


Obesity and Risk of Liver and Biliary Tract Cancer: Does Timing and Trajectory Matter?

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The evidence linking obesity—as measured at a single point in time—and future risk for liver cancer has been classified as strong and convincing for several years (1). Obesity is one of the driving forces in the sharply rising liver cancer incidence rates over the past 20 years (2). Current obesity rates are more than 40% in the United States, and class III obesity has been rising at a faster rate in rural and underserved settings (3). Without any indication that rising obesity rates will be curbed, and in light of the prolonged latency of liver cancer and the grim prognosis, this intersection represents a looming crisis in cancer outcomes. Strategies to combat obesity are imperative, yet prevention and treatment remain major public health challenges with inadequate resources. Therefore, data on weight change trajectories and liver cancer risk are needed to identify critical windows for prevention and to help target resources when and where they are most needed.

In this issue of *JNCI Cancer Spectrum*, Yang and colleagues (4) present data on liver and biliary tract cancer risk by body mass index (BMI) at various ages, by weight gain thresholds across adulthood, and by BMI trajectories among 138 922 participants enrolled in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. After adjusting for sex, other sociodemographic characteristics, smoking, aspirin use, and family history of liver and/or biliary tract cancer, the authors found that a BMI of 25 kg/m² or more by age 20 years resulted in a twofold increased risk of both liver cancer and biliary tract cancer. Furthermore, independent of BMI at age 20 years, participants with weight gain of more than 20 kg from age 20 to 50 years had 2.2-fold increased risk of liver cancer and 1.9-fold increased risk for biliary tract cancer compared with those who were weight stable (within 5 kg). Participants with weight gain of 10 kg to less than 20 kg had 1.8-fold increased risk of liver cancer, whereas weight gain less than 10 kg did not statistically significantly influence risk. The authors further identified 4 BMI trajectories from age 20 years to an average age of 62 years (at study enrollment), the most common being normal BMI to overweight (48%) followed by normal to obese (19%). Trajectories that resulted in obesity

were associated with increased risk for liver and biliary tract cancer compared with a stable normal BMI trajectory.

These findings make an important contribution to the field by extending a growing body of evidence demonstrating a statistically significant relationship between liver and biliary tract cancer with early adult onset of obesity as well as excessive weight gain during early to mid-adulthood independent of early adult BMI (5–7). Yang et al. (5) used similar latent-class group-based trajectory modeling with data from the National Cancer Institute–AARP cohort and identified 5 trajectories from age 18 years to an average age of 62 years, 3 of which ended in class I, II, or III obesity. Trajectories ending in obesity, regardless of obesity class, resulted in 70%–80% higher liver cancer risk compared with stable normal BMI trajectory. The implications of these emerging consistencies across cohorts highlight the importance of effective weight gain prevention interventions beginning prior to young adulthood, as well as preventing further weight gain regardless of weight status upon entering adulthood. Early identification of individuals' active weight gain trajectories is another important window to address the underlying causes and reverse or prevent continued gain past thresholds for cancer risk.

Interpreting the magnitude of the associations in the current study presents challenges because of different ways that confounding by covariates were handled. The current study conducted sensitivity analyses further adjusting for diabetes, hypertension, diverticulitis, cirrhosis, gallstones, alcohol consumption, and diet quality, which attenuated many of the positive associations toward nonstatistical significance. In contrast, using data from the Nurses' Health Study and Health Professionals Follow-up Study, Simon et al. (6) adjusted their primary analyses for diabetes, hypertension, dyslipidemia, alcohol consumption, diet quality, physical activity, and smoking and found statistically significant twofold associations that remained very similar in sensitivity analyses that further adjusted for cirrhosis and hepatitis C and B viral infections. Using the National Cancer Institute–AARP cohort, Yang et al. (5)

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adjusted only for variables that changed hazard ratio estimates by more than 10%, which included diabetes, physical activity, smoking status, alcohol, and red meat consumption.

The study does not address the mechanistic link between obesity, weight gain, and liver cancers, but obesity-related fatty liver disease is likely to be the dominant effect. The risk of liver cancer is elevated in nearly all forms of chronic liver disease and particularly high in cirrhosis. Some of the factors associated with this risk are chronic inflammation; oxidative stress with subsequent DNA damage; mutations in several driver gene pathways such as p53, β -catenin, and telomerase reverse transcriptase (TERT); and a dysregulated hepatocellular regenerative response that is characteristic of cirrhosis (8). Although hepatitis C and B viral infections are directly carcinogenic, a strong causative link exists between metabolic steatohepatitis and liver cancer risk both with or without cirrhosis (9). The risk is approximately tenfold higher in cirrhotic vs noncirrhotic individuals, and thus underdiagnosis of cirrhosis could be a confounding factor in this study. In fact, unrecognized cirrhosis and advanced fibrosis in populations with obesity have been estimated to be as high as 2%-4% of those unaware of any liver disease (10,11). Future investigations should consider disentangling confounding by lifestyle factors (eg, smoking, alcohol, diet, physical activity) vs intermediate conditions between obesity and liver cancer (eg, diabetes, nonalcoholic fatty liver disease, cirrhosis).

Bias in weight recall over the lifespan is another potential confounder, especially if self-report bias varies by current weight status or by different time frames being recalled (eg, greater underestimation of weight at age 20 years vs age 50 years) (12). Moreover, the degree of underestimation of current or past weight has been shown to be greater for those with higher BMI (12,13). However, the magnitude of the underestimation is likely small enough to minimally influence assignment to categorical obesity exposure variables.

Weight trajectories based on weights at 3-4 timepoints over the life course do not take into account weight cycling with bouts of intentional weight loss followed by varying degrees of regain over months or years. Overall weight gain from young to middle adulthood is most often gradual but especially common following major life transitions (14). However, weight loss attempts are also very common. About 50% of US adults report attempting weight loss in a given year (15), and the annual probability of more than 5% weight loss among adults with obesity is estimated to be 1 out of 5 to 1 out of 12 individuals (16). Weight loss from lifestyle modification that is followed by gradual regain may have long-term benefits for liver cancer risk (eg, by preventing or delaying diabetes for at least 10 years) (17). Prospective cohorts with annual weight data, as well as current levels of relevant biomarkers, are needed to examine more nuanced BMI trajectories, obesity exposure across the lifespan, and weight loss bouts, as well as short- or long-term changes in related lifestyle behavioral factors. This further evidence is needed to better understand critical windows and intervention opportunities to control liver cancer risk.

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