Article:
Barrett, JH orcid.org/0000-0002-1720-7724 (2016) Telomere length and melanoma - is there a straightforward relationship? British Journal of Dermatology, 175 (5). pp. 865-866. ISSN 0007-0963

https://doi.org/10.1111/bjd.14892

Telomere length and melanoma – is there a straightforward relationship?

Telomeres are of major importance to human health, protecting against chromosomal rearrangements and helping to maintain genomic integrity. Telomere length (TL) declines markedly with age, and numerous epidemiological studies have shown an association between shorter telomeres and increased risk of cardiovascular[1] and other chronic disease. However the simple conclusion that longer telomeres are better for human health has been challenged by the observation of a more complex relationship with cancer. Although shorter telomeres are associated with increased risk of some cancers, *longer* telomeres have been associated with increased risk of other cancers[2], including melanoma[3]. The reasons for this are not yet well understood; possibly longer telomeres delay senescence of melanocytic naevi, allowing a higher probability of progression to melanoma[4].

Besides genuine differences of effect, there are many possible reasons for inconsistency in the literature on TL[5]. One problem is that TL is not easy to measure, and there are few large studies. In addition most studies are cross-sectional rather than prospective, and hence may be affected by differences in sample handling or reverse causality. They are also almost always based on measurements of leukocyte TL, relying on this as a proxy for TL in more relevant tissue. However some genetic predictors of leukocyte TL, which have themselves been reliably measured in much larger data sets, also show differences in direction of association between cancers[6]. The genetic studies generally support the evidence for the association between long telomeres and increased risk of melanoma, the strength of the association suggesting telomere genes play a particularly important role in melanoma[7].

In this issue of the BJD, Menin *et al*.[8] report on a cross-sectional study of TL in melanoma cases and controls, where they observe a difference in direction of association with familial and sporadic melanoma. They suggest that this heterogeneity may explain inconsistencies in the published findings for melanoma, some of which are based on more familial and some sporadic cases. There is no doubt that melanoma is a heterogeneous disease[9]; the disease may arise through different aetiological pathways, where UV exposure, nevus phenotype, pigmentation and overall genetic predisposition are of differing importance. In addition, given the complex role of telomeres in oncogenesis[10], evidence for different directions of effect in different subtypes of melanoma would not be altogether surprising. That the important subtypes could be simply identified by those with and without a first degree affected relative would perhaps be more of a surprise.

The findings reported by Menin *et al.*[8] are thus very intriguing, if not totally convincing, based as they are on quite a small sample size. Larger studies are needed to confirm or refute their findings. Understanding the role of telomere length in melanoma could help in understanding disease heterogeneity and also pave the way to providing a useful biomarker of disease risk.

Jenny Barrett
Professor of Statistical Genetics
University of Leeds, Leeds, UK
ORCID number: 0000-0002-1720-7724

Acknowledgements

Thanks to Dr Mark Iles for constructive comments on this note.

This research was supported by Cancer Research UK Programme Award C588/A19167.
There are no conflicts of interest.

References

1. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A and Willeit P (2014) Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 349: g4227.

2. Zhu X, Han W, Xue W, Zou Y, Xie C, Du J and Jin G (2016) The association between telomere length and cancer risk in population studies. Scientific Reports 6: 22243.

3. Caini S, Raimondi S, Johansson H, de Giorgio V, Zanna I, Palli D and Gandini S (2015) Telomere length and the risk of cutaneous melanoma and non-melanoma skin cancer: a review of the literature and meta-analysis. Journal of Dermatological Science 80: 168-174.

4. Nan H, Du M, De Vivo I, Manson JE, Liu S, McTiernan A, Curb JD, Lessin LS, Bonner MR, Guo Q, Qureshi AA, Hunter DJ, Han J (2011) Shorter telomeres associate with a reduced risk of melanoma development. Cancer Res 71:6758-6763.

5. Barrett JH, Iles MM, Dunning AM and Pooley KA (2015) Telomere length and common disease: study design and analytical challenges. Hum Genetics; 134: 679-689.

6. Bojesen SE, Pooley KA, Johnatty SE et al (2013) Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet 45:371-84

7. Iles MM, Bishop DT, Taylor JC, Hayward NK, Brossard M, Cust AE, Dunning AM, Lee JE, Moses EK, Akslen LA; AMFS Investigators, Andresen PA, Avril MF, Azizi E, Scarrà GB, Brown KM, Dębniak T, Elder DE, Friedman E, Ghiorzo P, Gillanders EM, Goldstein AM, Gruis NA, Hansson J, Harland M, Helsing P, Hočevar M, Höiom V; IBD investigators, Ingvar C, Kanetsky PA, Landi MT, Lang J, Lathrop GM, Lubiński J, Mackie RM, Martin NG, Molven A, Montgomery GW, Novaković S, Olsson H, Puig S,

Puig-Butille JA; QMEGA and QTWIN Investigators, Radford-Smith GL, Randerson-Moor J; SDH Study Group, van der Stoep N, van Doorn R, Whiteman DC, MacGregor S, Pooley KA, Ward SV, Mann GJ, Amos CI, Pharoah PD, Demenais F, Law MH, Newton Bishop JA, Barrett JH; GenoMEL Consortium (2014) The effect on melanoma risk of genes previously associated with telomere length. Journal of the National Cancer Institute; 106(10).

8. Menin et al. (2016) Differences in telomere length between sporadic and familial cutaneous melanoma. British Journal of Dermatology.

9. Whiteman DC, Pavan WJ and Bastian BC (2011) The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res.; 24: 879–897.

10. Cesare AJ and Reddel RR (2010) Alternative lengthening of telomeres: models, mechanisms and implications. Nature Reviews Genetics 11: 319-330.