased pancreatic cancer and colorectal cancer (CRC) risks in Chinese population[57]. About 900 pancreatic cancer cases, 300 CRC cases and 900 controls were included in the study. Both cases with longer LTL ($p = 0.004$) and shorter LTL ($p = 8.50 \times 10^{-6}$) showed higher pancreatic cancer risks. The TLV was found to be associated with increased pancreatic cancer risk ($p = 0.006$).

ROLE OF HUMAN TELOMERASE REVERSE TRANSCRIPTASE (hTERT)

Telomerase is expressed in early human development and then becomes silenced in most normal tissues[60]. Human telomerase reverse transcriptase (hTERT) plays a central role in telomere lengthening for continuous cell proliferation, but it remains unclear how extracellular cause regulate telomerase lengthening of telomeres. Young human cells with long telomeres have been reported to show repressed hTERT epigenetic status, but this status is altered when telomeres become short. This change correlated with altered expression of TERT and genes near to TERT[60]. Various researches reported involvement of hTERT in telomere alteration[61-65].The Table 2 depicted the studies reporting the association of hTERT with telomere length alterations.

hTERT expression was found to be significantly higher in tissue from cancer-adjacent polyps (CAP) in comparison to cancer-free polyps (CFP) ($p = 0.05$). Interestingly, CAP tissues had shorter telomeres and polyp TLs of aggressive CAPs were significantly different from the polyps of non-aggressive CAPs, ($p = 0.01$)[66]. Bone Morphogenetic Protein-7 (BMP7) has been reported to increase telomere shortening and cell aging by involving BMPRII receptor and Smad3- mediated repression of the hTERT gene[67]. In a recent study, quantitative PCR identified hTERT promoter mutation in 36% of patients with HNSCC which had shorter telomeres in early stage tumors[68]. rs2736100 polymorphism of the hTERT gene has been found involved in the regulation of hTERT expression and telomere length[43,41]. On the contrary, RTL has been found to be shorter in familial non-medullary thyroid cancer affected members but was not associated with altered copy number or expression of hTERT[69].

HMGB1 knockdown in MCF-7 cells inhibited telomerase activity and cell proliferation[69]. Single nucleotide polymorphisms in the region of hTERT gene were found to be associated with various malignancies. Telomerase RNA gene hTERT genotypes were recently linked to TL. A study analyzed 21 polymorphisms in the hTERT gene and RTL at average age 50 and 60 in 959 individuals with repeated blood samples.

Table 2: Studies reporting the association of hTERT with telomere length alterations

Cancer type	Inference	References
Intra uterine growth restriction placentas	Decreased hTERT mRNA leads to decreased protein expression and reduced telomere elongation	Biron-Shental *et al.*[61]
Breast cancer	BMP7 induces the hTERT gene repression	Cassar *et al.*[62]
Gastric cancer	rs2736100 polymorphism of the hTERT gene associated with TL alteration	Choi *et al.*[41]
HNSCC	hTERT promoter mutation may influence TL	Barczak *et al.*[67]
Familial non-medullary thyroid cancer	Shorter RTL is not associated with hTERT expression	He *et al.*[68]
Breast cancer	Knockdown of HMGB1 in MCF-7 cells inhibit telomerase activity	Ke *et al.*[69]

BMP7: Cytokine bone morphogenetic protein-7, hTERT: human telomerase reverse transcriptase; HMGB1: High mobility group box 1, MCF-7: Michigan cancer foundation-7, RTL: Relative telomere length, TL: Telomere length

Mean RTL was associated with four genetic variants of the hTERT gene at age 60 (rs2736100, rs2853672, rs2853677 and rs2853676), two of which reported to be associated with cancer risk[70].

CONCLUSION

Telomere length variations have been reported in varied tumour types in comparison to control tissues. Genetic variations and SNPs of telomere associated gene ACYP2 have been reported to be associated with lung cancer. Long telomeres have also been found associated with higher risk of developing recurrence of lung cancer, especially in women. Long telomeres in peripheral white blood cells may depict increased risk of lung cancer. Telomere shortening may represent a genetic risk factor for the development of cirrhosis. Positive correlation was found between *Helicobacter pylori* infection and telomere shortening in human gastric mucosa, increasing the gastric cancer risk. Telomere shortening has also been observed in the early stages of pancreatic carcinogenesis. Moreover, a weak positive correlation between long leukocyte telomere length and pancreatic cancer risk has been reported. Conclusively, telomere length alterations may be used as novel biomarkers in relation to particular cancer types, but further studies are highly recommended to strengthen the association.

SIGNIFICANCE STATEMENT

Telomere length governs the lifespan of a cell by acting as a biological clock. Telomere alterations have been reported to be associated with different cancer types. The present paper reflects these associations including telomere shortening and extreme elongations in varied cancer subtypes. Paper also discusses the role of human telomerase reverse transcriptase in telomere length alterations. This paper will be useful for the researchers and practitioners in the field of cancer biomarkers and telomere biology.

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