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An Assessment of the Mutation Rate or Normal Colorectal Epithelium in Patients with Cancer Compared to Patients Without

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It is thought that half of somatic mutations present in colorectal cancers have arisen previously in the epithelium. In order to become fixed, these mutations must occur in colonic stem cells which can then replace the crypt. To study the mutation rate we used a neutral clonal marker, MAO-A. It is located on the X chromosome and truncating mutations result in loss of staining of the protein with immunohistochemistry allowing for direct visualisation of fixed mutations.

Normal colonic mucosa was examined from cancer patients (cancer-associated normal, CAN) N=9 and patients who had resections for non-neoplastic and non-inflammatory indications (non-neoplastic normal, NNN) N=6. Slides were stained for MAO-A and digitally scanned. The total mucosal area was measured and 300 random points were scored as either epithelium, lamina propria or non-relevant. Next 50 randomly selected crypts per slide were measured to estimate the average crypt size and the total crypt number.

For the CAN group the average mutation rate was 1 in 2646 crypts. The 6 samples of NNN had an average mutation rate of 1 in 6737; this meant a 2.6 fold difference for CAN compared to NNN. This difference was significant (p=0.0198). The average age of the patients in the two groups was not significantly different; CAN=72years, NNN=69years, p=0.516. The mutation rate increased with increasing age in both groups; the lowest mutation rate was 1 in 12842 for a patient aged 44 and the highest rate was 1 in 901 crypts for patient aged 88.

Mutations accumulate throughout the colorectal epithelium during a person's lifetime and are present in histologically normal mucosa before cancer occurs. By using a neutral clonal marker, MAO-A, we have shown a difference in the mutation rate of the normal mucosa from patients with cancer and without. Although a relatively low sample size, we have still demonstrated a clear difference of 3.6-fold. This may indicate more genetic damage occurring in the colorectum of cancer patient.