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Editorial

EDITORIAL

# Understanding Adiposity at Different Times Across the Life Course and Cancer Risk: Is Evidence Sufficient to Act?

Graham A. Colditz, MD, DrPH,[1,2,*]

[1]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St Louis, MO, USA and [2]Alvin J. Siteman Cancer Center, Barnes-Jewish Hospital and Washington University School of Medicine, St Louis, MO, USA

*Correspondence to: Graham A. Colditz, MD, DrPH, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, 660 South Euclid Ave, Campus Box 8100, St Louis, MO 63110, USA (e-mail: colditzg@wustl.edu).

Fang et al. (1) raise several important considerations in understanding adiposity and cancer risk. First, the extensive summary of Mendelian randomization (MR) evidence helps bring together the literature on timing of adiposity in relation to cancer risk at different sites. Second, although 5 years ago the International Agency for Research on Cancer (IARC) evaluation of the cancer preventive effect of absence of excess body fatness concluded that there was sufficient evidence that absence of excess body fatness prevents cancers of the esophagus, gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast cancer, corpus uteri, ovary, renal cell cancer of the kidney, meningioma, thyroid, and multiple myeloma in humans (2,3), since that report was published, the evidence has shown that childhood adiposity is inversely related to breast cancer. And third, despite these advances in understanding relations with adiposity, the mechanistic insights are not yet in place to translate these associations to pathways for prevention or interception of breast cancer.

Fang et al. (1) provide an extensive summary review of the potential contributions of MR studies to deciphering the effects of obesity on cancer and pay particular attention to the life course issues in this exposure. A number of strategies have been employed to address timing of adiposity and cancer risk. Arnold (4) used a measure of years of adiposity and showed very strong effects for duration and extent of excess adiposity for endometrial cancer but not ovarian. Meanwhile working with Dr Rosner (5), we have separated out adiposity in childhood and adolescence from adult adiposity by breaking out weight gain from initial measuresof adiposity at ages 10 years and 18 years. This avoids the correlation between body mass index (BMI) across life that confounds the interpretation of studies that control for BMI at age 18 years, for example. We reported the correlation between weight at 18 years and at menopause is 0.56 [Supplementary Table 2 in (5)], and somatotype at age 10 years is −0.11 with weight change during premenopausal years. More consistent approaches to analysis of adiposity, weight change, and cancer risk will help refine understanding of adiposity measures that are not highly correlated and can distort interpretation.

This issue of interpreting life course adiposity and cancer risk was of major concern to the IARC Working Group on the Evaluation of Cancer-Preventive Interventions: Absence of Excess Body Weight, a review panel I chaired in April 2016 (some 5 years ago). The committee considered MR analyses to help draw conclusions on adiposity and cancer risk. Consensus was difficult to achieve. IARC reviews bring together evidence from human studies, animal models, and mechanistic data to suggest a causal cancer preventive effect (2). Because we identified that some meta-analyses are incomplete (6), we gave priority to studies that combine individual participant data from multiple prospective cohorts. The Cochrane methods group considers these analyses to be the "gold standard" because they can improve the quality of the dataand the type of analyses reported (7,8) compared with combining summary measures from reports in the literature. Fang et al. (1) draw largely on an umbrella review that has known limitations (9) but extended the data sources to include additional meta-analyses, filling gaps in evidence.

Of note, the data on childhood adiposity and cancer risk are sparse, and the IARC 2016 work group struggled to reach consensus on the interpretation of evidence either with or without the added insights from the MR data and their implications for childhood adiposity in relation to breast cancer risk. "BMI in early adulthood (generally reported at age 18 years) is either not associated or modestly inversely associated with postmenopausal breast cancer risk" (3). The conclusion on adiposity in childhood and early adult years was thus muted for breast cancer (3).

The past 5 years have seen more widespread use of MR approaches and as Fang et al. (1) summarize, these studies can start to refine our understanding of the impact of timing of adiposity on cancer risk. Further additional prospective cohort data point to the strong inverse association of adiposity at age 10 years and breast cancer that is independent of adiposity at age 18 years or later in life. Further insights on pathways include several studies of mammographic breast density and tissue features (10-12). It is estimated that some 26% of the effect of childhood somatotype and breast cancer risk is mediated through

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breast density (13). As we noted recently (14), transcriptomic analyses also point to nonhormonal pathways for adiposity and breast cancer, including immune response and inflammatory markers (15) that are now being extensively studied in the National Cancer Institute Human Tumor Atlas Network (16). Refining insights into pathways that are set by childhood adiposity and independent from adult adiposity and that potentially offer lifelong reduction in breast cancer risk is urgent given the global burden that is already high and rising with economic development. Deeper understanding of the pathways through which childhood lifestyle and adiposity modify breast cancer risk can open new avenues for preventive interventions for this, the leading cancer diagnosis in women.

Other associations directly linking childhood and adolescent adiposity to increasing incidence of adult malignancies demands more attention to the role of lifestyle excess weight gain in childhood and adolescence. Pancreatic cancer incidence is rising, even in adults younger than 50 years. Pooled cohort data indicate that individuals who are overweight in late adolescence have a more than 50% increased risk of pancreatic cancer compared with no overweight, adding to the evidence from MR studies that a 1-time measure of adiposity in epidemiologic studies may underestimate the magnitude of association and the population burden attributed to excess weight and obesity. To reap the reward from past research, we must act to implement effective strategies to reduce childhood and adolescent adiposity, reduce excess weight gain in adult years, and maintain a healthy weight. This will require us to change the way we live, but COVID-19 has shown we can make changes to how we live and work. Let us keep the changes we have already made, or take on new ones, that will cut our collective cancer toll.

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