OXFORD

JNCI J Natl Cancer Inst (2021) 113(1): djaa059

doi: 10.1093/jnci/djaa059
First published online April 28, 2020
Editorial

Oh GxE! The Complexity of Body Mass Index and Colon Cancer Risk

Joanne Ngeow, MBBS, MPH,[1,2,3,4] Charis Eng, MD, PhD [4,5,6,7,8,*]

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [2]Cancer Genetics Service, Division of Medical Oncology, National Cancer Centre, Singapore; [3]Oncology Academic Clinical Program, Duke-NUS Medical School, Singapore; [4]Genomic Medicine Institute, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA; [5]Center for Personalized Genetic Healthcare, Cleveland Clinic Community Care and Population Health, Cleveland, OH, USA; [6]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [7]Stanley Shalom Zielony Institute of Nursing Excellence, Cleveland Clinic, Cleveland, OH, USA and [8]Department of Genetics and Genome Sciences, and CASE Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, USA

[*]**Correspondence to:** Charis Eng, MD, PhD, Genomic Medicine Institute, Cleveland Clinic, 9500 Euclid Ave, NE-50, Cleveland, OH 44195, USA (e-mail: engc@ccf.org) .

Complexity is the prodigy of the world.—Gang Yu

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women worldwide with 1.8 million new cases reported in 2018 (1). CRC has a complex etiology involving genetic, environmental, and behavioral interactions that are poorly understood. The association between body mass index (BMI) and outcomes in patients diagnosed with CRC has been previously described, and analyses of other surrogates of obesity, for example, waist circumference and/or waist-to-hip ratio, have shown a similar relationship to CRC. The relationship of BMI with CRC cancer risk, however, remains nuanced, complex, and debatable.

In this issue of the Journal, Campbell et al. (2) explored these nuances through testing for multiplicative statistical interactions between approximately 2.7 million single nucleotide polymorphisms and BMI with risk of colorectal adenocarcinoma using 14 059 CRC or advanced adenoma cases and 14 416 controls. They identified that each 5-kg/m^2 increase in BMI was associated with a higher risk of CRC, more pronounced in men than women (odds ratio = 1.26 vs 1.14). They further identified an interaction for women, but not men, between BMI and a common intronic variant in *SMAD7* at 18q21.1 (rs4939827). A statistically significant higher risk for those with the rs4939827-*CC* genotype than those with the rs4939827-*CT* genotype was observed. The results of this study are notable because they further validate rs4939827 as a common variant risk locus for CRC. TGFβ-SMAD signaling pathway's role in CRC tumorigenesis has been previously established, in part through understanding the roles of *SMAD4* and *BMPR1A* in hereditary and then in sporadic CRCs. SMAD7's role in CRC tumorigenesis is yet to be understood with very limited functional data available. Furthermore, rs4939827 is known to be in linkage disequilibrium with 4 other functional SNPs as well as a newly identified one (rs34007497) that may have allele-specific enhancer activity in the colon. These insights should be explored by basic and translational researchers as future large cohorts if we are to shed light on what role SMAD7 fundamentally plays.

Perhaps more important, this study also highlights the challenges researchers are faced with in trying to understand complex interactions among genetic, environmental, and behavioral factors. With more than 28 000 case and control participants, the study detected a statistically significant interaction between BMI and *SMAD7*-rs4939827 in women but, almost as notably, little else. Campbell et al. (2), by design, limited the study to only participants of Northern and Western European genetic ancestry. To further preserve as much cross-collaboration data as possible for analyses, harmonization through multistep data harmonization procedures at coordinating centers was undertaken in this study, which is in itself no small endeavor. Yet despite these efforts, as the authors note, they remain underpowered to explore other risk factors, including tumor phenotypic profiles, which may be important given recent studies demonstrating that the relation between BMI and Microsatellite instability-high CRC in women seems to be stronger than that between BMI and microsatellite-stable CRC (3). It is unfortunate that this study was unable to retrospectively correlate cases with adenoma or tumor molecular phenotype, which could provide clues the role rs4939827 plays mechanistically.

BMI as a phenotype is dynamic with age-specific BMI, average BMI, body weight change, and BMI trajectory all having been reported to be a statistically significant positive relationship between increased BMI and CRC risk (4). The mechanisms through which BMI can affect outcomes in patients with CRC are stage dependent, and many factors can lead to the differential outcomes reported. In advanced-stage CRC patients, the weight loss and cachexia that are part of the disease process may affect patients who are malnourished and/or normal BMI more than overweight or obese patients. Thereby, a high BMI may potentially be protective in specific clinical scenarios. Furthermore, few studies considered pre- or postdiagnosis weight or BMI change as a variable to estimate the prognosis of CRC. Given BMI is a dynamic variable, the impact of a decrease in BMI or weight on survival of CRC patients needs to be further

Received: April 13, 2020; **Revised:** Month 0, 2020; **Accepted:** April 16, 2020

elucidated through longitudinal studies for us to truly understand the clinical significance of any candidate gene-environment interactions such as rs4939827.

Population cohort studies are a major, costly, long-term commitment for participants, study teams, and funders, but their strength is in their ability to identify multiple risk factors over time. This is particularly relevant in assessment of exposures that cannot be randomized, notably health behaviors such as exercise and social circumstance, both of which affect BMI levels. Such studies are costly to conduct and have historically led to disparities in study populations. To address some of these inherent problems, many contemporary population cohorts obtain consent to link participants to routine health records, which reduces loss to follow-up and recall bias and is less expensive than active follow-up; some use remote data capture through the internet. The developing fields of life-course epidemiology and exposomics, whereby the totality of environmental exposures from conception onwards are evaluated, are a novel and exciting approach to studying the role of the environment and behavioral factors in disease development. Although awareness of cohorts and sharing of data and samples are already policy for some national funders, there can be greater efforts for disease and population cohorts globally to be included in online directories and appropriate meta-data provided. Cohorts should use standardized and validated approaches, where possible, to facilitate cross-cohort comparisons.

We are writing this editorial at the peak of the COVID-19 pandemic, and there are lessons learned even for cancer etiology and control. During this pandemic, we have seen how expedient and impactful coordinated transparent data collection can be when dealing with dynamic and complex disease-related interactions, indeed, not dissimilar to understanding cancer etiology.

Out of complexity, find simplicity.—Albert Einstein

Funding

JN is funded by the National Medical Research Council Singapore Clinician Scientist Award. CE is the Sondra J. and Stephen R. Hardis Chair of Cancer Genomic Medicine at the Cleveland Clinic and is an American Cancer Society Clinical Research Professor.

Notes

Role of the funder: The funders had no role in the writing of this editorial or decision to submit it for publication.

Conflict of interest: No author had any financial or personal relationships that could inappropriately influence or bias this work.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
2. Campbell PT, Li Y, Bien S, et al. Association of body mass index with colorectal cancer risk by genome-wide variants. *J Natl Cancer Inst*. 2021;113(1):38–47.
3. Carr PR, Amitay EL, Jansen L, et al. Association of BMI and major molecular pathological markers of colorectal cancer in men and women. *Am J Clin Nutr*. 2020;111(3):562–569.
4. Zheng R, Du M, Zhang B, et al. Body mass index (BMI) trajectories and risk of colorectal cancer in the PLCO cohort. *Br J Cancer*. 2018;119(1):130–132.