Are young people eating their way to bowel cancer?

Jacqui Keenan, Alan Aitchison, Frank Frizelle

The rate per capita of colorectal cancer (CRC) in New Zealand is currently one of the highest in the world, and while there is encouraging evidence that the incidence of this disease is starting to decline in those aged 50 to 80 years, this is partially offset by a significant increase in the number of under 50 year olds. Specifically, between 1995 and 2012, the incidence of distal colonic cancer in men increased by 14% per decade, the incidence of rectal cancer in men increased by 18% and that in women by 13% in patients aged under 50 years. This is in line with a rising incidence of early-onset CRC in young people worldwide, the reason for which is currently unknown.

Studies to date suggest that most early onset CRC develop in the distal large bowel (including the rectum) and again New Zealand is no exception. In molecular terms, proximal and distal cancers are generally considered to present as distinct subtypes, with proximal cancers more likely to display a high degree of microsatellite instability (MSI-H) while retaining a wildtype APC tumour suppressor gene (APC-wt). In contrast, protein truncating mutations in the APC gene that characterise the classic adenoma-carcinoma pathway are more often present in microsatellite stable (MSS) distal cancers. However, this generalised proximal/distal model for CRC molecular subtypes is now being challenged with evidence that young people are presenting with APC-wt/MSS cancers. It is possible that the presence of a wild-type APC gene in a young person presenting with a distal cancer may simply reflect insufficient time for an APC mutation to develop. However, evidence that APC-mutant/MSS cancers of the distal colon in young people have a better prognosis than APC-wt/MSS early onset CRCs in this location suggests these cancers more likely comprise two distinct molecular subtypes, and that the patients presenting with APC-wt/MSS distal cancers may have a different genetic risk profile for CRC development.

Histological examination reveals that a disproportionate percentage of early onset cancers present with a mucinous phenotype and that a subset of these cancers are classified as signet ring based on more than 50% of cells showing evidence of intracellular mucin accumulation. This is exemplified by a recent study of early onset CRC in New Zealand, which identified eight of the 50 cases as mucinous (16%) and a further five cases (10%) as signet ring cell cancers in under 25 year olds presenting with CRC. Signet ring cell cancers are typically characterised by markedly reduced or absent E-cadherin expression, which renders the cells unable to maintain cell-cell contact, and the presence of signet ring cells in carcinomas with mucinous differentiation is associated with poor prognosis. Thus, reduced or absent expression of the E-cadherin tumour suppressor gene may prove to be an underappreciated risk factor in the genesis of early onset CRC. This may reflect a germline mutation in the CDH1 (E-cadherin) gene, similar to that identified as the primary risk factor for patients presenting with familial gastric cancer. However, the worldwide increase in early onset CRC coupled with the finding that a family history of CRC is not necessarily a risk factor for this disease hints more at the involvement of environmental and/or lifestyle factors, and this is reinforced by studies which find that people who migrate from low- to high-risk areas of the world rapidly assume the CRC risk of the host country.

We are particularly interested in diet as a potentially modifiable factor associated with increased risk of early onset CRC in New Zealand. For example, the global obesity pandemic that is being driven by the increased supply of cheap, sweet, energy-
dense foods is one risk factor that stands out in this age group,8 and a meta-analysis of glycaemic index and glycaemic load suggests there is an overall direct association between carbohydrate-rich diets and human CRC.9 Moreover, evidence that obesity can drive epigenetic change in the mouse colon10 hints at epigenetic modification of promoter regions of genes resulting in altered gene expression in the absence of altered DNA sequence. Thus, the reduced expression of E-cadherin in early onset CRC could potentially link back to diet. We also have preliminary evidence of a role for gut bacteria in the aetiology of this disease. Our research shows the presence of Bacteroides fragilis, that are capable of expressing a toxin that targets and cleaves E-cadherin, more often in stool samples from CRC patients when compared to age-matched controls.11 Moreover, these bacteria are associated with increased risk of colon carcinogenesis in a Canterbury cohort,12 and we are currently determining whether the B. fragilis toxin is also capable of epigenetic modification of the E-cadherin gene.

Collectively, these studies demonstrate that the incidence of early onset CRC in New Zealand is increasing and that a better understanding of what drives carcinogenesis in these young individuals is needed if we want to reverse this trend in the future.

Competing interests:
Nil.

Author information:
Jacqueline Keenan, Senior Research Fellow, Department of Surgery, University of Otago, Christchurch; Alan Aitchison, PhD Student, Department of Surgery, University of Otago, Christchurch; Frank Frizelle, Colorectal Surgeon, Department of Surgery, University of Otago, Christchurch.

Corresponding author:
Jacqueline Keenan, Senior Research Fellow, Department of Surgery, University of Otago, Riccarton Avenue, Christchurch 8011。
jacqui.keenan@otago.ac.nz

URL:

REFERENCES:


