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REPLY: Imaging-Based Obesity Assessment for Risk Factor Stratification and Prognostication in Malignancy

We thank Mr Cowan and colleagues for their insightful comments on our paper.[1] The authors underscore an important finding from our study suggesting that body mass index is an imperfect measure of fat mass, limiting its ability to elucidate associations between excess adiposity and future risk for cancer. We agree that deeper phenotyping, including larger imaging-based studies examining specific adipose depots or tissue characteristics, may better capture adiposity-related risk, as we demonstrate using computed tomography.

As highlighted in the letter, our findings specifically around lung cancer illustrate this point: a higher body mass index appeared protective, whereas abdominal adiposity assessed via waist circumference was not associated with future risk for lung cancer. Indeed, when examining specific adipose depots using imaging, greater visceral adiposity and higher levels of C-reactive protein were positively associated with lung cancer incidence. Taken together, these observations support the idea that visceral adipose tissue specifically may underlie disease risk.

In addition to what the authors highlight, we believe that circulating biomarker assessments that reflect adiposity-related pathways may complement imaging-based assessments to elucidate potential underlying mechanisms. For example, we recently showed that beyond C-reactive protein, other biomarkers of inflammation, immune activation, and fibrosis were associated with future cancer risk, including growth differentiation factor-15 and stromal cell-derived factor-1.[2] Other studies have identified adipokines, such as leptin, as key players in tumor pathogenesis.[3] With the widespread use of metabolomic and proteomic platforms enabling comprehensive molecular phenotyping, future studies may further enhance our mechanistic understanding of the association of adiposity with cancer risk, with the ultimate goal of disease prevention and identification of therapeutic targets. For example, metformin has been associated with lower cancer incidence and increased survival across various observational studies.[4] Whether targeting cardiometabolic disease and visceral adiposity with therapies such as metformin and others may prevent future cancer development remains to be studied.

Last, Mr Cowan and colleagues suggest a potential role for imaging-based assessments of adipose tissue to inform cancer risk stratification on the basis of the important and complex relationship between adiposity and cancer prognosis. We agree that risk prediction may be another possible clinical application of imaging-based assessments of adipose depots, although it is important to acknowledge that present data do not support widespread clinical utility for prognostication, which will need to be studied and established in future investigations.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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