Research Article

Lymphocyte Telomere Length Is Long in \textit{BRCA1} and \textit{BRCA2} Mutation Carriers Regardless of Cancer-Affected Status

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Abstract

**Background:** Telomere length has been linked to risk of common diseases, including cancer, and has previously been proposed as a biomarker for cancer risk. Germline \textit{BRCA1} and \textit{BRCA2} mutations predispose to breast, ovarian, and other cancer types.

**Methods:** We investigated telomere length in \textit{BRCA} mutation carriers and their non-carrier relatives and further examined whether telomere length is a modifier of cancer risk in mutation carriers. We measured mean telomere length in DNA extracted from whole blood using high-throughput quantitative PCR. Participants were from the EMBRACE study in United Kingdom and Eire ($n=4,822$) and comprised \textit{BRCA1} ($n=1,628$) and \textit{BRCA2} ($n=1,506$) mutation carriers and their non-carrier relatives ($n=1,688$).

**Results:** We find no significant evidence that mean telomere length is associated with breast or ovarian cancer risk in \textit{BRCA} mutation carriers. However, we find mutation carriers to have longer mean telomere length than their non-carrier relatives (all carriers vs. non-carriers, $P_{\text{trend}}=0.0018$), particularly in families with \textit{BRCA2} mutations (BRCA2 mutation carriers vs. all non-carriers, $P_{\text{trend}}=0.0016$).

**Conclusions:** Our findings lend little support to the hypothesis that short mean telomere length predisposes to cancer. Conversely, our main and unexpected finding is that \textit{BRCA} mutation carriers (regardless of cancer status) have longer telomeres than their non-mutation carrier, non-cancer-affected relatives. The longer telomere length in \textit{BRCA2} mutation carriers is consistent with its role in DNA damage response. Overall, it seems that increased telomere length may be a consequence of these mutations, but it is not itself directly related to the increased cancer risk in carriers.

**Impact:** The finding that mutation carriers have longer mean telomere lengths than their non-carrier relatives is unexpected but biologically plausible and could open up new lines of research into the functions of the BRCA proteins. To our knowledge, this is the largest study of telomere length in \textit{BRCA} mutation carriers and their relatives. The null cancer-risk association supports recent large prospective studies of breast and ovarian cancer and indicates that mean telomere length would not be a useful biomarker in these cancers. *Cancer Epidemiol Biomarkers Prev; 23(6); 1018–24. ©2014 AACR.*
Introduction

Human chromosomes are capped and stabilized by telomeres, comprising several thousand (TTAGGG)$_n$ repeats and a plethora of structural proteins (1–3). Telomere length shortens with each cell division, leading to a progressive decrease with age (4–7) and rare mutations in telomere maintenance genes, such as TERT, can cause dramatically shortened telomeres and premature aging (8, 9). It has therefore been hypothesized that short mean telomere length may predispose to a number of diseases of aging, including cardiovascular disease (10–13) and cancer, and thus could be used as a biomarker of disease risk (14). The association of cancer risk with mean telomere length, measured in DNA from leukocytes, has been evaluated in a number of studies, but the results have been inconclusive. Retrospectively collected studies, where blood samples for telomere length analysis have been taken after cancer diagnosis, have generally found patients with cancer to have shorter telomeres than unaffected controls (15–18). However, results from more appropriate prospective study designs, with blood collected before diagnosis, have been largely null (16, 19–21).

In fact, the largest prospective study yet published, of 3,142 cancers from a general population study of 47,102 Danish individuals, reported a correlation between shorter telomere length and a very modest yet significant increase in cancer risk (22). Mutations in BRCA1 and BRCA2 confer high risks of breast, ovarian, and other cancers. BRCA1 and BRCA2 are integral to the early stages of DNA damage recognition and repair (23). BRCA1 is activated by ATR and is involved in cell-cycle arrest and replication fork stalling (with CHEK2), and breakage site stabilization (with BRIP1 and BARD1) through directly binding the damaged DNA (24, 25). BRCA2 is activated by ATM and recruited to the repair site indirectly via BRCA1, where it stimulates the recruitment of RAD51, a protein integral to repair through homologous recombination and Holliday junction formation (26).

To date, few other studies have examined telomere length in BRCA1 and BRCA2 mutation carriers. Martínez-Delgado and colleagues (27) reported shorter telomere length in cancer in BRCA1 and BRCA2 carriers compared with sporadic breast cancer, and an earlier age of cancer onset, and shorter age-adjusted telomere length, in successive generations of patients with cancer. The same group recently reported retrospectively collected sporadic ($n = 178$) and hereditary ($n = 168$) ovarian cancer cases to have shorter telomeres when compared with 267 control samples (28).

In this study, we have evaluated the hypothesis that short telomere length predisposes to breast or ovarian cancer by examining mean telomere length in BRCA1 and BRCA2 mutation carriers from the EMBRACE study in United Kingdom and Eire. We have compared mean telomere length between mutation carriers who have been diagnosed with breast or ovarian cancer, and as yet unaffected carriers (who remain at high risk of developing cancer in the future). To further evaluate the hypothesis that mutation carriers (affected or unaffected) might display shortened telomeres, we have compared mean telomere length between BRCA1 and BRCA2 mutation carriers and unaffected, mutation-free members from the same families.

Materials and Methods

Study populations

Mean telomere length was determined in blood DNA from participants in the EMBRACE study, an epidemiologic study of BRCA1 and BRCA2 mutation carriers and their relatives (29). The study began recruiting in 1996 through clinical genetics centers in United Kingdom and Eire. Eligible participants were either confirmed mutation carriers, had been (or were in the process of being) tested for BRCA mutations (in families where a pathogenic mutation had been found), had been found to be a non-carrier, or had attended genetic counseling, or had been offered testing, but had declined. The present analysis is based on only proven mutation carriers and non-carrier relatives from EMBRACE.

All participants were over 18 years old and were asked at baseline recruitment to provide a blood sample for DNA analysis, and to complete a comprehensive lifestyle and general health questionnaire. These data were collected to identify any genetic or environmental factors, or surgical interventions, that may modify cancer risks for BRCA1 and BRCA2 mutation carriers and their relatives.

In total, mean telomere length data were available for 4,822 subjects; 3,134 mutation carriers (1,628 with BRCA1 mutations and 1,506 BRCA2 mutations) and 1,688 non-carrier relatives. Of these 3,134 mutation carriers, 439 were male and 2,695 were female. Of the female carriers, 1,494 were known to have been diagnosed with breast or ovarian cancer and 1,201 were unaffected. Further details are given in Table 1. Twelve percent of the total cancer cases studied presented with ovarian cancer, with the majority of 88% having breast cancer as the primary diagnosis, so the two cancer types were pooled for analysis. Cancer diagnoses were predominantly at baseline recruitment (94% of breast cancer cases and 85% of ovarian cancer...
cases) rather than by follow-up or flagging, but all cases were eligible for our analysis, regardless of the timing of presentation as we had much less power to detect effects in the follow-up and flagging groups separate from baseline. Ethical approval was obtained and all participants gave informed consent.

Telomere length measurement
Relative mean telomere length was ascertained by a SYBR Green real-time PCR using a version of the published quantitative PCR protocols (15, 30) modified as described previously (16). In brief, genomic DNA was extracted from whole blood, and telomere length was ascertained through the ratio of detected fluorescence from the amplification of telomere repeat units (TEL) relative to that of a single-copy reference sequence from the β-Globin gene (CON). Telomere and control reactions were performed separately. For each assay, the PCR cycle at which each reaction crossed a predefined fluorescence threshold was determined ($C_t$ value). The difference in the $C_t$ values, $D_{C_t} = C_t^{TEL} - C_t^{CON}$, was the measure of telomere length used in the analysis. We were not able to generate absolute telomere length values using these data as calibration samples of known length were not available. Sixteen percent of the study was run in duplicate, with repeated samples assayed in a secondary run during the experiment, using a separately prepared mix of PCR reagents. Failed PCR reactions were not repeated. A standard plate of “test” samples was additionally assayed with each study. This plate consisted of 94 high-yield DNA samples and was assayed in each PCR batch, performed as a method of interexperiment quality control.

**Table 1.** Summary characteristics for the BRCA1 and BRCA2 carriers and non-carrier relatives used in the analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-carriers</th>
<th>BRCA1 carriers</th>
<th>BRCA2 carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unaffected</td>
<td>Affected</td>
<td>Unaffected</td>
</tr>
<tr>
<td>Total number</td>
<td>1,636</td>
<td>52</td>
<td>797</td>
</tr>
<tr>
<td>Males</td>
<td>306</td>
<td>6</td>
<td>198</td>
</tr>
<tr>
<td>Females</td>
<td>1330</td>
<td>46</td>
<td>599</td>
</tr>
<tr>
<td>Age at blood draw (mean, SE)</td>
<td>45.9 (0.3)</td>
<td>55.4 (1.5)</td>
<td>42.8 (0.5)</td>
</tr>
<tr>
<td>Age at censure (mean, SE)</td>
<td>44.5 (0.3)</td>
<td>54.1 (1.5)</td>
<td>39.6 (0.4)</td>
</tr>
<tr>
<td>Relative telomere length (mean, SE)</td>
<td>n/a</td>
<td>n/a</td>
<td>39.0 (0.5)</td>
</tr>
</tbody>
</table>

**Table 2.** Cancer status and quartile of mean telomere length in female BRCA1 and BRCA2 mutation carriers

<table>
<thead>
<tr>
<th>Relative telomere length</th>
<th>BRCA1 mutation carriers</th>
<th>BRCA2 mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>614 affected, 471 unaffected</td>
<td>499 affected, 459 unaffected</td>
</tr>
<tr>
<td>Q1 longest</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Q2</td>
<td>0.91 (0.67–1.25), 0.57</td>
<td>1.26 (0.87–1.84), 0.23</td>
</tr>
<tr>
<td>Q3</td>
<td>1.27 (0.71–2.28), 0.42</td>
<td>1.89 (0.90–3.98), 0.09</td>
</tr>
<tr>
<td>Q4 shortest</td>
<td>0.85 (0.37–1.98), 0.71</td>
<td>1.27 (0.49–3.34), 0.62</td>
</tr>
<tr>
<td>Per quartile</td>
<td>0.96 (0.76–1.22)</td>
<td>1.17 (0.88–1.56)</td>
</tr>
<tr>
<td>$P_{\text{trend}}$</td>
<td>0.76</td>
<td>$P_{\text{trend}}$ = 0.27</td>
</tr>
</tbody>
</table>

**Note:** Differences in telomere length (by quartile of length) between cancer-affected and unaffected mutation carriers are shown. Associations are presented as HR with 95% CI. Analyses are adjusted for age, study plate, and relatedness. Weights were generated for this study based on time at risk before age at censoring, affected status, and mutation type (BRCA1 or BRCA2).
The correlation between repeated ΔCt measurements of the same study subjects, assayed in separate PCR batches, was 0.87. The Spearman rank order correlation of the triplicate "test" plate ΔCt measurements was 0.71. More than 93% of the samples attempted gave useable mean telomere length measurements. In unaffected subjects, ΔCt increased with age at blood draw was 0.0033 [95% confidence interval (CI), 0.0015–0.0051]; P = 2.8 × 10−4, after adjustment for carrier status, study plate, relatedness, and gender. This is consistent with the established reduction in mean telomere length with age, and the magnitude of the change is consistent with that observed in previous studies.

**Statistical analysis**

The intraexperimental quality control comparisons of duplicated samples were assessed using the Pearson product-moment correlation coefficient. The interexperimental comparison of standard "test" plates, for assurance of batch-to-batch quality control, was assessed using Spearman rank correlation coefficient. Before all analyses, "outlier" samples were removed if the CON PCR Ct value was more than two SDs from the mean, and these reactions were considered "fails.

The association of ΔCt with age at blood draw was evaluated in cancer-free individuals using linear regression, adjusting for age, study plate, gender, and clustered by relatedness. Similarly, the association between mutation carrier status and mean telomere length (ΔCt) was analyzed using linear regression, showing the difference in mean telomere length (ΔΔCt) comparing mutation carriers with non-carriers, with associated 95% CI. The analysis was adjusted for age, study plate, gender, and clustered by relatedness.

The association between disease status in female mutation carriers and telomere length was assessed using a weighted cohort analysis (31–33) Individuals were censored at the age of the first breast cancer diagnosis, ovarian cancer diagnosis, bilateral prophylactic mastectomy, or the age at last observation. Weighted Cox regression was used to adjust for the nonrandom sampling of the mutation carriers with respect to disease status (33). For this purpose, affected and unaffected individuals were allocated differential weights according to breast or ovarian cancer status, such that the weighted cohort mimics a "true" cohort of mutation carriers (32, 33). These weights were generated for this study based on the time at risk before age at censoring, affected status (breast or ovarian), and mutation type (BRCA1 or BRCA2). This approach has been shown to provide unbiased estimates of the relative risks, adjusting for the oversampling of affected individuals, while utilizing the whole dataset. Subjects were

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**Table 3. BRCA1 and BRCA2 mutation carrier status and mean telomere length in all study individuals**

<table>
<thead>
<tr>
<th>Relative telomere length</th>
<th>All carriers 3,134 carriers, 1,688 non-carriers</th>
<th>BRCA1 mutation carriers 1,628 carriers, 1,688 non-carriers</th>
<th>BRCA2 mutation carriers 1,506 carriers, 1,688 non-carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>All none-carriers</td>
<td>0.00 (ref.)</td>
<td>0.00 (ref.)</td>
<td>0.00 (ref.)</td>
</tr>
<tr>
<td>All carriers</td>
<td>−0.056 (−0.091 to −0.021)</td>
<td>−0.038 (−0.079 to 0.003)</td>
<td>−0.067 (−0.108 to −0.026)</td>
</tr>
<tr>
<td>P</td>
<td>0.0018</td>
<td>0.068</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

**Table 4. BRCA1 and BRCA2 mutation carrier status and mean telomere length in EMBRACE in all unaffected individuals**

<table>
<thead>
<tr>
<th>Relative telomere length</th>
<th>All unaffected carriers 1,588 carriers, 1,636 non-carriers</th>
<th>BRCA1 mutation carriers 797 carriers, 1,636 non-carriers</th>
<th>BRCA2 mutation carriers 791 carriers, 1,636 non-carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-carriers</td>
<td>0.00 (ref.)</td>
<td>0.00 (ref.)</td>
<td>0.00 (ref.)</td>
</tr>
<tr>
<td>Carriers</td>
<td>−0.056 (−0.098 to −0.013)</td>
<td>−0.041 (−0.094 to 0.011)</td>
<td>−0.069 (−0.123 to −0.016)</td>
</tr>
<tr>
<td>P</td>
<td>0.011</td>
<td>0.12</td>
<td>0.011</td>
</tr>
</tbody>
</table>

**NOTE:** Differences in telomere length (ΔΔCt) between BRCA1 mutation carriers and BRCA2 mutation carriers and non-carrier relatives in each study are shown. Associations are presented as β-coefficients with 95% CI. Estimates are shown for all unaffected non-carriers compared with all carriers. Analyses are adjusted for age, study plate, relatedness, and gender.
categorized into quartiles for telomere length, the boundaries of which were defined by the continuous distribution of ΔCt in the unaffected mutation carrier sample population; the Q1 reference quartile group had the longest mean telomere length and the Q4 quartile group had the shortest. The analysis was additionally adjusted for study plate and age at blood draw, and clustered by family to allow for the nonindependence between family members. Male mutation carriers (n = 439), carriers of unknown cancer status, and individuals on whom appropriate censoring data were not available were excluded from these analyses.

All analyses were performed using Intercooled Stata 11.2 statistical package (Stata).

Results

The association of mean telomere length with cancer status in BRCA1 and BRCA2 mutation carriers

The differences in telomere length between mutation carriers diagnosed with breast or ovarian cancer and unaffected mutation carriers are shown in Table 2. In a weighted Cox regression analysis, no significant associations were detected between telomere length quartiles and the risk of developing either breast or ovarian cancer in BRCA1 or BRCA2 mutation carriers (Table 2). In addition, no significant trends were observed by quartile of mean telomere length (P(trend) = 0.76 for BRCA1, P(trend) = 0.27 for BRCA2).

Comparison of mean telomere length in BRCA1 and BRCA2 mutation carriers and their non-carrier relatives

The estimated differences in telomere length between BRCA1 and BRCA2 mutation carriers and non-carriers, adjusted for age, study plate, relatedness, and gender, are shown in Tables 3 and 4. Heterozygous carriers of BRCA1 and BRCA2 mutations had longer telomeres than non-carriers (as shown by a negative covariate-adjusted β-coefficient; ΔΔCt = −0.056; 95% CI, −0.091 to −0.021; P = 0.0018; Table 3). This association was more significant for BRCA2 mutation carriers (vs. all non-carriers; ΔΔCt = −0.067; 95% CI, −0.108 to −0.026; P = 0.0016) compared with those with BRCA1 mutations (vs. all non-carriers; ΔΔCt = −0.038; 95% CI, −0.079 to −0.003; P = 0.068). The effect sizes for associations between telomere length and mutation status remained virtually unchanged when the analysis was restricted to BRCA1 and BRCA2 mutation carriers who had not developed breast or ovarian cancer (but remained at high risk of doing so) and cancer-free, non-carrier relatives (Table 4; P(trend) = 0.011).

Discussion

In this study, we found no significant associations between mean telomere length, as measured in blood leukocytes, and cancer status amongst BRCA1 and BRCA2 mutation carriers; that is, we see no evidence that cancer cases from these families have differences in mean telomere length compared with their unaffected, mutation-carrying relatives. This is in agreement with recent studies of telomere length and sporadic cancer risk in the general population (16, 19–22). Unexpected, however, was the identification of a significant difference in mean telomere length between carriers and non-carriers of mutations in the BRCA1 and BRCA2 genes. In our study, mutation carriers (regardless of whether cancer-affected or unaffected) have longer telomeres than individuals from the same families without mutations. This was particularly apparent in families with BRCA2 mutations (P(trend) = 0.0016). Expressed another way, BRCA2 mutation carriers were 50% more likely to have a mean telomere length measurement in the longest quartile for length, compared with the shortest, than non-carriers; OR [Q1 (longest) vs. Q4 (shortest, referent)] = 1.50 (95% CI, 1.25–1.77; P = 0.001). This finding seems initially counter intuitive, as the prevailing hypothesis has been that people at higher risk of developing cancer would have shorter telomeres than people at low risk.

Published literature does lend support to our findings. BRCA1 or BRCA2 knockdown or mutation is reported to variously increase TERT expression, increase telomerase activity, and increase telomere length, but also to reduce the structural stability of the telomere and increase genomic rearrangement. Overexpression of BRCA1 has been shown to inhibit TERT expression and cause telomere shortening in human cancer cell lines (34, 35). Conversely, others report that decreased BRCA1 expression can regulate mean telomere length both by increasing telomerase expression and by increasing telomere length, even in cells lacking telomerase activity (36). In addition to binding the “shelterin” complex of proteins, the telomere is also protected by its tertiary architecture and the T-loop formed using the G-rich single-stranded overhang at the 3’ telomere end. The length of this overhang, and thus the stability of the telomere, are regulated by BRCA1 and RAD50 such that overexpression of either protein increases T-loop length (36). BRCA1 expression knockdown by siRNA, in mammery epithelial cells in vitro, has also been shown to increase the frequency of chromosomal rearrangements, increase telomere attrition, and lead to defective telomere capping (37–40).

Similarly, it has been reported that breast tumors in BRCA2 mutation carriers have significantly more numerous complex chromosomal changes compared with non-carriers, and chromosomal abnormalities characteristic of alternative lengthening of telomeres activity have also been seen in BRCA2−/− cell lines (41–43). BRCA2 (together with RAD51) associates with the telomere during S phase of the cell cycle (44), and mutations in BRCA2 (more so than BRCA1) can induce telomere fragility and shortening, suggesting an important role for BRCA2 in chromosome and telomere stability. BRCA2 is also reportedly important in the replication of the G-rich 3’ lagging strand and, consequently, in telomere length homeostasis (41). On the basis of these observations, it is not surprising that BRCA1 and/or BRCA2 carrier status has a pleiotropic effect on telomere length, independent of any association with cancer risk.
In our analysis of telomere length in cancer-affected versus unaffected BRCA1 and BRCA2 mutation carriers, there is little evidence of an association between mean telomere length and breast or ovarian cancer occurrence. Our findings do not support those of a smaller study, reported by Martinez-Delgado (28), in which telomere length was associated with ovarian cancer status, most significantly in women ages 41 to 50 years ($P_{\text{trend}} = 4.9 \times 10^{-10}$).

One of the major advantages of the EMBRACE study design is that subjects were recruited as part of families that contained carriers, both affected and unaffected, and non-carriers. These samples have been treated identically from collection to storage, so there is less chance of these findings being due to artifacts in DNA processing. For the analysis of telomere length against disease risk, we utilized a weighted cohort approach. While the EMBRACE study is not a true cohort, the weighted cohort approach provides unbiased relative risk estimates while adjusting for the oversampling of affected carriers. A weakness of the current study is that cancer-affected individuals were sampled after diagnosis. It is therefore possible that the comparison of telomere length between cases and controls could be biased if the measurement is affected by the diagnosis of the disease or treatment. This potential bias is similar to that in many case–control studies of telomere length. There may also be survivor bias if women with poor prognosis, and hence are less likely to be, have longer or shorter mean telomere length; however, studies to date have not shown consistent associations between telomere length and survival. A preferable study design would be to utilize samples from carriers taken before diagnosis, and evaluate the association with cancer risk prospectively. Unfortunately, the number of cancers diagnosed prospectively in cohorts of carriers, including EMBRACE, is currently too small to permit prospective analyses, but such analyses should be possible in the future. Notwithstanding, our results suggest that, if there is any association between telomere length and breast cancer risk in carriers, it is likely to be weak. As such, our results are consistent with the results from prospective studies in the general population, and not consistent with previous findings from retrospective case–control studies suggesting a strong association between telomere length and cancer risk. Thus, any previous consideration of telomere length as a potential biomarker for cancer risk seems misplaced (14).

It is possible that in BRCA1 and BRCA2 mutations carriers, longer telomere lengths (compared with their age-adjusted relatives) are maintained by derepression of telomerase but, evidently, maintaining telomere length is insufficient to protect BRCA mutation carriers from cancer development. In a recent study, we found that single-nucleotide polymorphisms (SNP) in the TERT gene (encoding the major subunit of telomerase), which control mean telomere length, are largely independent of other TERT locus SNPs that alter risks of breast and ovarian cancer in the general population, as well as in BRCA1 mutation carriers (45). The roles of TERT in maintaining telomere length and affecting cancer risk are largely separate. Evidence is thus mounting against the hypothesis that measures of mean telomere length (or genetic variants that control mean telomere length) could act as biomarkers for cancer risk.

In conclusion, our main and unexpected finding is that BRCA1 and BRCA2 mutation carriers have longer telomeres than their non-mutation carrier, non–cancer-affected relatives. These results suggest that telomere length is altered in BRCA1 and BRCA2 mutation carriers, but that this is not related to its effect on cancer risk. Our findings lend little support to the hypothesis that shorter mean telomere length predisposes to cancer, and indicate that mean telomere length measurements in blood DNA are unlikely to be useful biomarkers for cancer prediction.

Disclosure of Potential Conflicts of Interest

R. Eeles has honoraria from speakers' bureau from Succinct Communications and Janssen. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: K.A. Pooley, R. Eeles, A.M. Dunning
Development of methodology: K.A. Pooley, A.M. Dunning
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.A. Pooley, A.C. Antoniou, D.F. Easton, A.M. Dunning
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. McGuffog, D. Barrowdale, D. Frost, R. Platte, E. Fineberg, S.D. Ellis
Study supervision: Z. Miedzybrodzka, R. Eeles, A.M. Dunning

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