Cancer and Environment Literature

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, cancers can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the cancer and the environment.
[Smith MH. **Cancer and Environment Literature.** *Cancer Biology* 2012;2(1):15-34]. (ISSN: 2150-1041). http://www.cancerbio.net. 3

Keywords: cancer; biology; life; disease; research; literature

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Ames, B. N. and L. S. Gold (1998). "The causes and prevention of cancer: the role of environment." Biotherapy **11**(2-3): 205-20.

The idea that synthetic chemicals such as DDT are major contributors to human cancer has been inspired, in part, by Rachel Carson's passionate book, Silent Spring. This chapter discusses evidence showing why this is not true. We also review research on the causes of cancer, and show why much cancer is preventable. Epidemiological evidence indicates several factors likely to have a major effect on reducing rates of cancer: reduction of smoking, increased consumption of fruits and vegetables, and control of infections. Other factors are avoidance of intense sun exposure, increases in physical activity, and reduction of alcohol consumption and possibly red meat. Already, risks of many forms of cancer can be reduced and the potential for further reductions is great. If lung cancer (which is primarily due to smoking) is excluded, cancer death rates are decreasing in the United States for all other cancers combined. Pollution appears to account for less than 1% of human cancer; yet public concern and resource allocation for chemical pollution are very high, in good part because of the use of animal cancer tests in cancer risk assessment. Animal cancer tests, which are done at the maximum tolerated dose (MTD), are being misinterpreted to mean that low doses of synthetic chemicals and industrial pollutants are relevant to human cancer. About half of the chemicals tested, whether synthetic or natural, are carcinogenic to rodents at these high doses. A plausible explanation for the high frequency of positive results is that testing at the MTD frequently can cause chronic cell killing and consequent cell replacement, a risk factor for cancer that can be limited to high doses. Ignoring this greatly exaggerates risks. Scientists must determine mechanisms of carcinogenesis for each substance and revise acceptable dose levels as understanding advances. The vast bulk of chemicals ingested by humans is natural. For example, 99.99% of the pesticides we eat are naturally present in plants to ward off insects and other predators. Half of these natural pesticides tested at the MTD are rodent carcinogens. Reducing exposure to the 0.01% that are synthetic will not reduce cancer rates. On the contrary, although fruits and vegetables contain a wide variety of naturally-occurring chemicals that are rodent carcinogens, inadequate consumption of fruits and vegetables doubles the human cancer risk for most types of cancer. Making them more expensive by reducing synthetic pesticide use will increase cancer. Humans also ingest large numbers of natural chemicals from cooking food. Over a thousand chemicals have been reported in roasted coffee: more than half of those tested (19/28) are rodent carcinogens. There are more rodent carcinogens in a single cup of coffee than potentially carcinogenic pesticide residues in the average American diet in a year, and there are still a thousand chemicals left to test in roasted coffee. This does not mean that coffee is dangerous but rather that animal cancer tests and worst-case risk assessment, build in enormous safety factors and should not be considered true risks. The reason humans can eat the tremendous variety of natural chemical "rodent carcinogens" is that humans,

like other animals, are extremely well protected by many general defense enzymes, most of which are inducible (i.e., whenever a defense enzyme is in use, more of it is made). Since the defense enzymes are equally effective against natural and synthetic chemicals one does not expect, nor does one find, a general difference between synthetic and natural chemicals in ability to cause cancer in high-dose rodent tests. The idea that there is an epidemic of human cancer caused by synthetic industrial chemicals is false. In addition, there is a steady rise in life expectancy in the developed countries. Linear extrapolation from the maximum tolerated dose in rodents to low level exposure in humans has led to grossly exaggerated mortality forecasts. Such extrapo

Barron, J. J., M. J. Cziraky, et al. (2009). "HER2 testing and subsequent trastuzumab treatment for breast cancer in a managed care environment." Oncologist **14**(8): 760-8.

BACKGROUND: Degree of physician adherence to 2001 guidelines recommending routine testing of human epidermal growth factor receptor 2 (HER2) status among newly diagnosed, recurrent, and metastatic breast cancer (BC) cases, and frequency of trastuzumab use in HER2-positive patients are not well documented. METHODS: Patients newly diagnosed with BC managed by an identifiable hematologist/oncologist between June 1, 2005 and June 30, 2006 were identified from an administrative claims database of three health plans (n = 3,521). From these, a subset of 380 patients was identified for medical chart review. HER2 testing (occurrence, type of test used), HER2 status (positive, negative, unknown), and trastuzumab usage were evaluated. RESULTS: HER2 testing occurred in 88% of all newly diagnosed patients with BC and in 98.1% of those with stage 1 or higher breast cancer (n = 322), for whom testing is recommended. Among those with HER2 testing performed (n = 335), 21.5% were positive (HER2(+)), 77.3% were negative (HER2(-)), and 1.2% were unknown. Of the 52 patients who used trastuzumab, only one patient did not have documented HER2 overexpression. Of the 45 HER2(+) women who had stage 2 or higher BC, 13% did not receive trastuzumab. CONCLUSIONS: HER2 testing status was extremely high among newly diagnosed BC patients treated by hematologists/oncologists in a managed care environment. There was almost no evidence of inappropriate prescribing of trastuzumab, but 1 of every 7.5 patients with HER2-overexpressing stage 2 or higher breast cancer did not receive the agent.

Bernstein, J. L., B. Langholz, et al. (2004). "Study design: evaluating gene-environment interactions in the etiology of breast cancer - the WECARE study." Breast Cancer Res **6**(3): R199-214.

INTRODUCTION: Deficiencies in cellular responses to DNA damage can predispose to cancer. Ionizing radiation can cause cluster damage and double-strand breaks (DSBs) that pose problems for cellular repair processes. Three genes (ATM, BRCA1, and BRCA2) encode products that are essential for the normal cellular response to DSBs, but predispose to breast cancer when mutated. DESIGN: To examine the joint roles of radiation exposure and genetic susceptibility in the etiology of breast cancer, we designed a case-control study nested within five population-based cancer registries. We hypothesized that a woman carrying a mutant allele in one of these genes is more susceptible to radiation-induced breast cancer than is a non-carrier. In our study, 700 women with asynchronous bilateral breast cancer were individually matched to 1400 controls with unilateral breast cancer on date and age at diagnosis of the first breast cancer, race, and registry region, and counter-matched on radiation therapy. Each triplet comprised two women who received radiation therapy and one woman who did not. Radiation absorbed dose to the contralateral breast after initial treatment was estimated with a comprehensive dose reconstruction approach that included experimental measurements in anthropomorphic and water phantoms applying patient treatment parameters. Blood samples were collected from all participants for genetic analyses. CONCLUSIONS: Our study design improves the potential for detecting gene-environment interactions for diseases when both gene mutations and the environmental exposures of interest are rare in the general population. This is particularly applicable to the study of bilateral breast cancer because both radiation dose and genetic susceptibility have important etiologic roles, possibly by interactive mechanisms. By using counter-matching, we optimized the informativeness of the collected dosimetry data by increasing the variability of radiation dose within the case-control sets and enhanced our ability to detect radiation-genotype interactions.

Bertelsen, L., L. Bernstein, et al. (2008). "Effect of systemic adjuvant treatment on risk for contralateral breast cancer in the Women's Environment, Cancer and Radiation Epidemiology Study." J Natl Cancer Inst **100**(1): 32-40.

BACKGROUND: Results from randomized trials indicate that treatment with tamoxifen or chemotherapy for primary breast cancer reduces the risk for contralateral breast cancer. However, less is known about how long the risk is reduced and the impact of factors such as age and menopausal status.

METHODS: The study included 634 women with contralateral breast cancer (case patients) and 1158 women with unilateral breast cancer (control subjects) from the Women's Environment, Cancer and Radiation Epidemiology Study. The women were younger than age 55 when they were first diagnosed with breast cancer during 1985-1999. Rate ratios (RRs) and 95% confidence intervals (CIs) for contralateral breast cancer after treatment with chemotherapy or tamoxifen were assessed by multivariable adjusted conditional logistic regression analyses. RESULTS: Chemotherapy was associated with a lower risk for contralateral breast cancer (RR = 0.57, 95% CI = 0.42 to 0.75) than no chemotherapy. A statistically significant association between chemotherapy and reduced risk for contralateral breast cancer persisted up to 10 years after the first breast cancer diagnosis and was stronger among women who became postmenopausal within 1 year of the first breast cancer diagnosis (RR = 0.28, 95% CI = 0.11 to 0.76). Tamoxifen use was also associated with reduced risk for contralateral breast cancer (RR = 0.66, 95% CI = 0.50 to 0.88) compared with no use, and the association was statistically significant for 5 years after the first diagnosis. CONCLUSION: The associations between chemotherapy and tamoxifen treatment and reduced risk for contralateral breast cancer appear to continue for 10 and 5 years, respectively, after the initial breast cancer is diagnosed. Ovarian suppression may have a role in the association between chemotherapy and reduced risk for contralateral breast cancer.

Borie, F., J. P. Daures, et al. (2002). "Influence of environment and healthcare structures on the survival of patients with colorectal cancer: a French population-based study." J Surg Oncol **80**(3): 137-42.

BACKGROUND AND OBJECTIVES: Colorectal cancer is one of the highest-ranking cancers in France, both sexes combined, with 33000 new cases per year. To report on the practice and the efficiency of the healthcare system, an evaluation of the therapeutic management of colorectal cancer was carried out in the department of the Herault, in the south of France. METHODS: Cases of colorectal cancer in 1992 (344 colorectal cancer incidental cases) in the department of the Herault were reviewed. The diversity of the therapeutic choices and survival were evaluated for the different types of healthcare facilities (private hospitals, nonspecialized and specialized hospitals) and residential areas (rural, semi-urban, urban). RESULTS: Two hundred seventy-one patients with colorectal cancer (78.8%) and 234 patients with colorectal cancer (67.7%) were respectively diagnosed and treated in the private sector. Sixteen cases (23.5%) in the public sector (29.7% in the university hospital) and 24 cases (19%) in the private sector involved surgical emergencies (peritonitis, intestinal obstructions) (P = 0.003). Radiotherapy was performed in 59% of patients with rectal cancer. Preoperative radiotherapy was used primarily in specialized hospitals (80% of radiated rectal cancer; P = 0.002), as opposed to postoperative radiotherapy, which was used predominantly in private hospitals (P = 0.005). Forty-five percent of the patients with colorectal cancer who had lymph node involvement have been treated with chemotherapy. In multivariate analysis, lymph node metastasis and the presence of metastases (Dukes stage) were the most important independent pejorative prognostic factors, followed by the initial treatment in nonspecialized hospitals, complicated colorectal cancer (intestinal obstruction, peritonitis), lack of histological differentiation, and rural and urban residential areas. CONCLUSIONS: Apart from independent prognostic factors, such as parietal, ganglionic, or metastatic extensions, the lack of histological differentiation, and the complicated forms, heterogeneity and inequality persist in the distribution, treatment for, and the survival of patients with colorectal cancer based on the type of healthcare facility and the living area of this French population.

Bronte, V., S. Cingarlini, et al. (2006). "Leukocyte infiltration in cancer creates an unfavorable environment for antitumor immune responses: a novel target for therapeutic intervention." Immunol Invest **35**(3-4): 327-57.

The interaction between tumor cells and the nearby environment is being actively investigated to explore how this interplay affects the initiation and progression of cancer. Host-tumor relationship results in the production of pro-inflammatory cytokines and chemokines that promote the recruitment of leukocytes within and around developing neoplasms. Cancer cells, together with newly recruited tumor-infiltrating cells, can also activate fibroblast and vascular responses, thus resulting in a chronic microenvironment perturbation. In this complex scenario, interactions between innate and adaptive immune cells can be disturbed, leading to a failure of immune-mediated tumor recognition and destruction. On the basis of the recent awareness about tumor promotion and immune deregulation by immune/inflammatory cells, novel anti-cancer strategies can be exploited.

Cartmel, B., L. J. Loescher, et al. (1992). "Professional and consumer concerns about the environment, lifestyle, and cancer." Semin Oncol Nurs **8**(1): 20-9.

Although it cannot be said that "everything causes cancer," our environment will never be

carcinogen-free. As a result, there are many substances we come in contact with daily that could be potentially harmful to our health. Even with the growing knowledge of the mechanisms of carcinogenesis, it is difficult to single out the exact cancer-causing or -promoting effects of single substances. The confusion that exists about the environment, lifestyle, and cancer can be overwhelming for everyone. Garfinkel offered the following suggestions for health care providers to use in putting this issue into better perspective for consumers: (1) no single study of cancer risk factors should be used as a basis for writing or changing public health policy; (2) animal studies should be supportive of findings in epidemiological studies; (3) any environmental factor-cancer effect relationship should be demonstrated biologically; (4) regulatory agencies such as the EPA tend to be conservative in their interpretation of study results, and may suggest caution even when the risk of developing cancer is low; (5) regulatory agencies have been known to extrapolate future effects of carcinogen exposure from current incomplete or limited information about the carcinogen in question. With the knowledge that we do have, we must strive to take personal control over life-style factors that may cause cancer.

Cox, K. (2000). "Setting the context for research: exploring the philosophy and environment of a cancer clinical trials unit." J Adv Nurs **32**(5): 1058-65.

This paper describes a process of context setting that was undertaken prior to designing a study to assess the psychosocial impact of participation in phase I and II anticancer drug trials from the patient's perspective. The paper outlines how and why this context setting was undertaken and highlights important aspects of the culture and organization of cancer clinical trials that may influence patients' experiences in trial recruitment and participation. In this way, the context setting proved to be an invaluable tool for providing an orientation to the environment where patients received their care and treatment as well as identifying issues that would need to be taken into consideration later in the research study design.

Coyle, Y. M. (2004). "The effect of environment on breast cancer risk." Breast Cancer Res Treat **84**(3): 273-88.

Environmental factors are believed to explain a large proportion of breast cancer incidence. Known risk factors for breast cancer, which are related to the reproductive life of women, and other factors, such as inheritance and socioeconomic status, explain only about half of the breast cancer cases in the US. Ionizing radiation is a well established environmental risk factor for breast cancer. Chemicals that induce mammary cancer in rodents have served as leads for studies in humans, but occupational and environmental exposure to these chemicals have for the most part lacked association with breast cancer risk. However, there is recent evidence in rats that cadmium at very low doses acts as an estrogen mimic, indicating a need to investigate the effects of metals on breast cancer risk. Studies suggest that circadian rhythm disruption is linked with breast cancer, but too few studies have been done to be conclusive. Over the years, cigarette smoking as a risk factor for breast cancer has remained controversial. However, recent research has found passive smoke exposure to be associated with increased breast cancer risk, which is hypothesized to be accounted for on the basis of an antiestrogenic effect of smoking. Solar radiation has been noted to be associated with reduced breast cancer, supporting the hypothesis that vitamin D plays a protective role in reducing this risk. Although, most of the environmental factors discussed in this review have not been convincingly found to influence breast cancer risk, research suggests that environmental exposure in combination with genetic pre-disposition, age at exposure, and hormonal milieu have a cumulative effect on breast cancer risk.

Davila, J. A., J. M. Brooks, et al. (2004). "The effect of physician characteristics and their practice environment on surgical referral patterns for early-stage breast cancer in Iowa." Am J Med Qual **19**(6): 266-73.

The objective of this article was to examine whether characteristics of referring physicians and their practice environment were associated with surgical referral behavior for early-stage breast cancer patients. A total of 2801 women diagnosed with early-stage breast cancer and their referring physicians were identified from the Iowa Surveillance, Epidemiology, and End Results (SEER) database during 1989-1996. The Iowa Physician Inventory was used to collect information on characteristics of referring physicians. Multiple logistic regression analyses were conducted to evaluate characteristics of the referring physicians and their practice environment to explain surgical referral behavior. Affiliation with physicians' networks and professional diversity among area specialists were associated with increased referrals to surgeons more likely to perform breast-conserving surgery. Promoting interaction among physicians, particularly among those with different specialties, may increase the diffusion of new behaviors into clinical practice.

DeRosa, C. T., Y. W. Stevens, et al. (1993). "Cancer policy framework for: public health assessment of

carcinogens in the environment." Toxicol Ind Health **9**(4): 559-75.

Cancer remains at the forefront of public health concerns in the United States and throughout the world. Over the past 20 years a wide range of federal agencies and other organizations have been involved in developing policy statements, classification strategies, and assessment methods to address carcinogenesis and health risks. Each of these documents was developed in response to issues confronted by those organizations in pursuing their mission, often as a direct function of legislative mandates. In pursuing its mandated responsibilities, the Agency for Toxic Substances and Disease Registry (ATSDR) must address public health concerns associated with exposure to carcinogens in the context of all available relevant information. This information includes both technical data as well as science policy positions adopted by the range of organizations with programs germane to the assessment and/or regulation of carcinogens. Because of distinct differences in perspective, practice, and policy dictated by the mandated activities of these organizations and the rapidly evolving understanding of carcinogenesis, apparently divergent positions may be reflected in their conclusions. The differences outlined above, coupled with requests from the public, other agencies, and the private sector for a statement reflecting the Agency's position on science and science policy issues related to cancer, prompted the development of this policy. This document is intended to serve as a framework to guide the Agency in its programs and actions regarding carcinogens and to harmonize such efforts with those of other federal agencies and relevant organizations. This framework reflects an assessment of current practice within the Agency and defines the appropriate roles of conclusions derived by other groups, professional judgment, and emerging scientific principles in ATSDR's public health assessments of exposures to carcinogens. This Cancer Policy Framework is not intended to encompass the development of operational guidelines per se, although the Agency recognizes the utility of such efforts. A central theme of this Cancer Policy Framework is the use of risk analysis as an organizing construct based on sound biomedical and other scientific judgment to define plausible exposure ranges of concern rather than single numerical conclusions that may convey an artificial sense of precision. The development and use of innovative tools for exposure and dose response assessment (with particular emphasis on molecular epidemiology) are also endorsed.

Desoubeaux, N., C. Herbert, et al. (1997). "Social environment and prognosis of colorectal cancer patients: a French population-based study." Int J Cancer **73**(3): 317-22.

Colorectal cancer is a major public health problem in industrialised countries. Several studies have shown that social environment influences survival in cancer patients in many countries, but the causes remain unknown. In France, very little work has been done in this area. Our aim was to assess whether social environment influences survival of colorectal cancer patients in a well-defined French population and, if so, to what extent this could be explained by differences in stage at diagnosis or in treatment. The study population consisted of 1,642 colorectal cancer patients diagnosed between 1978 and 1987 in the French department of Calvados. Socio-demographic characteristics were assessed in terms of socio-professional category, place of residence (urban vs. rural) and distance from the place of residence to a specialised health-care centre. The relation between social environment, clinical factors and survival was studied using 2 multivariate methods (Cox model and relative survival method). Patients with poorer prognosis were found to be farmers of both sexes and individuals without occupation among males. Differences in survival were not explained entirely even when variations in stage at diagnosis and in treatment were taken into account.

Freitas, V. M., M. Rangel, et al. (2008). "The geodiamolide H, derived from Brazilian sponge Geodia corticostylifera, regulates actin cytoskeleton, migration and invasion of breast cancer cells cultured in three-dimensional environment." J Cell Physiol **216**(3): 583-94.

We are investigating effects of the depsipeptide geodiamolide H, isolated from the Brazilian sponge Geodia corticostylifera, on cancer cell lines grown in 3D environment. As shown previously geodiamolide H disrupts actin cytoskeleton in both sea urchin eggs and breast cancer cell monolayers. We used a normal mammary epithelial cell line MCF 10A that in 3D assay results formation of polarized spheroids. We also used cell lines derived from breast tumors with different degrees of differentiation: MCF7 positive for estrogen receptor and the Hs578T, negative for hormone receptors. Cells were placed on top of Matrigel. Spheroids obtained from these cultures were treated with geodiamolide H. Control and treated samples were analyzed by light and confocal microscopy. Geodiamolide H dramatically affected the poorly differentiated and aggressive Hs578T cell line. The peptide reverted Hs578T malignant phenotype to polarized spheroid-like structures. MCF7 cells treated by geodiamolide H exhibited polarization compared to controls. Geodiamolide H induced striking phenotypic

modifications in Hs578T cell line and disruption of actin cytoskeleton. We investigated effects of geodiamolide H on migration and invasion of Hs578T cells. Time-lapse microscopy showed that the peptide inhibited migration of these cells in a dose-dependent manner. Furthermore invasion assays revealed that geodiamolide H induced a 30% decrease on invasive behavior of Hs578T cells. Our results suggest that geodiamolide H inhibits migration and invasion of Hs578T cells probably through modifications in actin cytoskeleton. The fact that normal cell lines were not affected by treatment with geodiamolide H stimulates new studies towards therapeutic use for this peptide.

Gagne, P., A. Akalu, et al. (2004). "Challenges facing antiangiogenic therapy for cancer: impact of the tumor extracellular environment." Expert Rev Anticancer Ther **4**(1): 129-40.

It is well known that angiogenesis plays an important role in malignant tumor progression. Thus, a great deal of effort has been focused on the development and evaluation of novel angiogenesis inhibitors for the treatment of human malignancies. In this review, the role of angiogenesis in tumor growth will be examined, as well as efforts to develop and use antiangiogenic therapies to treat malignant tumors. In particular, focus will be on the extracellular environment and the challenges of using antiangiogenic therapy in the clinical setting, in terms of toxicities, potential mechanisms of tumor resistance and optimization of clinical trial design. Attention will be focused upon a mechanistic understanding of the variability and dynamic nature of individual tumor microenvironments, and the potential impact this has on antiangiogenic therapies.

Germain, P. (2007). "Barriers to the optimal rehabilitation of surgical cancer patients in the managed care environment: an administrator's perspective." J Surg Oncol **95**(5): 386-92.

Ensuring that surgical cancer patients obtain optimal rehabilitation care (defined here as all care provided post-operatively following cancer surgery) can be challenging because of the fragmented nature of the U.S. healthcare delivery and payment systems. In the managed care environment, surgical cancer patients' access to rehabilitation care is likely to vary by type of health insurance plan, by setting, by type of provider, and by whether care is provided in-network or out-of-network. The author of this article, who negotiates managed care contracts for the Roswell Park Cancer Institute (RPCI), gives examples of strategies used with some success by RPCI to collaborate with local payers to ensure that surgical cancer patients get optimal rehabilitation care, especially as they make the transition from hospital to outpatient care. She suggests that further collaborations of healthcare providers, payers, consumers, and policymakers are needed to help ensure optimal rehabilitation care for surgical cancer patients.

Giarelli, E. and L. A. Jacobs (2005). "Modifying cancer risk factors: the gene-environment interaction." Semin Oncol Nurs **21**(4): 271-7.

OBJECTIVES: To examine the concept of risk modification in the context of cancer prevention. DATA SOURCES: Published articles and research studies on genetic and environmental factors. CONCLUSION: How the environment is defined frames how the gene-environment interaction is studied and understood. The development of a workable model for risk modification flexible enough to be individualized for a patient is an important step in making primary prevention the goal in cancer care. IMPLICATIONS FOR NURSING PRACTICE: Nurses working in cancer care are well placed to advise patients on risk-management strategies, and to increase public awareness of the interdependence of environment and genomics on cancer risk.

Giordano, A., A. Fucito, et al. (2007). "Carcinogenesis and environment: the cancer stem cell hypothesis and implications for the development of novel therapeutics and diagnostics." Front Biosci **12**: 3475-82.

Stem cell research has greatly contributed to the field of oncology with the identification and isolation of cancer stem cells from a variety of tumors. The discovery of rare subpopulations of cancer stem cells has indeed entirely changed the focus of cancer research. Normal adult stem cells and cancer stem cells can both self-renew and undergo a differentiation program that, in turn, gives rise to a high number of differentiated cells. Adult stem cells and their malignant counterparts share almost all of the same intrinsic and extrinsic factors to regulate self-renewal, differentiation and proliferation pathways. Fractions of normal and cancer stem cells are naturally more resistant to toxic injuries than any other cell type. Overall, these observations lead to the conclusion that adult stem or progenitor cells can eventually become malignant by generating cancer stem cells, which are responsible for the development and maintenance of the tumor mass. In addition, chemo-resistant cancer stem cells may cause the relapse of the disease following an apparent beneficial treatment. Indeed, the study of the biology of cancer stem cells might lead to the improvement of preventive cancer diagnosis and to the development of novel therapeutics, which must be designed to selectively target malignant stem cells without affecting normal adult stem cells.

Gutt, C. N., Z. G. Kim, et al. (2001). "CO2 environment influences the growth of cultured human cancer cells dependent on insufflation pressure." Surg Endosc **15**(3): 314-8.

BACKGROUND: Experimental and clinical studies, have suggested that the CO2 pneumoperitoneum influences the development of intraabdominal tumor dissemination and port site metastases. Previous experiments performed both in vitro and in vivo have proved that CO2 insufflation stimulates malignant cell growth. Therefore, we designed a study to investigate the influence of CO2 insufflation administered at different pressures on the growth of cultured human tumor cells. METHODS: Two human tumor cell lines (CX-2 colon adenocarcinoma, DAN-G pancreas adenocarcinoma) were exposed to a CO2 environment maintained at different pressures (0 mmHg, 6 mmHg, 12 mmHg). Tumor growth was determined at different times after exposure to CO2 using fluorescence photometry. Cytotoxity of the CO2 environment different pressures was investigated using flow cytometry. RESULTS: At 1-4 days after exposure to CO2 insufflation, CX-2 and DAN-G tumor cell growth was decreased significantly ($p < 0.01$). Proliferation of pancreatic adenocarcinoma DAN-G increased significantly from day 5 to day 15 independent of the insufflation pressure ($p < 0.01$). Proliferation of colon adenocarcinoma CX-2 increased significantly from day 5 to day 15 but was found to be dependent on the insufflation pressure. CX-2 growth increased significantly with higher pressures ($p < 0.05$). CONCLUSION: CO2 insufflation influences the growth of cultured human tumor cells. After a short period of suppression, the CO2 environment stimulates malignant cell growth. The insufflation pressure may also have additional effects in promoting tumor growth.

Heavey, P. M., D. McKenna, et al. (2004). "Colorectal cancer and the relationship between genes and the environment." Nutr Cancer **48**(2): 124-41.

Colorectal cancer (CRC) is a significant cause of morbidity and mortality in developed countries, with both genetic and environmental factors contributing to the etiology and progression of the disease. Several risk factors have been identified, including positive family history, red meat intake, smoking, and alcohol intake. Protective factors include vegetables, calcium, hormone replacement therapy, folate, nonsteroidal anti-inflammatory drugs, and physical activity. The interaction between these environmental factors, in particular diet and genes, is an area of growing interest. Currently, oncogenes, tumor suppressor genes, and mismatch repair genes are believed to play an essential role in colorectal carcinogenesis. When considering the genetics of CRC, only 10% of cases are inherited and only 2-6% can be ascribed to the highly penetrant genes, such as APC, hMLH and hMSH2. Lower penetrance genes combined with a Western-style diet contribute to the majority of sporadic CRCs. The purpose of this article is to give a brief overview of the epidemiologic studies that have been conducted and present the major findings. Here, we examine the molecular events in CRC, with particular focus on the interaction between genes and environment, and review the most current research in this area.

Heiney, S. P., S. A. Adams, et al. (2006). "Subject recruitment for cancer control studies in an adverse environment." Cancer Nurs **29**(4): 291-9; quiz 300-1.

Subject recruitment in an adverse environment prompted researchers to identify a novel method to gain a different perspective on the problem. Lewin's Model of Change was used in a post hoc examination of recruitment strategies from 5 cancer control studies of breast or prostate cancer. Based on this evaluation, driving and restraining forces in recruitment were identified. Lessons learned and recommendations are discussed based on this evaluation. Five categories of restrainers were identified from this evaluation and include sociocultural, institutional, individuals, budget, and study design. Conversely, only 3 categories of drivers were elucidated by the examination: sociocultural, institutional, and individuals. Lessons and recommendations ranged from addressing institutional barriers to capitalizing on public relations. Researchers entering a new environment for recruitment would benefit from using Lewin's force field analysis before writing a proposal or implementing a project. This approach better directs energy and resources and enhances the ability of the investigator to maintain a broad, less biased perspective.

Hesse, B. W. (2005). "Harnessing the power of an intelligent health environment in cancer control." Stud Health Technol Inform **118**: 159-76.

In 1971, when Congress declared "war on cancer," the public's perception was driven by an image of a single cure for a single disease. What researchers have learned since that time is that cancer is a formidable enemy made up of more than 100 different disease etiologies. The war on cancer became a war of the 21st century; a war to be fought on multiple fronts against a diffuse enemy and for which prevention was the most judicious path to victory. To fight this new war on cancer, the National Cancer Institute must seek to harness the power of health informatics to create a supportive environment for transforming science, delivering safe and patient-

centric health care, and creating an environment of personal empowerment in public health. Three different types of health informatics applications are implicated: (a) applications in bioinformatics, which are intended to revitalize the engine of scientific discovery; (b) applications in medical informatics, which will create a safer and more effective environment for delivery; and (c) applications in consumer informatics, which will enable individuals to advance the charge of their own ongoing health care over the course of their lives. To keep these applications on track, health care administrators must take a sociotechnical approach to implementation. The new systems must be built into the health care environment in such a way that they support human capacities, provide failsafe backups in the face of cognitive and physical limitations, and support continuous quality improvement.

Hinds, P. S., M. Hockenberry, et al. (2007). "Nocturnal awakenings, sleep environment interruptions, and fatigue in hospitalized children with cancer." Oncol Nurs Forum **34**(2): 393-402.

PURPOSE/OBJECTIVES: To describe nocturnal awakenings and sleep environment interruptions experienced by children and adolescents hospitalized for two to four days to receive chemotherapy and to assess the relationships among nocturnal awakenings, sleep environment interruptions, sleep duration, and fatigue. DESIGN: Longitudinal, descriptive design. SETTING: St. Jude Children's Research Hospital and Texas Children's Cancer Center. SAMPLE: 25 patients with solid tumors and 4 with acute myeloid leukemia. METHODS: Actigraphy, fatigue instruments, sleep diary, room entry and exit checklists, and blood samples. MAIN RESEARCH VARIABLES: Nocturnal awakenings, sleep environment interruptions, sleep duration, and fatigue. FINDINGS: The number of nocturnal awakenings per night as measured by actigraphy ranged from 0-40. The number of room entries and exits by a staff member or parent was 3-22 times per eight-hour night shift. The number of nocturnal awakenings was related to fatigue by patient report; patients who experienced 20 or more awakenings had significantly higher fatigue scores than those with fewer awakenings. Nocturnal awakenings also were significantly associated with sleep duration by patient and parent report. CONCLUSIONS: Hospitalized pediatric patients with cancer who experience more nocturnal awakenings are more fatigued and sleep longer. IMPLICATIONS FOR NURSING: Nurses may be able to control some of the factors that contribute to nocturnal awakenings and sleep environment interruptions that affect fatigue and sleep duration in hospitalized pediatric patients with cancer.

Hursting, S. D. (1997). "Experimental models of gene-environment interaction for cancer chemoprevention studies." Curr Opin Oncol **9**(5): 487-91.

The recent development of mouse strains with cancer-related genes overexpressed or inactivated has provided investigators with new models for testing chemoprevention strategies to offset specific genetic susceptibilities to cancer. This review focuses on the three genetically altered mouse models that have been the most widely used in chemoprevention studies: Min mice, which carry a mutation in the adenomatous polyposis coli (APC) gene; APC-knockout mice; and p53-knockout mice. Studies with the Min and APC-knockout mice provide the strongest evidence to date that the enzyme cyclooxygenase-2 plays a major role in colon carcinogenesis, and that nonsteroidal anti-inflammatory drugs that target cyclooxygenase-2 have great potential as colon cancer chemopreventive agents. In addition, chemoprevention studies in mice deficient of the p53 tumor-suppressor gene, the most commonly altered gene in human cancer, suggest that the increased susceptibility to cancer resulting from the loss of p53 function may be offset by preventive approaches. Other recently developed transgenic and knockout models of potential interest for chemoprevention studies will also be discussed.

Ide, T., Y. Kitajima, et al. (2007). "The hypoxic environment in tumor-stromal cells accelerates pancreatic cancer progression via the activation of paracrine hepatocyte growth factor/c-Met signaling." Ann Surg Oncol **14**(9): 2600-7.

BACKGROUND: Pancreatic cancer is one of the representative solid tumors, in which the hypoxic microenvironment plays a crucial role in malignant progression. We previously demonstrated that tumor-stromal interaction under hypoxia enhances the invasiveness of pancreatic cancer cells through hepatocyte growth factor (HGF)/c-Met signaling. METHODS: We investigated the immunohistochemical expression of hypoxia inducible factor-1alpha (HIF-1alpha) c-Met, and HGF in both cancer and stromal cells using 41 pancreatic cancer tissue specimens, and tried to identify any correlations with the clinical features and survival. RESULTS: Positive staining for HIF-1alpha was observed in both pancreatic cancer and the surrounding stromal cells in more than 30% of the cases, and it significantly correlated with lymph node metastasis ($P < .05$). A significant correlation was observed between the expression of HIF-1alpha and HGF in stromal cells ($P < .05$). In addition, the c-Met expression in cancer cells was found to significantly correlate with the

HGF expression in not only cancer but also stromal cells. The disease-free survival rates of the patients with HIF-1alpha in cancer, stromal, c-Met in cancer, and an HGF expression in stromal cells was significantly worse than those without such expressions (P < .05). CONCLUSIONS: These data suggest that the HGF/c-Met signaling via HIF-1alpha ?may therefore negatively affect the prognosis in patients with pancreatic cancer, and targeting tumor stroma under hypoxia might thus be potentially useful as a novel therapy for this cancer.

Jennbacken, K., H. Gustavsson, et al. (2009). "The prostatic environment suppresses growth of androgen-independent prostate cancer xenografts: an effect influenced by testosterone." Prostate **69**(11): 1164-75.

BACKGROUND: Interactions between prostate cancer cells and their surrounding stroma play an important role in the growth and maintenance of prostate tumors. To elucidate this further, we investigated how growth of androgen-dependent (AD) LNCaP and androgen-independent (AI) LNCaP-19 prostate tumors was affected by different microenvironments and androgen levels. METHODS: Tumor cells were implanted subcutaneously and orthotopically in intact and castrated immunodeficient mice. Orthotopic tumor growth was followed by magnetic resonance imaging (MRI). Gene expression in the tumors was evaluated by means of microarray analysis and microvessel density (MVD) was analyzed using immunohistochemistry. RESULTS: The results showed that LNCaP-19 tumors grew more rapidly at the subcutaneous site than in the prostate, where tumors were obviously inhibited. Castration of the mice did not affect ectopic tumors but did result in increased tumor growth in the prostatic environment. This effect was reversed by testosterone treatment. In contrast to LNCaP-19, the LNCaP cells grew rapidly in the prostate and castration reduced tumor development. Gene expression analysis of LNCaP-19 tumors revealed an upregulation of genes, inhibiting tumor growth (including ADAMTS1, RGS2 and protocadherin 20) and a downregulation of genes, promoting cell adhesion and metastasis (including N-cadherin and NRCAM) in the slow-growing orthotopic tumors from intact mice. CONCLUSIONS: The results show that the prostatic environment has a varying impact on AD and AI tumor xenografts. Data indicate that the androgen-stimulated prostatic environment limits growth of orthotopic AI tumors through induction of genes that inhibit tumor growth and suppression of genes that promote cell adhesion and metastasis.

Karan, D., J. B. Thrasher, et al. (2008). "Prostate cancer: genes, environment, immunity and the use of immunotherapy." Prostate Cancer Prostatic Dis **11**(3): 230-6.

Prostate cancer remains the most prevalent noncutaneous cancer, leading to almost 30,000 deaths every year in men in the United States. A large body of knowledge emphasizes a strong influence of epidemiological factors such as lifestyle, environment and diet, on the development of prostate cancer. Although risk reduction of prostate cancer has been somewhat successful, effective prevention is still lacking. Immunotherapeutic approaches, although moderately complicated, remain promising in an effort to control the progression and development of the disease. Taken together, the parameters of epidemiological studies and immunotherapeutic regimens might eventually be the most effective and preventive approach for prostate cancer. This review highlights some of the events associated with the development and prevention of prostate cancer.

Koeneman, K. S., F. Yeung, et al. (1999). "Osteomimetic properties of prostate cancer cells: a hypothesis supporting the predilection of prostate cancer metastasis and growth in the bone environment." Prostate **39**(4): 246-61.

BACKGROUND: Unlike most other malignancies, prostate cancer metastasizes preferentially to the skeleton and elicits osteoblastic reactions. METHODS: We present a hypothesis, based upon results obtained from our laboratory and others, on the nature of progression of prostate cancer cells and their predilection to growth and metastasis in the bone microenvironment. We propose the hypothesis that osseous metastatic prostate cancer cells must be osteomimetic in order to metastasize, grow, and survive in the skeleton. The reciprocal interaction between prostate cancer and bone stromal growth factors, including basic fibroblast growth factor (bFGF), hepatocyte growth factor/scatter factor (HGF/SF), and especially the insulin growth factor (IGF) axis initiates bone tropism, and is enhanced by prostate secreted endothelin-1 (ET-1) and urokinase-type plasminogen activator (uPA). Growth factors and peptides that have differentiating activity, such as transforming growth factor beta (TGF-beta), parathyroid hormone-related protein (PTH-rp), and the bone morphogenetic proteins (BMPs), can shift local homeostasis to produce the characteristic blastic phenotype, via interaction with prostate-secreted human kalikrein 2 (hK2), and prostate-specific antigen (PSA). This proposal asserts that altering the expression of certain critical transcription factors, such as Cbfa and MSX in prostate cancer cells, which presumably are under the inductive influences of prostate or bone stromal cells, can confer profiles of gene expression, such as osteopontin (OPN),

osteocalcin (OC), and bone sialoprotein (BSP), that mimic that of osteoblasts. RESULTS AND CONCLUSIONS: Elucidation of common proteins, presumably driven by the same promoters, expressed by both prostate cancer and bone stromal cells, could result in the development of novel preventive and therapeutic strategies for the treatment of prostate cancer skeletal metastasis. Agents developed using these strategies could have the potential advantage of interfering with growth and enhancing apoptosis in both prostate cancer and bone stromal compartments. The selective application of gene therapy strategy, driven by tissue-specific and tumor-restricted promoters for the safe delivery and expression of therapeutic genes in experimental models of prostate cancer metastasis, is discussed.

Koifman, S. and R. J. Koifman (2003). "Environment and cancer in Brazil: an overview from a public health perspective." Mutat Res **544**(2-3): 305-11.

This paper presents the current pattern of cancer incidence in Brazil by analyzing the country's cancer epidemiological profile. The authors highlight the observed overlapping distribution of cancer incidence in Brazil in tumor sites normally associated with higher socioeconomic status (cancers of the breast, prostate, and colon/rectum, among others) and poverty (cervix, stomach, oral cavity, and penis). In addition to analyzing the demographic and social characteristics associated with current epidemiological distribution of cancer in Brazil, the authors present several of the most important environmental risk factors (smoking and exposure to radiation, pesticides, and other chemicals) and discuss their respective exposure levels in the Brazilian context. The article concludes with an evaluation of the principal challenges facing environmental cancer control programs in Brazil, particularly focusing on smoking and exposure to chemicals.

Kotnis, A., S. Kannan, et al. (2008). "Case-control study and meta-analysis of SULT1A1 Arg213His polymorphism for gene, ethnicity and environment interaction for cancer risk." Br J Cancer **99**(8): 1340-7.

Cytosolic sulphotransferase SULT1A1 plays a dual role in the activation of some carcinogens and inactivation of others. A functional polymorphism leading to Arg(213)His substitution (SULT1A1*2) affects its catalytic activity and thermostability. To study the association of SULT1A1*2 polymorphism with tobacco-related cancers (TRCs), a case-control study comprising 132 patients with multiple primary neoplasm (MPN) involving TRC and 198 cancer-free controls was carried out. One hundred and thirteen MPN patients had at least one cancer in upper aerodigestive tract including lung (UADT-MPN). SULT1A1*2 showed significant risk association with UADT-MPN (odds ratio (OR)=5.50, 95% confidence interval (CI): 1.09, 27.7). Meta-analysis was conducted combining the data with 34 published studies that included 11 962 cancer cases and 14 673 controls in diverse cancers. The SULT1A1*2 revealed contrasting risk association for UADT cancers (OR=1.62, 95% CI: 1.12, 2.34) and genitourinary cancers (OR=0.73, 95% CI: 0.58, 0.92). Furthermore, although SULT1A1*2 conferred significant increased risk of breast cancer to Asian women (OR=1.91, 95% CI: 1.08, 3.40), it did not confer increased risk to Caucasian women (OR=0.92, 95% CI: 0.71, 1.18). Thus risk for different cancers in distinct ethnic groups could be modulated by interaction between genetic variants and different endogenous and exogenous carcinogens.

Lakshmanaswamy, R., R. C. Guzman, et al. (2008). "Hormonal prevention of breast cancer: significance of promotional environment." Adv Exp Med Biol **617**: 469-75.

Early full-term pregnancy reduces the risk of mammary cancer in humans. Rats and mice also exhibit this phenomenon of parity protection. Short-term treatment with pregnancy levels of estradiol (E2) is also highly effective in preventing mammary carcinogenesis. Earlier it has been demonstrated that parous rats treated with carcinogen develop latent microscopic mammary tumors that do not progress further to form overt mammary cancers. In the current investigation, we wanted to find out if short-term treatment with pregnancy levels of E2 also prevents mammary carcinogenesis similar to parity. Rats were injected with N-methyl-N-nitrosourea at 7 weeks of age and treated with 20 microg, 100 microg, 200 microg, or 30mg of E2 in silastic capsules for 3 weeks. 100 microg (17%), 200 microg (17%), and 30mg (17%) doses of E2 resulted in levels of E2 equivalent to pregnancy level and were effective in preventing overt mammary cancer incidence compared with control (100%) or 20 microg (73%) E2 treatment, which did not result in pregnancy levels of E2 in the circulation. Although a significant reduction of overt cancers was observed in the pregnancy levels of E2 treated groups, there was no difference in the incidence of latent microscopic mammary cancers between the E2 treated and the controls. Proliferation of latent microscopic mammary cancers was examined using immunohistochemistry for cyclin D1 expression. Proliferation in the latent microscopic mammary cancers of the protected groups was significantly lower (approximately 2.0-3.0-fold) than the latent microscopic mammary cancers in the unprotected groups. These findings indicate that mammary cancer development can be blocked by

inhibiting or blocking promotion and progression of carcinogen initiated cells.

Landi, M. T., D. Consonni, et al. (2008). "Environment And Genetics in Lung cancer Etiology (EAGLE) study: an integrative population-based case-control study of lung cancer." BMC Public Health **8**: 203.

BACKGROUND: Lung cancer is the leading cause of cancer mortality worldwide. Tobacco smoking is its primary cause, and yet the precise molecular alterations induced by smoking in lung tissue that lead to lung cancer and impact survival have remained obscure. A new framework of research is needed to address the challenges offered by this complex disease. METHODS/DESIGN: We designed a large population-based case-control study that combines a traditional molecular epidemiology design with a more integrative approach to investigate the dynamic process that begins with smoking initiation, proceeds through dependency/smoking persistence, continues with lung cancer development and ends with progression to disseminated disease or response to therapy and survival. The study allows the integration of data from multiple sources in the same subjects (risk factors, germline variation, genomic alterations in tumors, and clinical endpoints) to tackle the disease etiology from different angles. Before beginning the study, we conducted a phone survey and pilot investigations to identify the best approach to ensure an acceptable participation in the study from cases and controls. Between 2002 and 2005, we enrolled 2101 incident primary lung cancer cases and 2120 population controls, with 86.6% and 72.4% participation rate, respectively, from a catchment area including 216 municipalities in the Lombardy region of Italy. Lung cancer cases were enrolled in 13 hospitals and population controls were randomly sampled from the area to match the cases by age, gender and residence. Detailed epidemiological information and biospecimens were collected from each participant, and clinical data and tissue specimens from the cases. Collection of follow-up data on treatment and survival is ongoing. DISCUSSION: EAGLE is a new population-based case-control study that explores the full spectrum of lung cancer etiology, from smoking addiction to lung cancer outcome, through examination of epidemiological, molecular, and clinical data. We have provided a detailed description of the study design, field activities, management, and opportunities for research following this integrative approach, which allows a sharper and more comprehensive vision of the complex nature of this disease. The study is poised to accelerate the emergence of new preventive and therapeutic strategies with potentially enormous impact on public health.

Launoy, G., X. Le Coutour, et al. (1992). "Influence of rural environment on diagnosis, treatment, and prognosis of colorectal cancer." J Epidemiol Community Health **46**(4): 365-7.

STUDY OBJECTIVE: Several studies have shown that residential location (urban or rural) influences the incidence of colorectal cancer. The aim was to investigate the influence of rural environment on colorectal cancer history and survival in a well defined population. DESIGN: Patients with colorectal cancer diagnosed in the department of Calvados (France) were classified by place of residence (urban/rural) and information on clinical symptoms, tumour extension, treatment, and survival was collected. SETTING: The study was population based, in the department of Calvados in France. PATIENTS: During 1978-1984, 1445 colorectal cancers were collected by the Digestive Tract Cancer Registry of Calvados, 1047 with an urban place of residence (544 males and 503 females) and 284 with a rural place of residence (134 males and 150 females). MEASUREMENTS AND MAIN RESULTS: In both sexes, rural patients with colorectal cancers were treated less frequently in a specialised health care centre (40.0%) than patients from an urban population (53.4%). The difference was mainly but not entirely explained by distance from the specialised health care centre. In females in the rural population, cancers were diagnosed more frequently at the stage of severe clinical symptoms (22.1%) and metastases (18.8%) than they were in the urban population (15.5% and 12.3%). In addition among females a rural environment appeared to confer a worse prognosis (relative risk = 1.3). CONCLUSIONS: Our findings suggest an inequality between rural and urban populations, especially for women. The loneliness of rural women leads to a delay in diagnosis and worse survival. In health education campaigns on colorectal cancer, efforts must be made to provide medical information to rural women in order to reduce the delay in diagnosis and improve survival.

Legorreta, A. P., X. Liu, et al. (2000). "Examining the use of breast-conserving treatment for women with breast cancer in a managed care environment." Am J Clin Oncol **23**(5): 438-41.

At a National Institutes of Health Consensus Conference in 1991, conservation treatment was considered preferable for patients with early-stage breast cancer. In the early and mid-1990s, however, less than half of the eligible patients received this treatment and the rates varied with patient and provider characteristics. This study explores whether

more eligible patients with breast cancer received conservation treatment in recent years in a managed care environment compared to reports in the literature, and if patient and hospital characteristics affected the rate of acceptance. The study population included 753 women with breast cancer in clinical stages 0, I, or II. Patients with Stage III or IV tumors or with tumors larger that 5.0 cm were excluded. A multiple logistic regression incorporated in a mixed-effect model was used to estimate the effect of patient and facility characteristics on the likelihood of using breast-conserving surgery controlling for clinical stages and demographics such as age, race, and marital status. Among the 753 eligible patients, 474 (62.9%) received conservation surgery. Only Hispanic ethnicity and clinical stage significantly affected the likelihood of receiving conservation treatment. Factors such as patient age, hospital size, and teaching status that had been found to be significant predictors in earlier studies were not statistically significant in this study, although conservation treatment was more frequent in younger women and in teaching hospitals. A larger proportion of eligible patients received conservative treatment in this study than in previous reports. This treatment became available in a broader range of institutions, moving from large, academic teaching centers to smaller community hospitals.

Low, Y. L., A. M. Dunning, et al. (2006). "Implications of gene-environment interaction in studies of gene variants in breast cancer: an example of dietary isoflavones and the D356N polymorphism in the sex hormone-binding globulin gene." Cancer Res **66**(18): 8980-3.

Studies to identify common genetic variants contributing to breast cancer risk often yield inconsistent results. Breast cancer is a complex disease involving both genetic and environmental determinants. Dietary isoflavones are thought to reduce breast cancer risk by stimulating circulating sex hormone-binding globulin (SHBG) levels. The SHBG gene contains a D356N polymorphism and the N variant is associated with reduced SHBG clearance compared with the D variant. In this study, we show a significant gene-environment interaction between SHBG D356N polymorphism and dietary isoflavone exposure on circulating SHBG levels in 1,988 postmenopausal women. SHBG levels were positively associated with isoflavones in women carrying the N variant (etap2 = 1.9%; P = 0.006) but not in women carrying only the D variant (etap2 = 0.0%; P = 0.999; P(interaction) = 0.019). This finding shows that the subtle effects of some genetic variants may be magnified and only become detectable in the presence of certain exposures. This gene-environment interaction might explain heterogeneity in studies associating SHBG gene variants and soy consumption with breast cancer risk in Far East population exposed to high isoflavone levels compared with populations with lower levels.

Maskarinec, G. (2000). "Breast cancer--interaction between ethnicity and environment." In Vivo **14**(1): 115-23.

The risk to develop breast cancer varies at least five fold around the world. Migrant women from low incidence countries to the United States experience an increase in risk over several generations. The objectives of this paper are to describe ethnic differences in breast cancer incidence and to review research related to risk factors that may explain these variations. Although ethnic differences can be partially explained by established risk factors, a large proportion of the increase in risk remains unexplained. Hormonal factors, including estrogens, insulin, and growth factors, may offer an explanatory mechanism how increasing caloric intake, decreasing physical activity, changes in nutrients, increasing height, and adiposity affect breast cancer risk. Future research on polymorphisms in genes coding for enzymes that are involved in the chemical activation and detoxification of environmental carcinogens, dietary agents, and endogenous hormones may contribute to the understanding of ethnic differences in breast cancer risk.

Micke, P. and A. Ostman (2005). "Exploring the tumour environment: cancer-associated fibroblasts as targets in cancer therapy." Expert Opin Ther Targets **9**(6): 1217-33.

Stroma cells contribute to the microenvironment that is essential for cancer growth, invasion and metastatic progression. Fibroblasts, often termed myofibroblasts or cancer-associated fibroblasts (CAFs), represent the most abundant cell type in the tumour stroma. The demonstrated tumour-promoting capacities of CAFs has increased the interest to exploit them as drug targets for anticancer therapy. Although single factors, such as platelet-derived growth factor, transforming growth factor-beta1, hepatocyte growth factor and matrix metalloproteinases have been identified as mediators in the fibroblast tumour interaction, the morphological and functional differences of CAFs compared with their normal counterparts are only incompletely understood. Recently, novel global methods for gene expression profiling were applied to comprehensively characterise CAFs from breast, pancreas, colon and basal cell cancer in their in situ environment. The analysis of different CAF preparations revealed regulated genes that were previously not described in the tumour-stroma context. Additionally, besides a

few striking overlaps, the comparison of the gene lists indicates a high level of heterogeneity in the expression pattern of CAFs from different tumour types. Together, these studies emphasise the importance of cross-talk between stromal and malignant cells of the tumour. It is likely that the continued characterisation of this interaction, and the molecular identification of key mediators, will provide insights into tumour biology and suggest novel therapeutic options.

Mihich, E., H. Bartsch, et al. (2001). "The twentieth international symposium of the Sapporo Cancer Seminar Foundation: gene environment interaction and cancer prevention." Cancer Res **61**(6): 2788-92.

The main goal of this Symposium was to discuss new information that could be used for the development of effective and novel approaches in cancer prevention. Mounting evidence indicates that genetic predisposition to cancer plays an important role in the etiology of the disease and that multistage carcinogenesis is for the most part based on multiple genetic changes, favoring cell survival. It is also evident that a variety of environmental factors lead to carcinogenic changes and determine cancer-causative or cancer-facilitative genetic changes; these factors may be endogenous in origin, as for example those that are endocrinologic in nature, or may come from the external environment, as for example products in tobacco smoke or in industrial pollution. It is therefore obvious that gene-environment interactions play a pivotal role in carcinogenesis and consequently may offer specific sites of intervention that may be useful for the development of cancer prevention. In general, cancer prevention can be implemented through Public Health measures, as is typically the case for intervention on smoking, industrial pollution, aflatoxin B contamination or, when we know more about it, dietary habits. On the other hand, it should become possible to design more rational chemoprevention and immunoprevention trials as more becomes known about the genetic changes predisposing to cancer and about the gene products that are responsible for the phenotypic changes leading to neoplasia.

Ohtsubo, T., H. Igawa, et al. (2001). "Acidic environment modifies heat- or radiation-induced apoptosis in human maxillary cancer cells." Int J Radiat Oncol Biol Phys **49**(5): 1391-8.

PURPOSE: The effects of hyperthermia or irradiation on cell killing and induction of apoptosis were evaluated using human maxillary carcinoma IMC-3 cells and low pH (pH 6.8) adapted cells (IMC-3-pH). METHODS AND MATERIALS: Cellular heat-sensitivity or radiosensitivity was determined using the clonogenic assay. Apoptosis was assessed on the basis of a flow cytometric determination of the DNA content, DNA fragmentation, and poly(ADP-ribose)polymerase cleavage. RESULTS: When IMC-3 cells or IMC-3-pH cells were exposed to heat at 44 degrees C in pH 6.8 medium, an increase in thermosensitivity was observed compared with when the IMC-3 cells were exposed to heat at 44 degrees C in pH 7.4 medium. However, the selective reduction in survival was not observed after irradiation. In IMC-3 cells, apoptosis after heating at 44 degrees C for 60 min in pH 7.4 medium occurred earlier than that after 8 Gy irradiation, although both thermal and irradiated doses decreased the cell count to 10%. The degree of apoptosis after heating at pH 6.8 in IMC-3 cells or IMC-3-pH cells was greater than that at pH 7.4 in IMC-3 cells. However, the degree of apoptosis after 8 Gy irradiation at pH 6.8 in IMC-3 cells or IMC-3-pH cells was smaller than that at pH 7.4 in IMC-3 cells. CONCLUSION: Hyperthermia treatment is more effective at inducing apoptosis than radiation is in tumors that contain a population of low pH adapted cells.

Pandit, T. S., W. Kennette, et al. (2009). "Lymphatic metastasis of breast cancer cells is associated with differential gene expression profiles that predict cancer stem cell-like properties and the ability to survive, establish and grow in a foreign environment." Int J Oncol **35**(2): 297-308.

Although lymphatic dissemination is a major route for breast cancer metastasis, there has been little work to determine what factors control the ability of tumor cells to survive, establish and show progressive growth in a lymph node environment. This information is of particular relevance now, in the era of sentinel lymph node biopsy, where smaller intranodal tumor deposits are being detected earlier in the course of disease, the clinical relevance of which is uncertain. In this study, we compared differentially expressed genes in cell lines of high (468LN) vs. low (468GFP) lymphatic metastatic ability, and related these to clinical literature on genes associated with lymphatic metastatic ability and prognosis, to identify genes of potential clinical relevance. This approach revealed differential expression of a set of genes associated with 'cancer stem cell-like' properties, as well as networks of genes potentially associated with survival and autonomous growth. We explored these differences functionally and found that 468LN cells have a higher proportion of cells with a cancer stem cell-like (CD44+/CD24-) phenotype, have a higher clonogenic potential and a greater ability to survive, establish and grow in a foreign (lymph node and 3D Matrigel) microenvironment, relative to 468GFP cells. Differentially expressed genes which reflect these

functions provide candidates for investigation as potential targets for therapy directed against early lymphatic metastasis.

Perera, F. P. (1997). "Environment and cancer: who are susceptible?" Science **278**(5340): 1068-73.

Acting in concert with individual susceptibility, environmental factors such as smoking, diet, and pollutants play a role in most human cancer. However, new molecular evidence indicates that specific groups-characterized by predisposing genetic traits or ethnicity, the very young, and women-may have heightened risk from certain exposures. This is illustrated by molecular epidemiologic studies of environmental carcinogens such as polycyclic aromatic hydrocarbons and aromatic amines. Individual genetic screening for rare high-risk traits or for more common, low-penetrant susceptibility genes is problematic and not routinely recommended. However, knowledge of the full spectrum of both genetic and acquired susceptibility in the population will be instrumental in developing health and regulatory policies that increase protection of the more susceptible groups from risks of environmental carcinogens. This will necessitate revision of current risk assessment methodologies to explicitly account for individual variation in susceptibility to environmental carcinogens.

Reed, P. I., B. J. Johnston, et al. (1991). "Effect of ascorbic acid on the intragastric environment in patients at increased risk of developing gastric cancer." IARC Sci Publ(105): 139-42.

Ascorbic acid has been shown to decrease nitrosation in vivo, and epidemiological data suggest that the consumption of foods rich in this vitamin is associated with a reduced risk for gastric cancer. In order to study this suggestion further, fasting gastric juice samples were obtained from 62 high-risk patients (seven with atrophic gastritis, ten with pernicious anaemia, ten with partial gastrectomy, 21 with vagotomy and drainage and 14 with highly selective vagotomy), before, during four weeks' treatment with 1 g ascorbic acid four times daily, and four weeks after treatment. Samples were analysed for pH, total and nitrate-reducing bacterial counts, nitrite and N-nitroso compounds. Treatment with ascorbic acid lowered the median pH only in the vagotomized patients (p less than 0.001) but resulted in a reduction in median nitrate-reducing bacterial counts and in nitrite and N-nitroso compound concentrations in all groups, except for an increase in the nitrate-reducing bacterial count in atrophic gastritis patients and in nitrite in those with pernicious anaemia. These data suggest that treatment with a high dose of ascorbic acid reduces the intragastric formation of nitrite and N-nitroso compounds.

Robson, B. (1996). "Conferences point to growing concern about possible links between breast cancer, environment." Cmaj **154**(8): 1253-5.

Evidence is growing that there may be a connection between certain chemicals in the environment and the rising incidence of breast cancer in North America. Two recent Canadian conferences have been held to disseminate information and another is planned for 1996. "We have a situation that is similar to global warming, " Devra Lee Davis, founder of the US Breast Cancer Prevention Collaborative Research Group, warned people attending a conference in Niagara Falls, Ont. "Breast cancer continues to increase. The increase is greatest among older women who have fewer of the known risk factors. It makes sense to try to limit exposure to things that could be promoting the disease."

Rogers, L. Q., S. J. Markwell, et al. (2009). "Exercise preference patterns, resources, and environment among rural breast cancer survivors." J Rural Health **25**(4): 388-91.

CONTEXT: Rural breast cancer survivors may be at increased risk for inadequate exercise participation. PURPOSE: To determine for rural breast cancer survivors: (1) exercise preference "patterns," (2) exercise resources and associated factors, and (3) exercise environment. METHODS: A mail survey was sent to rural breast cancer survivors identified through a state cancer registry, and 483 (30%) responded. FINDINGS: The majority (96%) were white, with mean education of 13 (+/-2.5) years and mean 39.0 (+/-21.5) months since diagnosis. Most participants (67%) preferred face-to-face counseling from an exercise specialist (27%) or other individual (40%). A third (31%) preferred home-based exercise with non face-to-face counseling from someone other than an exercise specialist. Participants preferring face-to-face counseling were more apt to prefer supervised exercise (38% vs 9%, $P < 0.001$) at a health club (32% vs 8%, $P < 0.001$). Home exercise equipment was reported by 63%, with 97% reporting home telephone and 67% reporting Internet access. Age, education, self-efficacy, treatment status, and exercise behavior were associated with exercise resources. The physical environment was often not conducive to exercise but a low crime rate and high trust in neighbors was reported. CONCLUSIONS: Rural health education programs encouraging exercise should offer multiple programming options while considering the physical environment and capitalizing on available resources and beneficial social environmental characteristics.

Ronnov-Jessen, L., O. W. Petersen, et al. (1995). "The origin of the myofibroblasts in breast cancer. Recapitulation of tumor environment in culture unravels diversity and implicates converted fibroblasts and recruited smooth muscle cells." J Clin Invest **95**(2): 859-73.

The origin of myofibroblasts in stromal reaction has been a subject of controversy. To address this question definitively, we developed techniques for purification and characterization of major stromal cell types. We defined a panel of markers that could, in combination, unequivocally distinguish these cell types by immunocytochemistry, iso-electric focusing, immunoblotting, and two-dimensional gel electrophoresis. We then devised an assay to recapitulate in culture, within two weeks of incubation, critical aspects of the microenvironment in vivo including the typical tissue histology and stromal reaction. When confronted with tumor cells in this assay, fibroblasts readily converted into a graded pattern of myogenic differentiation, strongest in the immediate vicinity of tumor cells. Vascular smooth muscle cells (VSMC), in contrast, did not change appreciably and remained coordinately smooth muscle differentiated. Midcapillary pericytes showed only a slight propensity for myogenic differentiation. Analysis of ten primary tumors implicated converted fibroblasts (10/10), vascular smooth muscle cells (4/10), and pericytes (1/10) in the stromal reaction. Tumor cells were shown to specifically denude the venules both in culture and in vivo, explaining the VSMC phenotype in the stroma. The establishment of this assay and clarification of the origin of these cells pave the way for further analysis of the mechanisms of conversion, and of the consequence of such heterogeneity for diagnosis and treatment.

Rowlands, J. and S. Noble (2008). "How does the environment impact on the quality of life of advanced cancer patients? A qualitative study with implications for ward design." Palliat Med **22**(6): 768-74.

It is well recognized that the ward environment has an effect on patients' quality of life and may, therefore, impact on the quality of end of life care. The body of evidence that informs ward design policy recommends single-bedded rooms on grounds of reduced infection risk, noise and versatility. Considering the majority of anticipated patient deaths occurring in hospitals, the quality of life aspects of ward design should also be considered. The aim of this study is to explore the views of patients with advanced cancer on the effect the ward environment has on their overall well-being. Semi-structured interviews exploring the experiences of 12 inpatients at a regional cancer centre were recorded and transcribed verbatim. Transcripts were analysed for emerging themes until theoretical saturation. Four major themes emerged: staff behaviours, the immediate environment, single vs. multi-bedded rooms and contact with the outside environment. The attitude, competence and helpfulness of the staff creates the atmosphere of the ward regardless of layout, furnishings, equipment and decor. The majority of the patients in this study expressed a strong preference for a multi-bedded room when they were well enough to interact and a single cubicle when they were very ill or dying, which opposes the current advice for building new hospitals with all single rooms. Although the current policy recommends the use of single-bedded rooms, this study suggests the need for a mix of multi-bedded wards and single rooms with respect to the impact of the environment on patient quality of life.

Shaham, D., R. Breuer, et al. (2006). "Computed tomography screening for lung cancer: applicability of an international protocol in a single-institution environment." Clin Lung Cancer **7**(4): 262-7.

BACKGROUND: The purpose of this study was to assess the applicability of an annual low-dose computed tomography (CT) screening program for lung cancer in a single institution in Israel, which has a relatively lower prevalence of lung cancer compared with other Western countries, and to examine stage distribution of detected lung cancers. PATIENTS AND METHODS: A cohort of 842 former and current smokers underwent baseline low-dose CT screening and a total of 942 annual repeat screenings over a period of 68 months. The definition of positive results on baseline and repeat screening and their diagnostic workup were guided by the common International Early Lung Cancer Action Program protocol. Recommendations for biopsy of suspicious nodules were based on nodule size, nodule growth, non-resolution following antibiotic therapy, and positron emission tomography scan. RESULTS: The test result was positive in 102 of the 842 baseline screenings (12%) and in 45 of the 942 annual repeat screenings (5%), and biopsy was recommended in 12 baseline and 2 annual screenings. Twelve of the 14 cancers diagnosed (86%) were stage I tumors. CONCLUSION: Our study indicates that the adoption of a common international protocol is feasible, even in a very different clinical setting, yielding a high proportion of early-stage lung cancers.

Tabori, U., H. Jones, et al. (2007). "Low prevalence of complications in severe neutropenic children with cancer in the unprotected environment of an overnight camp." Pediatr Blood Cancer **48**(2): 148-51.

BACKGROUND: The high risk of infection and other complications in severely neutropenic pediatric oncology patients receiving chemotherapy has led to development of a variety of preventive measures including isolation and diet restrictions. In order to examine the potential impact of these measures, we evaluated the outcomes of such patients attending a recreational summer camp. METHODS: We collected data on all children who attended an overnight summer camp for children with cancer during the years 1999-2004, and who were either severely neutropenic or at a high-intensity phase of chemotherapy. Outcome measures included fever, bleeding, hospitalization, and clinical or laboratory evidence of infection. The observation period included both, the 2-week camp experience and 30 days post-camp. RESULTS: The study group was comprised of 34 patients. Although nine (24%) were hospitalized for management of fever and neutropenia, only one patient had clinical or culture-positive evidence of an invasive infectious agent. No bleeding episode was recorded and most patients attended all camp activities. CONCLUSIONS: Our results support the safety and feasibility of severely neutropenic patients with cancer to attend the non-isolated, non-sterile environment of a summer camp. These findings may be applicable to school and other social settings.

Tan, X. L., A. Nieters, et al. (2007). "Genetic polymorphisms in TP53, nonsteroidal anti-inflammatory drugs and the risk of colorectal cancer: evidence for gene-environment interaction?" Pharmacogenet Genomics **17**(8): 639-45.

OBJECTIVE: Substantial evidence indicates that nonsteroidal anti-inflammatory drugs protect against colorectal cancer by altering cell cycle progression and/or inducing apoptosis, whereas p53 protein is crucial to maintaining cell-cycle arrest and regulating DNA repair, differentiation, and apoptosis. Genetic variants in TP53 gene might therefore influence colorectal cancer risk and modify the effects of nonsteroidal anti-inflammatory drugs. We assessed the association of TP53 Arg72Pro and p53PIN3 polymorphisms with colorectal cancer risk and their possible interaction with nonsteroidal anti-inflammatory drug use. METHODS: We included 467 cases and 563 controls from a population-based case-control study. Multivariate logistic regression analysis was used to estimate the association between genotypes, environmental exposures and colorectal cancer risk, adjusting for potential confounders. RESULTS: Odds ratios of colorectal cancer were 0.75 (95% confidence interval, 0.57-0.99) for TP53 72Pro carriers compared with those homozygous for the TP53 72Arg allele and 0.78 (95% confidence interval, 0.58-1.05) for p53PIN3 A2 carriers compared with p53PIN3 A1A1. Risks differed by nonsteroidal anti-inflammatory drug use. For both investigated TP53 polymorphisms, we found that the colorectal cancer risk associated with regular nonsteroidal anti-inflammatory drug use was statistically significantly modified by the TP53 genotype (P values for interaction=0.049 and 0.034, respectively), whereby a substantial protective effect of nonsteroidal anti-inflammatory drug use was observed for homozygous carriers of the 72Arg allele and of the PIN3 A1 allele (odds ratio 0.44; 95% confidence interval, 0.30-0.65 and odds ratio, 0.45; 95% confidence interval, 0.31-0.65). The interaction between nonsteroidal anti-inflammatory drugs and TP53 genetic polymorphisms was confirmed by haplotype analysis. CONCLUSIONS: These data suggest that the TP53 genotype may modify the influence of nonsteroidal anti-inflammatory drug use on the risk of colorectal cancer. A direct proof of functional analysis is warranted to confirm these findings.

Thomas, S., J. Atchley, et al. (2009). "Audit of the introduction of CT colonography for detection of colorectal carcinoma in a non-academic environment and its implications for the national bowel cancer screening programme." Clin Radiol **64**(2): 142-7.

AIM: To compare the sensitivity of double-contrast barium enema (DCBE) with computed tomography colonography (CTC) to determine whether CTC is superior for the detection of colorectal cancer (CRC) locally, and to compare the results to those of a national barium enema audit. MATERIALS AND METHODS: All patients undergoing diagnostic DCBE or CTC between January 2003 and December 2005 were identified from the picture archiving communication system (PACS). Patients with a confirmed diagnosis of CRC were identified from the local cancer registry. Patients who were not diagnosed as having CRC on imaging were assumed true negatives if they were not listed in the cancer registry by December 2007, giving a minimum of 2 years follow-up. DCBE and CTC reports of all patients with CRC were analysed, and cancer detection was considered to have occurred (positive test result) if the report stated the definite presence of CRC or possible CRC requiring further investigation. RESULTS: 2520 DCBEs and 604 CTCs were included. Twenty-one of 33 patients with CRC were detected using DCBE (incidence 1.31%, sensitivity 63.7%). Thirty-two of 33 patients with CRC were -detected using CTC (incidence 5.46%, sensitivity 97.7%). CONCLUSION: CTC is more sensitive for the detection of CRC, and its introduction in a district general hospital is justified. However, there has been a consequent decline in DCBE sensitivity, which, if

reflected nationally, suggests CTC is the preferential screening test for CRC.

Tominaga, K., J. Andow, et al. (1998). "Family environment, hobbies and habits as psychosocial predictors of survival for surgically treated patients with breast cancer." Jpn J Clin Oncol **28**(1): 36-41.

Many psychosocial factors have been reported to influence the duration of survival of breast cancer patients. We have studied how family members, hobbies and habits of the patients may alter their psychosocial status. Female patients with surgically treated breast cancer diagnosed between 1986 and 1995 at the Tochigi Cancer Center Hospital, who provided information on the above-mentioned factors, were used. Their subsequent physical status was followed up in the outpatients clinic. The Cox regression model was used to evaluate the relationship between the results of the factors examined and the duration of the patients' survival, adjusting for the patients' age, stage of disease at diagnosis and curability, as judged by the physician in charge after the treatment. The following factors were revealed to be significant with regard to the survival of surgically treated breast cancer patients: being a widow (hazard ratio 3.29; 95% confidence interval 1.32-8.20), having a hobby (hazard ratio 0.43; 95% confidence interval 0.23-0.82), number of hobbies (hazard ratio 0.64; 95% confidence interval 0.41-1.00), number of female children (hazard ratio 0.64; 95% confidence interval 0.42-0.98), smoker (hazard ratio 2.08; 95% confidence interval 1.02-4.26) and alcohol consumption (hazard ratio 0.10; 95% confidence interval 0.01-0.72). These results suggest that psychosocial factors, including the family environment, where patients receive emotional support from their spouse and children, hobbies and the patients' habits, may influence the duration of survival in surgically treated breast cancer patients.

Volkman, J. E. and K. J. Silk (2008). "Adolescent females and their mothers: examining perceptions of the environment and breast cancer." J Health Psychol **13**(8): 1180-9.

Recent research indicates environmental factors and personal behaviors are related to breast cancer risk, but adopting a healthy lifestyle as early as adolescence can serve a protective function. To investigate perceptions of breast cancer risk and the environment, 10 focus groups (N = 91) were conducted with adolescent females (n = 55) and mothers (n = 36) across four counties in the Midwest, USA. The Uncertainty Management Theory provides a framework for discussing statements, and results suggest that uncertainty is maintained through ambiguity about environmental risk factors and breast cancer. Recommendations for prevention messages are presented.

Wang, L. and S. J. Chen (2001). "Environment, genome and cancer." C R Acad Sci III **324**(12): 1085-91.

Cancer is one of the most serious diseases that threaten human being today. To some degree, it is a genetic disease but environmental and other nongenetic factors clearly play a role in many stages of neoplastic process. Genetic factors by themselves are thought to explain only about 5% of all cancer. The remainder can be attributed to external, 'environment' factors that act in conjunction with both genetic and acquired susceptibility. Of note, part of the susceptibility is owing to the variety of human genome. So, environment, human genome and cancer have much to do with each other. Combining all of the information from epidemiology and from research works in laboratory with policy-making and clinical works, purifying the environment, giving special protection to the high risk population, the mortality of cancer may decrease gradually in the future.

Wertel, I., B. Barczynski, et al. (2008). "The role of dendritic cells in cytotoxic immune response regulation in ovarian cancer micro-environment." Front Biosci **13**: 2177-90.

Ovarian cancer is the most lethal gynecological malignancy. At the time of diagnosis most patients present with an advanced stage of the disease and require multidisciplinary systemic treatment, including surgery and adjuvant chemotherapy. Despite good initial response to cytostatics, the vast majority of patients develops a recurrence and will need novel therapeutic strategies, as relapsed ovarian cancer is still incurable. One promising treatment option is the use of dendritic cells (DCs) which might induce effective anti-tumor immunity. The ability of DCs to generate an anti-cancer response has been documented in various kinds of human tumors, including malignant melanoma, renal cell carcinoma, and breast cancer tumors. Although DCs were identified in the micro-environment of ovarian cancer, lack of clearly defined ovarian-specific tumor antigens capable of being recognized by T cells is considered the major prohibiting factor in ovarian cancer vaccine development. There is therefore a strong need to identify and employ attractive candidates for tumor-specific antigens. In this review we will focus on current knowledge of the influence of DC mechanisms of cytotoxic T-cell responses and recent advances in DC identification in ovarian cancer patients, in addition to summarizing the data on DC vaccinations in these patients.

Wu, M. S., C. J. Chen, et al. (2005). "Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer." Cancer Epidemiol Biomarkers Prev **14**(8): 1878-82.

Revelation of the connection between Helicobacter pylori infection and gastric adenocarcinoma has prompted new investigations pertaining to its basic and clinical aspects. H. pylori-induced persistent and uncontrolled gastric inflammation nearly always precedes the development of cancer and is instrumental in initiating a multistep process leading to carcinogenesis. Despite initial optimism about the potential of combination anti-H. pylori therapy to ultimately eradicate gastric adenocarcinoma, recent investigations suggest its use should be targeted and tailored to a selected patient group considering the multifaceted role of H. pylori in disease and the disease heterogeneity of gastric adenocarcinoma. The clinical spectrum of H. pylori infection ranges from asymptomatic gastritis and peptic ulcer to gastric malignancies. The occurrence of one versus another is the result of differences in the magnitude of gastritis, and the current disease paradigm suggests gastric inflammation is common to all H. pylori-associated gastroduodenal diseases. Therefore, the host inflammatory responses to environmental triggers, rather than to bacteria or environmental factors per se, would dictate the variable outcomes of H. pylori infection. Putative factors that are expected to play an important role in stimulating inflammatory pathways and modulating the cross-talk between host and environment are age at the time of infection, environmental cofactors, H. pylori virulence, and host genetics. Elucidation of the intimate relationship between host-environment interaction and gastric inflammation, although currently a formidable task, is essential in the development of new prevention and treatment strategies. Such knowledge might provide clues that allow more accurate prediction of variable outcomes of gastric inflammation and appropriate adjustment of treatment strategies, and might open up novel areas for studying gastric carcinogenesis. The evolving new technologies, such as microarray, proteomic, and functional genomic analyses, promise to shed new light on the immense complexity of the presumed host-environment interactions and will reveal more useful markers for the diagnosis and prognosis of gastric adenocarcinoma.

Yang, S. Z., I. A. Eltoum, et al. (2006). "Enhanced EGR1 activity promotes the growth of prostate cancer cells in an androgen-depleted environment." J Cell Biochem **97**(6): 1292-9.

During anti-hormonal therapy for prostate cancer, a major clinical problem is the development of androgen-independent disease. The molecular mechanisms underlying the transition to androgen independence are the subject of intense investigation. In many prostate tumors, the activity of the transcription factor EGR1 (early growth response gene 1) is elevated due to overexpression of EGR1 and/or downregulation of the co-repressor, NAB2. We have modeled these alterations by expressing active EGR1 that does not bind NAB co-repressor proteins in human prostate carcinoma cells. We show here that active EGR1 expression enhances the androgen-independent growth of prostate carcinoma cells in vitro and in vivo. Employing RNAi and expression analyses, we show that EGR1 mediates its effects, at least in part, through the AR signaling pathway. These findings support a role for enhanced EGR1 activity in regulating the transition from androgen-dependent to androgen-independent prostate cancer.

Yeo, T. P., R. H. Hruban, et al. (2009). "Assessment of "gene-environment" interaction in cases of familial and sporadic pancreatic cancer." J Gastrointest Surg **13**(8): 1487-94.

INTRODUCTION: Pancreatic cancer (PC) is the fourth leading cause of cancer death in the United States. This study characterizes one of the largest national registries of familial PC (FPC) and sporadic PC (SPC), focusing on demographics, clinical factors, self-reported environmental and occupational lifetime exposures, and survival status. BACKGROUND: Reported risk factors for PC include advancing age, a family history of PC, high-risk inherited syndromes, cigarette, cigar, and pipe smoking, exposure to occupational and environmental carcinogens, African-American race, high fat/high cholesterol diet, obesity, chronic pancreatitis, and diabetes mellitus. PATIENTS AND METHODS: This retrospective cross-sectional, case-only analysis includes cases of FPC (n = 569) and SPC (n = 689) from the Johns Hopkins National Familial Pancreas Tumor Registry (NFPTR) enrolled between 1994 and 2005. RESULTS: FPC smokers with environmental tobacco smoke (ETS) exposure were diagnosed at a significantly younger mean age (63.7 years) as compared to FPC non-smokers without ETS exposure (66.6 years; $p = 0.05$). Non-smoker ETS-exposed cases were diagnosed with PC at a significantly younger mean age (64.0 years) compared to non-smoker non-ETS-exposed cases (66.5 years) ($p < 0.0004$). The mean age at diagnosis for Ashkenazi Jewish SPC subjects was significantly younger (by 2.1 years) than Ashkenazi Jewish FPC cases ($p = 0.05$). In

addition, Ashkenazi Jewish FPC subjects who smoked were diagnosed 5.9 years earlier than Ashkenazi Jewish FPC non-smokers (p = 0.05). The median length of survival for unresected FPC cases was significantly shorter (168 days) as compared to unresected SPC cases (200 days) (p = 0.04). Survival was improved in resected cases, 713 days for FPC cases and 727 days for SPC cases, but was not significantly different between the groups (p = 0.4). Mild to moderate multiplicative interaction was found between a family history of PC and exposure to asbestos, environmental radon, and environmental tobacco smoke (ETS), as evidenced by odds ratios >1.0. CONCLUSIONS: These are the first data to show that occupational and environmental exposures may act synergistically with inherited or acquired genetic polymorphisms, resulting in earlier occurrence of PC. Exposure to cigarette smoking and ETS exposure in non-smokers when younger than 21 years of age are associated with a younger mean age of diagnosis in FPC and SPC cases and Ashkenazi Jewish smokers, when compared to non-exposed cases. Risk prediction models which take into account environmental exposures as well as family history may more accurately predict the risk of PC. High-risk individuals will likely benefit from early identification of pre-malignant lesions and molecular profiling, as methods of early detection, prevention, and personalized therapy.

Young, G. P., Y. Hu, et al. (2005). "Dietary fibre and colorectal cancer: a model for environment--gene interactions." Mol Nutr Food Res **49**(6): 571-84.

As environmental factors are clearly associated with risk for colorectal cancer, we set out to model how dietary fibre, or the effects of its ingestion, might impact upon the complex events that characterise colorectal oncogenesis. The diverse nature of dietary fibre and its resultant fate in the gut is outlined. The evidence indicates that different types of fibre create different conditions in different regions of the gut. This is reflected in different effects on oncogenesis especially in animal models. Data from animal models show that insoluble fibre is protective. Evidence from human studies are not consistent, especially considering the interventional studies. However, all such studies have been dependent on biomarkers short of cancer formation, for measurement of an effect. The biological and molecular events characteristic of colorectal oncogenesis are reviewed in an effort to identify how fibre ingestion might regulate oncogenesis. While several mechanisms might account for protection, the results of fermentation and especially butyrate production provide examples of how genomic instability might be controlled. Activation of apoptosis and cell cycle arrest seem likely to be mechanisms that would enable correction of genomic events that drive oncogenesis. Butyrate itself can regulate gene expression by both epigenetic and direct effects.

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8/9/2011