Journal Of The National Cancer Institute, 2023, **115(2),** 120–121
https://doi.org/10.1093/jnci/djac216
Advance Access Publication Date: 29 November 2022
Editorial

Editorial

Combined individual participant data: highest-level evidence on obesity and colorectal cancer molecular subtypes

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In this issue of the Journal, Murphy and colleagues (1) draw on data from 11 observational studies to evaluate obesity in relation to molecular pathways to colorectal cancer (CRC). Like other groups of investigators interrogating pathways and molecular mechanisms to cancer (2), initial studies were inconsistent. Yet, by combining data and harmonizing measures, the large team of collaborating investigators shows that the association of body mass index (BMI) was remarkably consistent across KRAS, BRAF, CpG island methylator phenotype, and Jass classification. Lynch syndrome was defined consistently across contributing studies as Jass type 5 CRC cases (microsatellite instability high, CpG island methylator phenotype low/negative, BRAF wild type, KRAS wild type). Only Jass type p5 or Lynch syndrome was not related to BMI. This is definitive evidence on the consistency of the BMI association across Jass subtypes and the exception of Lynch syndrome.

This analysis by Murphy et al. (1) is important because the long-standing association between obesity and CRC raised questions of mechanisms and potential pathways for prevention. BMI was deemed a causal factor for CRC in the International Agency for Research on Cancer report in 2002 (3), and subsequent studies have further extended insights into this association. Initial studies of mechanisms generated interest in insulin pathways (4,5). The current finding of higher BMI consistently associated with elevated risks of Jass types 1-4 CRC suggests that obesity influences all major pathways. This may then strengthen the implications for prevention through strategies to promote and support the avoidance of weight gain in adult years. The World Health Organization, American Cancer Society, World Cancer Research Fund, and other organizations consistently recommend avoiding weight gain and maintaining a healthy weight to reduce risk of cancer. Societal barriers to achieving this goal, including lack of access to safe space for exercise, the structure of our neighborhoods and cities, and ready access to inexpensive energy-dense foods and drinks, combine to limit the overall achievement of this goal.

This individual participant combined data (IPD) analysis has overcome limitations of sample size and publication bias and lack of consistent molecular characterization in prior studies. As others have noted, IPD can overcome reporting gaps in the original studies and so results in improved overall quality of evidence (6). This is an important distinction from merely estimating a weighted average from reported results in a classic meta-analysis approach. Like findings that motivated the initial breast and colon cancer cohort consortium to harmonize data and analytic approaches across the contributing cohort data sets (2), the advantages of the combined individual participant data analysis cannot be ignored. As the Cochrane Collaboration notes, this is the highest level of evidence available to inform policy and practice. Initiated as an approach to combine clinical trials comparing breast cancer treatment and variable follow-up durations some 35 years ago (7), the methods have evolved from that work (8), and IPD analysis of observational data has matured (9) and now informs International Agency for Research on Cancer and other evidence synthesis reports (10,11). Likewise, IPD analysis of trials data has increased generalizability of findings and applicability to subsets of the at-risk population (12). Although IPD collaborations harmonizing data across studies are time-consuming, this approach reduces sources of heterogeneity. This has been demonstrated through the collaborative study of hormones and breast cancer resolving inconsistent definitions and analysis of menopause and age at menopause when evaluating the association of hormone therapy with breast cancer (13). Again, IPD analysis demonstrates the added value and return on investment from the initial studies with the added contribution to the IPD. Random fluctuation is reduced, common definitions of variables are used, and finer categories of risk factors can be interrogated and reported.

Returning to the implications of these results by Murphy et al. (1), weight gain in adult years remains a global priority for prevention of CRC (14) and the other weight- and obesity-related cancers (10). Multifaceted approaches should support general recommendations for individuals to keep weight within the healthy range and avoid weight gain in adult life through healthy diet, physical activity, and limiting sugar-sweetened beverages.

Funding

This work was supported by the Siteman Biostatistics Shared Resource at the Alvin J. Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital in

Received: November 16, 2022. **Accepted:** November 21, 2022

St. Louis, MO. The Siteman Cancer Center is supported in part by an NCI Cancer Center Support Grant #P30 CA091842.

Notes

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

Author disclosures: The author has no disclosures. GAC, a *JNCI* Associate Editor and author of this editorial, was not involved in the editorial review or decision to publish this editorial.

Author contributions: Conceptualization, Writing—original draft, Writing—review & editing: GAC.

Data availability

No data were generated or analyzed for this editorial.

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