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ALSO IN THIS ISSUE



SP312

SHIFT TO YOUNGER PATIENTS. Two review articles published in the past year, including one in *JAMA Network Open*, have highlighted how cancers related to obesity are increasingly appearing in younger patients. The shift has implications for payers, [SP312](#).

LACK OF DIVERSITY LIMITS TRIALS. A study in *JAMA Oncology* finds that African American and Hispanic patients are underrepresented in clinical trials, which limits the ability to develop personalized approaches for patients, [SP314](#).

VOLUNTARY FIRST.

The American Society of Radiation Oncologists responds to CMS' proposed Radiation Oncology Model, which the group says would unduly punish practices that are already efficient. A board member calls for a voluntary-first approach and other changes to the proposal, [SP317](#).



ENGAGE, ENABLE, EMPOWER. The most recent session of the Institute for Value-Based Medicine in Philadelphia challenged cancer care leaders to give health systems the tools to measure how well quality care is being delivered, and then charge physicians with improving care based on how well they fare against benchmarks, [SP322](#).

PATIENT-REPORTED OUTCOMES (PROS).

A session at the National Comprehensive Cancer Network's fall policy conference in Washington, DC, looked at the importance of PROs and the challenge of comparing them across different groups of cancer patients, [SP319](#).



OVERVIEW

Obesity and Cancer Risk: A Public Health Crisis

Alexander J. Alvarnas; and Joseph C. Alvarnas, MD

OBESITY IS BECOMING AN increasingly common health condition in the United States and other Western nations. This condition is defined as an individual having a body mass index (BMI) of 30 kg/m² or greater.¹ Although some data suggest that other measures of obesity, such as percentage of body fat or fat mass index, might be better predictors of obesity-related complications such as metabolic syndrome, BMI is still the most commonly used metric to estimate individual obesity.² A BMI greater than 40 kg/m² indicates extreme obesity.³

The United States has the highest obesity rates in the world.⁴ According to a *JAMA* paper published in 2016 based on data from 26,468 participants from 2 previous National Health and Nutritional Examiner Survey (NHANES) trials, the crude rate of obesity for data year 2013 was 35.2% for men and 40.5% for women. The overall age-adjusted obesity rate was 37.7%. The prevalence of class 3 obesity (BMI ≥40 kg/m²) was 5.5% for men and 9.9% for women.⁵ When comparing obesity rates in 2015 with those of the 1980s, one study found that average body weight had increased by 10%.⁶ By comparison, in 1990, the US obesity rate of obesity was just 15%.

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ADVOCACY PERSPECTIVE

NASH and Liver Cancer: The New Cancer Headline

Donna Cryer, JD

DESPITE MUCH PROGRESS in the war on cancer, the continued rise of obesity in the United States remains a significant contributing factor to cancer incidence and death.¹ The term *obesogenic cancers*, which refers to cancers driven by our fat-promoting environment, nutritional policies, and lifestyle, is still relatively unfamiliar outside the medical literature. However, this issue needs to be at the top of the agenda for public health, policy, and payer professionals.

Obesogenic cancers include esophageal, colon, breast, and liver cancer. The most common primary liver cancer, hepatocellular carcinoma (HCC), driven by fatty liver disease, is among the most prevalent and deadly of obesogenic cancers.² In 2014, overweight- and obesity-associated cancers accounted for 40% of cancer diagnoses in the United States, totaling about 630,000 diagnoses.³ Rising rates of overweight and obesity parallel increased obesogenic cancer rates, which increased 7% between 2005 and 2014.³ With nonobesogenic cancer rates declining over the same period, it is evident that there is cause for concern.³

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PATT

INTERVIEW

How Obesity Affects Cancer Treatment—and How to Talk With Patients About Prevention

An Interview With Debra Patt, MD, MPH, MBA, by Jaime Rosenberg

AS OBESITY RATES HAVE CLIMBED in the United States over the past 2 decades, so has the incidence of cancers related to obesity.^{1,2} Debra Patt, MD, MPH, MBA, an oncologist who specializes in breast cancer and who serves as executive vice president at Texas Oncology, sees this phenomenon among her patients in the Austin, Texas, area. Patt spoke with *Evidence-Based Oncology*™ (*EBO*) about the effect that obesity has on cancer rates and how it can reduce the effectiveness of some therapies, as well as the need for clinicians to encourage

patients to eat healthy food and exercise to both improve outcomes and prevent recurrence.

Patt, a member of the editorial board of *EBO*, is a national leader in healthcare policy and clinical informatics who has testified before Congress about the importance of protecting access to care for Medicare beneficiaries.³ She is the editor-in-chief of the *Journal of Clinical Oncology—Clinical Cancer Informatics*.

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NASH and Liver Cancer: The New Cancer Headline

Donna Cryer, JD



CRYER

Donna Cryer, JD, is president and chief executive officer of the Global Liver Institute.

CONTINUED FROM COVER

Fatty Liver Disease: The Link Between Obesity and Liver Cancer

The obesity epidemic in the United States has been highlighted over the past few decades, with obesity rates consistently increasing. In 2011-2014, more than 70% of adults were classified as overweight or obese, compared with 56% in 1988-1994.²

A strong relationship between fatty liver disease and obesity has been discovered. Investigators found that between 30% and 90% of obese patients had nonalcoholic fatty liver disease (NAFLD).⁴ In severely obese patients having bariatric surgery, more than 90% had NAFLD.^{4,5} For NAFLD to be diagnosed, there must be imaging or histology evidence of hepatic steatosis (HS) and the lack of a secondary cause of hepatic fat accumulation.⁵ The more advanced form of fatty liver disease, nonalcoholic steatohepatitis (NASH), is marked by the presence of $\geq 5\%$ HS and inflammation with injury to liver cells.⁵

Compared with individuals who have a normal body mass index (BMI), overweight patients have a greater than 20% increased risk of developing liver cancer. Likewise, obese patients have an 87% increased risk of developing the disease compared with those of normal BMI.

NAFLD and NASH are widely considered the hepatic manifestations of metabolic syndrome, alongside diabetes and high cholesterol. NAFLD affects up to 30% to 40% of adults in the United States, and NASH affects 3% to 12%.³ Although these numbers are high, just a small percentage of NASH cases are diagnosed, with even fewer confirmed by biopsy.⁵ More concerning: The number of patients presenting with 2 or more risk factors for NAFLD or NASH, including obesity, type 2 diabetes, high cholesterol, and high triglycerides, is steadily increasing.^{4,5}

NAFLD and NASH are not the only liver diseases marked by alarming trends. Liver cancer has the fastest-rising incidence in men and women of any cancer type in the United States.⁶ This year, more than 42,000 people in the United States will receive a diagnosis of liver cancer,⁶ and nearly 32,000 people will die from the disease.⁵ Additionally, at 18%, the 5-year survival rate for liver cancer is among the lowest of any cancer type in the United States.⁶ When liver cancer is diagnosed at later stages with distant metastasis, the 5-year survival rate drops to just 2%.⁶

Historically, the majority of HCC cases have been viral hepatitis related. As the number, effectiveness, and accessibility of hepatitis C virus (HCV) curative treatments rises, the number of cases of HCV-related cirrhosis and HCC falls. With HCV-related HCC decreasing in incidence and prevalence, experts have been examining the roles that obesity, metabolic syndrome, and NAFLD/NASH play in the development of HCC.⁷

Although the exact mechanisms associating NAFLD and NASH and the development of liver cancer need further investigation, research has consistently shown a relationship between the diseases. NAFLD has been recognized as a trigger for liver cancer, with related risk factors for both diseases including elevated body mass index (BMI), abdominal obesity, insulin resistance, and other metabolic factors.^{7,8} In fact, compared with individuals who have a normal BMI, overweight patients have a greater than 20% increased risk of developing liver cancer.⁸ Likewise, obese patients have an 87% increased risk of developing the disease compared with those of normal BMI.⁸

Current Challenges

The liver cancer world has been marked by challenges, including but not limited to cost burden, fragmentation in healthcare and health policy, and issues associated with liver cancer risk factors, especially related to obesity, NAFLD, and NASH.

The direct and indirect costs of managing liver cancer, especially obesity-related liver cancer, are significant. In 2014, direct and indirect obesity healthcare costs in the United States reached \$1.42 trillion, with an estimated \$63 million in liver cancer costs attributable to obesity.⁹ Of those costs, \$35 million reflect direct liver cancer medical treatment cost and \$28 million represent indirect costs, including the combination of absenteeism, or lost workdays, and productivity loss or underperformance at work due to the disease.⁹ Costs associated with NAFLD and NASH are also marked with high, and are increasing. Current estimates state that in the United States, annual direct costs associated with NAFLD have reached \$103 billion.¹⁰

The worlds of healthcare and health policy have been divided over liver issues in the past. This is especially evident in screening policies and programs for patients at risk of developing HCC. Although some experts recommend screening for at-risk patients every 6 months, using ultrasounds with or without serum α -fetoprotein, these recommendations do not hold consistent across liver and oncologic specialties.^{11,12}

Liver diseases have been marked by clinical and research difficulties, and NAFLD and NASH present a new set of challenges. Although it is estimated that one-third of adults in the United States have NAFLD, very few people know what the disease is or that they may be at risk. NAFLD and NASH are largely asymptomatic diseases that go undiagnosed. Because of the lack of both public education and awareness and troubling symptoms, patients are progressing to later-stage disease before intervention occurs.

Another challenge we face is the lack of simple, noninvasive, cost-effective diagnostics in NAFLD and NASH, leading to late diagnosis and patient burden. The gold standard diagnostic test is a liver biopsy, a procedure that is invasive and burdensome and carries risk, including death. Noninvasive technologies for diagnosis do exist, but their adoption is likely years away due to regulatory pressure, clinical inertia, and health system procurement processes.

Meeting the Challenges

The Global Liver Institute, other advocacy groups (cancer, liver disease, and obesity), patients, and clinical experts are collaborating to meet these challenges and change the trajectory of

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obesogenic liver cancer. Massive strides have been made in the past few decades in the fights against cancer and obesity. Public awareness and education organizations and campaigns, increased funding for research and innovation, and policy changes are leading to progress in cancer and obesity.

To tackle obesity-driven liver cancer, we must address the link between NAFLD and NASH; then we may see an increase in disease management and treatment and a decrease in patients developing NAFLD- and NASH-associated liver cancer. The first step in this process is public awareness and education, a need that has been met by advocacy organizations across the globe. With campaigns, educational materials, events, and now an international awareness day, held on June 12, the public is gaining more and more access to information.

Another pillar in the fight against NAFLD and NASH involves overcoming barriers to diagnosis. This is addressed in *Beyond the Biopsy*, an awareness-raising campaign with the goals of speeding the acceptance and adoption of noninvasive technologies as an alternative to liver biopsy.¹³ As NAFLD and NASH become more prevalent, it is imperative that patients have access not only to accurate diagnoses but also to diagnoses that do not require the invasiveness, burden, and risk associated with liver biopsy.

Other stakeholders involved in noninvasive technologies include the Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE)¹⁴ and Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS)¹⁵, operating in the United States and the European Union, respectively. The NIMBLE project aims to standardize and validate a set of noninvasive biomarkers to the diagnosis and staging of NASH and identify patients at risk of disease progression to cirrhosis and in need of intervention. The LITMUS project's goal is to develop, validate, and advance toward regulatory qualification biomarkers that diagnose, risk stratify, and monitor NAFLD and NASH progression and fibrosis stage.

Targeting the disease states that lead to liver cancer offers hope that the number of obesity-driven liver cancer diagnoses will begin to drop, but liver cancer must be a target, as well. Cancer screening saves lives, and when HCC is diagnosed at an early stage, there is the greatest hope for curative treatment.^{11,12}

October is Liver Cancer Awareness Month, celebrated with #OctoberIs4Livers, a monthlong awareness campaign that addresses topics in the liver cancer continuum. The campaign delves into liver cancer basics, diagnostics, treatment options, research, and support. This year, #OctoberIs4Livers revolves around a common goal of doubling the 5-year survival rate for liver cancer to 36%. The current 18% rate means that this year, more than 30,000 people will die of the disease.⁶ Recent trends in liver cancer drug approvals and research are promising, but more effective therapies and screening protocols are needed to ensure that all liver cancer patients have access to these lifesaving resources.^{11,12}

Continuing to grow the nation's investment in liver cancer research will be pivotal in reaching our goals

and improving health outcomes in this population. In 2019, the first liver cancer Specialized Program of Research Excellence (SPORE) was established at Mayo Clinic in Rochester, Minnesota.¹⁶ We look forward to additional liver cancer SPORE programs gaining approval and coming online quickly to continue the movement of basic science findings into the clinical setting.

The Liver Illness Visibility, Education, and Research (LIVER) Act of 2019 (HR 3016), introduced in May, is crucial to progressing liver cancer research.¹⁷ The LIVER Act will authorize funds for liver cancer and hepatitis B research at the National Institutes of Health and elevate the Liver Diseases Branch of the National Institute of Diabetes and Digestive and Kidney Diseases to a division. The act would also direct the National Cancer Institute to establish an interinstitute working group and create programs to coordinate research agendas focused on finding better outcomes and cures for liver cancer and other liver diseases. In addition, the act authorizes funds for prevention and awareness grants at the CDC, including grants for screening, vaccination, and treatment for liver cancer, NAFLD, and cirrhosis of the liver.

Another step forward in health policy comes from Hawaii, where Hawaii House Bill 654 was signed into law.¹⁸ It appropriates funds to the University of Hawaii Cancer Center in Honolulu to determine the etiologies of the high incidence of liver and bile duct cancer in the state and establishes reporting requirements. The bill also highlights NASH as a cause of liver cancer.

More research is needed to understand the relationship between the NAFLD and NASH epidemic and liver cancer incidence and mortality trends so that more can be done to elevate and, ideally, solve these related health problems. Peter Campbell, PhD, strategic director of gastrointestinal tract cancer research at the American Cancer Society states, "Along with reducing known risks—excess alcohol consumption and hepatitis infection—maintaining a healthy body weight, eating healthy, and staying physically active to reduce the risk of diabetes may be important preventive strategies to reduce the risk of liver cancer."⁸

If policy and research trends continue in the right direction, we expect to see liver cancer diagnoses and deaths steadily decrease. But this won't come without widespread public awareness and education on liver cancer, NAFLD, and NASH. Looking forward, policy makers, thought leaders, research experts, clinicians, and patients must come together to change the narrative of liver cancer and alter the trajectory of this disease while saving lives. ♦

AUTHOR INFORMATION

Donna R. Cryer, JD, has channeled her personal experience as an irritable bowel disease and liver transplant patient into professional advocacy as founder of CryerHealth, LLC consulting firm on patient-industry partnerships; the Global Liver Institute (GLI), the only patient-driven liver health non-profit operating in the United States and Europe; and now as interim executive director of the People-Centered Research Foundation, the central office for PCORnet. In addition to leading the GLI Liver Cancer Council, Cryer's oncology experience includes serving as a managing director for the Association of Community Cancer Centers, building a multicultural clinical trial recruitment function for a public relations agency, and assessing patient advocacy and public affairs capabilities and opportunities for top pharmaceutical clients in the oncology space. She is a frequent speaker on patient centrality in research and healthcare delivery at meetings of major pharmaceutical, biotechnology, and oncology research and industry organizations.

REFERENCES

1. Does body weight affect cancer risk? American Cancer Society website. [cancer.org/cancer/cancer-causes/diet-physical-activity/body-weight-and-cancer-risk/effects.html](https://www.cancer.org/cancer/cancer-causes/diet-physical-activity/body-weight-and-cancer-risk/effects.html). Updated January 4, 2018. Accessed September 3, 2019.
2. Obesity and cancer. National Cancer Institute website. [cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet#r32](https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet#r32). Updated January 17, 2017. Accessed August 21, 2019.
3. Cancers associated with overweight and obesity make up 40 percent of cancers diagnosed in the United States [press release]. Atlanta, GA: CDC; October 3, 2017. [cdc.gov/media/releases/2017/p1003-vs-cancer-obesity.html](https://www.cdc.gov/media/releases/2017/p1003-vs-cancer-obesity.html). Accessed August 21, 2019.
4. Definition & facts of NAFLD & NASH. National Institute of Diabetes and Digestive and Kidney Diseases website. [niddk.nih.gov/health-information/liver-disease/nafl-d-nash/definition-facts](https://www.niddk.nih.gov/health-information/liver-disease/nafl-d-nash/definition-facts). Published November 2016. Accessed August 21, 2019.
5. Chalasani N, Younossi Z, Lavine JE, et al; American Gastroenterological Association; American Association for the Study of Liver Diseases; American College of Gastroenterology. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases. *Gastroenterology*. 2012;142(7):1592-1609. doi: 10.1053/j.gastro.2012.04.001.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34. doi: 10.3322/caac.21551.
7. Aleksandrova K, Stelmach-Mardas M, Schlesinger S. Obesity and liver cancer. *Recent Results in Cancer Res*. 2016;208:177-198. doi: 10.1007/978-3-319-42542-9_10.
8. Tarkan L. Being overweight increases risk of liver cancer. EndocrineWeb website. [endocrineweb.com/news/obesity/55627-being-overweight-increases-risk-liver-cancer](https://www.endocrineweb.com/news/obesity/55627-being-overweight-increases-risk-liver-cancer). Updated October 28, 2016. Accessed August 22, 2019.
9. Waters H, Devol R. Weighing down America: the health and economic impact of obesity. Milken Institute website. [assets1b.milkeninstitute.org/assets/Publication/ResearchReport/PDF/Weighing-Down-America-WEB.pdf](https://www.milkeninstitute.org/assets/Publication/ResearchReport/PDF/Weighing-Down-America-WEB.pdf). Published November 2016. Accessed August 22, 2019.
10. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology*. 2016;64(5):1577-1586. doi: 10.1002/hep.28785.
11. Covey AM. Hepatocellular carcinoma: updates to screening and diagnosis. *J Natl Compr Can Netw*. 2018;16(5S):663-665. doi: 10.6004/jnccn.2018.0052.
12. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Clin Liver Dis*. 2019;13(1):1-1. doi:10.1002/cld.802.
13. Global Liver Institute. Beyond the biopsy. static1.squarespace.com/static/53bafd3ce4b0ae714af7153f/t/5cdc83aec153600011c0e85/1557955502787/btb-2019.pdf. Accessed September 3, 2019.
14. Non-invasive biomarkers of metabolic liver disease. Foundation for the National Institutes of Health Website. [fnih.org/what-we-do/biomarkers-consortium/programs/nimble](https://www.fnih.org/what-we-do/biomarkers-consortium/programs/nimble). Accessed September 3, 2019.
15. Antsee QM. LITMUS: Liver Investigation: Testing Marker Utility in Steatohepatitis. HIV Forum website. [hivforum.org/storage/documents/2016/LF5/08_Antsee.pdf](https://www.hivforum.org/storage/documents/2016/LF5/08_Antsee.pdf). Published August 2016. Accessed September 3, 2019.
16. NCI funds SPORE for liver and bile duct cancer research. *Forefront*. March 2019. [mayo.edu/research/forefront/nci-funds-spore-for-liver-and-bile-duct-cancer-research](https://www.mayo.edu/research/forefront/nci-funds-spore-for-liver-and-bile-duct-cancer-research). Accessed September 3, 2019.
17. Liver Illness Visibility, Education, and Research Act of 2019, HR 3016, 116th Cong, 1st Sess (2019). HB 654, 30th leg (HI 2019).



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Read more at: <http://www.curetoday.com/link/248>