# Spotlight

1. **Implementation of Risk-reducing Strategies for Breast Cancer is Long Overdue**
   Victor G. Vogel
   See related article, p. 131

# Commentary

5. **Clearing the Haze: What Do We Still Need to Learn about Electronic Nicotine Delivery Systems?**
   Lisa M. Fucito, Hannah Malinosky, Stephen R. Baldassarri, and Roy S. Herbst

# Research Brief

11. **Hallmark Circulating Tumor-Associated Cell Clusters Signify 230 Times Higher One-Year Cancer Risk**
   Anantbhushan Ranade, Amit Bhatt, Raymond Page, Sewanti Limaye, Timothy Crook, Dadasaheb Akolkar, and Darshana Patil
   The study evaluated a blood test that can determine if healthy (‘asymptomatic’) individuals without a history of cancer have an increased risk of developing cancer within the next one year. This test can significantly minimize radiological or invasive screening in the majority individuals who do not have any increased risk.

# Research Articles

17. **Targeting the Cholecystokinin Receptor: A Novel Approach for Treatment and Prevention of Hepatocellular Cancer**
   Martha D. Gay, Anita Safronenka, Hong Cao, Felice H. Liu, Zoe X. Malchiodi, Robin D. Tucker, Alexander Kroemer, Narayan Shivapurkar, and Jill P. Smith
   This investigation demonstrates the role of the gastrointestinal peptide cholecystokinin (CCK) in hepatocellular carcinoma (HCC) and how CCK-BR blockade reverses the premalignant state of the hepatic extracellular matrix hence, rendering it less susceptible to the development of HCC. Thereby, CCK-BR blockade is a novel approach for the prevention/treatment of HCC.

31. **Reducing Fatty Acid Oxidation Improves Cancer-free Survival in a Mouse Model of Li-Fraumeni Syndrome**
   Ping-Yuan Wang, Jin Ma, Jie Li, Matthew F. Starost, Michael J. Wolfgang, Komudi Singh, Mehdi Pirooznia, Ju-Gyeong Kang, and Paul M. Hwang
   Mildly inhibiting the increased fatty acid oxidation observed in a mouse model of Li-Fraumeni syndrome, a cancer predisposition disorder caused by inherited mutations of TP53, dampens aberrant pro-tumorigenic cell signaling and improves the survival time of these mice, thereby revealing a potential strategy for cancer prevention in patients.

41. **Genome-wide Association Analysis of Proinflammatory Cytokines and Gene- Lifestyle Interaction for Invasive Breast Cancer Risk: The WHI dbGaP Study**
   Su Yon Jung, Peter A. Scott, Jeanette C. Papp, Eric M. Sobel, Matteo Pellegrini, Herbert Yu, Sihao Han, and Zuo-Feng Zhang
   The top GWA-SNPs associated with pro-inflammatory biomarkers have implications for breast carcinogenesis by interacting with obesity factors. Our findings may suggest interventions for women who carry the inflammatory-risk genotypes to reduce breast cancer risk.

55. **Sleep Characteristics and Risk of Ovarian Cancer Among Postmenopausal Women**
   Xiaoyun Liang, Holly R. Harris, Michael Hendryx, Aladdin H. Shadyab, Lauren Hale, Yueyao Li, Tracy E. Crane, Elizabeth M. Cespedes Feliciano, Marcia L. Stefanick, and Juhua Luo
   This study shows no association between sleep duration, sleep quality, or insomnia with the risk of overall ovarian cancer among postmenopausal women. However, restful sleep quality was associated with a lower risk of invasive serous ovarian cancer, and insomnia was associated with a higher risk of invasive serous ovarian cancer.
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ABOUT THE COVER

Nonalcoholic steatohepatitis (NASH) is a severe form of fatty liver disease characterized by inflammation, steatosis, and fibrosis and balloon degeneration from hepatocyte injury. NASH increases the risk for development of cirrhosis and hepatocellular carcinoma (HCC). Currently, there are no FDA-approved agents to reverse hepatic fibrosis and NASH. In this issue, an investigation by Gay and colleagues (starting on page 17) demonstrates a novel approach to preventing HCC by treatment with a cholecystokinin receptor antagonist, proglumide. Treatment of mice with proglumide reversed NASH; lowered hepatic inflammatory cytokines and chemokines; reduced oxidative stress; and prevented HCC. The anti-fibrotic, anti-inflammatory, and anti-proliferative effects of proglumide may provide hope for future studies to reverse hepatic fibrosis and prevent HCC. Proglumide has a broad safety profile in human subjects and could therefore easily be repurposed for prevention of HCC. The cover histological images show periportal fibrosis altering the microenvironment in the liver of a mouse with NASH (left panel) and prevention of these histologic changes with proglumide therapy (right panel).