

## EDITORIAL

## What Is Driving Early-Onset Colorectal Cancer?



As far back as 2009—and even before this—a series of studies began to report that while the incidence of colorectal cancer (CRC) was declining in adults aged 50 years and more, there was an increase in CRC incidence among individuals aged less than 50 years (20–49) in the United States.<sup>1,2</sup> This observation has been repeatedly confirmed in the United States and in many other—although not all—regions around the world.<sup>2–4</sup> This has captured the attention of those who study this disease, prompted a change in the age at which we begin screening for colorectal neoplasia (down to age 45 years), and has led many groups to investigate the possible explanation for these observations.

Perhaps the simplest explanation for this is that environmental and/or gut microbiome-related factors are driving colorectal neoplasia (adenomatous polyps and CRCs) in all age groups and that the recommendation to screen everyone aged 50 years or more for CRC has been effective in controlling the increase in CRC cases in those aged more than 50 years, but that the groups aged less than 50 years have not received that benefit. No data available thus far can seriously discount this possibility. Alternatively, there could be changes in lifestyle-related exposures that are unique to the younger birth cohorts that are responsible for the change in CRC incidence. This would be a more interesting and important finding because it could lead to a deeper understanding of the pathogenesis of CRC and possibly suggest some novel preventive measures.

In this issue of *GastroHep Advances*, a group from Northern Ireland led by Dr Ashleigh Hamilton has examined the clinical and molecular profiles in Stage II and III early-onset CRC (EOCRC), compared them to a CRC cohort aged 60–69 years, correlated the molecular alterations with the clinical features of the cancers, and then performed a systematic review of the literature on the subject. Importantly, they found that EOCRC patients (aged < 50 years, 5.4% of the entire cohort) did not have a significantly increased risk of CRC-related deaths compared to older CRC patients. The number of EOCRC patients was small ( $n = 35$ ), with no significant increase in mortality, as has been reported in some, but not all, prior studies.<sup>5</sup>

Microsatellite instability (MSI), the genetic signature indicating defective DNA mismatch repair activity—and suggesting the presence of Lynch syndrome in the younger cohort—was present in 25.7% of the EOCRC group in the Hamilton study. The presence or absence of MSI in this group had no significant effect on mortality but again the cohort was small and the confidence intervals wide. Of note, a report in 2000 by Gryfe et al<sup>6</sup> of 607 CRC patients aged  $\leq 50$  years indicated that the presence of MSI in the tumor was associated with a significantly reduced mortality, independent of the cancer stage (Hazard ratio 0.42,

0.27–0.67). The search for mutations in the *BRAF* and *KRAS* genes in the early-onset group yielded results compatible with what has been previously reported ( $\sim 1\%$  *BRAF* mutations and  $\sim 32\%$  with *KRAS* mutations) but did not provide novel diagnostic or mechanistic insights to EOCRC.

The authors then undertook a systematic review and meta-analysis from the published literature. A pooled analysis of 32 individual studies (which curiously did not include the Gryfe study) yielded an estimate that about 10% of presumed sporadic EOCRC patients had tumors with MSI—suggesting a more limited role of Lynch syndrome in early-onset disease. Two prior reports had suggested that the familial forms of CRC may have accounted for 20%–35% of the EOCRC<sup>7,8</sup> (similar to the Hamilton study cohort), but the 2 studies with this finding were reported from familial cancer clinics, so the likelihood of selection bias is embedded in those estimates. The search for mutations in *BRAF*, *KRAS*, *NRAS*, and *PIK3CA* produced no surprises. *BRAF* mutations are associated with MSI and acquired biallelic methylation (and silencing) of the *MLH1* gene in older patient cohorts and are uncommon in EOCRC.<sup>9</sup> The estimate that about 25.7% of apparently “sporadic” EOCRC in Hamilton’s population-based study suggests that these represent Lynch syndrome but that still leaves 74.3% without an explanation.<sup>7,10</sup>

What makes this a complicated issue is that, in spite of multiple efforts from several groups, it remains unclear whether some or all of EOCRC represent a different type of cancer than what is occurring in the older cohorts. As one studies large cohorts of CRC patients, the likelihood of Lynch syndrome causing the CRC is highest in the youngest groups (25–49) and goes down with advancing age. The frequency of *BRAF* mutations (and acquired mismatch repair deficiency) in the tumors goes up with advancing age. Older patients with MSI in their CRCs are substantially more likely to have the sporadic (nonfamilial) form of the disease, which is driven by *BRAF* mutations and the CpG island methylator phenotype.<sup>11</sup> Also, as many as 90% of the older-onset MSI CRCs occur in the proximal colon, whereas EOCRC tends to be a distal disease.<sup>2</sup> So, there clearly are some age-related differences in CRCs. If one is not taking the familial and epigenetic (methylation) aspects into account, the data can be confusing.

One interesting feature is that methylation of DNA in human DNA goes up in a linear manner with age, compatible with the rising frequency of hypermethylation, CpG island methylator phenotype, and *MLH1* methylation in the normal colonic tissues and CRCs in the older cohorts.<sup>11</sup> Methylation of DNA in normal tissues is a type of molecular clock. It has been reported that significantly more EOCRCs demonstrate global hypomethylation (using *LINE-1* sequences as a

measure) in the tumor cells when compared with the older-aged cohorts.<sup>12</sup> Interestingly, this hypomethylation leads to the re-expression of at least 3 oncogenes that are normally silenced by methylation.<sup>13</sup> This might simply be a simple issue of the epigenetics of aging, but in this study, hypomethylation had an adverse effect on outcome.<sup>12</sup> The complete meaning of this observation remains to be explained.

There will no doubt be continued efforts to better understand the issue of EOCRC, in particular because of different societal implications of advanced CRC in a 45-year-old vs a 75-year-old. No doubt we will learn more with time.

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