Lifestyle Factors and Microsatellite Instability in Colorectal Cancer: The Evolving Field of Molecular Pathological Epidemiology

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Colorectal cancer is not a single disease. It encompasses heterogeneous diseases with different sets of genetic and epigenetic alterations. Each tumor arises and behaves in a unique fashion that is unlikely to be exactly recapitulated by any other tumor (1). Nevertheless, we classify colorectal cancers into a limited number of groups (e.g., microsatellite instability [MSI]-high vs microsatellite stability [MSS]) because we assume that tumors with similar characteristics have arisen through common mechanisms and behave in a similar fashion (1).

Traditional epidemiology research has typically investigated factors that are associated with the overall risk of colorectal cancer, although distinct risk factors have long been recognized for colon and rectal cancers. Traditional pathology research has explored histopathologic and molecular characteristics to predict prognosis and response to specific treatment (2). More recently, these two approaches have converged to improve our understanding of how particular exposures influence carcinogenesis by examining molecular pathological marks of tumor initiation or progression, in relation to exposures of interest, for both etiology (3–27) and prevention.

In this issue of *Journal*, Campbell et al. (35) describe a case–control study of body mass index (BMI) and colorectal cancer risk in relation to tumor MSI status. As others have found (36,37), the authors showed that prediagnosis BMI was associated with an increased risk of colorectal cancer. In addition, they showed that this excess risk was limited to MSS tumors (for a BMI increment of 5 kg/m², adjusted odds ratio = 1.38, 95% confidence interval = 1.24 to 1.54); BMI was not associated with the risk of MSI-high tumors (adjusted odds ratio = 1.05; 95% confidence interval = 0.84 to 1.31).

Two previous case–control studies have examined the relationship between BMI and colon cancer risk by MSI status (5,10). Slattery et al. (5) examined 118 MSI-high and 696 MSS tumors and found that high BMI was associated with the risk of MSS tumors but not with the risk of MSI-high tumors among men; they observed no such difference in women. Satia et al. (10) examined 49 MSI-high and 437 MSI-low or MSS tumors and found that high BMI before diagnosis was associated with the risk of MSI-low or MSS tumors but not with the risk of MSI-high tumors. These results are generally consistent with those of Campbell et al. (35), providing further evidence for the specific relationship between obesity and the risk of MSS cancer. The specificity of this link not only reinforces a causal interpretation but also points the way to a specific mechanism.

Experimental evidence supports the link between obesity and gastrointestinal tumorogenesis in *Apc*-mutant mice (38). In human colorectal cancer, *APC* mutations and WNT/CTNNB1 (β-catenin) activation are inversely associated with the CpG island methylator phenotype (CIMP) (39,40), which is strongly associated with MSI (41–44). CIMP is the most common cause of MSI, which occurs through epigenetic inactivation of a mismatch repair gene *MLH1* (43,44). CIMP status and MSI status are major determinants of epigenomic and genomic characteristics (1) and are associated with many specific molecular events (1,43,44). For example, tumor expression of fatty acid synthase (FASN) is positively associated with MSI (45,46). FASN is inhibited by AMP-activated protein kinase (47,48), which is activated by a deficiency of cellular energy source ATP. Obesity is associated with reduced survival among colon cancer patients (49,50), and this association appears to be limited to patients with FASN-expressing tumors (28). Thus, obesity likely interacts with FASN in colorectal cancer cells to modify tumor behavior (28). The differential influence of obesity with respect to MSI vs MSS colorectal cancer incidence suggested by Campbell et al. (35) could potentially be explained by FASN. Alternatively, MSI status might serve as a surrogate for CIMP status or other molecular changes in colorectal cancer. Further studies are necessary to resolve this issue.

The results of Campbell et al. suggest that the increased risk of colorectal cancer associated with obesity is restricted to MSS tumors. Along with the findings by other investigators (3–27), these molecular pathological epidemiology data imply that molecular markers (such as MSI) can be used to classify colorectal cancers into distinct subtypes, which have implications for both etiology and prevention.

Molecular pathological epidemiology is a promising approach to investigate molecular mechanisms of carcinogenesis. Nonetheless, it faces all of the challenges inherent in epidemiological and pathology research as well as some unique limitations. For example, analyses are limited to case subjects for whom tumor tissue specimens are available. Thus, the size of any given sample in a molecular pathological epidemiology study will always be smaller than that of the parent study. Differential tissue availability...
can be a source of selection bias. The potential for bias will vary by many factors that may affect availability of tissue. Molecular pathological epidemiology, by definition, is based on subset analyses by tumor subtype, which further limits the sample size. Therefore, for adequate statistical power, large sample sizes are necessary. Also, the subset analyses exacerbate the potential for false-positive findings because of multiple hypothesis testing. If one crosses a wide range of lifestyle and other factors with a variety of molecularly defined tumor types, the likelihood for a nominally statistically significant chance finding is high. Thus, lack of clearly defined a priori causal hypotheses can be another caveat that may be more problematic in molecular pathological epidemiology than in traditional epidemiology. Such prior hypotheses could be based on earlier exploratory findings (35) or on the underlying biology. For example, it would be reasonable to consider a causal relation between one-carbon nutrients and genetic and epigenetic alterations (5–8,11,17–23,27) because one-carbon reactions are essential for both DNA methylation and synthesis. However, the relationship between obesity (and associated metabolic conditions) and tumor MSI status appears to be indirect. Often, findings on molecular subtypes are exploratory, and the data should be interpreted with caution. Hypotheses generated by epidemiological research with multiple hypothesis testing should be validated in independent datasets.

In summary, the article by Campbell et al. (35) represents a prototypical study in the evolving field of molecular pathological epidemiology. This approach will continue to provide useful insights on carcinogenic processes and help us improve cancer prevention and therapeutic strategies.

References


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