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Editorial

EDITORIAL

Causality Inference of Obesity and Cancer Risk by Mendelian Randomization Analysis: Are We There Yet?

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Strong epidemiological evidence supports an association of excessive body fatness with increased risk of 13 cancer types (1). It is estimated that 6% of cancers in adults are attributed to overweight and obesity, placing it as 1 of the most important cancer risk factors, second only to smoking (2). However, association does not equate to causality. Body fatness, commonly assessed by body mass index (BMI), is determined by a myriad of genetic and environmental factors. Confounding effects by those factors are difficult to completely refute in observational studies. A randomized trial to experimentally test the causality between BMI and cancer risk is apparently also out of the question. However unsatisfying it may sound, we still are uncertain whether obesity causes cancer.

In recent years, Mendelian randomization (MR) analysis has gained considerable attention as an alternative approach to interrogate disease etiology (3). Instead of testing an exposure with disease directly, MR analysis tests the association with an instrumental variable constructed based on germline genetic determinants of the exposure. For traits such as BMI that undergo dynamic change through the life course, regression of disease risk to the static genetic component of an exposure is conceptually appealing. Compared with a single measure of BMI at a time that may or may not be relevant to disease etiology, genetically determined BMI represents a lifetime expectancy of body fatness. Because genetic variants are randomly assigned at conception and remain unchanged, MR analysis minimizes the concerns of confounding effects and reverse causality. Earlier MR studies relied on single genetic variants as instrumental variables. With the maturation of genome-wide association study findings, polygenic risk scores (PRSs) aggregating multiple variants, from a few dozen to a few million, has become the mainstay genetic instrument in MR analysis (4).

In this issue, Fang et al. (5) performed a comprehensive literature review of MR studies on BMI and the risk of 12 cancer types. Summary statistics of the associations from representative MR studies for each cancer type were compared with those derived mostly from a meta-analysis of observational studies commission by the World Cancer Research Fund (WCRF) and American Institute of Cancer Research(1). Concordant results between the 2 methods were found for 6 cancer types, including esophagus, colorectum, endometrium, ovary, kidney, and pancreas. In all cases, the risk estimates were notably stronger in MR studies than observational studies. The findings for breast cancer were less straightforward, however. Whereas the WCRF report linkedhigher adult BMI to increased risk of postmenopausal breast cancer, MR studies revealed an inverse association with both premenopausal and postmenopausal cancers. When BMI in early life was concerned, results with breast cancer risk were again concordant between the 2 methods.

The findings from this review are consistent with an earlier report by Mariosa et al. (2). Despite different data sources and PRSs for BMI used, the concordance between the 2 independent analyses, as well as between MR and observational studies, is remarkable. They provide the strongest evidence so far to settle the question of a cause-effect relationship between obesity and risk of these cancer types. The notably stronger risk estimates from MR studies compared with those from observational studies also provide validation for one of the presumptions of MR analysis: when confounding biases are minimized, stronger associations emerge. Nonetheless, like any good research, answering 1 question always leads to more questions.

One such question is the temporal effect of genetically determined BMI. Although genetic variants are fixed, their impact on BMI and cancer risk may change with time. The best example of this effect may be seen in breast cancer. Between MR studies and observational studies, findings are consistent for an inverse relationship of early-life BMI with overall breast cancer risk as well as adult BMI with premenopausal cancer risk. But the relationships are in opposite directions for adult BMI and postmenopausal cancer risk. Obesity in later life is well established for associations with higher risk of postmenopausal breast cancer (1). It is thus puzzling for MR studies to show an inverse

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association with genetically determined BMI. Fang et al. (6) attributed that to high correlation between early-life and adult BMI, whereas the increased postmenopausal cancer risk may be better explained by weight gain, a phenotype not well captured by PRS for BMI (7). In fact, the strength of the association between genetic variants and BMI was shown to erode during aging (8). Although MR analysis shines by taking temporality out of the equation when assessing disease etiology, caution in interpretation should be taken due to possible washout of genetic effects over time.

A second issue that warrants attention is that most current PRSs were developed based on genotype data from populations of European ancestry. The ability of those PRSs to predict risk in other ancestry groups or even within the same ancestry is uncertain, as is the generalizability of MR findings to non-European populations (9).

Of the 13 cancer types linked to obesity in the WCRF report, data are still insufficient or lacking for causality inference by MR analysis for 6 cancer types, including stomach, liver, gallbladder, meningioma, thyroid, and multiple myeloma. For lung cancer and prostate cancer, data from observational studies are inconclusive (1), yet MR studies now provide evidence for positive and inverse association with obesity, respectively (10,11). An ensuing question then is, without supporting data from observational studies, can we make causal inference based on genetic analysis only? Moreover, when considering all cancer types together, the causal impact of obesity may be weak, if any at all, because breast cancer and prostate cancer, the 2 most common cancer types, are inversely related to genetically determined obesity, as recently shown in an MR analysis based on UK Biobank data (12). Therefore, for a seemingly straightforward question of whether excessive body fatness causes cancer, the answer may not be straightforward after all. How to craft a simple public health message to convey the complexity and nuances of the relationships may be a challenge to be grappled with going forward.

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