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Can We Change the Past for Colorectal Cancer Patients and How Do We Move Forward?

Justin Y. Jeon, Ph.D and

Department of Sport and Leisure Studies, Yonsei University, Yonsei-Ro, Seodaemun-gu, Seoul Korea, 120-749

Jeffrey A. Meyerhardt, MD, MPH

Department of Medical Oncology, Dana Farber Cancer Institute, 450 Brookline Ave, Boston, MA, USA 02215

Justin Y. Jeon: jjeon@yonsei.ac.kr

Numerous studies support the hypothesis that diet and lifestyle are associated with the incidence and, more recently, prognosis of colorectal cancer [1–3]. Since many lifestyle factors are modifiable, there is great interest whether changing these factors could have potential preventive benefits in those without colorectal cancer and adjuvant benefits for those with the disease. These modifiable lifestyle factors include diet, physical activity, smoking, alcohol consumption and adiposity. Among these modifiable lifestyle factors, diet, physical activity and body mass index (BMI) are linked to energy balance and metabolic dysregulation of the insulin-glucose axis [4]. Recent analyses of the Framingham Heart Study-Offspring Cohort showed that exposure to impaired fasting glucose (IFG) more than 20 years was associated with significantly increased hazard ratio (HR) for developing colon cancer of 3.26 [95% confidence interval (CI):1.73–6.14], when adjusted for age, sex, alcohol, smoking and BMI [5]. Another recent meta-analysis, which analyzed 49 data sets with 11,462 cancer cases, reported that metabolic syndrome was associated with an increased risk of colorectal cancer incidence in both men (RR:1.33, 95% CI: 1.18–1.50) and women (RR:1.41, 95% CI: 1.18–1.70) [6]. In addition to lifestyle factors linked to energy balance, other lifestyle factors such as alcohol consumption (RR: 1.63 95% CI: 1.25–1.79) and smoking (RR: 1.15, 95% CI: 1.00–1.32) also influence the incidence of colorectal cancer [7]. While there is a large body of evidence supporting that physical activity, diet and BMI influences incidence of colorectal cancer, the influence of these lifestyle factors on prognosis and mortality of colorectal cancer patients has only recently been studied using cohorts that either have collections on prediagnosis or postdiagnosis exposures or both, leading to mixed results [2].

In this issue of *Cancer*, Colleen et al (NEED REFERENCE FROM JOURNAL) studied the association between pre-diagnostic lifestyle factors and survival after colon and rectal cancer patient. They found that prediagnosis smoking and obesity was associated with an increased risk of five-year all-cause mortality, a 19% increased risk of death from any cause and about 84% increased risk of cardiovascular disease-related death in colon cancer. In patients with

rectal cancer, prediagnosis smoking and healthy eating pattern were associated with risk of all-cause mortality. On the other hand, they did not find any association of prediagnosis physical activity and alcohol consumption with survival outcomes among colon and rectal cancer.

While most studies have examined individual exposures and associations with outcomes, Colleen et al went one step further to try to look at an overall “healthy lifestyle”, as measured by a composite scores composed of BMI, smoking, alcohol consumption, diet pattern and physical activity, on survival outcomes. Higher composite lifestyle scores, which represent healthier lifestyle, were associated with reduced all-cause mortality among colon and rectal cancer while higher composite lifestyle scores were associated with reduced risk of colorectal cancer mortality in rectal cancer cases, but not among colon cancer patient.

Several issues are raised when considering how to fit the data from Colleen and colleagues into our care of colorectal cancer patients. First, when someone is diagnosed with cancer, they cannot alter the past but seek to understand what they can do moving forward to improve their outcomes. The NIH-AARP Diet and Healthy Study is not a cohort that can answer the question of “what can I do now”. There are cohort studies that have looked at the postdiagnosis exposures and demonstrated associations between increased physical activity, avoidance of obesity and healthier diets and improved outcomes in colorectal cancer survivors [8] [9].

Second, given that the results of Colleen et al primarily demonstrate that individual exposures and healthier composite lifestyle are associated with improved overall and/or cardiovascular mortality, these data remind clinicians that colorectal cancer survivors are at risk for other comorbidities that are associated with increased mortality. Specifically, obesity, lack of physical activity, smoking and certain dietary habits are associated with increased risk of diabetes and cardiovascular disease as well as colorectal cancer [10]. For those patients whose colorectal cancer was influenced by one or more of these exposures, other metabolic syndrome-related diseases may already be part of their medical history at diagnosis or become a medical issue after diagnosis. Thus, the care of colorectal cancer survivors must not only focus on the treatment of the cancer, but also the treatment of the whole patient, even beyond the initial surgery and chemotherapy period.

Finally, demonstrating associations between exposures prior to diagnosis and outcomes may reflect the biology of the tumor that developed. Specifically, if prediagnosis adiposity is associated with increased risk of colorectal cancer-specific mortality in colorectal cancer survivors, it may be that the tumor that developed in a patient with increased BMI is more aggressive or has higher potential for metastases. Our understanding of the interaction between gene and environment in the development and progression of colorectal cancer is very limited. For example, Campbell and colleagues reported a positive association between increasing BMI and the risk of microsatellite stable and microsatellite instability-low colorectal tumors, but not with the risk of microsatellite instability-high tumors.[11] Another example is the study of a cohort of colorectal cancer survivors in which physical activity was significantly associated with improved colon cancer mortality in tumor with expression of cyclin-dependent kinase inhibitor 1B (CDKN1B or p27) but not in those with loss of

expression.[12] Additionally, given the growing interest and understanding of the field of epigenetics, the question is raised whether lifestyle factors result in epigenetic changes which may also influence prognosis of colorectal cancer? [13] Unlike genetic alterations, which are essentially unchangeable, epigenetic changes are intrinsically reversible and gene expression can be turned on and off. There is growing evidence supporting the hypothesis that epigenetic alteration is the driving force of some drug resistance [14] and the DNA demethylating drugs 5-azacitidine and 5-aza-2'deoxyctidine are already in use clinically for cancer treatment and myelodysplastic syndrome [15] [16]. There are ample evidence of lifestyle factors, including smoking, drinking, diet and physical activity, causing alterations to DNA, such as histone modifications, DNA methylation, expression of microRNAs and changes of the chromatin structure [17–20]. Thus, much of lifestyle and cancer links could be contributed to epigenetic changes. A critical question is how one can influence this association once a cancer develops.

In conclusion, Colleen and colleagues have provided another piece of evidence to back up a usual recommendation to our cancer patients: healthier lifestyle will result in healthier life regardless of their cancer. While we cannot change the biology of a tumor, understanding how to impact tumors with biology that are at least partially influenced by diet and lifestyle factors will be critical to increasing cure rates and survival of colorectal cancer patients.

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