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   Victor G. Vogel

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## 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.

    
    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.
Inflammation Modulation by Vitamin D and Calcium in the Morphologically Normal Colorectal Mucosa of Patients with Colorectal Adenoma in a Clinical Trial
David Corley Gibbs, Veronica Fedirko, John A. Baron, Elizabeth L. Barry, W. Dana Flanders, Marjorie L. McCullough, Rami Yacoub, Tapasya Raavi, Robin E. Rutherford, March E. Seabrook, and Roberd M. Bostick
Supplemental calcium and vitamin D reduce indicators of cancer-promoting inflammation in normal colorectal tissue in humans, thus furthering our understanding of how they may help prevent colorectal cancer.

Risk of Skin Cancer Associated with Metformin Use: A Meta-Analysis of Randomized Controlled Trials and Observational Studies
Michael S. Chang, Rebecca L. Hartman, Junchao Xue, Edward L. Giovannucci, Hongmei Nan, and Kening Yang
Meta-analyses of RCT and cohort studies showed no significant association between metformin and skin cancer, although suggestive evidence of modestly reduced skin cancer risks among metformin users was observed. These findings suggest metformin use should not influence current medical decision making for diabetes patients at risk of developing skin cancer.

Changes in Dietary Inflammatory Index Patterns with Weight Loss in Women: A Randomized Controlled Trial
Catherine Duggan, Jean de Dieu Tapsoba, Nitin Shivappa, Holly R. Harris, James R. Hébert, Ching-Yun Wang, and Anne McTiernan
Diet high in saturated fats and low in fruit and vegetable intake are associated with increased inflammation, which increases cancer risk. This study showed that changes in diet quality had effects on factors associated with cancer; however, the majority of beneficial effects were associated with weight loss rather than diet quality.

Association of Aspirin, Metformin, and Statin Use with Gastric Cancer Incidence and Mortality: A Nationwide Cohort Study
Mi Hee Cho, Tae Gon Yoo, Su-Min Jeong, and Dong Wook Shin
Long-term use of aspirin was independently associated with reduced incidence and mortality of gastric cancer in the general population. Metformin or statin use, however, was only associated with a reduction of gastric cancer risks among metformin users was observed. These findings suggest metformin use should not influence current medical decision making for diabetes patients at risk of developing skin cancer.

The Acceptability and Preference of Vaginal Self-sampling for Human Papillomavirus (HPV) Testing among a Multi-ethnic Asian Female Population
Su Pei Khoo, Wen Tzien Lim, Reena Rajasuriar, Nazrila Hairizan Nasir, Patti Gravitt, and Yin Ling Woo
Organized cervical cancer screening remains unachievable in many countries. Self-sampling HPV testing is an evidence-based method that can remove barriers to cervical screening. This is particularly important for developing countries in order to achieve the WHO global strategy to accelerate cervical cancer elimination.
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).