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Altered Telomere Length as a Biomarker Associated with Ovarian and Prostate Cancer

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Abstract **Review Article**

Telomerase activity is known to be a characteristic feature of malignancy. In the present paper, telomeric length alterations have been presented as biomarker or ovarian and prostate cancer diagnosis. Pre-diagnostic telomere length determination may prove to be helpful in diagnosing ovarian cancer development. In tubo-ovarian dysplasia, telomeres were found to be significantly shorter than BRCA1 or BRCA2 mutations. Telomeric length and stability were found to be influenced by proteins including telomerase which is encoded by TERT gene. Short telomere patients exhibited more unplanned hospital admissions and were found to be at higher risk of serious events. Telomere shortening in stromal cells has been found to be associated with risk of prostate gland. Moreover, telomere lengthening has been reported as a risk factor for hereditary prostate cancer. Conclusively, telomere length alterations could serve as a biomarker to predict future cancer risk.

Keywords: Telomere; Telomerase; Ovarian cancer; Tumour marker; Prostate cancer; EGFR; TERT.

INTRODUCTION

Telomeric dysfunction, by any means, initiates genomic instability which increases the risk of cancer. Individuals with short telomeres are at increased risk for cancer. However, individuals with long telomeres also display an increased risk for major cancers [1]. Epidermal growth factor receptor (EGFR) pathway has been shown to regulate telomerase function [2]. 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 [3]. But a faulty telomerase action may result in genomic instability that may lead to cancer.

Various researchers have reported the relationship of telomere length (TL) and different cancer types including ovarian cancer [4-10] and prostate cancer [11-15]. In this review paper, an attempt has been made to compile up the studies reporting the association of TL and the above two mentioned cancer types. A wide literature search was done to compile the studies. A number of search attempts were made with different keywords related to telomeric length and cancer types. Various keyword combinations were also used to search the papers. Databases used were PubMed and Google Scholar. The retrieved studies were grouped with respect to the cancer types.

Alteration in telomere length has been observed in most human cancers and is known to be a feature of malignancy [16]. Short telomeres lead to genomic instability [1]. Individuals with short telomeres are at an increased risk for cancer. Length of telomeres may be used as biomarker for the prediction and progression of a particular cancer type. The studies reporting alteration of TL in relation to ovarian and prostate cancer types are discussed below.

Ovarian cancer

Genetic instability plays an important role in ovarian carcinogenesis [17]. Pre-diagnosis LTL may reflect an early event in the ovarian cancer development and could serve as a biomarker to predict future risk [10]. Andreassi *et al.* [18] compared dose response curves for TL and MN frequency in peripheral blood lymphocytes exposed to high energy pulses and X-ray radiations. Cell viability was monitored in the OVCAR-3 ovarian cancer cell line. Effects of tumour cell survival after exposure to laser driven electron pulse were also evaluated and compared to electron beams produced by conventional radiofrequency accelerator commonly used for radiotherapy. Relative biological effectiveness (RBE) for micronucleus induction was

calculated from the alpha coefficients for electrons. Mean TL was found to be reduced in a significant dose-dependent manner. The RBE values obtained were 1.3 and 1.2 after comparing the alpha values. Results revealed a radiobiological response, shortening of telomere and reduction of cell survival in blood samples and cancer cells exposed in-vitro to laser-generated electron bunches. Chene *et al.* [17] investigated the level of telomere shortening and genomic instability in early and pre-invasive stages of ovarian cancer, serous tubal intraepithelial carcinoma (STIC), and tubo-ovarian dysplasia (TOD). The results were obtained from the analysis of 51 TOD from prophylactic salpingo-oophorectomies with BRCA1 or 2 mutation, 12 STICs, 53 tubo-ovarian high-grade serous carcinoma, and 36 noncancerous controls. TOD showed marked telomere shortening compared to non-cancerous controls ($P < 10^{-7}$). STICs had even shorter telomeres than TOD (P = 0.0008). Ovarian carcinoma had shorter telomeres than controls but longer than STICs and dysplasia. In TOD, telomeres were significantly shorter in those with BRCA1 mutation than in those with BRCA2 mutation (P = 0.005).

Association between TERT-locus SNPs and leucocyte telomere measures with multiple cancer risks was investigated [4]. Approximately, 480 SNPs at the TERT locus in breast (n = 103,991), ovarian (n = 39,774) and BRCA1 mutation carrier (n = 11,705) cancer cases were analysed by using the Illumina custom genotyping array. Most associations clustered into three independent peaks. The minor allele at the peak 1 SNP rs2736108 associated with longer telomeres ($P = 5.8 \times 10^{-7}$), lower risks for estrogen receptor (ER)-negative ($P = 1.0 \times 10^{-8}$), BRCA1 mutation carrier ($P = 1.1 \times 10^{-5}$) breast cancers and altered promoter assay signal. The minor allele at the peak 2 SNP rs7705526 associated with longer telomeres ($P = 2.3 \times 10^{-14}$), higher risk of low-malignant-potential ovarian cancer ($P = 1.3 \times 10^{-15}$) and greater promoter activity. Cancer risk alleles of rs2242652 and rs 10069690, respectively were reported to increase silencing and generate a truncated TERT splice variant. TL and stability are also reported to be influenced by proteins, including telomerase which is partially encoded by the TERT gene [6]. Falandry *et al.* [5] also reported TL as a prognostic biomarker in elderly advanced ovarian cancer patients. They tested the hypothesis that TL could predict patient vulnerability and outcome with cancer treatment. Short telomere patients were found to be at higher risk of serious adverse events (OR = 2.7; P = 0.02) and had more unplanned hospital admissions (OR = 2.1; P = 0.08). On the other hand, Kotsopoulos *et al.* [7] suggested no significant correlation of TL with ovarian cancer-specific mortality (P log-rank test = 0.55). Hazard Ratio (HR) for women in the highest three quartiles of TL z score combined was found to be 0.88 (95% CI, 0.77 – 1.10) and the corresponding estimates for serous as well as non-serous tumours were found to be 0.68 (95% CI, 0.66 – 1.13) and 1.13 (95% CI, 0.71 – 1.79) respectively.

Telomere maintenance genes have been investigated for their association with ovarian cancer [6]. A total of 417 ovarian cancer cases and 417 matched controls were included in a study. Strongest association was found with TNKS gene (rs10093972, hazard ratio = 1.88; 95% CI: 1.20 – 2.92; P = 0.006, Q = 0.076). Thus it is suggestive that genetic variations in telomere-maintenance genes may be associated with ovarian cancer risk and outcome [9]. Yang *et al.* [10] investigated the association of LTL with ovarian cancer risk. A total of 442 cases and 727 controls were included in the study. A decreased risk of ovarian cancer with longer LTL was found. The women with ovarian cancer in the top quartile of LTL had an odds ratio (OR) of 0.67 (95% CI, 0.46 – 0.97) in comparison to the women in the bottom quartile. Inverse associations were stronger for non-serous cases (OR quartile 4 vs. quartile 1 of LTL = 0.55, 95% CI, 0.33 – 0.94) and cases who died within 3 years of diagnosis (OR quartile 4 vs. quartile 1 of LTL = 0.55, 95% CI, 0.32 – 0.95). Sarkar *et al.* [8] found that G-rich T-oligos (GT-oligos; oligonucleotides with homology to telomeres) induced transcript expression of the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors DR-4 and DR-5, which are generally silenced in ovarian cancer cells.

Prostate cancer

Telomere shortening in stromal cells has been found associated with prostate cancer risk [14]. A total number of 32 cases and 50 controls were included in the study. As a result, men with short stromal cell TL (below median) had 2.66 (95% CI 1.04-3.06; P = 0.04) times the odds of prostate cancer as compared to men who had longer lengths (at or above median). Moreover, no statistically significant associations were observed for short TLs in normal-appearing basal (OR = 2.15, 95% CI 0.86-5.39; P= 0 .10) or luminal (OR = 1.15, 95% CI 0.47-2.80; P = 0.77) cells. Another study [13] also reported that the combination of higher telomere length alterations in cancer cells and telomere shortening in cancer-associated stromal (CAS) cells was related with induced metastasis and prostate cancer death. Griebling [12] suggested that telomere lengthening is a risk factor for hereditary prostate cancer.

Table-1: Studies reporting the association of telomere length alterations with ovarian and prostate cancer types

Sr. No.	Authors	Year	Cancer type	Results	Reference
1.	Andreassi *et al.*	2016	Ovarian cancer	Induction of micronuclei and shortening of telomere in blood samples and cancer cells exposed in-vitro to laser-generated electron bunches	[18]
2.	Chene *et al.*	2013	Ovarian cancer	TOD showed marked telomere shortening compared to noncancerous controls ($P < 10^{-7}$), STICs had shorter telomeres than TOD ($P = 0.0008$) and ovarian carcinoma had shorter telomeres than controls but longer than STICs and TOD	[17]
3.	Bojesen *et al.*	2013	Ovarian cancer	Multiple independent variants at TERT locus are correlated with TL in ovarian and BC risks	[4]
4.	Falandry *et al.*	2015	Ovarian cancer	TL is a predictive biomarker in elderly advanced patients of ovarian cancer	[5]
5.	Harris *et al.*	2012	Ovarian cancer	Positive correlation found between genetic variation in five telomere maintenance genes and ovarian cancer	[6]
6.	Sun *et al.*	2017	Ovarian cancer	Genetic variants in telomere maintenance genes are correlated with ovarian cancer risk and outcome	[9]
7.	Kotsopoulos *et al.*	2014	Ovarian cancer	No significant correlation of TL with ovarian cancer-specific mortality (P log-rank test = 0.55)	[7]
8.	Sarkar *et al.*	2013	Ovarian cancer	Telomere-homologous G-rich oligonucleotides sensitize human ovarian cancer cells to TRAIL-induced growth inhibition and apoptosis	[8]
9.	Yang *et al.*	2017	Ovarian cancer	Increased LTL may be associated with a decreased ovarian cancer risk	[10]
10.	Heaphy *et al.*	2015	Prostate cancer	Telomere shortening in normal stromal cells is associated with prostate cancer risk	[19]
11.	Chen *et al.*	2017	Prostate cancer	No specificity of telomere-binding protein TRF2 in prostate cancer found; TRF1 may be associated with prostate cancer progression	[11]
12.	Griebling	2015	Prostate cancer	TL is a risk factor for hereditary prostate cancer	[12]
13.	Heaphy *et al.*	2013	Prostate cancer	Telomere shortening in CAS cells was strongly associated with induced metastasis and prostate cancer death	[13]
14.	Heaphy *et al.*	2015	Prostate cancer	Telomere shortening in normal stromal cells is associated with prostate cancer risk	[14]
15.	Hurwitz *et al.*	2014	Prostate cancer	Shorter LTL may be associated with higher odds of prostate cancer in pre-diagnostic samples	[15]
16.	Julin *et al.*	2015	Prostate cancer	longer LTL was modestly associated with higher risk of prostate cancer	[20]
17.	Ornish *et al.*	2013	Prostate cancer	RTL increased from baseline by a median of 0.06 telomere to single-copy gene ratio (T/S)units in the lifestyle intervention group, but decreased in the control group	[21]
18.	Reddy *et al.*	2015	Prostate cancer	DDR signalling pathway inhibitors may enhance the potency of AR-targeted therapies for prostate cancer	[22]
19.	Sharpley *et al.*	2017	Prostate cancer	Positive correlation found between decreased TL, depressed mood, anhedonia and peevishness in prostate cancer patients	[23]
20.	Svenson *et al.*	2017	Prostate cancer	Long LTL in prostate cancer patients at diagnosis is associated with poor metastasis-free and cancer-specific survival	[24]
21.	Wark *et al.*	2017	Prostate cancer	3D telomere analysis of CTCs can identify disease heterogeneity providing better treatment to high-risk prostate cancer patients	[25]
22.	Weber *et al.*	2016	Prostate cancer	Maternal and neonate factors had no correlation with cord blood TL; TL did not differ by race	[26]
23.	Wulaningsih *et al.*	2017	Prostate cancer	Positive correlation was found between PSA and LTL contributing to prostate cancer progression	[27]

Chen *et al.* [11] investigated TRF1 and TRF2 (telomere repeat binding factor 1 and 2) expressions in prostate cancer and their associations with clinic-pathological features. A total of 50 prostate cancer tissues and paired benign prostate hyperplasia tissues were analysed. TRF1 expression was found to be higher in prostate cancer tissue as compared to benign prostate hyperplasia tissue (chi2 = 62.69, P < 0.01). Moreover, a positive association of TRF1 expression with surgical capsular invasion (Spearman's r = 0.43, P = 0.002), seminal vesicle invasion (Spearman's r = 0.35, P = 0.01), lymph nodes metastases (Spearman's r = 0.41, P = 0.003), total prostate specific antigen (r = 0.61, P < 0.05) and Gleason score (r = 0.47, P = 0.01) was observed. Elevated levels of TRF2 were identified in both prostate cancer and benign prostate hyperplasia tissue (chi2 = 1.13, P = 0.76). Hence, TRF1 was reported to be correlated with increased prostate cancer risk. Telomeric length in leukocytes has been found associated with higher prostate cancer risk. Hurwitz *et al.* [15] reported that shorter LTL may be associated higher odds of prostate cancer when analysed in pre-diagnostic samples whereas another prospective study [20] presented that longer LTL was associated with increased prostate cancer risk in a nested case control study which included 922 cases and 935 controls. Svenson *et al.* [24] also reported that prostate cancer patients with long LTL at diagnosis is associated with poor metastasis-free and cancer-specific survival.

A small pilot study was conducted including a total of 10 cases and 25 controls [21]. Blood samples were taken at 5 years and compared RTL and telomerase enzymatic activity per viable cell with those at baseline and their association to the degree of lifestyle changes was analyzed. RTL increased from baseline by a median of 0.06 telomere to single-copy gene ratio (T/S) units (IQR -0.05 to 0.11) in the lifestyle intervention group but reduced in the control group (-0.03 T/S units, -0.05 to 0.03, difference p = 0.03). At 5 years, telomerase activity had reduced from baseline by 0.25 (-2.25 to 2.23) units in the lifestyle intervention group and by 1.08 (-3.25 to 1.86) units in the control group (p = 0.64) and was not found associated with any lifestyle changes (relative risk 0.93, 95% CI: 0.72 – 1.20, p = 0.57). Reddy *et al.* [22] proposed that resistors of DNA damage response signalling pathways may offer a strange accommodation to enhance the potency of AR (Androgen receptor)-targeted therapies for the treatment of androgen-sensitive and castration-resistant prostate cancer. A study by Weber *et al.* [26] revealed that maternal and neonate factors were not in correlation with cord blood TL. TL did not differ by race. TL at birth does not explain the prostate cancer racial disparity when venous umbilical cord blood leukocyte RTL was measured by qPCR in 38 black and 38 white full-term male neonates. Another study found a positive correlation between prostate-specific antigen (PSA) and LTL contributing to prostate cancer progression [27].

CONCLUSION

Telomere biology is related to cancer initiation and prognosis. Both telomere shortening and extreme elongation have been found in correlation with different type of cancer progressions. Studies retrieved for the present review revealed telomeric length variations to be characteristic of ovarian and prostate cancer types. Pre-diagnostic telomere length determination may prove to be helpful in diagnosing ovarian cancer development. Telomeres have been found shorter than BRCA1 or BRCA2 mutations in case of tubo-ovarian dysplasia. Short telomere patients have been found at higher risk of serious events and unplanned hospital admissions. Telomere shortening in stromal cells has been found to be associated with risk of prostate gland. Telomere lengthening has been reported as a risk factor for hereditary prostate cancer. Conclusively, telomere length alterations can be used as biomarkers or ovarian and prostate cancer diagnosis. Further studies are recommended so as to strengthen this association.

Authors' contribution

ZS conceived the study. PK participated in the design of the study. Both the authors drafted the manuscript. Both authors read and approved the final manuscript.

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