Letter to the Editor

Title: Epiphenomenon of telomere lengths – lessons from Ulcerative colitis

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We read with great interest the article by Jones et al (*Gut 2012;61:248-54)* detailing *TERC* polymorphisms, longer telomeres and increased risk of colorectal cancer (CRC). Indeed, it is accepted that shorter telomere lengths (measured from peripheral leucocytes) have been shown in senescent somatic cells and also to predispose to cancer. The biological rationale is that telomeres which form a protective cap at the end of chromosomes can be disrupted to undergo double strand breaks, inefficient repair and eventually chromosomal instability. The latter is a well established precursor to cancer development. Thus the authors finding of longer telomeres associated with risk of CRC is particularly intriguing.

It is worth noting certain similarities and contrasts in ulcerative colitis (UC) for example, which, is a chronic inflammatory condition with a risk of developing CRC. In UC, studies have consistently shown shorter telomere lengths (peripheral leucocytes and mucosal colonocytes) in those with UC with and without mucosal dysplasia (1). In fact we have shown decreased colonic *hTERT* (telomerase reverse transcriptase) and shortened telomere lengths in those with UC (2). Moreover although telomere attrition was noted, it was not accelerated as has been noted in senescent somatic cells. Jones et al in their cohort of CRC patients did not find an association between *TERT* polymorphism and telomere lengths supporting our previously proposed hypothesised of an alternative molecular pathway for development of UC associated CRC (1).

Our experiments with ex-vivo cultured rectal fibroblasts have shown relatively slower telomere shortening in those with late onset UC (3). This suggests that those who develop UC later in life perhaps have more efficient anti-oxidant systems that protect against telomere damage. Nevertheless in UC, rather than focusing on telomere attrition as a biomarker, attention has been diverted to look at the stability complex of telomeres (‘T’ loop or shelterin complex). The shelterin complex consists of important regulatory telomere binding proteins (TBPs). Cells deficient in functional TBPs undergo striking chromosomal instability. For example, we have found reduced TRF2 mRNA expression (one of the TBPs) in peripheral lymphocytes in UC as well as an association between mRNA expression of RAP1 (another TBP) and 5 aminosalicylate consumption (4). These findings serve to suggest that perhaps TBPs should be explored further in CRC particularly its role as a prognostic marker.

Telomere lengths are useful intermediate biomarkers but it is likely to be an epiphenomenon in the pathogenesis of cancer including CRC. Whilst there may be other polymorphisms of *TERT* to explore in CRC the benefits remain unclear as in UC. Like UC, exploration of the

stability of telomere binding proteins and development of cancer may prove to be illuminating.

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