Mitochondrial mutations and colorectal cancer prognosis

Human mitochondrial DNA (mtDNA) is thought to be more prone to mutations than nuclear DNA, and mutations within this 16,569 base-pair genome have been reported in different types of cancers. Lièvre and colleagues have now identified a mutational 'hotspot' within the non-coding, displacement-loop (D-loop) region of the mitochondrial genome; their recent paper relates these findings to the clinicopathologic characteristics of a series of patients with colorectal cancer.

To search for mutational hotspots, the investigators amplified and sequenced the entire mitochondrial genome using DNA isolated from 11 colorectal tumors. In order to differentiate between germline and somatic mutations, matched healthy tissue—taken from the surgical margins—was also analyzed. A total of 10 somatic mutations were found in 7 of the tumor samples, and 8 of these were in the D-loop region of the mtDNA. Specifically, the mutations occurred within the D310 sequence of the D-loop region in six (54%) of the patients; the authors therefore considered this region to be a hotspot of mtDNA mutations in patients with colorectal cancer.

The team went on to amplify and sequence the D-loop region of the mtDNA in an additional 365 patients who underwent colorectal cancer resection. A somatic D-loop mutation was found in 142 (39%) of the tumors, and the D310 sequence was affected in 132 cases (36%). Three-year survival was significantly lower in patients with a D-loop mutation than in those without (53.5% vs 62.1%, $P = 0.05$). This corresponded to a 40% increase in the risk of death, after adjusting for factors such as age and disease stage. In addition, the presence of a D-loop mutation was associated with resistance to adjuvant chemotherapy in patients with stage III colon cancers.

In summary, the D-loop region of the human mitochondrial genome appears to be a hotspot for somatic mutations in colorectal cancer, and mutations in this region are linked to poor clinical outcomes.

Original article Lièvre A *et al.* (2005) Clinical value of mitochondrial mutations in colorectal cancer. *J Clin Oncol* **23:** 3517–3525

Does participation in a trial affect clinical outcome?

A systematic review published in the *British Medical Journal* has asked whether participation in randomized controlled trials (RCTs) influences clinical outcomes. By comparing outcomes of RCT participants with those of individuals receiving similar treatments outside of trials, the researchers demonstrated that RCTs were associated with neither a harmful nor a beneficial effect.

There has been some debate over whether participation in a randomized trial increases a patient's risk of a bad outcome, and whether the benefit of such studies is restricted to future patients. Furthermore, the applicability of clinical trial results to normal clinical practice has been questioned. Several studies have been undertaken to address these questions, but no single study has provided conclusive evidence. Vist *et al.* carried out a systematic review of 50 non-randomized cohort studies, and five clinical trials in which patients were randomized to participation or the option of participation. The studies were in the fields of oncology, obstetrics and gynecology, cardiology or other internal medicine, psychology and drug misuse, pediatrics, and respiration. The studies included data on a total of 31,140 RCT participants and 20,380 comparable non-participants who received similar treatment.

Of 73 dichotomous main outcomes studied, the majority (59) showed no statistically significant difference between RCT participants and non-participants, whereas 10 showed significantly better outcomes and 4 showed significantly worse outcomes for RCT participants. The pooled results for 18 continuous outcomes showed no statistically significant difference between those treated inside or outside of RCTs.

In summary, this systematic review indicates that participation in RCTs is associated with neither benefit or harm, compared with the use of similar interventions outside trials. These findings support the idea that the results of RCTs are generally applicable to clinical practice.

Original article Vist GE *et al.* (2005) Systematic review to determine whether participation in a trial influences outcome. *BMJ* **330:** 1175