EDITORIALS |

Colon Cancer Recurrence: Insights From the Interface Between Epidemiology, Laboratory Science, and Clinical Medicine

Neal J. Meropol, Nathan A. Berger

Correspondence to: Neal J. Meropol, MD, Division of Hematology and Oncology, University Hospitals Case Medical Center, 11100 Euclid Ave, Lakeside 1200, Cleveland, OH 44106–5065 (e-mail: neal.meropol@case.edu).

In spite of advances in screening and prevention, early detection, adjuvant therapy, and treatment of metastatic disease, colorectal cancer remains the second leading cause of cancer death in the United States, with approximately 143,000 cases and 52,000 deaths expected in 2012 (1). When confined to the bowel and regional lymph nodes, colorectal cancer is highly curable, with a combination of local (ie, surgery and radiation) and systemic therapies. Among patients with stage III colon cancer, approximately 70% can be cured with surgery followed by adjuvant chemotherapy. More than 20 years of clinical trials have delivered us to this point, yet recent unsuccessful attempts to build upon the backbone of a fluoropyrimidine plus oxaliplatin with the addition of drugs that target the epidermal growth factor receptor or vascular endothelial growth factor pathway have been sobering (2,3). We must look beyond these traditional approaches.

It is well recognized that colorectal cancers are molecularly heterogeneous, arising via multiple pathways (4), with each tumor characterized by a panoply of genetic changes (5). Our increasing sophistication in profiling individual tumors introduces a major opportunity for tailoring of adjuvant treatment, but not without enormous challenges related to both interpretation of complex genomic data and clinical trial design. Although clearly worth pursuing, this focus on intrinsic characteristics of tumor cells does not account for influences on micrometastases that are present in the tumor microenvironment.

Whereas the role of the cancer epidemiologist has historically been focused on testing hypotheses related to cancer predisposition and cancer risk, recent studies have provided insights into potential therapeutic approaches. In particular, observations about cancer natural history after surgical treatment for early stage colorectal cancer raise the possibility that behavioral factors may influence risk of recurrence by affecting the extracellular milieu that drives tumor proliferation and survival. Insofar as behaviors may be modified, therapeutic interventions may be developed and tested.

In this issue of the Journal, Meyerhardt et al. (6) report an analysis of prospectively collected dietary data to address a secondary objective within a phase III randomized clinical trial in patients with stage III colon cancer. The primary objective of the parent study was to determine whether the addition of irinotecan to a backbone of 5-fluorouracil plus leucovorin improves survival in the adjuvant setting; no improvement was observed, thus permitting arms to be combined for this dietary study (7). To explore an association between food consumption and clinical outcomes, a representative sample of 1001 patients completed a 131-item semiquantitative

dietary questionnaire midway through adjuvant therapy and six months after the completion of treatment. Meyerhardt et al. previously reported that red meat, processed meat, refined grains, and sugary desserts—a so-called Western diet—was associated with recurrence and inferior survival in this population (hazard ratio for relapse free survival = 2.85; 95% confidence interval = 1.75–4.63) (8). The new report seeks to further define the dietary components responsible for the observed outcomes. The authors found that dietary glycemic load and carbohydrate intake were both associated with poorer disease-free, recurrence-free, and overall survival. The magnitude of these associations was clinically meaningful. However, an interaction was observed that suggested the association was restricted to patients with higher body mass index.

These clinical findings are consistent with multiple molecular and biochemical observations. Warburg first observed that tumor cells metabolize glucose by anaerobic fermentation (glycolysis) rather than aerobic respiration, even under aerobic conditions (9), thus rendering them less efficient (10). The Warburg effect, in which glucose is processed to lactate, while limiting entrance of pyruvate into the tricarboxylic acid cycle, leads to increased glucose uptake by tumor cells to generate sufficient ATP for energy-dependent processes (10–12). However, the increased uptake facilitates more glucose to be diverted toward generating biomass using pathways such as the pentose phosphate shunt to produce ribose for nucleotide synthesis and reduction of NADP to NADPH to facilitate fatty acid synthesis for membrane formation (10–12). The requirement to build biomass and consequently produce ATP by a less-efficient process than in normal cells explains why cancer cells become avid sugar consumers. The need for high sugar levels also provides an explanation for the recent observation that low glucose availability may drive the development of mutations in *KRAS* or *BRAF*, each of which facilitates increased glucose uptake (13,14). Insulin is a mediator of this growth-promoting effect (15,16), and hyperinsulinemia, commonly associated with obesity, may account for the observation that the adverse effect of high glycemic diets was mainly observed in overweight and obese persons (6). Thus, the combined effects of high glycemic load leading to hyperglycemia, thereby providing more fuel and building blocks for tumor growth, and hyperinsulinemia, which drives both glucose utilization and growth pathways via PI3K, AKT and mTOR (17), may conspire to increase colon cancer recurrence risk. As previously reported, exercise, another modulator of glucose metabolism and energy balance, is also associated with reduced risk of colon cancer recurrence in the patients in this cohort (18).

Is the current evidence sufficient to warrant dietary recommendations for our patients who ask the simple question, "How can I keep my cancer from coming back"? We agree with an American Cancer Society expert panel that advises colorectal cancer survivors "to maintain a healthy weight, participate in regular physical activity, and eat a well-balanced diet consistent with guidelines for cancer and heart disease prevention" (19). Although not definitive regarding the impact on colorectal cancer recurrence, the convergence of clinical observations and biology provides a compelling justification to test hypothesis-driven interventions in prospective randomized clinical trials. These interventions should include behavioral modifications [eg, dietary modification, exercise (20)] as well as more traditional pharmacologic approaches that target pathways involved in glucose metabolism. The report by Meyerhardt et al. (6) reminds us that the epidemiologist is an essential member of the translational science team in oncology. Ongoing transdiciplinary interactions between epidemiologists, laboratory investigators, and clinical scientists promise to improve understanding of host–tumor interactions and expand the evidence that will help us address our patients' "simplest" queries and improve their outcomes.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
2. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. *JAMA*. 2012;307(13):1383–1393.
3. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol*. 2011;29(1):11–16.
4. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. *N Engl J Med*. 2009;361(25):2449–2460.
5. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;487(7407):330–337.
6. Meyerhardt JA, Sato K, Niedzwiecki D. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J. Natl Cancer Inst*. 2012;104(22).
7. Saltz LB, Niedzwiecki D, Hollis D, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. *J Clin Oncol*. 2007;25(23):3456–3461.
8. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. *JAMA*. 2007;298(7):754–764.
9. Warburg O. On respiratory impairment in cancer cells. *Science*. 1956;124(3215):269–270.
10. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*. 2009;324(5930):1029–1033.
11. Vander Heiden MG, Locasle JW, Swanson KD, et al. Evidence for an alternative glycolytic pathway in rapidly proliferating cells. *Science*. 2010;329(5998):1492–1499.
12. Kim JW, Dang CV. Cancer's molecular sweet tooth and the Warburg effect. *Cancer Research*. 2006;66(18):8927–8930.
13. Yun J, Rago C, Cheong I, et al. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. *Science*. 2009;325(5947):1555–1559.
14. Bunz F, Papadopoulos N. Ras/Raf and their influence in glycolysis in colon cancer. In Markowitz SD, Berger NA, eds. *Energy Balance and Gastrointestinal Cancer*. New York: Springer, 2012;131–139.
15. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J. Nutr*. 2001;131(11):3109S–3120S.
16. Wolpin BM, Meyerhardt JA, Chan AT, et al. Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. *J Clin Oncol*. 2009;27(2):176–185.
17. Nock NL, Berger NA. Obesity and cancer: overview of mechanisms. In: Berger NA, ed. *Cancer and Energy Balance, Epidemiology and Overview*. New York: Springer, 2010;129–179.
18. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol*. 2006;24(22):3535–3541.
19. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243–274.
20. Courneya KS, Booth CM, Gill S, et al. The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. *Curr Oncol*. 2008;15(6):279–285.

Human Papillomavirus Vaccines for Cervical Cancer Prevention: Translating Possibility Into Reality

Vikrant V. Sahasrabuddhe, Mark E. Sherman

Correspondence to: Vikrant V. Sahasrabuddhe, MBBS, DrPH, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Blvd, EPS 5032, Rockville, MD 20852 (e-mail: vikrant.sahasrabuddhe@nih.gov).

In this issue of the Journal, Van de Velde et al. apply a mathematical model, "HPV-ADVISE" (human papillomavirus agent-based dynamic model for vaccination and screening evaluation), to project anticipated reductions in the incidence of HPV-associated cancers