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Telomere Length and Mortality Following a Diagnosis of Ovarian Cancer

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Abstract

Background—Telomeres are essential for the maintenance of chromosomal integrity. Telomere shortening leads to genomic instability which is hypothesized to play a role in cancer development and prognosis. No studies to date have evaluated the prognostic significance of telomere length for ovarian cancer.

Methods—We examined whether relative telomere length in peripheral blood leukocytes was associated with survival following a diagnosis of ovarian cancer. We analyzed data from a large population-based study of incident ovarian cancer conducted in Ontario between 1995 and 2004. Telomere length was measured using the quantitative PCR (qPCR)-based relative telomere length assay and vital status was determined by computerized record-linkage and by chart review (n = 1,042). Proportional hazard models were used to estimate ovarian cancer-specific survival hazard

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Disclosure/Conflict of Interest
The authors declare no conflicts of interest.

ratios (HRs) and 95% confidence intervals (CI) associated with quartiles of telomere length *z* score.

Results—We found no significant relationship between telomere length and ovarian cancer-specific mortality (*P* log-rank test = 0.55). Compared to women in the lowest quartile of telomere length *z* score, the HR for women in the highest three quartiles of telomere length *z* score combined was 0.88 (95%CI 0.77–1.10). The corresponding estimates for serous and non serous tumors were 0.68 (95%CI 0.66–1.13) and 1.13 (95%CI 0.71–1.79), respectively.

Conclusions—Our data provide preliminary evidence that telomere length likely does not predict outcome after a diagnosis of ovarian cancer.

Impact—This represents the first study to suggest no prognostic role of telomere length for ovarian cancer.

Keywords

ovarian cancer; prognosis; telomere length; survival

Introduction

Telomeres are essential for the maintenance of chromosomal integrity and telomere shortening is hypothesized to play a role in cancer risk and prognosis (1). Studies of ovarian tumor tissue suggest that telomerase activity and telomere shortening may play an important role in ovarian carcinogenesis, particularly for high-grade serous tumors (2–4); however, no studies have evaluated the prognostic significance of telomere length among ovarian cancer patients. Thus, we sought to examine the degree of association between telomere length in peripheral blood leukocytes (PBLs) and ovarian cancer survival.

Materials and Methods

All patients in Ontario, Canada, diagnosed from January 1995-December 1999 and January 2002-December 2004 with invasive epithelial ovarian cancer were identified by monitoring acquisitions of the Ontario Cancer Registry (OCR) (see (5) for further detail on study population and sample collection). Survival status was determined both by computerized linkage to death certificate records of the OCR and by chart review at local hospitals.

Relative telomere length in genomic DNA from PBLs was measured using a modified high-throughput version of a quantitative PCR-based method (6). This assay quantifies the ratio of telomere repeat copy number to a single-gene copy number (T/S). Each sample was analyzed in triplicate and the relative telomere length was the average exponentiated T/S ratio corrected for a reference sample.

We computed relative telomere length *z* scores within each batch to minimize the impact of potential batch shift. Telomere length *z* scores were then combined and divided into quartiles based on the distribution in the entire cohort. Ovarian cancer-specific survival was defined as the duration from date of diagnosis until date of death from ovarian cancer. Survival was censored at death from another cause or September 30, 2010, the most recent

limit of available death-certificate information (if alive). We performed a left-truncated survival analysis to ensure that each woman only contributed person-years from the date of blood draw and employed Cox proportional hazards models to estimate adjusted survival curves, hazard ratios (HRs) and 95% confidence intervals (CIs) (5). All analyses were carried out using SAS Version 9.1 (SAS Institute, Cary, NC, USA). All *P*-values are two-sided.

Results

Table 1 displays characteristics of the 1,042 women included in the current study, according to category of telomere length *z* score. Age at blood draw, age at diagnosis, histology, and chemotherapy status differed significantly according to quartile of telomere length *z* score ($P \leq 0.04$).

There was no significant relationship between telomere length *z* score and survival (Table 2). Compared to women in the lowest quartile of telomere length *z* score, risk of death for women in the highest three quartiles of telomere length *z* score combined was 0.85 (95%CI 0.69–1.05) in the reference model and 0.88 (95%CI 0.77–0.10) in the multivariate model. There was no significant relationship between telomere length and risk of death among women diagnosed with a serous (HR = 0.86; 95%CI 0.66–1.13) or non-serous tumor (HR = 1.13; 95%CI 0.71–1.79). Telomere length was not associated with survival among women with *BRCA* mutations (data not shown).

Discussion

We found no significant relationship between longer telomere length and ovarian cancer-specific mortality. To our knowledge, this represents the first study that has evaluated the association of telomere length on survival following a diagnosis of ovarian cancer.

Three case-control studies have evaluated the relationship between PBL telomere length and risk of ovarian cancer: two reported shorter telomere length among ovarian cancer patients compared with controls while one reported no relationship between telomere length and ovarian cancer risk (3, 4, 7). Two groups have reported significantly shorter telomeres in serous tubal intraepithelial carcinomas, the putative precursor of high-grade serous ovarian carcinoma, compared with high-grade serous ovarian cancers or control samples, supporting the hypothesis for a state of genomic instability during the pre-invasive stage of ovarian carcinogenesis (2, 8).

Strengths of the current study include the large number of cases, long follow-up, use of triplicate measurements, and the ability to adjust for confounders. Although DNA from PBL may not reflect telomere length in the tumor itself, telomere length is said to be highly synchronized in a variety of tissues (1, 3) and significant correlations between leukocyte DNA and matched tissues have previously been reported (1). We cannot exclude the possible influence of reverse causation with telomere attrition as a direct consequence of the cancer itself or of its treatment (1).

In summary, our findings suggest that telomere length in PBLs likely does not predict mortality following diagnosis of ovarian cancer, although these findings require replication. Future studies that evaluate telomere length in ovarian tumors are warranted given the promising results of trials with telomerase inhibitors and telomerase immunotherapy (1).

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Table 1

Selected Characteristics of 1,042 Epithelial Ovarian Cancer Cases, by Relative Telomere Length *z* Score

Characteristic	Quartile 1 N=260	Quartile 2 N=261	Quartile 3 N=260	Quartile 4 N=261	*p*[c]
Age at blood, mean (SD[a])	62.2 (10.8)	61.5 (10.8)	59.7 (11.5)	55.7 (12.1)	<0.0001
Age at diagnosis, mean (SD)	59.8 (10.8)	59.1 (10.8)	57.4 (11.5)	53.3 (12.1)	<0.0001
Body mass index 5 years in past (kg/m^2), mean (SD)	26.4 (5.6)	26.7 (10.1)	25.8 (5.8)	26.2 (8.8)	0.62
Smoking status, ever, n (%)	124 (50)	132 (53)	122 (50)	113 (47)	0.60
Histology, n (%)					
Serous	154 (59)	156 (60)	133 (51)	126 (48)	
Mucinous	13 (5)	17 (7)	27 (10)	33 (13)	
Endometrioid	50 (19)	50 (19)	59 (23)	60 (23)	
Other[b]	43 (17)	38 (17)	41 (16)	42 (16)	0.04
Stage, n (%)					
I	35 (14)	38 (15)	52 (20)	62 (24)	
II	45 (1)	48 (18)	53 (20)	45 (17)	
III	137 (53)	132 (51)	126 (49)	115 (44)	
IV	42 (16)	43 (17)	29 (11)	38 (15)	0.06
Chemotherapy (yes), n (%)	119 (87)	115 (79)	117 (77)	101 (69)	0.003
BRCA1 mutation, n (%)	19 (8)	19 (8)	12 (5)	16 (6)	0.53
BRCA2 mutation, n (%)	14 (6)	12 (5)	12 (5)	9 (4)	0.75

[a] SD = standard deviation.

[b] Other includes the following tumor types: clear cell, mixed histology, epithelial not otherwise specified, and adenocarcinomas.

[c] Differences between clinical or pathologic characteristics of the subjects by category of telomere length were assessed using the t-statistic or χ^2 statistic, as appropriate.

N.B: The coefficient of variation (CV) for the average exponentiated T/S ratio of the quality control samples was 14%. For further quality control, we calculated the exponentiated T/S ratio for each sample replicate and excluded samples with a replicate CV of >20% (n=36).

Table 2

Ovarian-Cancer Specific Mortality by Relative Telomere Length *z* Score Quartiles Among Ovarian Cancer Patients.

Relative TL *z* score	Reference Model[a] HR[b] (95%CI)	*P*	Multivariate Model HR[c] (95%CI)	*P*
Quartile 1	1.00 (ref)		1.00 (ref)	
Quartile 2	0.79 (0.60–1.02)	0.07	0.80 (0.60–1.05)	0.11
Quartile 3	0.90 (0.69–1.17)	0.43	0.94 (0.71–1.25)	0.66
Quartile 4	0.88 (0.67–1.07)	0.35	0.92 (0.69–1.23)	0.57
Quartile 2+3+4	0.85 (0.69–1.05)	0.13	0.88 (0.77–1.10)	0.25
***P* – trend**	0.97 (0.89–1.06)	0.55	0.99 (0.90–1.09)	0.83
Serous tumors				
Quartile 1	1.00 (ref)		1.00 (ref)	
Quartile 2	0.90 (0.67–1.23)	0.50	0.88 (0.63–1.23)	0.47
Quartile 3	0.86 (0.63–1.18)	0.36	0.84 (0.60–1.17)	0.29
Quartile 4	0.88 (0.64–1.20)	0.42	0.87 (0.62–1.22)	0.41
Quartile 2+3+4	0.88 (0.68–1.14)	0.33	0.86 (0.66–1.13)	0.28
***P* – trend**	0.96 (0.88–1.06)	0.40	0.95 (0.85–1.06)	0.38
Non-serous tumors				
Quartile 1	1.00 (ref)		1.00 (ref)	
Quartile 2	0.89 (0.53–1.51)	0.67	0.97 (0.55–1.70)	0.91
Quartile 3	1.19 (0.71–1.98)	0.51	1.33 (0.76–2.33)	0.32
Quartile 4	0.98 (0.56–1.70)	0.94	1.13 (0.63–2.03)	0.67
Quartile 2+3+4	1.01 (0.66–1.55)	0.96	1.13 (0.71–1.79)	0.62
***P* – trend**	1.03 (0.86–1.22)	0.77	1.04 (0.45–2.41)	0.92

[a] Reference HR adjusted for age at blood (continuous), batch (batch 1, batch 2) and stage (I, II, III, IV).

[b] HR = hazard ratio; CI = confidence interval.

[c] Multivariate HR adjusted for adjusted for age at blood (continuous), batch (batch 1, batch 2), stage (I, II, III, IV), age at diagnosis (continuous), *BRCA* mutation status (carrier/non-carrier), histologic subtype (serous, mucinous, endometrioid, other), BMI five years prior to the cancer diagnosis (continuous), smoking history (ever/never) and chemotherapy (yes/no).