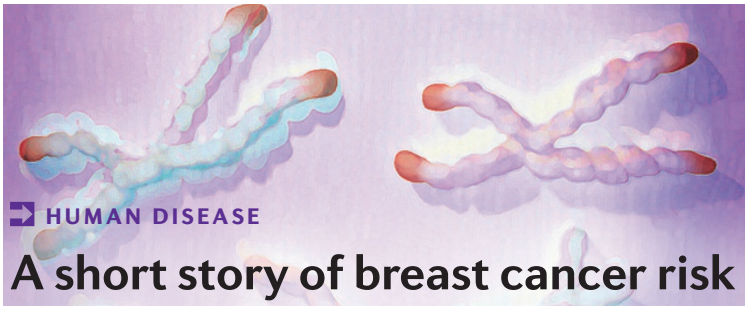

HUMAN DISEASE

A short story of breast cancer risk

A study of blood cells shows that patients with familial breast cancer have shorter telomeres than those found in the general population, and that progressive telomere shortening across generations might explain the genetic anticipation that is seen in families with hereditary breast cancer.

Shorter telomeres have been linked to susceptibility to various cancers, as they predispose the genome to instability and thus to malignant transformation. Separate lines of evidence from genetic diseases other than cancer have implicated telomere shortening in genetic anticipation: the earlier age of onset or increased severity of a disease across generations. Martinez-Delgado *et al.* put together these two observations and hypothesized that telomere shortening could explain both predisposition to hereditary breast cancer and the genetic anticipation of this condition.

The authors studied three groups of patients — from 623 families — who had familial breast and ovarian cancer (FBOC): those with mutations in *BRCA1*, those with mutations in *BRCA2* and those without either mutation (*BRCAX*). Age at diagnosis was much earlier (by 6.8–12.3 years) in daughters than in mothers across these three groups compared to healthy controls. Additionally, studies of blood leukocytes in 198 patients revealed telomeres to be shorter in FBOC cases than in non-FBOC controls and than in sporadic breast cancers. Hereditary breast cancer therefore shows anticipation and is linked to shorter telomeres.

In *BRCA1* or *BRCA2* mutation carriers, telomere shortening seems to be directly linked to the presence of these mutations, as the telomere lengths of the *BRCA1*- or *BRCA2*-mutation-negative sisters of the probands were indistinguishable from those seen in the general population. In *BRCAX* families, most cases (50–70%) are seen in families with the shortest telomere length (those in the first quartile). This finding points to a link between shorter telomere length and breast cancer incidence in *BRCAX* families, even though the heterogeneous genetic factors that are involved in these cases are, of course, unknown. Moreover, the longest telomeres were seen in *BRCAX* families in which the cancer had been detected in one generation only, again suggesting that telomere shortening could be occurring in later generations.

Further support for the authors' hypothesized link between telomere shortening and anticipation of hereditary breast cancer risk came from studying mother–daughter pairs: affected mothers and their *BRCA1*- or *BRCA2*-mutation-carrying daughters, who were either affected or unaffected, and unaffected mother–daughter controls. Telomere length decreased in the *BRCA1*- or *BRCA2*-mutation-carrying daughters of affected mothers, irrespective of whether the daughter was affected, showing that the telomere shortening results from transmission of the mutation rather than from the disease itself.

Although more work needs to be done to explain the mechanistic link between telomere length and the onset of hereditary breast cancer (do cancer-predisposing mutations lead to earlier cancer onset independently of shorter telomeres or by inducing shorter telomeres?), telomere length could already have a use in clinical surveillance.

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ORIGINAL RESEARCH PAPER
Martinez-Delgado, B. *et al.* Genetic anticipation is associated with telomere shortening in hereditary breast cancer. *PLoS Genet.* **7**, e1002182 (2011)
FURTHER READING Cesare, A. J. & Reddel, R. R. Alternative lengthening of telomeres: models, mechanisms and implications. *Nature Rev. Genet.* **11**, 319–330 (2010)