Contents

Cancer Prevention Research

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PERSPECTIVE

897 **Estrogen Receptors in Colorectal Cancer: Goalkeepers, Strikers, or Bystanders?**
Johan Hartman and Jan-Åke Gustafsson
See article p. 910

REVIEW

900 **Chemoprevention of Head and Neck Cancer with Green Tea Polyphenols**
Joseph W. Kim, A.R.M. Ruhul Amin, and Dong M. Shin

RESEARCH ARTICLES

910 **Estrogen Stimulates the Expression of Mismatch Repair Gene hMLH1 in Colonic Epithelial Cells**
Peng Jin, Xiao-juan Lu, Jian-qiu Sheng, Lei Fu, Xiao-ming Meng, Xin Wang, Tai-ping Shi, Shi-rong Li, and Jianyu Rao
See perspective p. 897

917 **Validation of a Novel Statistical Model for Assessing the Synergy of Combined-Agent Cancer Chemoprevention**
Junya Fujimoto, Maiying Kong, J. Jack Lee, Waun Ki Hong, and Reuben Lotan

929 **Preclinical Colorectal Cancer Chemopreventive Efficacy and p53-Modulating Activity of 3′,4′,5′-Trimethoxyflavonol, a Quercetin Analogue**
Lynne M. Howells, Robert G. Britton, Marco Mazzoletti, Peter Greaves, Massimo Broggini, Karen Brown, William P. Steward, Andreas J. Gescher, and Stewart Sale

940 **Dual Inhibition of Both the Epidermal Growth Factor Receptor and erbB2 Effectively Inhibits the Promotion of Skin Tumors during Two-Stage Carcinogenesis**
Kaoru Kiguchi, Takuya Kitamura, Tricia Moore, Mohammad Rumi, Hsiang-Chun Chang, Devon Treece, Lynnsie Ruffino, Kevin Connolly, and John DiGiovanni

953 **New Role of (–)-Epicatechin in Enhancing the Induction of Growth Inhibition and Apoptosis in Human Lung Cancer Cells by Curcumin**
Achinto Saha, Takashi Kuzuhara, Noriko Echigo, Masami Suganuma, and Hirota Fujiki

963 **Novel Application of Proton Pump Inhibitor for the Prevention of Colitis-Induced Colorectal Carcinogenesis beyond Acid Suppression**
Yoon Jae Kim, Jeong Sang Lee, Kyung Sook Hong, Jun Won Chung, Ju Hyun Kim, and Ki Baik Hahm

975 **1,4-Phenylenebis(Methylene) Selenocyanate, but Not Selenomethionine, Inhibits Androgen Receptor and Akt Signaling in Human Prostate Cancer Cells**
Nicole D. Facompre, Karam El-Bayoumy, Yuan-Wan Sun, John T. Pinto, and Raghu Sinha

985 **Green Tea Polyphenols and Metabolites in Prostatectomy Tissue: Implications for Cancer Prevention**
Piwen Wang, William J. Aronson, Min Huang, Yanjun Zhang, Ru-Po Lee, David Heber, and Susanne M. Henning

994 **Proteomic Profiling of Potential Molecular Targets of Methyl-Selenium Compounds in the Transgenic Adenocarcinoma of Mouse Prostate Model**
Jinhui Zhang, Lei Wang, Lorraine B. Anderson, Bruce Witthuhn, Yanji Xu, and Junxuan Lü

1007 **No Association between Endogenous Retinoic Acid and Human Papillomavirus Clearance or Incident Cervical Lesions in Brazilian Women**
Erin M. Siegel, Jason L. Salemi, Neal E. Craft, Luisa L. Villa, Alex S. Ferenczy, Eduardo L. Franco, and Anna R. Giuliano

1015 **Cryptotanshinone Inhibits Cancer Cell Proliferation by Suppressing Mammalian Target of Rapamycin–Mediated Cyclin D1 Expression and Rb Phosphorylation**
Wenxing Chen, Yan Luo, Lei Liu, Hongyu Zhou, Baoshan Xu, Xiuzhen Han, Tao Shen, Zhijun Liu, Yin Lu, and Shile Huang

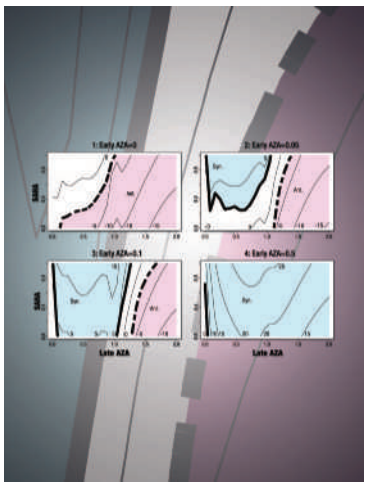
1026 **Factors Affecting the Decision of Breast Cancer Patients to Undergo Contralateral Prophylactic Mastectomy**
Min Yi, Kelly K. Hunt, Banu K. Arun, Isabelle Bedrosian, Angelica Gutierrez Barrera, Kim-Anh Do, Henry M. Kuerer, Gildy V. Babiera, Elizabeth A. Mittendorf, Kaylene Ready, Jennifer Litton, and Funda Meric-Bernstam

1035 **Oral Selenium Supplementation Has No Effect on Prostate-Specific Antigen Velocity in Men Undergoing Active Surveillance for Localized Prostate Cancer**
M. Suzanne Stratton, Amit M. Algotar, James Ranger-Moore, Steven P. Stratton, Elizabeth H. Slate, Chiu-Hsieh Hsu, Patricia A. Thompson, Larry C. Clark, and Frederick R. Ahmann

MEETING REPORT

1044 **Conference Report: Eighth Annual AACR International Conference on Frontiers in Cancer Prevention Research**
Abenaa M. Brewster, Sherri L. Patterson, Michele R. Forman, Chanita Hughes-Halbert, Paul J. Limburg, Frank G. Ondrey, Electra D. Paskett, David W. Wetter, and Ernest T. Hawk

ABOUT THE COVER



The cover image of four contour plots reflects a novel statistical methodology for assessing the chemopreventive synergy of combined agents (epigenetic modulators in this case). Standard statistics for two-drug combinations are limited for addressing complex dose-response patterns of chemopreventive combinations, which can involve nonmonotonic, or nonlinear, relationships with a plateau effect or U-shaped curve. The Emax and recently developed semiparametric statistical models can address such complexities. Each contour plot shows the growth-inhibition effects of a demethylating agent (AZA) plus a histone deacetylase inhibitor (SAHA) at different doses and/or schedules in tumorigenic human bronchial epithelial cells without serum. AZA was added to cells at an early (Early AZA) and late (Late AZA) time point, whereas SAHA was added only at the late time point. The *x* axis (AZA) and *y* axis (SAHA) show doses in μmol/L. The complex dose-response relationships included only an additive (white area) or antagonistic (Ant., pink area) relationship of late AZA plus SAHA with no early AZA (top-left panel) and increasingly synergistic effects (Syn.) when adding low doses of late AZA to SAHA plus increasing doses of early AZA (light-blue areas in the top-right, lower-left, and lower-right panels). Numbers adjacent to the contour lines indicate beyond-additive growth inhibition, i.e., differences between the observed and predicted growth inhibition. The graph data were generated via the Emax and Loewe-additivity models (predicted additive growth inhibition) and the semiparametric model (beyond-additive growth inhibition and confidence bands). These results are part of a comprehensive set of experiments and analyses that validated this novel statistical approach for assessing the synergy of combined chemopreventive drugs. See article by Fujimoto et al. (beginning on page 917) for more information.

Cancer Prevention Research

3 (8)

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