

Cancer Prevention and Population Sciences Program

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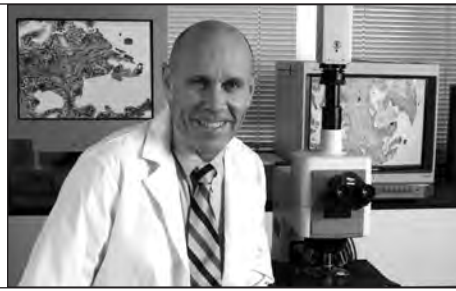
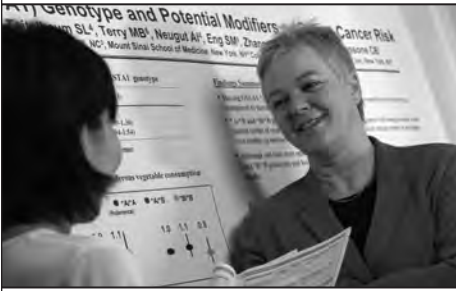
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*Professor and Chair, Cancer Prevention & Control
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Overview

The primary goal of the Cancer Prevention and Population Sciences Program is to prevent cancer morbidity and mortality by identifying exposures and genetic factors that interact to affect cancer risk and prognosis and develop interventions for cancer prevention at the primary, secondary, and tertiary levels. The Program seeks to translate findings to human populations. This translation requires that the Program integrate basic science with the understanding of cancer risk in human populations so that prevention efforts can be focused most effectively. Cancer progresses along a continuum from exposures to early genetic alterations, to clinically detectable lesions, to diagnosis and treatment, to outcome. Prevention strategies can be

designed to intervene at multiple points along this continuum, from identification and prevention of carcinogen exposure, to interventions in high-risk populations or those with premalignant lesions, to identification of factors that affect treatment-related toxicity and mortality. The primary aim of the Program is to elucidate factors that increase or decrease risk of cancer and affect cancer prognosis, and to extend these findings to the community. At each point on this continuum, genetic factors interacting with environmental ones can play a role. The Program seeks to understand the interaction of environment, diet, and lifestyle exposures with genetic variability and the role of genetic variation in treatment outcome.

In the late 1940s, when cigarette manufacturers ran ads that featured alleged physicians touting the health benefits of smoking, real doctors at RPCI published an article in the *Journal of the American Medical Association* linking smoking with lung cancer. Research at RPCI contributed significantly to an understanding of the role of smoking in lung cancer and solidified its international leadership role in tobacco control research and education. Today, most medical professionals agree that diet is important in cancer prevention. Initial studies of diet and cancer done at RPCI in the 1950s today provide the basis for its chemoprevention, epidemiology, and pharmacology and therapeutics research that continues to explore the role of diet in cancer risk.

A commitment to translational research by building prevention linkages to basic science distinguishes the Cancer Prevention Program at RPCI. Top-tier laboratory scientists in genetics, biochemistry, pharmacology, toxicology and immunology are being recruited to collaborate with prevention experts to explore scientific leads and develop more effective prevention strategies. Like a sidewalk between bench and bedside, preven-

tion incorporates both basic science and behavioral research into biomedical chemoprevention efforts. RPCI clinicians work with primary care doctors, nurses, and other healthcare professionals in the community to enhance cancer control and screening, to track cancer patterns, and to develop clinical interventions for prevention. Current efforts include a program to increase colorectal screening and to understand the dynamics of physician practices to determine what factors distinguish those practices in which screening is most pervasive. Prevention and early detection initiatives are also evaluating new approaches for cancer education of women, minorities and high-risk populations.

Opportunities for prevention occur at three points in the cancer continuum—exposure, early alterations, and clinical disease. To that end, our research programs develop along three themes: primary prevention, secondary prevention, and post-treatment cancer control. Primary prevention focuses on identifying and preventing exposures, secondary prevention includes interventions in high-risk individuals, and post-treatment cancer control examines short- and long-term side effects and predictors of recurrence and survival.

Themes

To address the overarching goal to prevent cancer morbidity and mortality, the Program's research is focused around three intersecting themes: 1) Nutrition and Chemoprevention in Cancer Risk and Prognosis; 2) Understanding Cancer Susceptibility; and 3) Tobacco Epidemiology and Translation into Policy.

Theme 1: NUTRITION AND CHEMOPREVENTION IN CANCER RISK AND PROGNOSIS

Dr. Clement Ip's leadership in the biochemistry and metabolism of selenium continues. His group has shown that a key to selenium activity in prostate cancer is androgen receptor signaling suppression. His analysis of selenium activity in the cell has enabled him to propose use of methylselenocysteine (MSC) as the best source of the critical selenium metabolite, methyl selenol. He and Dr. Marshall were selected by NCI (NWU04-4-02) to undertake the single-dose pharmacokinetic analyses of MSC.

Dr. Ambrosone's findings that genetic variants related to lower protection from reactive oxygen species were associated with better survival but greater toxicities led her to question if a similar relationship would exist for use of antioxidant supplements during chemotherapy – that use of antioxidants might reduce toxicities, but also interfere with drug efficacy. This is a highly contested area in the research and clinical community, particularly in light of the growing evidence that high dose supplements potentiate the effects of chemotherapy. This led to a funded R01 (R01 CA116395) to query women enrolled on a large SWOG/Intergroup trial of cyclophosphamide, adriamycin and paclitaxel for high-risk breast cancer.

Dr. McCann's work on the effects of dietary lignans on breast cancer risk has evolved from observations to a translational intervention among women at high risk for breast cancer. She first found that high dietary lignan intake reduced risk of ER negative breast cancer in premenopausal women, which led to an intervention with lignans to determine effects on hormones. In that study, flaxseed consumed over 7 days resulted in a significant increase in the ratio of 2OHE1 to 16OHE1, associated with lower risk of breast cancer. This change in hormone metabolites was most notable among women with specific genotypes in hormone metabolizing enzymes, COMT and CYP1B1. Based upon these results, Dr. McCann was recently funded by NIH to assess the effects of flaxseed given in a neoadjuvant setting on proliferative markers in women having surgery for breast cancer.

Theme 2: UNDERSTANDING CANCER SUSCEPTIBILITY

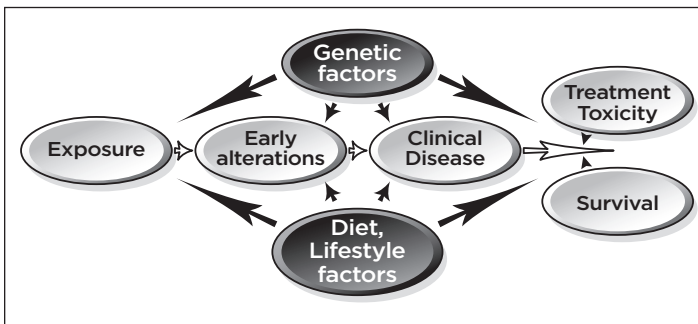
Drs. Ambrosone and McCann have been studying the effects of genetics on relationships between diet and cancer risk. Using data and specimens from the Long Island Breast Cancer Study, Dr. Ambrosone showed that while there was reduction of breast cancer risk among women with genotypes resulting in lower levels of ROS, the risk was observed only among women who were higher consumers of fruits and vegetables. Similar associations were noted for diet and catalase genotypes, with a significant multiplicative interaction ($P_{\text{interaction}} = 0.02$) for the CC genotype and high fruit intake (odds ratio = 0.59, 95% Confidence Interval (CI): 0.38, 0.89). Similar effects were observed for MPO genotypes; when consumption of fruits and vegetables were dichotomized at the median, inverse associations with either GA or AA genotypes were most pronounced among women who consumed higher amounts of total fruits and vegetables (odds ratio, 0.75; 95% CI: 0.58-0.97); this association was not noted among the low-consumption group ($P_{\text{interaction}} = 0.04$). These findings demonstrate the important interactions between inherent genetics, diet, and cancer risk, and underline the complexity of these relationships. The modifying effects of genetic variability on exposures are clear when applied to metabolism of chemotherapeutic agents and treatment outcomes. Drs. Ambrosone and Moysich, with colleagues in the Southwest Oncology Group, investigated the role of pharmacogenetics in treatment outcomes among elderly patients with AML. When investigating the effects of DNA repair capabilities on patient outcomes, those with XPD genotypes associated with reduced repair were more likely to have complete response (OR=3.06; CI: 1.44-6.70) and less likely to have resistant disease (OR=0.32, CI: 0.14-0.72) than those with better repair capabilities. XPD genotypes, as well as those for XRCC3 and ERCC1 that result in reduced DNA repair capabilities were also associated with greater risk of lung and metabolic toxicities. Similar relationships were noted for genotypes in the glutathione S-transferases; those with genotypes related to reduced Phase II activity were at greater risk of toxicity.

Theme 3: TOBACCO EPIDEMIOLOGY AND TRANSLATION INTO POLICY

The Transdisciplinary Tobacco Use Research Center (TTURC) has focused on evaluation of public policy interactions at the population level including statistics on product labeling, smoke-free policies, tobacco marketing and counter marketing, product regulation, and pricing effects. The Tobacco Group has demonstrated the greater effectiveness of more prominent pictorial product warnings. Measuring levels of smoke particulates, they have also shown that indoor-smoking regulation has a significant impact. Their work has had immediate implications for public policy around the globe including New York, as they have shown that access to untaxed cigarettes as obtained from other states and from Indian reservations is associated with a decidedly decreased rate of smoking cessation. Research on the prevalence and impact of low/untaxed cigarette sales in New York State documented that the availability of less expensive cigarettes reduces the frequency of quit attempts resulting in poorer health outcomes and at least \$500 million per year in uncollected tax revenue in New York State. These findings

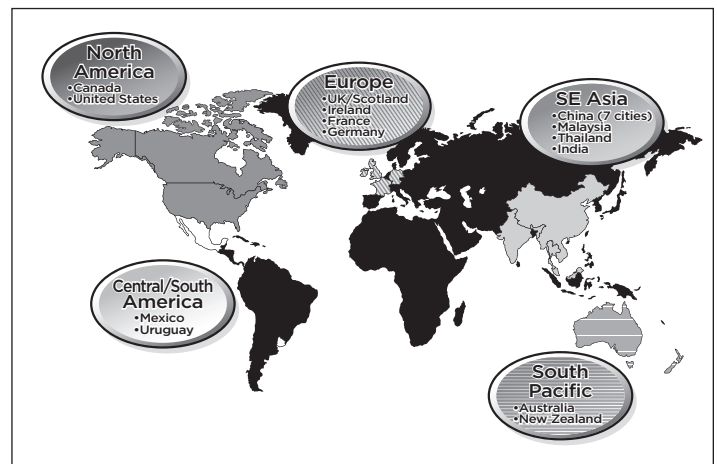
played an instrumental role in bringing the issue of cigarette tax inequities to the forefront during the 2006 NYS Legislative session where measures to reduce the tax differentials were debated and some measures were implemented into law (New York State Department of Health, Cigarette Purchasing Patterns among New York Smokers: Implications for Health, Price, and Revenue 2006). The Tobacco Epidemiology and Translation group has conducted several studies evaluating interventions that impact the demand for stop smoking services. Their research on the distribution of free nicotine replacement therapy (NRT) to smokers calling their quitline demonstrated that giving out free patches increased call volume 5-15-fold and improved quit success. The cost-effectiveness of this intervention has influenced what other state quitlines are now doing. Before our studies were completed, few quitlines provided NRT; now about 1/3 do. (Miller *et al.*, Lancet 2005; 365:1849; Cummings *et al.*, Am J Prev Med 2006; 31:181; Hawk *et al.*, J Public Health Manag Pract 2006; 12(1):52).

Cancer Susceptibility: Etiology, Morbidity and Mortality



Theme 2 focuses on investigation of the role of genetics and other factors in susceptibility not only to risk of cancer, but also to morbidity following diagnosis and treatment.

Countries participating in TTURC



Roswell Park's Transdisciplinary Tobacco Use Research Center, TTURC, focuses on worldwide policy and has active collaborations with investigators in these countries.

Selected Scientific Accomplishments

Christine Ambrosone, PhD

*Professor and Chair, Cancer Prevention & Control
Data Bank and BioRepository Resource Director*

In an inter-institutional collaboration built on the Cancer and Retinol (CARET) study with collaborators at the Fred Hutchinson Cancer Research Center, Dr. Ambrosone investigated potential associations between prostate cancer risk and polymorphisms in *MnSOD*, *CAT*, and *GPX1* resulting in reduced protection against ROS (R01 CA096789). Although no single SNP was associated with increased risk of prostate cancer, men with more than 4 risk alleles had more than twofold the risk of prostate cancer compared to men with less than 5 risk alleles (Choi *et al.*, *Cancer Epidemiol Biomarkers Prev* 2007; 16: 1115-20). Results were strongest among men who were not users of vitamin supplements. Members have also been investigating the role of oxidative stress-related genotypes in prostate cancer etiology in relation to consumption of dietary and supplemental iron. When genotypes were considered as potential modifiers of association between iron intake and prostate cancer risk, a significant interaction was noted for *MnSOD* ($P_{\text{interaction}}=0.013$ in overall; $P_{\text{interaction}}=0.016$ in aggressive cases). Among men with *MnSOD* TT genotypes, high iron intake (3rd versus 1st tertile) was associated with an overall twofold increase in risk, OR= 2.1 (95% CI=1.10-4.03); among men with aggressive prostate cancer, the OR was 2.6 (95% CI=1.06-6.54). In contrast, among men with CC genotype, the ORs were 0.6 (95% CI=0.28-1.16) and 0.8 (95% CI= 0.30-2.19) for overall and aggressive prostate cancer, respectively. These patterns were similar for MPO genotypes although the $P_{\text{interaction}}$ was not significant. Oxidative stress in prostate cancer etiology is also a focus of a project that Dr. Ambrosone co-leads, embedded in the Prostate Cancer Prevention Trial (P01 CA1086964).

K. Michael Cummings, PhD

Professor and Chair, Health Behavior

Dr. K. Michael Cummings leads the Transdisciplinary Tobacco Use Research Center (TTURC) [www.roswelltturc.org]. The Roswell Park TTURC ("Building the Evidence Base for Tobacco Control Policies" – P50 CA111236) is an international research collaborative conducting studies on the psychosocial, behavioral, and product-related impact of the tobacco control policies of the World Health Organization's Framework Convention on Tobacco Control (FCTC). The FCTC is the first international treaty devoted to a health issue and has recently placed national-level tobacco control policies in the spotlight. The goal of the RPCI TTURC is to expand and disseminate the science base for policy approaches for controlling tobacco by fostering transdisciplinary research that can lead to rigorous evaluation of the psychosocial and behavioral effects of national-level tobacco control policies in multiple developed and developing countries. Currently, the Roswell Park TTURC includes over 50 independent investigators from 20 institutions in 13 countries including the United States, United Kingdom, Canada, Australia, Ireland, Malaysia, Thailand, South Korea, China, Poland, Mexico, New Zealand, and Uruguay. Dr. Cummings is the Director of this Center, which is funded at about \$1.4M per year for 5 years. However, the overall project is much larger with multiple governments and several private research foundations contributing resources to support the research. Last year, the resources linked to the Center's operation were valued at over \$10 million.

Theresa Hahn, PhD

Assistant Professor, Medicine

Hypotheses related to pharmacogenetics and oxidative stress are being tested by Theresa Hahn, PhD among blood and marrow transplant (BMT) patients. Dr. Hahn, working with Philip McCarthy, MD (TII) holds an ACS Career Development Award to evaluate the effect of homozygous deletions in *GSTM1* and/or *GSTT1* on overall survival, treatment-related mortality and risk of toxicity post-BMT (MSRG 05-198-01). Regimen-related toxicity was selected as an outcome measure, since morbidity due to moderate or severe but non-fatal toxicity increases length of stay, cost, and the need for therapeutic intervention and decreases quality-of-life for post-BMT patients. *GSTM1* and *GSTT1* individually did not predict overall survival in autologous (self) or allogeneic (related or

unrelated donor) BMT patients. However, patients who were homozygous null for both genes had a trend toward increased overall survival in allogeneic but decreased overall survival in autologous BMT patients which suggested differential response to regimen intensity and/or immunomodulatory effects of graft-versus-host disease in the allogeneic BMT setting. *GSTM1* deletion was associated with a significantly increased risk of moderate, severe or fatal toxicity (RR=1.7, 95% CI 1.02, 2.7; p=0.04), with the same trend seen in both autologous and allogeneic BMT subgroups. *GSTT1* deletion alone or in combination with *GSTM1* null was not associated with toxicity. Individual organ toxicity was also assessed: *GSTM1* deletion was associated with increased risk of grade 2-4 stomatitis (RR=1.6, 95% CI 0.99, 2.6; p=0.056); *GSTT1* deletion was associated with increased risk of grade 2-4 gastrointestinal toxicity (RR=3.7, 95% CI 0.96, 14.3; p=0.058). Genotype analysis of SNPs in additional metabolic enzyme gene pathways and multivariate statistical analyses are ongoing.

Andrew Hyland, PhD

*Associate Professor, Health Behavior
Survey Research and Data Acquisition Resource Director*

Tobacco price policies and price marketing influence the purchase habits and smoking practices of consumers. For example, tax avoidance varies considerably across countries and is more frequent among younger, non-white, male, higher-income smokers who smoke more cigarettes per day. The increasing prevalence of roll-your-own cigarettes in some countries also appears to be a response to higher cigarette prices. The use of low and untaxed sources of cigarettes is associated with a lower likelihood of quitting smoking. Dr. Hyland and others estimate that, because of availability of low/untaxed cigarettes from other states, Indian Reservations, and the Internet, New York State fails to collect approximately \$500 million each year in cigarette taxes (R01 CA100802). Eliminating these sources of cheaper cigarettes would drop the smoking prevalence in the state by 2 to 3 percentage points [Implications for Health, Price, and Revenue; New York State Department of Health, March 2006]. Release of this report has stimulated political debate in New York State to help address the problem of untaxed tobacco products. (Hyland *et al.*, *Am J Public Health* 2005; 95(6):994; Hyland *et al.*, *Tob Control* 2006; 15:iii59).

Clement Ip, PhD

Professor, Cancer Prevention & Control

Clement Ip, PhD, an internationally recognized authority on selenium biochemistry and metabolism, leads an active selenium research group; members include Yan Dong, PhD, Haitao Zhang, PhD and Drs. Marshall, Gao (PR), Mohler (PR), and Kuettel (CSBT). This work, which has made important contributions at the basic science level, now also involves intervention studies and clinical trials. Selenium investigators are focused on developing new selenium-based strategies for prostate cancer prevention, translating information generated from the laboratory to human intervention trials. Dr. Ip developed a new selenium analog, methyl selenocysteine (MSC), which was chosen by NCI for further development using the RAPID program. Dr. C. Ip showed that MSC is metabolized more readily to the key chemopreventive selenium metabolite, methylselenol than the more common organoselenium, selenomethionine. Dr. Clement Ip and Dr. Marshall were funded by the NCI Division of Cancer Prevention to perform the initial phase I pharmacokinetic, single-dose study of methylselenocysteine (NWU04-4-02).

Margot Ip, PhD

Professor, Pharmacology & Therapeutics

Margot Ip, PhD and Clement Ip, PhD have a long-standing interest in conjugated linoleic acid (CLA). CLA is a fatty acid found either naturally in dairy products as the c9,t11-isomer, or synthetically as a mixture of c9,t11- and t10,c12-isomers. Both c9,t11-CLA and t10,c12-CLA inhibit mammary carcinogenesis in a rat model and lung metastasis in a transplantable mouse model. The two isomers also inhibit angiogenesis, an effect attributed at least in part to a decrease in VEGF and, for t10,c12-CLA, a decrease in leptin. Subsequent studies found that t10,c12-CLA, but not c9,t11-CLA, induced remodeling of the mouse mammary gland, with a loss of most of the adipocyte stroma, leukocyte infiltration, and a marked increase in the fibroblast component surrounding the ductal epithelium. These changes, similar to those seen in the inflammatory stroma of human breast cancer, suggested that t10,c12-CLA might not be appropriate for use in humans. To investigate this further, a transgenic mouse model was used to ask whether the two CLA isomers differentially affected mammary tumorigenesis in mice which

overexpress erbB2/her2 in the mammary epithelium (a significant proportion of human breast cancer overexpresses erbB2). Unexpectedly, t10,c12-CLA stimulated mammary tumorigenesis and lung metastasis. These data suggest that it would be prudent to avoid the widely available CLA supplements (sold in health food stores and supermarkets) containing the t10,c12-isomer. It also led to the cancelling of a planned intervention trial in women at high risk for breast cancer for which a well-defined mixture of the two CLA isomers was to be utilized. On the other hand, although c9,t11-CLA is not able to overcome the strong oncogenic signal from erbB2 overexpression, supplements containing only c9,t11-CLA may be safe and efficacious in breast cancer prevention based on its proven ability to suppress the progression of premalignant lesions in the mammary gland. Ongoing studies are focused on the molecular and biochemical mechanisms by which CLA exerts its effects (NIH RO1 CA061763, Komen BCTR0201524, AICR 05B020, Avon-AACR International Scholar Award, DOD Breast Cancer Predoctoral Grant BC050029). (Russell *et al.*, *J Nutr* 2007; 137:1200; Ou *et al.*, *Biochem Biophys Res Commun* 2007; 356:1044; Ip *et al.*, *Carcinogenesis* 2007; *in press*)

Martin Mahoney, MD, PhD

Associate Professor, Health Behavior

Daniel Green, MD (Pediatric Oncology) and Dr. Mahoney have been following a cohort of young adults treated for cancer as children in an inter-institutional effort. This research is funded by two grants, "Late Effects of Wilms Tumor Survivors and Offspring" (RO1 CA054498) and "Childhood Cancer Survivor Study" (U24 CA055727). In the study of Wilms Tumor survivors, Dr. Green and collaborators are evaluating pregnancy outcomes and breast-feeding practices, congestive heart failure, and second malignancies. Dr. Green, who chairs the Fertility and Reproductive Outcomes Workgroup of the Childhood Cancer Survivor Study, is examining fecundity and fertility in the female CCSS participants. He and his collaborators recently updated their analysis of 15-year survivors. Secondary malignancies are the most frequent cause of death among these patients. They are currently looking at secondary malignancies in survivors of Hodgkin disease. Determination of why some patients develop second cancers while others remain disease-free will be an important area for future research; understanding the interactional roles of genetic variants and treatment will be critical.

James Marshall, PhD

*Professor and Senior Vice President,
Cancer Prevention & Population Sciences
Associate Director for Cancer Prevention*

Dr. Marshall is protocol chair of SWOG 9917/CALGB 70004/ECOG S9917, which is funded by NCI as a pivotal chemoprevention trials (U10 CA77178). Selenium 200 mcg/day is being tested for its ability to prevent the progression of high-grade prostatic intraepithelial neoplasia (HGPIN) to prostate cancer. In addition to providing an evaluation of the chemopreventive potential of selenium among men with a premalignant lesion, this study will be one of the largest of the natural history of HGPIN among men who have been carefully examined for the presence of occult prostate cancer. This trial has completed recruitment; follow-up will conclude in 2009. (Marshall *et al.*, *Cancer Epi Bio Prev* 2006; 15(8):1479).

Susan McCann, PhD

Associate Professor, Cancer Prevention & Control

Dr. McCann's research focuses on phytochemicals, and she has a broad program to evaluate the effects of dietary lignans on cancer risk and prognosis. In an earlier epidemiologic study, Dr. McCann, with Drs. Ambrosone, Freudenheim, Marshall and Moysich, showed that higher intake of lignans was associated with more than two-fold decreased risk of both prostate cancer and estrogen receptor (ER) negative premenopausal breast cancer. Dr. McCann received a career development training award (K07 CA089123) to evaluate further these relationships in another breast cancer case control study, and to conduct an intervention study in which postmenopausal women consume flaxseed for 7 days. Estrogens are metabolized to catechol estrogens, and the 2-hydroxyestrone (2-OHE1) metabolite may be anti-estrogenic and decrease breast cancer risk, while 16 α hydroxyestrone (16 α -OHE1) may increase risk of breast cancer. After the intervention, women's levels of 2-OHE1 increased and the ratio of 2 to 16 OHE1 increased. (McCann *et al.*, *Nutr Cancer* 2005; 53(1):33; McCann *et al.*, *Cancer Epidemiol Biomarkers Prev* 2004; 13(9):1480; McCann *et al.* *Cancer Epidemiol Biomarkers Prev* 2007; 16(2):256) Dr. McCann used these pilot findings to assemble an interprogrammatic and institutional collaboration with Dr. Lillian Thompson (University of Toronto), David Hicks, MD (GN), Swati Kulkarni, MD and Stephen Edge, MD, to evaluate the effects of a 2-week flaxseed intervention in a 2x2 factorial design pilot study with and without aromatase inhibitors among women with breast cancer. The hypothesis of

the proposed study is that proliferative indices will be reduced with flaxseed, and that the effect will be greatest when given with aromatase inhibitors. Proliferative markers will be compared in tissue obtained at biopsy versus at surgery. This NCCAM-funded (R21 AT004024) therapeutic trial arose from interactions among scientists from genetics, pathology and prevention and surgical oncologists in the Breast DSRG. Dr. McCann is also collaborating with Drs. Freudenheim, Ambrosone, Moysich and Hong to implement a new case control study of breast cancer in Puerto Rico. This study funded by the Department of Defense Minority Institution Training Partnership will correlate lignan intake with risk in a population with high overall but variable lignan intake.

Kirsten Moysich, PhD

Associate Professor, Cancer Prevention & Control

Dr. Moysich is conducting studies of genetically determined variability in drug metabolism in treatment outcomes among patients with leukemia or ovarian cancer. RPCI has a large bank of bone marrow samples from cancer patients; however, the usefulness of DNA from diseased bone marrow is unknown, and chromosomal changes resulting from disease or treatment may impact classification of inherited genotypes. In work supported in part with CCSG Developmental funds, Dr. Moysich compared DNA from bone marrow and from buccal cells from patients with leukemia. In an inter-programmatic collaboration with Maria Baer, MD (MTET) and Javier Blanco, PhD (MTET) (R03 CA121881) genotype data agreed ($\kappa > 0.75$) between bone marrow and buccal samples in nearly all genes under investigation (i.e., *ABCB1*, *ABCC1*, *ABCG2*, *CAT*, *GPX*, *SOD2*, *MPO*, *GSTA1*, *GSTM1*, *GSTT1*, *CYP3A4*, *CYP2C8*, and *CDA*). Bone marrow appears a suitable source of biological material for pharmacogenetic studies in AML. Dr. Moysich recently secured R03 funding to conduct a similar methodological study in ovarian cancer. In related research, members have been examining the role of variants in genes related to protection from oxidative stress and DNA repair in the context of two SWOG clinical trials in elderly patients with AML.

Mary Reid, PhD

Assistant Professor, Cancer Prevention & Control

Mary Reid, PhD has established a cohort of high risk lung cancer patients at RPCI and has initiated a program of chemoprevention of lung cancer. At RPCI, there is a lung cancer screening program for high risk patients; this program employs autofluorescence bronchoscopy and low dose spiral CT of the chest for early detection of lung cancer. Patients are screened on the basis of known risk factors for lung cancer (smoking, obstructive lung disease, prior aerodigestive cancer and asbestos exposure), and followed prospectively with multiple biopsies taken for pathologic and biomarker assessment. Lung cancer is characterized as a multi-step process involving sequential histopathological changes and the accumulation of numerous epigenetic and genetic alterations caused mostly by chronic exposure to tobacco carcinogens. Recent analysis of 350 screened patients demonstrates that premalignant lesions, including metaplasia and dysplasia are present in 53% of all patients screened. On subsequent bronchoscopies, 25% of these patients continue to have the same level of lesion and 18.2% progress to a higher grade lesion after an average of 11 months. These pathway alterations seen in these lesions represent potential targets for chemopreventive agents, such as vitamin D. Dr. Reid, in collaboration with Candace Johnson, PhD (PR) and Donald L. Trump, MD (MTET), has obtained NCI funding to conduct a randomized, placebo controlled clinical trial to supplement high risk former smokers with confirmed premalignant lesions of the lung to calcitriol (1,25 dihydroxycholecalciferol) to test the hypothesis that calcitriol will inhibit the progression or reduce the incidence of metaplastic or dysplastic lesions in the bronchial epithelium of former smokers (R01 CA112238). The work has led to the formation of an international registry of premalignant lesions of the lung, across 10 major institutions in the US, Canada, and Europe to track the natural history of premalignancy of the lung and to determine the role of these lesions in quantifying risk of lung cancer incidence. In collaboration with Alex Adjei, MD, PhD (MTET), this effort is supported by an \$800,000 named philanthropic effort and Institute developmental funds; it will yield numerous future research opportunities and information on the genetic and epigenetic factors that influence progression to lung cancer.

Haitao Zhang, PhD*Assistant Professor, Cancer Prevention & Control*

Testosterone, the major circulating androgen, is converted to dihydrotestosterone, the preferred ligand of AR, in the prostate by the enzyme 5 α -reductase. The Prostate Cancer Prevention Trial (PCPT) demonstrated that treatment with finasteride, an inhibitor of 5 α -reductase type 2, decreased prostate cancer incidence by 25% but increased the proportion of poorly differentiated prostate cancers. Based on the finding that selenium depresses AR level, Dr. H. Zhang is investigating whether the chemopreventive efficacy of finasteride could be enhanced by combining it with selenium. The dihydrotestosterone-AR complex is known to associate with and suppress the activity of FOXO transcription factors. In general, FOXO members up-regulate transcription of a variety of pro-apoptotic genes, and selenium increases expression of FOXO. The functional significance of restoring FOXO transactivation by decreasing the level of the ligand-AR complex with finasteride/selenium is being studied. Dr. H Zhang also discovered that finasteride binds directly to AR and repressed AR signaling. He is characterizing the AR antagonistic activity of finasteride and the effect of AR ligand-binding domain mutations on such activity. This information may provide useful guidelines for matching patients to therapy in future clinical practice.

Yuesheng Zhang, PhD*Professor, Cancer Prevention & Control*

Dr. Y. Zhang is evaluating isothiocyanate-enriched cruciferous vegetable extracts in preclinical models (R01 CA80962 and R01 CA100623). The bladder is particularly interesting in this regard because isothiocyanates are excreted in urine and accumulate in bladder tissues. Isothiocyanates, including sulforaphane and allyl isothiocyanate, and vegetable extracts rich in these compounds, demonstrate potent bladder cancer-preventive activity. These agents have carcinogen-detoxifying phase 2 enzyme activity and cause apoptosis and cell cycle arrest in both cell and animal models. These findings suggest that isothiocyanates are promising for prevention of both primary and recurrent human bladder cancer. An immediate goal is to evaluate this potential among bladder cancer patients at high risk for recurrence. In collaboration with Khurshid Guru, MD (PR), Drs. Zhang and Ambrosone are conducting an observational study, using data and urine samples from the Data Bank BioRepository (DBBR), to determine the association of cruciferous vegetable consumption with bladder cancer recurrence. These epidemiologic and preclinical findings will provide the basis for a clinical trial with ITCs for prevention of bladder cancer recurrence with Drs. Zhang, Guru and Michael Wong, MD, PhD (TII). Preliminary/pre-clinical studies have shown promising effects of isothiocyanates. Dr. Zhang, in a recently initiated international collaboration with Dr. Rex Munday of Ruakura Research Center, New Zealand, identified cyclopenta dithiolethione (a synthetic dithiolethione) as a potent inducer of carcinogen-detoxifying enzymes in the bladder and other organs in rodents. (Tang *et al.*, *Cur Drug Metal* 2004; 5:193; Tang *et al.*, *Anticancer Drugs* 2006; 17:297).

SELECTED PUBLICATIONS

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