# Table of Contents

## CANCER IMMUNOPREVENTION SERIES

95 Immunoprevention of Human Papillomavirus–Associated Malignancies


## COMMENTARY

105 Physical Inactivity and Low Fitness Deserve More Attention to Alter Cancer Risk and Prognosis

Fabian Sanchis-Gomar, Alejandro Lucia, Thomas Yvert, Ana Ruiz-Casado, Helios Pareja-Galeano, Alejandro Santos-Lozano, Carmen Fiuza-Luces, Nuria Garatachea, Giuseppe Lippi, Claude Bouchard, and Nathan A. Berger

## RESEARCH ARTICLES

111 Urinary Protein Biomarkers in the Early Detection of Lung Cancer

Brian M. Nolen, Aleksey Lomakin, Adele Marrangoni, Liudmila Velikokhatnaya, Denise Prosser, and Anna E. Lokshin

120 Chemoprevention Activity of 25-Hydroxyvitamin D in the MMTV-PyMT Mouse Model of Breast Cancer

Lionel Rossdeutscher, Jiarong Li, Aimée-Lee Luco, Ibtihal Fadhil, Benoit Ochietti, Anne Camirand, Dao Chao Huang, Timothy A. Reinhardt, William Muller, and Richard Kremer

129 Enhanced Antitumor Effects of Novel Intracellular Delivery of an Active Form of Menaquinone-4, Menahydroquinone-4, into Hepatocellular Carcinoma

Shuichi Setoguchi, Daisuke Watase, Kazuhsa Matsunaga, Misa Matsubara, Yohei Kubo, Mariko Kusuda, Nami Nagata-Akaho, Muneechika Enjoji, Manabu Nakashima, Morishige Takeshita, Yoshifumi Kanbe, and Jiro Takata

139 Combined Use of Vitamin D3 and Metformin Exhibits Synergistic Chemopreventive Effects on Colorectal Neoplasia in Rats and Mice

Wan Li, Qi-Long Wang, Xia Liu, Shu-Hong Dong, Hong-Xia Li, Chun-Yang Li, Li-Shu Guo, Jing-Miao Gao, Nathan A. Berger, Li Li, Ian Ma, and Yong-Jie Wu

149 Genomic Profiling of Human Penile Carcinoma Predicts Worse Prognosis and Survival

Ariane F. Busso-Lopes, Fabio A. Marchi, Hellen Kusane, Cristovam Scapulatempo-Neto, José Carlos S. Trindade-Filho, Carlos Márito N. de Jesus, Ademar Lopes, Gustavo C. Guimarães, and Silvia R. Rogatto

157 Spectrin Repeat Containing Nuclear Envelope 1 and Forkhead Box Protein E1 Are Promising Markers for the Detection of Colorectal Cancer in Blood


165 Salivary microRNAs Show Potential as a Noninvasive Biomarker for Detecting Resectable Pancreatic Cancer

Zijun Xie, Xiaoyu Yin, Bo Gong, Wenjing Nie, Bin Wu, Xuchao Zhang, Jian Huang, Pingyou Zhang, Zhiwei Zhou, and Zijun Li

174 Metformin Use and Lung Cancer Risk in Patients with Diabetes


AC icon indicates Author Choice

For more information please visit [www.aacrjournals.org](http://www.aacrjournals.org)
ABOUT THE COVER

Vitamin D3 and metformin are widely used in humans for regulating mineral metabolism and as an anti-diabetic drug respectively, and both of them have been shown to have chemopreventive effects against various tumors. Potential synergistic chemopreventive effects of vitamin D3 and metformin against the development of early colon neoplasia was investigated in two models: DMH-induced colon cancer rat model and DMH-DSS-induced colitis-associated colon neoplasia mouse model. The combination of vitamin D3 and metformin showed a more pronounced effect in reducing the numbers of aberrant crypt foci and tumor in the colon when compared to vitamin D3 or metformin alone (shown: macroscopic image of mucosal hyperplasia in rat colon). Results from this study showed that enhancement of metformin’s chemopreventive effects by vitamin D3 was associated with down-regulation of S6P expression, via the AMPK (IGF-1)/mTOR pathway. Furthermore, enhancement of vitamin D3’s chemopreventive effects by metformin was associated with inhibition of the protein expressions of c-Myc and Cyclin D1, via the vitamin D receptor/β-catenin pathway. These findings suggest that combined use of vitamin D3 and metformin exhibits synergistic effects against the development of early colon neoplasia and that its use may represent a novel strategy for chemoprevention of colorectal cancer. See article by Li et al. (beginning on page 139) for more information.