**HISTORICAL PERSPECTIVE**

1 Fifty Years of Tobacco Carcinogenesis Research: From Mechanisms to Early Detection and Prevention of Lung Cancer
Stephen S. Hecht and Eva Szabo

**COMMENTARY**

9 Physical Activity and Gastric Cancer: So What? An Epidemiologist’s Confession
Tim Byers
See article, p. 12

**RESEARCH ARTICLES**

12 Physical Activity Is Associated with Reduced Risk of Gastric Cancer: A Systematic Review and Meta-analysis
Siddharth Singh, Jithinraj Edakkanambeth Varayil, Swapna Devanna, Mohammad Hassan Murad, and Prasad G. Iyer
See commentary, p. 9

23 Clinical and Biochemical Studies Support Smokeless Tobacco’s Carcinogenic Potential in the Human Oral Cavity
Susan R. Mallery, Meng Tong, Gregory C. Michaels, Amber R. Kiyani, and Stephen S. Hecht

33 Regular Aspirin Use and Risk of Multiple Myeloma: A Prospective Analysis in the Health Professionals Follow-up Study and Nurses’ Health Study
Brenda M. Birmann, Edward L. Giovannucci, Bernard A. Rosner, and Graham A. Colditz

42 Nutrition and Physical Activity Cancer Prevention Guidelines, Cancer Risk, and Mortality in the Women’s Health Initiative
Cynthia A. Thomson, Marjorie L. McCullough, Betsy C. Wertheim, Rowan T. Chlebowski, Maria Elena Martinez, Marcia L. Stefanick, Thomas E. Rohan, JoAnn E. Manson, Hilary A. Tindle, Judith Ockene, Mara Z. Vitolins, Jean Wactawski-Wende, Gloria E. Sarto, Dorothy S. Lane, and Marian L. Neuhouser

54 Metformin Inhibits Skin Tumor Promotion in Overweight and Obese Mice
L. Allyson Checkley, Okkyoung Rho, Joe M. Angel, Jiyoung Cho, Jorge Blando, Linda Beltran, Stephen D. Hursting, and John DiGiovanni

65 Luteolin Nanoparticle in Chemoprevention: In Vitro and In Vivo Anticancer Activity

74 A Derivative of Chrysin Suppresses Two-Stage Skin Carcinogenesis by Inhibiting Mitogen- and Stress-Activated Kinase 1
Haidan Liu, Joonsung Hwang, Wei Li, Tae Woong Choi, Kangdong Liu, Zunnan Huang, Jae-Hyuk Jang, N.R. Thimmegowda, Ki Won Lee, In-Ja Ryoo, Jong-Seog Ahn, Ann M. Bode, Xinnin Zhou, Yifeng Yang, Raymond L. Erikson, Bo-Yeon Kim, and Zigang Dong

86 Kava Blocks 4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone–Induced Lung Tumorigenesis in Association with Reducing O6-methylguanine DNA Adduct in A/J Mice

97 Effect of a Low-Fat Fish Oil Diet on Proinflammatory Eicosanoids and Cell-Cycle Progression Score in Men Undergoing Radical Prostatectomy

105 Dynamic Tumor Growth Patterns in a Novel Murine Model of Colorectal Cancer

114 Temporal and Spatial Evolution of Somatic Chromosomal Alterations: A Case-Cohort Study of Barrett’s Esophagus
Xiaohong Li, Patricia C. Galipeau, Thomas G. Paulson, Carissa A. Sanchez, Jessica Arnaudo, Karen Liu, Cassandra L. Sather, Rumen L. Kostadinov, Robert D. Odze, Mary K. Kuhner, Carlo C. Malley, Steven G. Self, Thomas L. Vaughan, Patricia L. Blount, and Brian J. Reid
Folate Deficiency Induces Dysfunctional Long and Short Telomeres; Both States Are Associated with Hypomethylation and DNA Damage in Human WIL2-NS Cells
Caroline F. Bull, Graham Mayrhofer, Nathan J. O’Callaghan, Amy Y. Au, Hilda A. Pickett, Grace Kah Mun Low, Dimphy Zeegers, M. Prakash Hande, and Michael F. Fenech

Licochalcone A, a Natural Inhibitor of c-Jun N-Terminal Kinase 1
Ke Yao, Hanyong Chen, Mee-Hyun Lee, Haitao Li, Weiya Ma, Cong Peng, Nu Ry Song, Ki Won Lee, Ann M. Bode, Ziming Dong, and Zigang Dong

A Novel Molecular Pathway for Snail-Dependent, SPARC-Mediated Invasion in Non–Small Cell Lung Cancer Pathogenesis
Jeanette L. Grant, Michael C. Fishbein, Long-Sheng Hong, Kostyantyn Krysan, John D. Minna, Jerry W. Shay, Tonya C. Walser, and Steven M. Dubinett

Cognitive Factors Associated with Adherence to Oral Antiestrogen Therapy; Results from the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) Study
Heidi D. Klepin, Ann M. Geiger, Hanna Bandos, Joseph P. Costantino, Stephen R. Rapp, Kaycee M. Sink, Julia A. Lawrence, Hal H. Atkinson, and Mark A. Espeland

eRapa Restores a Normal Life Span in a FAP Mouse Model
Paul Hasty, Carolina B. Livi, Sherry G. Dodds, Diane Jones, Randy Strong, Martin Javors, Kathleen E. Fischer, Lauren Sloane, Kruthi Munthy, Gene Hubbard, Lishi Sun, Vincent Húrez, Tyler J. Curiel, and Zelton Dave Sharp

ABOUT THE COVER
In 2007, the International Agency for Cancer Research presented compelling evidence that linked smokeless tobacco use to the development of human oral cancer. While these findings imply vigorous local carcinogen metabolism, little is known regarding levels and distribution of Phase I, II, and drug egress enzymes in human oral mucosa. The current study integrated clinical data, imaging studies, and histopathologic analyses of an oral squamous cell carcinoma that arose at the site of smokeless tobacco quid placement. The cover depicts a three-dimensional iCAT image of the buccal aspect of the patient’s left mandibular body. The marked bone destruction associated with tobacco quid placement in the buccal vestibule adjacent to the patient’s second and first mandibular molars is readily apparent. Immunoblot and immunohistochemical (IHC) analyses were employed to identify tumor and normal human oral mucosal smokeless tobacco-associated metabolic bioactivation and detoxification enzymes. Human oral epithelium contains every known Phase I enzyme capable of nitrosamine oxidative bioactivation with ~2 fold interdonor differences in protein levels. IHC studies confirmed that oral mucosal nitrosamine metabolizing enzymes reside in the basal and suprabasilar regions, sites of ongoing keratinocyte DNA replication. Clearly, variations in product composition, capacity for nitrosamine oxidative metabolism and exposure duration will modulate clinical outcomes. The data presented here form a coherent picture consistent with the abundant experimental data that link tobacco-specific nitrosamines to human oral cancer. See article by Mallery and colleagues (beginning on page 23) for more information.