Cancer and Smoke Research Literatures

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Abstract: 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. This article introduces recent research reports as references in the cancer and smoke related studies.
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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.

The following introduces recent reports as references in the related studies.

Agudo, A., N. Sala, et al. "Polymorphisms in metabolic genes related to tobacco smoke and the risk of gastric cancer in the European prospective investigation into cancer and nutrition." Cancer Epidemiol Biomarkers Prev. 2006 Dec;15(12):2427-34.

Metabolizing enzymes, which often display genetic polymorphisms, are involved in the activation of compounds present in tobacco smoke that may be relevant to gastric carcinogenesis. We report the results of a study looking at the association between risk of gastric adenocarcinoma and polymorphisms in genes CYP1A1, CYP1A2, EPHX1, and GSTT1. A nested case-control study was carried out within the European Prospective Investigation into Cancer and Nutrition, developed in 10 European countries. The study includes 243 newly diagnosed cases of histologically confirmed gastric adenocarcinoma and 946 controls matched by center, age, sex, and date of blood collection. Genotypes were determined in nuclear DNA from WBCs. We found an increased risk of gastric cancer for homozygotes for C (histidine) variant in Y113H of EPHX1 (odds ratio, 1.91; 95% confidence interval, 1.19-3.07) compared with subjects with TC/TT. There was also a significant increased risk for smokers carrying at least one variant allele A in Ex7+129C>A (m4) of CYP1A1 and never smokers with null GSTT1 and allele A in the locus -3859G>A of CYP1A2. Most of these genes are involved in the activation and detoxification of polycyclic aromatic hydrocarbons, suggesting a potential role of these compounds in gastric carcinogenesis.

Ahern, T. P., T. L. Lash, et al. "Lifetime tobacco smoke exposure and breast cancer incidence." Cancer Causes Control. 2009 Dec;20(10):1837-44. doi: 10.1007/s10552-009-9376-1.

PURPOSE: We analyzed data from a case-control study to assess the association between lifetime tobacco smoke exposure and breast cancer incidence. METHODS: Incident breast cancer cases were identified in the Massachusetts Cancer Registry and population controls were sampled from state Medicare lists and driver's license rosters. Demographic, lifestyle, medical history, reproductive history, and passive and active smoking exposure variables were assessed by telephone interview. We defined passive and active tobacco smoke exposure categories reflective of lifetime exposure patterns, and compared breast cancer risk among these groups while adjusting for age, body mass index, menopausal status, parity, alcohol consumption, and family history of breast cancer. We also adjusted passive smoking associations for active smoking status and vice versa. RESULTS: We observed no association between ever being passively exposed to tobacco smoke and risk of incident breast cancer (adjusted OR: 1.2; 95% CI: 0.8, 1.8) nor between active smoking and breast cancer (adjusted OR for [23 pack-years compared to

nonsmokers: 0.9; 95% CI: 0.7, 1.3). Null effects persisted in finer categorizations of active and passive exposure. CONCLUSIONS: We observed no causal associations between active or passive tobacco smoke exposures and incident breast cancer, consistent with results from most prospective cohort studies.

Alberg, A. J., A. Kouzis, et al. "A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke." Am J Epidemiol. 2007 Mar 15;165(6):660-6. Epub 2007 Jan 4.

Active cigarette smoking is a major risk factor for bladder cancer. Secondhand exposure to cigarette smoke may also contribute to bladder carcinogenesis. The authors conducted a prospective cohort study to examine the influence of both active smoking and household exposure to secondhand smoke (SHS) on subsequent bladder cancer risk. The study population included persons from two cohorts established from private censuses conducted in Washington County, Maryland, in 1963 (n = 45,749; 93 cases) and 1975 (n = 48,172; 172 cases). Poisson regression models were fitted to estimate the relative risk of bladder cancer associated with active and passive smoke exposure in the two cohorts (referent category: never smokers who did not live with any smokers). Current smokers had an elevated risk of bladder cancer in both the 1963 cohort (relative risk (RR) = 2.7, 95% confidence limits (CL): 1.6, 4.7) and the 1975 cohort (RR = 2.6, 95% CL: 1.7, 3.9) after adjustment for age, education, and marital status. Among nonsmoking women, current household SHS exposure was associated with bladder cancer risk in the 1963 cohort (RR = 2.3, 95% CL: 1.0, 5.4) but not in the 1975 cohort (RR = 0.9, 95% CL: 0.4, 2.3). This study further solidifies the evidence that active smoking is causally associated with bladder cancer. Additional studies are needed to determine whether passive smoking is a risk factor for bladder cancer.

Al-Zoughool, M., J. Pintos, et al. "Exposure to environmental tobacco smoke (ETS) and risk of lung cancer in Montreal: a case-control study." Environ Health. 2013 Dec 18;12:112. doi: 10.1186/1476-069X-12-112.

BACKGROUND: The objective of the present study was to examine the association between environmental tobacco smoke (ETS) and risk of lung cancer among never smokers, defined as subjects who smoked less than 100 cigarettes in their lifetime. METHODS: We conducted a population-based case-control study on lung cancer in Montreal, Canada (1996-2000) including 1,203 cases and 1513 controls. The present analysis is restricted to the 44 cases and 436 population controls who reported never smoking and completed the questionnaire on lifetime ETS exposure. Collected information included duration and intensity of exposure from multiple sources: inside home (parents, spouses, roommates and any other co-resident) and outside homes (in vehicles, social settings, and workplace). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated between ETS and lung cancer, adjusting for age, sex, socioeconomic status (SES), and proxy respondent. RESULTS: Overall there was no association between ETS cumulative exposure from all sources (measured in pack-years) and lung cancer: OR = 0.98 (95%CI: 0.40-2.38), comparing upper with lower tertiles of exposure. While there were no elevated ORs associated with ever having lived with parents who smoked (OR = 0.62; 95%CI: 0.32-1.21) or with spouses who smoked (OR = 0.39; 95%CI: 0.18-0.85), ETS exposure from sources outside homes was associated with a slight, although non-significant increased risk: OR = 2.30 (95%CI: 0.85-6.19) for the upper 50% exposed. There were no clear differences in ORs by age at exposure to ETS or by histologic type of tumour, though numbers of subjects in subgroup analyses were too small to provide reliable estimates. CONCLUSION: No clear association between lifetime ETS exposure from all sources and increased risk of lung cancer was found in the current study.

An, Y., A. Kiang, et al. "Cigarette smoke promotes drug resistance and expansion of cancer stem cell-like side population." PLoS One. 2012;7(11):e47919. doi: 10.1371/journal.pone.0047919. Epub 2012 Nov 5.

It is well known that many patients continue to smoke cigarettes after being diagnosed with cancer. Although smoking cessation has typically been presumed to possess little therapeutic value for cancer, a growing body of evidence suggests that continued smoking is associated with reduced efficacy of treatment and a higher incidence of recurrence. We therefore investigated the effect of cigarette smoke condensate (CSC) on drug resistance in the lung cancer and head and neck cancer cell lines A549 and UMSCC-10B, respectively. Our results showed that CSC significantly increased the cellular efflux of doxorubicin and mitoxantrone. This was accompanied by membrane localization and increased expression of the multi-drug transporter ABCG2. The induced efflux of doxorubicin was reversed upon addition of the specific ABCG2 inhibitor Fumitremorgin C, confirming the role of ABCG2. Treatment with CSC increased the concentration of phosphorylated Akt, while addition of the PI3K inhibitor LY294002 blocked doxorubicin extrusion, suggesting that Akt activation is required for CSC-induced drug efflux. In addition, CSC was found to promote resistance to

doxorubicin as determined by MTS assays. This CSC-induced doxurbicin-resistance was mitigated by mecamylamine, a nicotinic acetylcholine receptor inhibitor, suggesting that nicotine is at least partially responsible for the effect of CSC. Lastly, CSC increased the size of the side population (SP), which has been linked to a cancer stem cell-like phenotype. In summary, CSC promotes chemoresistance via Akt-mediated regulation of ABCG2 activity, and may also increase the proportion of cancer stem-like cells, contributing to tumor resilience. These findings underscore the importance of smoking cessation following a diagnosis of cancer, and elucidate the mechanisms of continued smoking that may be detrimental to treatment.

Anantharaman, D., A. Chabrier, et al. "Genetic variants in nicotine addiction and alcohol metabolism genes, oral cancer risk and the propensity to smoke and drink alcohol: a replication study in India." PLoS One. 2014 Feb 5;9(2):e88240. doi: 10.1371/journal.pone.0088240. eCollection 2014.

BACKGROUND: Genetic variants in nicotinic acetylcholine receptor and alcohol metabolism genes have been associated with propensity to smoke tobacco and drink alcohol, respectively, and also implicated in genetic susceptibility to head and neck cancer. In addition to smoking and alcohol, tobacco chewing is an important oral cancer risk factor in India. It is not known if these genetic variants influence propensity or oral cancer susceptibility in the context of this distinct etiology. METHODS: We examined 639 oral and pharyngeal cancer cases and 791 controls from two case-control studies conducted in India. We investigated six variants known to influence nicotine addiction or alcohol metabolism, including rs16969968 (CHRNA5), rs578776 (CHRNA3), rs1229984 (ADH1B), rs698 (ADH1C), rs1573496 (ADH7), and rs4767364 (ALDH2). RESULTS: The CHRN variants were associated with the number of chewing events per day, including in those who chewed tobacco but never smoked (P = 0.003, P = 0.01 for rs16969968 and rs578776 respectively). Presence of the variant allele contributed to approximately 13% difference in chewing frequency compared to non-carriers. While no association was observed between rs16969968 and oral cancer risk (OR = 1.01, 95% CI = 0.83- 1.22), rs578776 was modestly associated with a 16% decreased risk of oral cancer (OR = 0.84, 95% CI = 0.72- 0.98). There was little evidence for association between polymorphisms in genes encoding alcohol metabolism and oral cancer in this population. CONCLUSION: The association between rs16969968 and number of chewing events implies that the effect on smoking propensity conferred by this gene variant extends to the use of smokeless tobacco.

Arndt, M., M. Rydzanicz, et al. "[Distribution of alcohol dehydrogenase (ADH1C) genotypes in subjects with tobacco smoke-associated laryngeal cancer]." Przegl Lek. 2008;65(10):466-9.

Laryngeal cancer in Poland is characterized by high levels of morbidity and mortality. The main risk factors for the larynx cancer are alcohol drinking and tobacco smoking. In contrary to well established tobacco-related evidence for an increased risk of larynx cancer, alcohol-related mechanisms of carcinogenesis remain unknown. Nevertheless the effect of alcohol is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism. Hence we investigated the ADH1C *1 genotype and allele frequency in a group of 102 larynx cancer patients with heavy alcohol consumption recruited from the Department of Otolaryngology and Laryngological Oncology of the University of Medical Sciences in Poznan. The data were compared with 112 non-cancer age-matched individuals consuming similar amounts of ethanol. Blood samples were used for analysis of restriction fragment length polymorphism. DNA was isolated from the whole blood leucocytes and PCR with specific primers was used to amplify polymorphic region of rs698 in the ADH1C gene. The method was based on allele detection by Sspl restriction enzyme digestion and after the incubation with enzyme, samples run on an electrophoresis. The statistic analysis was performed to calculate Odds Ratio (ORs), 95% confidence intervals (CIs) and significance. Results suggest a slightly increased risk of larynx cancer for individuals who have inherited the ADH1C *1 allele (rs 698), however they did not reach the level of statistic significance.

Arrieta, O., A. D. Campos-Parra, et al. "Clinical and pathological characteristics, outcome and mutational profiles regarding non-small-cell lung cancer related to wood-smoke exposure." J Thorac Oncol. 2012 Aug;7(8):1228-34. doi: 10.1097/JTO.0b013e3182582a93.

HYPOTHESIS: Although smoking is the major risk factor for non-small-cell lung cancer (NSCLC), other factors are also associated with lung carcinogenesis, such as wood-smoke exposure (WSE). This article has been aimed at suggesting that lung cancer related to cigarette smoking and lung cancer related to WSE have different clinical and genetic characteristics. EXPERIMENTAL DESIGN: A cohort of 914 lung cancer patients was prospectively studied; they had been treated at Mexico's National Cancer Institute between 2007 and 2010. The associations of

WSE and cigarette smoking with clinical characteristics, mutation profile, response to chemotherapy, and epidermal growth factor receptor tyrosine kinase inhibitors were analyzed, and overall survival (OS) rate was calculated. The trial was registered with ClinicalTrials.gov: NCT01023828. RESULTS: Of the lung cancer patients studied, 95.1% were classified as coming within the NSCLC histology subtype; 58% of the patients smoked cigarettes, 35% had a background of WSE (exposure to both cigarette smoke and wood smoke was documented in 12.1% of all patients), and 19.4% patients had no smoke-exposure background. WSE was associated with NSCLC and adenocarcinoma histology, and was also more frequently associated with epidermal growth factor receptor-mutations than cigarette-smoking patients were (50.0% cf. 19.4%), whereas KRAS mutations were less common in WSE patients (6.7%) than in smokers (21%). WSE patients had a higher epidermal growth factor receptor tyrosine kinase inhibitor response rate (39.7%) than smokers (18.8%). The NSCLC patient WSE group's OS was longer (22.7 months) than that for smokers (13.8 months). CONCLUSION: NSCLC patients who smoked tobacco/cigarettes differed from those having a background of WSE regarding tumor histology, mutation profile, response rate, and OS, indicating that different carcinogenic mechanisms were induced by these two types of smoke exposure.

Asomaning, K., D. P. Miller, et al. "Second hand smoke, age of exposure and lung cancer risk." Lung Cancer. 2008 Jul;61(1):13-20. doi: 10.1016/j.lungcan.2007.11.013. Epub 2008 Jan 8.

BACKGROUND: Exposure to second hand smoke (SHS) has been identified as a risk factor for lung cancer for three decades. It is also known that the lung continues to grow from birth to adulthood, when lung growth stops. We hypothesize that after adjusting for active cigarette smoking, if SHS exposure took place during the period of growth, i.e. in the earlier part of life (0-25 years of age) the risk of lung cancer is greater compared to an exposure occurring after age 25. METHOD: Second hand smoke exposure was self-reported for three different activities (leisure, work and at home) for this study population of 1669 cases and 1263 controls. We created variables that captured location of exposure and timing of first exposure with respect to a study participant's age (0-25, >25 years of age). Multiple logistic regressions were used to study the association between SHS exposure and lung cancer, adjusting for age, gender and active smoking variables. RESULT: For study participants that were exposed to SHS at both activities (work and leisure) and compared to one or no activity, the adjusted odds ratio (AOR) for lung cancer was 1.30 (1.08-1.57) when exposure occurred between birth and age 25 and 0.66 (0.21-1.57) if exposure occurred after age 25 years. Respective results for non-smokers were 1.29 (0.82-2.02) and 0.87 (0.22-3.38), and current and ex-smokers combined 1.28 (1.04-1.58) and 0.66 (0.15-2.85). CONCLUSION: All individuals exposed to SHS have a higher risk of lung cancer. Furthermore, this study suggests that subjects first exposed before age 25 have a higher lung cancer risk compared to those for whom first exposure occurred after age 25 years.

Balansky, R., G. Ganchev, et al. "Prenatal N-acetylcysteine prevents cigarette smoke-induced lung cancer in neonatal mice." Carcinogenesis. 2009 Aug;30(8):1398-401. doi: 10.1093/carcin/bgp128. Epub 2009 May 20.

Certain adult diseases may have their origin early in life, and perinatal exposures may contribute to cancers both during childhood and later in life. We recently demonstrated that mainstream cigarette smoke (MCS) induces a potent carcinogenic response in mice when exposure starts soon after birth. We also showed that the antioxidant N-acetylcysteine (NAC) prevents the extensive nucleotide and gene expression alterations that occur 'physiologically' at birth in mouse lung. The present study was designed to evaluate whether administration of NAC during pregnancy may affect the yield of tumors in mice exposed to MCS, starting after birth and continuing for 120 days. The results obtained showed that 210 days after birth, one adenoma only was detectable in sham-exposed mice. In contrast, as much as the 61.1% (33/54) of MCS-exposed mice born from untreated dams had lung tumors, including both benign tumors and bronchoalveolar carcinomas. Treatment with NAC during pregnancy strikingly inhibited the formation of benign lung tumors and totally prevented occurrence of carcinomas. In addition, prenatal NAC inhibited the MCS-induced hyperplasia of the urinary bladder epithelium. These findings demonstrate for the first time that treatment during pregnancy with an antioxidant chemopreventive agent can affect the induction of tumors consequent to exposure to a carcinogen after birth.

Band, P. R., N. D. Le, et al. "Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer." Lancet. 2002 Oct 5;360(9339):1044-9.

BACKGROUND: Results of epidemiological studies, assessing the relation between smoking and breast cancer, have been inconclusive. Our aim was to assess the carcinogenic and possibly antioestrogenic effects of cigarette smoke on risk of breast cancer. METHODS: We sent a questionnaire to 1431 women

younger than age 75 years who had breast cancer and were listed on the population-based British Columbia cancer registry between June 1, 1988, and June 30, 1989. We also sent questionnaires to 1502 age-matched controls, randomly selected from the 1989 provincial voters list. We obtained information on all known and suspected risk factors for breast cancer, and on lifetime smoking, alcohol consumption, and occupational history. We assessed the effect of smoking separately for premenopausal and postmenopausal women, adjusting for confounding variables. FINDINGS: 318 premenopausal women and 340 controls replied. Risk of breast cancer was significantly increased (adjusted odds ratio 1.69, 95% CI 1.13-2.51) in women who had been pregnant and who started to smoke within 5 years of menarche, and in nulliparous women who smoked 20 cigarettes daily or more (7.08, 1.63-30.8) and had smoked for 20 cumulative pack-years or more (7.48, 1.59-35.2). Postmenopausal women (700 breast cancer and 685 controls) whose body-mass index increased from age 18 to current and who started to smoke after a first fullterm pregnancy had a significantly reduced risk of breast cancer (0.49, 0.27-0.89). INTERPRETATION: Our results suggest that cigarette smoke exerts a dual action on the breast, with different effects in premenopausal and postmenopausal women. Our observations reinforce the importance of smoking prevention, especially in early adolescence, and draw attention to the timing of exposure in relation to susceptibility and refractory windows in the design of studies to investigate associations between environmental carcinogens or putative endocrine disruptors and risk of breast cancer.

Bazoes, A., M. Bower, et al. "Smoke and mirrors: HIV-related lung cancer." Curr Opin Oncol. 2008 Sep;20(5):529-33. doi: 10.1097/CCO.0b013e32830a4c99.

PURPOSE OF REVIEW: The introduction of highly active antiretroviral therapy has dramatically reduced AIDS-related illnesses and increased life expectancy for people living with HIV infection. At the same time, non-AIDS-defining cancers are becoming an increasing problem and now account for a large proportion of HIV-related deaths. Perhaps the most important and controversial of these is HIV-related lung cancer. There are a number of unresolved issues surrounding this illness, which are the subject of this review. RECENT FINDINGS: Smoking does not account for all of the increase in the incidence of lung cancer seen in HIV patients. Other factors accounting for the increased incidence remain undefined. Highly active antiretroviral therapy may not have had a beneficial effect on either the incidence or outcome of the disease, which needs further investigation. Early diagnosis and offering these patients potentially curative therapy wherever appropriate is of utmost importance. SUMMARY: HIV-related lung cancer is becoming an increasingly important problem as patients are living longer with HIV infection.

Ben-Zaken Cohen, S., P. D. Pare, et al. "The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism." Am J Respir Crit Care Med. 2007 Jul 15;176(2):113-20. Epub 2007 Apr 5.

Smoking-related lung diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer are growing epidemics in women in the United States and elsewhere. Although some of this disturbing trend in women can be attributed to changing smoking habits, there is emerging evidence that women may be biologically more susceptible to the harmful effects of cigarette smoke than are men. Estrogen and related compounds may up-regulate the expression of cytochrome P450 (CYP) enzymes in lungs and liver, which are involved in the metabolism of various constituents of cigarette smoke. Although metabolism of foreign substances is usually beneficial in eliminating potential toxins from the body, in some instances the metabolic process can transform harmless substances into toxic chemicals through a process called metabolic bioactivation. One important xenobiotic substrate for CYP enzymes in cigarette smoke is polycyclic aromatic hydrocarbon, which in its native form is relatively harmless in small doses but upon bioactivation by CYP enzymes, can become very toxic substances for the lungs. In this article, we explore CYP and other related pathways as potential mechanisms and targets of future research and novel discoveries to curb the growing epidemic of COPD and lung cancer in women.

Besaratinia, A. and S. Tommasi "Genotoxicity of tobacco smoke-derived aromatic amines and bladder cancer: current state of knowledge and future research directions." FASEB J. 2013 Jun;27(6):2090-100. doi: 10.1096/fj.12-227074. Epub 2013 Feb 28.

Bladder cancer is a significant public health problem, worldwide. In the United States, bladder cancer is the fourth most common cancer in men, and its recurrence rate is the highest among all malignancies. Tobacco smoking is the leading risk factor for bladder cancer. The risk of bladder cancer is directly related to the intensity and duration of smoking, while quitting smoking reduces this risk. The increased risk of smokers for developing bladder cancer is attributable to their exposure to aromatic amines, which constitute a family of known bladder carcinogens present in tobacco smoke. The underlying

mechanism of action of aromatic amines in the genesis of bladder cancer is not, however, fully delineated. Research has identified a genotoxic mode of action, specifically DNA adduction and mutagenicity, for aromatic amines, which may account for their carcinogenicity. The present review summarizes our current knowledge on the DNA adduction and mutagenicity of aromatic amines in relation to smoking-associated bladder cancer. For illustrative purposes, representative results from published research on aromatic amine-induced DNA adduction and mutagenesis are discussed. The direction of future research on the underlying mechanisms of tobacco smoke-associated bladder carcinogenesis is also outlined. Understanding the molecular mechanisms of bladder carcinogenesis is essential for improving future strategies for prevention, early detection, treatment, and prognosis of this malignancy.

Bhattacharyya, S., S. Mandal, et al. "Cannabis smoke can be a major risk factor for early-age laryngeal cancer-a molecular signaling-based approach." Tumour Biol. 2015 Aug;36(8):6029-36. doi: 10.1007/s13277-015-3279-4. Epub 2015 Mar 4.

Epidermal growth factor receptor (EGFR) and its downstream elements are overexpressed in most cases of the head and neck squamous cell carcinoma. This study investigated the expression pattern of key proteins linked to the EGFR pathway in laryngeal carcinoma patients with a history of cannabis smoking. We selected 83 male glottic cancer patients, aged between 45 to 75 years with three distinct populations-nonsmoker, cigarette smoker, and cannabis smoker. Immunohistochemical staining was performed for EGFR, protein kinase B (PKB or Akt), nuclear factor kappa B p50 (NF-capital KA, CyrillicB), and cyclooxygenase-2 (COX-2) followed by boolean scoring for statistical analysis. Experimental data showed upregulation of the selected EGFR cascade in tumor cells, stromal expression of EGFR, and nuclear localization of COX-2 in metaplastic gland cells of laryngeal cancer tissue sample. Statistical analyses indicated that overexpression of the EGFR cascade is significantly correlated to cannabis smoking. Cannabis smokers had higher expression ($p < 0.01$) of these onco-proteins with respect to both nonsmokers as well as cigarette smokers. Risk factor analysis showed high risk of these proteins expression in age <60 years (odds ratio (OR) > 1.5) as the lower age group had relatively higher number of cannabis smokers. This study provides evidence for a direct association between cannabis smoking and increased risk of laryngeal cancer. Higher expression of the EGFR cascade in cannabis smokers revealed that cannabis smoking may be a major cause for the early onset of aggressive laryngeal cancer.

Birrane, G., H. Li, et al. "Cigarette smoke induces nuclear translocation of heme oxygenase 1 (HO-1) in prostate cancer cells: nuclear HO-1 promotes vascular endothelial growth factor secretion." Int J Oncol. 2013 Jun;42(6):1919-28. doi: 10.3892/ijo.2013.1910. Epub 2013 Apr 17.

Prostate cancer is the second leading cause of male-cancer related death in the United States. Despite a number of evidence-based studies which strongly suggest an association between cigarette smoking and prostate cancer, the underlying biological mechanism is largely unknown. Heme oxygenase 1 (HO-1) has been implicated in maintaining cellular homeostasis, but also in tumor angiogenesis. Nuclear HO-1 protein expression has been observed in various types of tumors including prostate cancer. These studies, however, were reported as clinical and pathological observations, and failed to investigate nuclear HO-1 at the molecular level in cancer. The present study explores the relationship between cigarette smoke and nuclear HO-1-modulated promotion of vascular endothelial growth factor (VEGF) secretion. We have demonstrated that cigarette smoke medium (SM)-induced HO-1 mRNA expression and upregulated HO-1 protein levels in the prostate cancer cell lines DU145 and PC3. We also observed that SM significantly induced nuclear expression of HO-1, and enhanced secretion of VEGF in cells. Nuclear-directed expression of HO-1 activated the transcriptional activity of VEGF and promoted VEGF secretion in prostate cancer cells. This study provides new insights into the molecular mechanism by which cigarette smoke-induced nuclear translocation of HO-1 promotes VEGF secretion in prostate cancer cells. Nuclear HO-1 may, therefore, constitute an attractive therapeutic target to inhibit angiogenesis and the progression of prostate cancer.

Bjerregaard, B. K., O. Raaschou-Nielsen, et al. "Tobacco smoke and bladder cancer--in the European Prospective Investigation into Cancer and Nutrition." Int J Cancer. 2006 Nov 15;119(10):2412-6.

The purpose of the present study was to investigate the association between smoking and the development of bladder cancer. The study population consisted of 429,906 persons participating in the European Prospective Investigation into Cancer and Nutrition (EPIC), 633 of whom developed bladder cancer during the follow-up period. An increased risk of bladder cancer was found for both current- (incidence rate ratio 3.96, 95% confidence interval: 3.07-5.09) and ex- (2.25, 1.74-2.91) smokers, compared to never-smokers. A positive association

with intensity (per 5 cigarettes) was found among current-smokers (1.18, 1.09-1.28). Associations (per 5 years) were observed for duration (1.14, 1.08-1.21), later age at start (0.75, 0.66-0.85) and longer time since quitting (0.92, 0.86-0.98). Exposure to environmental tobacco smoke (ETS) during childhood increased the risk of bladder cancer (1.38, 1.00-1.90), whereas for ETS exposure as adult no effect was detected. The present study confirms the strong association between smoking and bladder cancer. The indication of a higher risk of bladder cancer for those who start smoking at a young age and for those exposed to ETS during childhood adds to the body of evidence suggesting that children are more sensitive to carcinogens than adults.

Boccia, S., F. A. Sayed-Tabatabaei, et al. "Polymorphisms in metabolic genes, their combination and interaction with tobacco smoke and alcohol consumption and risk of gastric cancer: a case-control study in an Italian population." BMC Cancer. 2007 Nov 8;7:206.

BACKGROUND: The distribution and the potential gene-gene and gene-environment interaction of selected metabolic genetic polymorphisms was investigated in relation to gastric cancer risk in an Italian population. METHODS: One hundred and seven cases and 254 hospital controls, matched by age and gender, were genotyped for CYP1A1, CYP2E1, mEH, GSTM1, GSTT1, NAT2 and SULT1A1 polymorphisms. Haplotype analysis was performed for EPHX1 exons 3 and 4, as well as CYP2E1 RsaI (*5 alleles) and CYP2E1 DraI (*5A or *6 alleles). The effect modification by alcohol and cigarette smoking was tested with the heterogeneity test, while the attributable proportion (AP) was used to measure the biological interaction from the gene-gene interaction analysis. RESULTS: Gastric cancer risk was found to be associated with the inheritance of GSTT1 null genotype (OR = 2.10, 95%CI: 1.27-3.44) and the SULT1A1 His/His genotype (OR = 2.46, 95%CI: 1.03-5.90). No differences were observed for the haplotype distributions among cases and controls. For the first time an increased risk was detected among individuals carrying the *6 variant allele of CYP2E1 if ever-drinkers (OR = 3.70; 95%CI: 1.45-9.37) with respect to never-drinkers (OR = 0.18; 95% CI: 0.22-1.46) (p value of heterogeneity among the two estimates = 0.001). Similarly, the effect of SULT1A1 variant genotype resulted restricted to ever-smokers, with an OR of 2.58 (95%CI: 1.27-5.25) for the carriers of His allele among smokers, and an OR of 0.86 (95%CI: 0.45-1.64) among never-smokers (p value of heterogeneity among the two estimates = 0.03). The gene-gene interaction analyses demonstrated that individuals with combined GSTT1 null and NAT2 slow acetylators had an additional increased risk of gastric cancer, with an OR of 3.00 (95%CI: 1.52-5.93) and an AP of 52%. CONCLUSION: GSTT1, SULT1A1 and NAT2 polymorphisms appear to modulate individual's susceptibility to gastric cancer in this Italian population, particularly when more than one unfavourable genotype is present, or when combined with cigarette smoke. The increased risk for the carriers of CYP2E1*5A or *6 alleles among drinkers need to be confirmed by larger prospective studies.

Borsoi, L., B. Leistikow, et al. "Tobacco smoke load and non-lung cancer mortality associations in Austrian and German males." Wien Klin Wochenschr. 2010 Dec;122(23-24):698-703. doi: 10.1007/s00508-010-1487-x. Epub 2010 Nov 15.

The millstone around the neck of tobacco control in Europe has been the influence of the tobacco industry on the governments of German speaking countries. This study attempts to estimate non-lung cancer mortality attributable to smoking in Austria during 1967-2006 and in Germany during 1973-2006. National estimates of the annual smoking-attributable fractions (SAF) were calculated for all ages in males, using lung cancer mortality rates as indicators of "tobacco smoke load" associated with cancer from active and passive smoking. In both countries non-lung cancer rates showed a nearly perfect linear correlation with lung cancer rates (R (2) = 0.95 in Austria and 0.94 in Germany) with a slope of 1.86 (95% confidence intervals [CI]: 1.71-1.99) in Austria and 1.77 (95% CI: 1.60-1.93) in Germany. In 2006 SAF of male cancer mortality for all ages were 61% in Austria (sensitivity range [SR]: 45%-70%) without autocorrelation and 61% in Germany (SR: 41-75%), if adjusted for possible autocorrelation. The similarity of the results is in line with the poor tobacco control measures in both countries until recently. Cancer prevention programs in Austria and Germany should focus on tobacco control, because 61% of male cancer mortality was associated with tobacco smoke load.

Bradbury, B. D., J. B. Wilk, et al. "Departure from multiplicative interaction for catechol-O-methyltransferase genotype and active/passive exposure to tobacco smoke among women with breast cancer." J Carcinog. 2006 Jan 17;5:3.

BACKGROUND: Women with homozygous polymorphic alleles of catechol-O-methyltransferase (COMT-LL) metabolize 2-hydroxylated estradiol, a suspected anticarcinogenic metabolite of estrogen, at a four-fold lower rate than women with no polymorphic alleles (COMT-HH) or heterozygous women (COMT-HL). We hypothesized that COMT-LL women

exposed actively or passively to tobacco smoke would have higher exposure to 2-hydroxylated estradiol than never-active/never passive exposed women, and should therefore have a lower risk of breast cancer than women exposed to tobacco smoke or with higher COMT activity. METHODS: We used a case-only design to evaluate departure from multiplicative interaction between COMT genotype and smoking status. We identified 502 cases of invasive incident breast cancer and characterized COMT genotype. Information on tobacco use and other potential breast cancer risk factors were obtained by structured interviews. RESULTS: We observed moderate departure from multiplicative interaction for COMT-HL genotype and history of ever-active smoking (adjusted odds ratio [aOR] = 1.6, 95% confidence interval [CI]: 0.7, 3.8) and more pronounced departure for women who smoked 40 or more years (aOR = 2.3, 95% CI: 0.8, 7.0). We observed considerable departure from multiplicative interaction for COMT-HL genotype and history of ever-passive smoking (aOR = 2.0, 95% CI: 0.8, 5.2) or for having lived with a smoker after age 20 (aOR = 2.8, 95% CI: 0.8, 10). CONCLUSION: With greater control over potential misclassification errors and a large case-only population, we found evidence to support an interaction between COMT genotype and tobacco smoke exposure in breast cancer etiology.

Brand, R. E., J. B. Greer, et al. "Pancreatic cancer patients who smoke and drink are diagnosed at younger ages." Clin Gastroenterol Hepatol. 2009 Sep;7(9):1007-12. doi: 10.1016/j.cgh.2009.06.008. Epub 2009 Jun 26.

BACKGROUND & AIMS: Cigarette smoking is an established risk factor for pancreatic cancer, but there is conflicting evidence regarding the effects of alcohol consumption. The effects of cigarettes and alcohol on age of sporadic pancreatic cancer diagnosis have not been examined; we evaluated the independent and synergistic effects of lifetime cigarette smoking and alcohol consumption on age at pancreatic cancer diagnosis in the United States. METHODS: We analyzed data on cigarette smoking and alcohol consumption from the IMPAC Services, Inc Cancer Information Resource File (CIRF), collected from June 1, 1993, to December 31, 2003, for 29,239 reported, histologically confirmed cases of pancreatic adenocarcinoma. We also analyzed data on cigarette smoking and alcohol consumption for 820 histologically confirmed cases of pancreatic adenocarcinoma from the University of Michigan Pancreatic Cancer Registry (UMPCR), collected from January 2004 to October 2007. RESULTS: Current cigarette smokers were diagnosed at significantly younger ages than never smokers, according to data from the CIRF and UMPCR (8.3 and 6.3 y, respectively); the UMPCR data indicated dose effects. Past and current alcohol consumption were associated with younger age at diagnosis in both databases. Current smokers who were current drinkers were diagnosed significantly earlier (CIRF, 10.2 y; UMPCR, 8.6 y) than abstainers. Past cigarette smoking was associated modestly with younger diagnosis age. CONCLUSIONS: Cigarette smoking and alcohol consumption were associated with younger age at pancreatic cancer presentation and have a combined effect on diagnosis age. Past cigarette smoking is less influential. Smoking cessation programs could help prevent pancreatic cancer.

Brennan, P., P. A. Buffler, et al. "Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies." Int J Cancer. 2004 Mar;109(1):125-31.

The interpretation of the evidence linking exposure to secondhand smoke with lung cancer is constrained by the imprecision of risk estimates. The objective of the study was to obtain precise and valid estimates of the risk of lung cancer in never smokers following exposure to secondhand smoke, including adjustment for potential confounders and exposure misclassification. Pooled analysis of data from 2 previously reported large case-control studies was used. Subjects included 1263 never smoking lung cancer patients and 2740 population and hospital controls recruited during 1985-1994 from 5 metropolitan areas in the United States, 11 areas in Germany, Italy, Sweden, United Kingdom, France, Spain and Portugal. Odds ratios (ORs) of lung cancer were calculated for ever exposure and duration of exposure to secondhand smoke from spouse, workplace and social sources. The OR for ever exposure to spousal smoking was 1.18 (95% CI = 1.01-1.37) and for long-term exposure was 1.23 (95% CI = 1.01-1.51). After exclusion of proxy interviews, the OR for ever exposure from the workplace was 1.16 (95% CI = 0.99-1.36) and for long-term exposure was 1.27 (95% CI = 1.03-1.57). Similar results were obtained for exposure from social settings and for exposure from combined sources. A dose-response relationship was present with increasing duration of exposure to secondhand smoke for all 3 sources, with an OR of 1.32 (95% CI = 1.10-1.79) for the long-term exposure from all sources. There was no evidence of confounding by employment in high-risk occupations, education or low vegetable intake. Sensitivity analysis for the effects of misclassification (both positive and negative) indicated that the observed risks are likely to underestimate the true risk. Clear dose-response relationships consistent with a causal association were

observed between exposure to secondhand smoke from spousal, workplace and social sources and the development of lung cancer among never smokers.

Browning, K. K., A. K. Ferketich, et al. "A psychometric analysis of quality of life tools in lung cancer patients who smoke." Lung Cancer. 2009 Oct;66(1):134-9. doi: 10.1016/j.lungcan.2008.12.018. Epub 2009 Jan 31.

Lung cancer is the leading cause of cancer death for both men and women in the United States. Patient quality of life (QOL) prior to cancer treatment is known to be a strong predictor of survival and toleration of treatment toxicities. A lung cancer patient's self-assessment of QOL is highly valued among clinicians as it guides treatment-related decisions and impacts clinical outcomes. Smokers are known to report a lower QOL. Limited research has been conducted on QOL outcomes in lung cancer patients who continue to smoke. To assess QOL, a reliable and valid QOL measure specific to lung cancer is required. The functional assessment of cancer therapy-lung cancer (FACT-L) and lung cancer symptom scale (LCSS) are instruments that specifically examine QOL among lung cancer patients. The LCSS is a focused QOL instrument that includes physical and functional domains of QOL and disease symptomatology. The FACT-L is a broader QOL instrument that includes physical, functional, social and emotional domains and disease symptomatology. Both are psychometrically valid and are widely used in the literature, but have not been exclusively evaluated in smokers. Furthermore, there is no 'gold standard' instrument since there has never been a correlation study to compare estimates of reliability and validity between these instruments. The purpose of this study is to report the internal consistency and convergence validity of the FACT-L and the LCSS among newly diagnosed lung cancer patients who smoke. This data were collected and analyzed from a larger study examining smoking behavior among newly diagnosed lung cancer patients (n=51). Descriptive statistics were calculated on the FACT-L and LCSS scores, internal consistency was assessed by estimating Cronbach's alpha coefficients, and Pearson correlation coefficients were estimated between the two scales. Internal consistency coefficients demonstrated good reliability for both scales, and the two instruments demonstrated a strong correlation, suggesting good convergence validity. Either of these instruments are appropriate measures for QOL in lung cancer patients who smoke. Given the conceptual difference between the two instruments, it is important to carefully consider the research aims when selecting the appropriate QOL measurement instrument.

Carpagnano, G. E., A. Spanevello, et al. "Cigarette smoke and increased COX-2 and survivin levels in exhaled breath condensate of lung cancer patients: how hot is the link?" Lung Cancer. 2010 Jan;67(1):108-13. doi: 10.1016/j.lungcan.2009.03.033. Epub .

One of the most current intriguing hypotheses on lung cancerogenesis envisages a role for inflammation as a possible trigger of both epithelial-mesenchymal transition and cancer development. Cigarette smoke has been suggested to be the main factor underlying the inflammation of the airways described in lung cancer patients. Cycloxygenase and survivin, a COX-2 dependent factor of apoptosis resistance, seem to play a key role in this regard. PURPOSE: The aim of this study was to study COX-2 and survivin in the airways of lung cancer patients and in those of a group of smokers in a view to increasing our understanding of the link between smoking, airway inflammation and lung cancer. PATIENTS AND METHODS: 70 NSCLC patients (28 smokers, 26 ex-smokers and 16 non-smokers) and 30 healthy subjects (20 smokers and 10 non-smokers) were enrolled in the study. Both COX-2 and survivin concentrations were measured in the exhaled breath condensates of all the subjects under study using EIA kits. RESULTS: Higher levels of exhaled survivin and COX-2 were found in NSCLC patients compared to healthy smokers and non-smokers. These levels were observed to be significantly elevated in smokers (patients with lung cancer and healthy) and ex-smokers compared to non-smokers and exhibited a positive correlation with the number of cigarettes smoked expressed as pack/year. A correlation was also found between exhaled COX-2 and survivin and the progression of cancer. CONCLUSIONS: We support the hypothesis that cigarette smoke be strongly connected to the inflammation of the airways observed in lung cancer patients. On the basis of the results obtained the use of exhaled breath condensate COX-2 and survivin levels could be suggested as two potential markers within an early non-invasive screening of populations of smokers at risk of lung cancer.

Chang-Claude, J., S. Kropp, et al. "Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk." Cancer Epidemiol Biomarkers Prev. 2002 Aug;11(8):698-704.

BACKGROUND: Polymorphisms in the N-acetyltransferase 2 (NAT2) gene influence the rate of metabolism of aromatic and heterocyclic amines present in tobacco smoke. Because the physicochemical composition of mainstream and

sidestream smoke differ, we conducted a case-control study to assess a possible differential effect of NAT2 genotype on the relationship between active/passive smoke exposure and breast cancer risk. METHODS: Breast cancer patients diagnosed by 50 years of age and population-sampled controls were interviewed to obtain detailed lifetime active and passive smoking history. NAT2 genotype was determined in 422 breast cancer patients and 887 controls. Multivariate logistic regression analysis was performed to estimate breast cancer risk in relation to smoking history by acetylator status and interaction effects. RESULTS: Compared with women never regularly exposed to tobacco smoke, odds ratios (ORs) for current smoking and ex-smoking were 1.7 [95% confidence interval (CI): 1.0-2.9] and 1.2 (95% CI, 0.7-2.0) in slow acetylators, and not increased in rapid acetylators. Active smoking variables, such as pack-years, duration of smoking, and time since cessation, showed significant dose-response relationships with breast cancer risk among slow acetylators but not rapid acetylators. In contrast, passive smoking was associated with higher risk in rapid than in slow acetylators, with ORs of 2.0 (95% CI, 1.0-4.1) and 1.2 (95% CI, 0.7-2.0), respectively. CONCLUSIONS: Our results suggest that the NAT2 status has a differential effect on the association of active and passive smoking with breast cancer and demonstrate the need to consider possible different mechanisms associated with exposure to main- and sidestream tobacco smoke.

Christmann, M. and B. Kaina "O(6)-methylguanine-DNA methyltransferase (MGMT): impact on cancer risk in response to tobacco smoke." Mutat Res. 2012 Aug 1;736(1-2):64-74. doi: 10.1016/j.mrfmmm.2011.06.004. Epub 2011 Jun 14.

Tobacco, smoked, snuffed and chewed, contains powerful mutagens and carcinogens. At least three of them, N-dimethylnitrosamine, N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, attack DNA at the O(6)-position of guanine. The resulting O(6)-alkylguanine adducts are repaired by the suicide enzyme O(6)-methylguanine-DNA methyltransferase (MGMT), which is known to protect against the mutagenic, genotoxic and carcinogenic effects of monofunctional alkylating agents. While in rat liver MGMT was shown to be subject to regulation by genotoxic stress leading to adaptive changes in its activity, in humans evidence of adaptive modulation of MGMT levels is still lacking. Several polymorphisms are known, which are suspected to impact on the risk of developing cancer. In this review we focus on three questions: (a) Has tobacco consumption by smoking or chewing an impact on MGMT expression and MGMT promoter methylation in normal and tumor tissue? (b) Is there an association between MGMT polymorphisms and cancer risk and is this risk related to smoking? (c) Does MGMT protect against tobacco-associated cancer? There are several lines of evidence for an increase of MGMT activity in the normal tissue of smokers compared to non-smokers. Furthermore, in tumors developed in smokers a tendency towards an increase of MGMT expression was found. The data points to the possibility that agents in tobacco smoke are able to trigger upregulation of MGMT in normal and tumor tissue. For MGMT promoter methylation data is conflicting. There is some evidence for an association between MGMT polymorphisms and smoking-induced cancer risk. The key question whether or not MGMT protects against tobacco smoke-induced cancer is difficult to answer since prospective studies on smokers versus non-smokers are lacking and appropriate animal studies with MGMT transgenic mice exposed to the complex mixture of tobacco smoke have not been performed, which indicates the need for further explorations.

Chuang, S. C., V. Gallo, et al. "Exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers in the European Prospective Investigation into Cancer and Nutrition." Cancer Causes Control. 2011 Mar;22(3):487-94. doi: 10.1007/s10552-010-9723-2. Epub 2011 Jan 30.

The association between childhood environmental tobacco smoke (ETS) exposure and adult cancer risk is controversial; we examined this relationship in never smokers within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Over an average of 10 years, 8,372 cases of cancer were diagnosed in 112,430 never smokers in EPIC. Childhood ETS was self-reported by participants at baseline, along with other lifestyle factors. Hazard ratios (HR) for ETS exposure in childhood and their 95% confidence intervals (CI) were estimated by Cox proportional hazards models stratified by age, sex, and study center and adjusted for education, alcohol drinking, body mass index, physical activity, non-alcoholic energy intake, fruit and vegetable intake, and adulthood ETS exposure. Models were further adjusted for reproductive factors for female cancers, for meat intake for digestive system cancers, and for diabetes status for pancreatic cancer. No association was observed between childhood ETS exposure and overall cancer risks (HR = 0.97, 95% CI = 0.92-1.02), and for selected sites. The only exception was pancreatic cancer, as previously reported by Vrieling et al., among those who had been exposed daily in childhood (overall HR = 2.09, 95% CI = 1.14-3.84). In conclusion, childhood

ETS exposure might not be a major risk factor for common cancers in adulthood.

Church, T. R., M. Haznadar, et al. "Interaction of CYP1B1, cigarette-smoke carcinogen metabolism, and lung cancer risk." Int J Mol Epidemiol Genet. 2010 Aug 5;1(4):295-309.

A previously published case-control study nested in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found a significant relationship of serum levels of total NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides) to prospective lung cancer risk. The present paper examines this relationship in the context of single-nucleotide polymorphisms (SNPs) in genes important in the metabolism of tobacco smoke carcinogens. DNA was extracted from the subjects' lymphocytes and analyzed for SNPs in 11 locations on four genes related to tobacco carcinogen metabolism. Logistic regressions on case-control status were used to estimate main effects of SNPs and biomarkers and their interactions adjusting for potential confounders. Of the 11 SNPs, only one, in CYP1B1, significantly interacted with total NNAL affecting risk for lung cancer. At low NNAL levels, the variant appeared protective. However, for those with the minor variant, the risk for lung cancer increased with increasing NNAL five times as rapidly compared to those without it, so that at high NNAL levels, this SNP's protection disappears. Analyzing only adenocarcinomas, the effect of the variant was even stronger, with the risk of cancer increasing six times as fast. A common polymorphism of CYP1B1 may play a role in the risk of NNK, a powerful lung carcinogen, in the development of lung cancer in smokers.

Coggins, C. R. "A further review of inhalation studies with cigarette smoke and lung cancer in experimental animals, including transgenic mice." Inhal Toxicol. 2010 Oct;22(12):974-83. doi: 10.3109/08958378.2010.501831.

CONTEXT: The lack of an effective animal model for pulmonary carcinogenesis in smokers is a continuing problem for researchers trying to design Potentially Reduced Risk Products for those smokers who are either unwilling or unable to quit smoking. The major failing of inhalation assays with cigarette smoke in laboratory animals is that these assays produce only small percentages of animals with pulmonary tumors (e.g. adenomas, with the occasional adenocarcinoma), as opposed to the highly invasive carcinomas (e.g. small cell and squamous cell) seen in smokers. OBJECTIVE: To update previous reviews on animal models, and to add different types of transgenic (Tg) mice to the review. METHODS: Reviews were made of articles retrieved from PubMed and elsewhere. RESULTS: The addition of Tg mice to the arsenal of tests used for the evaluation of the carcinogenic potential of cigarettes did not result in any better understanding of the inability of such testing to reflect the epidemiological evidence for lung cancer in smokers. CONCLUSION: As in previous reviews on the subject, the best assay providing support for the epidemiology data is still the 5-month whole-body exposure of male A/J mice to a combination of mainstream/sidestream smoke, followed by a 4-month recovery.

Cox, L. A., Jr. "Could removing arsenic from tobacco smoke significantly reduce smoker risks of lung cancer?" Risk Anal. 2009 Jan;29(1):3-17. doi: 10.1111/j.1539-6924.2008.01145.x. Epub 2008 Nov 5.

If a specific biological mechanism could be determined by which a carcinogen increases lung cancer risk, how might this knowledge be used to improve risk assessment? To explore this issue, we assume (perhaps incorrectly) that arsenic in cigarette smoke increases lung cancer risk by hypermethylating the promoter region of gene p16INK4a, leading to a more rapid entry of altered (initiated) cells into a clonal expansion phase. The potential impact on lung cancer of removing arsenic is then quantified using a three-stage version of a multistage clonal expansion (MSCE) model. This refines the usual two-stage clonal expansion (TSCE) model of carcinogenesis by resolving its intermediate or "initiated" cell compartment into two subcompartments, representing experimentally observed "patch" and "field" cells. This refinement allows p16 methylation effects to be represented as speeding transitions of cells from the patch state to the clonally expanding field state. Given these assumptions, removing arsenic might greatly reduce the number of nonsmall cell lung cancer cells (NSCLCs) produced in smokers, by up to two-thirds, depending on the fraction (between 0 and 1) of the smoking-induced increase in the patch-to-field transition rate prevented if arsenic were removed. At present, this fraction is unknown (and could be as low as zero), but the possibility that it could be high (close to 1) cannot be ruled out without further data.

De Matteis, S., D. Consonni, et al. "Are women who smoke at higher risk for lung cancer than men who smoke?" Am J Epidemiol. 2013 Apr 1;177(7):601-12. doi: 10.1093/aje/kws445. Epub 2013 Feb 20.

Worldwide lung cancer incidence is decreasing or leveling off among men, but rising among women. Sex differences in associations of tobacco carcinogens with lung cancer risk have been hypothesized, but the epidemiologic evidence is

conflicting. We tested sex-smoking interaction in association with lung cancer risk within a population-based case-control study, the Environment and Genetics in Lung Cancer Etiology (EAGLE) Study (Lombardy, Italy, 2002-2005). Detailed lifetime smoking histories were collected by personal interview in 2,100 cases with incident lung cancer and 2,120 controls. Odds ratios and 95% confidence intervals for pack-years of cigarette smoking were estimated by logistic regression, adjusted for age, residence area, and time since quitting smoking. To assess sex-smoking interaction, we compared the slopes of odds ratios for logarithm of pack-years in a model for men and women combined. Overall, the slope for pack-years was steeper in men (odds ratio for female-smoking interaction = 0.39, 95% confidence interval: 0.24, 0.62; P < 0.0001); after restriction to ever smokers, the difference in slopes was much smaller (odds ratio for interaction = 0.63, 95% confidence interval: 0.29, 1.37; P = 0.24). Similar results were found by histological type. Results were unchanged when additional confounders were evaluated (e.g., tobacco type, inhalation depth, Fagerstrom-assessed nicotine dependence). These findings do not support a higher female susceptibility to tobacco-related lung cancer.

Delgado, J., L. M. Martinez, et al. "Lung cancer pathogenesis associated with wood smoke exposure." Chest. 2005 Jul;128(1):124-31.

BACKGROUND: Tobacco is considered the most important cause of lung cancer, but other factors could also be involved in its pathogenesis. The aim of the present work was to establish an association between wood smoke exposure and lung cancer pathogenesis, and to analyze the effects of wood smoke on p53 and murine double minute 2 (MDM2) protein expression. DESIGN: Blood samples were obtained from 62 lung cancer patients, 9 COPD patients, and 9 control subjects. Of the 62 lung cancer patients, 23 were tobacco smokers (lung cancer associated with tobacco [LCT] group), 24 were exposed to wood smoke (lung cancer associated with wood smoke [LCW] group), and 15 could not be included in these groups. Western blot assays were performed to identify the presence of p53, phospho-p53, and murine double minute 2 (MDM2) isoforms in plasma samples. Densitometric analysis was used to determine the intensity of p53, phospho-p53, and MDM2 bands. RESULTS: Approximately 38.7% of the lung cancer patients examined had an association with wood smoke exposure, most of them women living in rural areas. Adenocarcinoma was present in 46.7% of these patients. The p53 and phospho-p53 proteins were significantly increased in LCW samples (56,536.8 +/- 4,629 densitometry units [DU] and 58,244.8 +/- 7,492 DU, respectively [+/- SD]), in comparison with the other groups. The 57-kD MDM2 isoform plasma concentration was very high in LCW and LCT samples (75,696.4 +/- 11,979 DU and 78,551.7 +/- 11,548 DU, respectively). MDM2-p53 complexes were present in a high concentration in control and COPD subjects. This allows p53 degradation and explains the low concentrations of p53 found in these groups. MDM2-phospho-p53 complexes were observed in COPD but not in the other samples. This correlates with the low concentration of p53 observed in the COPD group (13,657 +/- 2,012 DU), and could explain the different clinic evolution of this smoker population in comparison with the LCT subjects. CONCLUSION: This study suggests that there is a possible association of lung cancer with wood smoke exposure. Likewise, our findings demonstrate that wood smoke could produce similar effects on p53, phospho-p53, and MDM2 protein expression as tobacco.

Di Cello, F., V. L. Flowers, et al. "Cigarette smoke induces epithelial to mesenchymal transition and increases the metastatic ability of breast cancer cells." Mol Cancer. 2013 Aug 6;12:90. doi: 10.1186/1476-4598-12-90.

BACKGROUND: Recent epidemiological studies demonstrate that both active and involuntary exposure to tobacco smoke increase the risk of breast cancer. Little is known, however, about the molecular mechanisms by which continuous, long term exposure to tobacco smoke contributes to breast carcinogenesis because most previous studies have focused on short term treatment models. In this work we have set out to investigate the progressive transforming effects of tobacco smoke on non-tumorigenic mammary epithelial cells and breast cancer cells using in vitro and in vivo models of chronic cigarette smoke exposure. RESULTS: We show that both non-tumorigenic (MCF 10A, MCF-12A) and tumorigenic (MCF7) breast epithelial cells exposed to cigarette smoke acquire mesenchymal properties such as fibroblastoid morphology, increased anchorage-independent growth, and increased motility and invasiveness. Moreover, transplantation experiments in mice demonstrate that treatment with cigarette smoke extract renders MCF 10A cells more capable to survive and colonize the mammary ducts and MCF7 cells more prone to metastasize from a subcutaneous injection site, independent of cigarette smoke effects on the host and stromal environment. The extent of transformation and the resulting phenotype thus appear to be associated with the differentiation state of the cells at the time of exposure. Analysis by flow cytometry showed that treatment with CSE leads to the emergence of a CD44(hi)/CD24(low) population

in MCF 10A cells and of CD44+ and CD49f + MCF7 cells, indicating that cigarette smoke causes the emergence of cell populations bearing markers of self-renewing stem-like cells. The phenotypical alterations induced by cigarette smoke are accompanied by numerous changes in gene expression that are associated with epithelial to mesenchymal transition and tumorigenesis. CONCLUSIONS: Our results indicate that exposure to cigarette smoke leads to a more aggressive and transformed phenotype in human mammary epithelial cells and that the differentiation state of the cell at the time of exposure may be an important determinant in the phenotype of the final transformed state.

Emmons, K. M., K. Sprunck-Harrild, et al. "Provider advice about smoking cessation and pharmacotherapy among cancer survivors who smoke: practice guidelines are not translating." Transl Behav Med. 2013 Jun;3(2):211-7. doi: 10.1007/s13142-013-0202-7.

Smoking among childhood and young adult cancer survivors may increase risk for late effects of treatment, and survivors need assistance in quitting. This paper reports on the prevalence of discussions between childhood cancer survivors and their health care providers about smoking cessation and pharmacotherapy and explores factors that are associated with these discussions. This is a longitudinal study that included 329 smokers who were childhood or young adult cancer survivors, recruited from five cancer centers in the USA and Canada. Fifty-five percent of smokers reported receiving advice to quit smoking from their regular provider during the study period, and only 36 % of smokers reported discussing pharmacotherapy with their provider. Receipt of advice was associated with being female and having a heavier smoking rate. Pharmacotherapy discussions were associated with readiness to quit, heavier smoking rate, and previous provider advice to quit. Health care providers are missing key opportunities to advise cancer survivors about cessation and evidence-based interventions. Systematic efforts are needed to ensure that survivors who smoke get the treatment that they need.

Eng, L., J. Su, et al. "Second-hand smoke as a predictor of smoking cessation among lung cancer survivors." J Clin Oncol. 2014 Feb 20;32(6):564-70. doi: 10.1200/JCO.2013.50.9695. Epub 2014 Jan 13.

PURPOSE: Second-hand smoke (SHS; ie, exposure to smoking of friends and spouses in the household) reduces the likelihood of smoking cessation in noncancer populations. We assessed whether SHS is associated with cessation rates in lung cancer survivors. PATIENTS AND METHODS: Patients with lung cancer were recruited from Princess Margaret Cancer Centre, Toronto, ON, Canada. Multivariable logistic regression and Cox proportional hazard models evaluated the association of sociodemographics, clinicopathologic variables, and SHS with either smoking cessation or time to quitting. RESULTS: In all, 721 patients completed baseline and follow-up questionnaires with a mean follow-up time of 54 months. Of the 242 current smokers at diagnosis, 136 (56%) had quit 1 year after diagnosis. Exposure to smoking at home (adjusted odds ratio [aOR], 6.18; 95% CI, 2.83 to 13.5; P < .001), spousal smoking (aOR, 6.01; 95% CI, 2.63 to 13.8; P < .001), and peer smoking (aOR, 2.49; 95% CI, 1.33 to 4.66; P = .0043) were each associated with decreased rates of cessation. Individuals exposed to smoking in all three settings had the lowest chances of quitting (aOR, 9.57; 95% CI, 2.50 to 36.64; P < .001). Results were similar in time-to-quitting analysis, in which 68% of patients who eventually quit did so within 6 months after cancer diagnosis. Subgroup analysis revealed similar associations across early- and late-stage patients and between sexes. CONCLUSION: SHS is an important factor associated with smoking cessation in lung cancer survivors of all stages and should be a key consideration when developing smoking cessation programs for patients with lung cancer.

Fagan, P., E. T. Moolchan, et al. "Biomarkers of tobacco smoke exposure in racial/ethnic groups at high risk for lung cancer." Am J Public Health. 2015 Jun;105(6):1237-45. doi: 10.2105/AJPH.2014.302492. Epub 2015 Apr 16.

OBJECTIVES: We examined biomarkers of tobacco smoke exposure among Native Hawaiians, Filipinos, and Whites, groups that have different lung cancer risk. METHODS: We collected survey data and height, weight, saliva, and carbon monoxide (CO) levels from a sample of daily smokers aged 18-35 (n = 179). Mean measures of nicotine, cotinine, cotinine/cigarettes per day ratio, trans 3' hydroxycotinine, the nicotine metabolite ratio (NMR), and expired CO were compared among racial/ethnic groups. RESULTS: The geometric means for cotinine, the cotinine/cigarettes per day ratio, and CO did not significantly differ among racial/ethnic groups in the adjusted models. After adjusting for gender, body mass index, menthol smoking, Hispanic ethnicity, and number of cigarettes smoked per day, the NMR was significantly higher among Whites than among Native Hawaiians and Filipinos (NMR = 0.33, 0.20, 0.19, P </= .001). The NMR increased with increasing White parental ancestry. The NMR was not significantly correlated with social-environmental stressors. CONCLUSIONS: Racial/ethnic groups with higher rates of lung cancer had slower nicotine metabolism

than Whites. The complex relationship between lung cancer risk and nicotine metabolism among racial/ethnic groups needs further clarification.

Faraglia, B., S. Y. Chen, et al. "Evaluation of 4-aminobiphenyl-DNA adducts in human breast cancer: the influence of tobacco smoke." Carcinogenesis. 2003 Apr;24(4):719-25.

Breast cancer is one of the major cancers around the world but its etiology is still not well understood. Only approximately 50% of the disease is associated with known risk factors including highly penetrant genes and lifestyle factors. Thus, environmental carcinogens may play an important role in the etiology of breast cancer. The arylamine 4-aminobiphenyl (4-ABP) is a tobacco smoke constituent, an environmental contaminant, and a well-established bladder carcinogen in rodents and humans. In this study, we investigated the role of 4-ABP in the etiology of human breast cancer by measuring 4-ABP-DNA adducts using a monoclonal antibody based immunoperoxidase method that had been validated by comparison with gas chromatography/mass spectroscopy analysis of liver tissues from 4-ABP-treated mice. Adducts were analyzed in 150 paraffin-embedded breast tumors and in 55 adjacent normal tissues collected from cases in the Long Island Breast Cancer Study Project. The role of polymorphisms in genes involved in the metabolism of 4-ABP including N-acetyl transferase 2 (NAT2), cytochrome P4501A2 (CYP1A2) and glutathione S-transferase M1 (GSTM1) and the nucleotide excision repair gene XPD was also explored in the same patients. The mean log-transformed relative staining intensity for 4-ABP-DNA adducts was higher in normal (5.93 +/- 0.54) than in the corresponding tumor (5.44 +/- 0.62, $P < 0.0001$) tissues. However, a highly significant positive correlation was observed between the levels of 4-ABP-DNA in both tissues ($r = 0.72$, $P < 0.0001$). Smoking status was correlated with the levels of 4-ABP-DNA in tumor adjacent normal tissues with a significant linear trend ($P = 0.04$) for current, former and never smokers; adducts were not related to smoking status in tumor tissues. No correlation was observed between the levels of 4-ABP-DNA and polymorphisms in the genes analyzed even when subjects were stratified by smoking status. These results demonstrate that smoking is associated with increased levels of 4-ABP-DNA adducts in human mammary tissue. In this study, genetic polymorphisms did not significantly affect the formation of 4-ABP-DNA adducts in breast cancer cases, perhaps due to the small number of samples.

Fathy, M., M. Hamed, et al. "Association between environmental tobacco smoke exposure and lung cancer susceptibility: modification by antioxidant enzyme genetic polymorphisms." Mol Diagn Ther. 2014 Feb;18(1):55-62. doi: 10.1007/s40291-013-0051-6.

BACKGROUND: Environmental tobacco smoke (ETS) is the primary etiologic factor responsible for lung cancer. However, only 10-15 % of smokers develop lung cancer, suggesting a genetic role in modifying individual susceptibility to lung cancer. Antioxidant enzymes and genetic polymorphisms should be considered. AIM: The present study aimed to evaluate the role of antioxidant enzyme activity and genetic polymorphisms in modifying the susceptibility to lung cancer among individuals exposed to ETS. SUBJECTS AND METHODS: A total of 150 male subjects were divided into three groups: 50 lung cancer patients, 50 chronic smokers, and 50 passive smokers. Genotyping of microsomal epoxide hydrolase (mEH) exon 3 (Tyr(113)Hist) and exon 4 (Hist(139)Arg) polymorphisms were done by the polymerase chain reaction-restriction fragment length polymorphism technique. MnSOD (Val(16)Ala) polymorphism was detected by the real time-TaqMan assay. Erythrocyte MnSOD activity was measured spectrophotometrically. RESULTS: ETS-exposed individuals (both active and passive smokers) who carried the His allele of mEH exon3 have a 2.9-fold increased risk of lung cancer (odds ratio [OR] 2.9, $P < 0.001$). In addition, ETS-exposed carriers of the Arg allele of mEH exon 4 have a 2.1-fold increased risk of lung cancer (OR 2.1, $P = 0.024$). However, no association between the MnSOD Val(16)Ala polymorphism and lung cancer was detected among ETS-exposed individuals (OR 1.6, $P = 0.147$), although the lung cancer group had significantly lower MnSOD activity than the chronic or passive smoker groups ($P = 0.03$). CONCLUSIONS: Exons 3 and 4 polymorphisms of the mEH gene may contribute to lung cancer susceptibility through disturbed antioxidant balance. However, this was not the case with the MnSOD Val(16)Ala single-nucleotid polymorphism. Antioxidant enzymes may modulate the influence of ETS exposure on lung cancer risk.

Ferreccio, C., Y. Yuan, et al. "Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer." Epidemiology. 2013 Nov;24(6):898-905. doi: 10.1097/EDE.0b013e31829e3e03.

BACKGROUND: Millions of people worldwide are exposed to arsenic in drinking water, and many are likely coexposed to other agents that could substantially increase their risks of arsenic-

related cancer. METHODS: We performed a case-control study of multiple chemical exposures in 538 lung and bladder cancer cases and 640 controls in northern Chile, an area with formerly high drinking water arsenic concentrations. Detailed information was collected on lifetime arsenic exposure, smoking, secondhand smoke, and other known or suspected carcinogens, including asbestos, silica, and wood dust. RESULTS: Very high lung and bladder cancer odds ratios (ORs), and evidence of greater than additive effects, were seen in people exposed to arsenic concentrations >335 microg/L and who were tobacco smokers (OR = 16, 95% confidence interval = 6.5-40 for lung cancer; and OR = 23 [8.2-66] for bladder cancer; Rothman Synergy Indices = 4.0 [1.7-9.4] and 2.0 [0.92-4.5], respectively). Evidence of greater than additive effects were also seen in people coexposed to arsenic and secondhand tobacco smoke and several other known or suspected carcinogens, including asbestos, silica, and wood dust. CONCLUSIONS: These findings suggest that people coexposed to arsenic and other known or suspected carcinogens have very high risks of lung or bladder cancer.

Filippini, G., P. Maisonneuve, et al. "Relation of childhood brain tumors to exposure of parents and children to tobacco smoke: the SEARCH international case-control study. Surveillance of Environmental Aspects Related to Cancer in Humans." Int J Cancer. 2002 Jul 10;100(2):206-13.

The etiology of childhood brain tumors (CBTs) remains unknown. Tobacco smoke contains several known carcinogens and can induce DNA adducts in human placenta and hemoglobin adducts in fetuses. We present the results of an international case-control study to evaluate the association between CBTs and exposure of parents and children to cigarette smoke. The study was undertaken as part of the SEARCH program of the IARC. Nine centers in 7 countries were involved. The studies mainly covered the 1980s and early 1990s. Cases (1,218, ages 0-19 years) were children newly diagnosed with a primary brain tumor; there were 2,223 population-based controls. Most mothers who agreed to participate were interviewed in person at home. Odds ratios (ORs) were calculated by unconditional logistic regression, adjusted for age, sex and center, for all types of CBT combined, 4 CBT histotypes, 5 age groups and each center. There was no association between the risk of brain tumors in the child and parental smoking prior to pregnancy, maternal smoking or regular exposure to others' cigarette smoke during pregnancy at home or at work, or passive smoking by the child during the first year of life. These results did not change considering the child's age at diagnosis, the histologic type of tumor or center.

Filosto, S., C. R. Becker, et al. "Cigarette smoke induces aberrant EGF receptor activation that mediates lung cancer development and resistance to tyrosine kinase inhibitors." Mol Cancer Ther. 2012 Apr;11(4):795-804. doi: 10.1158/1535-7163.MCT-11-0698. Epub 2012 Feb 1.

The EGF receptor (EGFR) and its downstream signaling are implicated in lung cancer development. Therefore, much effort was spent in developing specific tyrosine kinase inhibitors (TKI) that bind to the EGFR ATP-pocket, blocking EGFR phosphorylation/signaling. Clinical use of TKIs is effective in a subset of lung cancers with mutations in the EGFR kinase domain, rendering the receptor highly susceptible to TKIs. However, these benefits are limited, and emergence of additional EGFR mutations usually results in TKI resistance and disease progression. Previously, we showed one mechanism linking cigarette smoke to EGFR-driven lung cancer. Specifically, exposure of lung epithelial cells to cigarette smoke-induced oxidative stress stimulates aberrant EGFR phosphorylation/activation with impaired receptor ubiquitination/degradation. The abnormal stabilization of the activated receptor leads to uncontrolled cell growth and tumorigenesis. Here, we describe for the first time a novel posttranslational mechanism of EGFR resistance to TKIs. Exposure of airway epithelial cells to cigarette smoke causes aberrant phosphorylation/activation of EGFR, resulting in a conformation that is different from that induced by the ligand EGF. Unlike EGF-activated EGFR, cigarette smoke-activated EGFR binds c-Src and caveolin-1 and does not undergo canonical dimerization. Importantly, the cigarette smoke-activated EGFR is not inhibited by TKIs (AG1478; erlotinib; gefitinib); in fact, the cigarette smoke exposure induces TKI-resistance even in the TKI-sensitive EGFR mutants. Our findings show that cigarette smoke exposure stimulates not only aberrant EGFR phosphorylation impairing receptor degradation, but also induces a different EGFR conformation and signaling that are resistant to TKIs. Together, these findings offer new insights into cigarette smoke-induced lung cancer development and TKI resistance.

Ford, J. S., E. Puleo, et al. "Perceptions of risk among childhood and young adult cancer survivors who smoke." Support Care Cancer. 2014 Aug;22(8):2207-17.

PURPOSE: Despite the fact that childhood and young adult cancer survivors are at increased risk for chronic health problems as a result of their cancer treatment, many use tobacco, thereby increasing their risks. Perceptions of risk related to tobacco use can be

targeted for interventions aimed at improving health behaviors for childhood, adolescent, and young adult cancer survivors. Understanding the covariates of perceptions of health risks among young adult survivors who smoke will help to determine targets for intervention. METHOD: Three hundred seventy-four participants who were diagnosed with cancer prior to age 35, currently between 18 and 55 years of age, and current smokers were recruited as part of a larger smoking cessation study, Partnership for Health-2 (PFH-2). Data were collected by telephone survey. RESULTS: Overall, women had the highest perception of risk for serious health problems, a second cancer, and heart problems. Additionally, those participants who were dependent on nicotine endorsed that they were at higher risk of serious health problems and second cancers, but not heart problems. Finally, Hodgkin lymphoma survivors reported that they were at increased risk for second cancers and heart problems compared to their "healthy" peers. CONCLUSION: Young adult cancer survivors who smoke correctly perceived some of their increased health risks. Additional motivation and education is needed for those young adult cancer survivors who perceive their increased health risks yet continue to smoke. Further education is needed for young survivors so they have a fully appropriate sense of risk, especially as it relates to their tobacco use.

Fukumoto, K., H. Ito, et al. "Cigarette smoke inhalation and risk of lung cancer: a case-control study in a large Japanese population." Eur J Cancer Prev. 2015 May;24(3):195-200. doi: 10.1097/CEJ.0000000000000034.

Several studies have shown that cigarette smoke inhalation is associated with an increased risk of lung cancer (LC) in European populations. The aim of our study was to clarify the relationship between cigarette smoke inhalation and the risk of LC in a Japanese population. We carried out a large case-control study of cigarette smoking and the risk of LC in Japan. Cases were newly diagnosed patients with histologically confirmed LC (n=653). Controls (n=1281) included hospital controls (n=453) and community-based controls (n=828). Odds ratios (OR) and 95% confidence intervals (CI) were derived from unconditional logistic regression analysis, adjusted for basic confounding variables including age, sex, drinking status, fruit and vegetable intake, family history of LC, occupation, and years of education. Compared with never smokers, ORs for ever smokers who do not inhale cigarette smoke (noninhalation) and ever smokers who inhale cigarette smoke (inhalation) were 1.72 (95% CI: 1.15-2.59) and 3.28 (95% CI: 2.38-4.53), respectively, when adjusted for basic confounding variables. When the analysis was restricted to ever smokers, the OR adjusted for basic confounding factors and pack-year of the risk of LC in the inhalation group was significantly higher than that in the noninhalation group. OR for the inhalation group compared with the noninhalation group was 1.52 (95% CI: 1.06-2.18, P=0.021). A similar pattern was observed in subcategory analyses for adenocarcinoma, squamous cell carcinoma and small cell carcinoma, and other histological types, although without statistical significance. Our case-control study showed that inhalation of cigarette smoke is a significant risk for LC independent from pack-years in a Japanese population.

Gallicchio, L., A. Kouzis, et al. "Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer." Prev Med. 2006 Mar;42(3):200-5. Epub 2006 Feb 3.

OBJECTIVE: The objective of this study was to examine the association between active cigarette smoking, household passive smoke exposure, and pancreatic cancer risk using a prospective cohort design. METHODS: Two cohorts were established in Washington County, Maryland in 1963 (n = 45,749) and 1975 (n = 48,172). The Washington County Cancer Registry was used to ascertain the occurrence of pancreatic cancer in the 1963 cohort from 1963-1978 and in the 1975 cohort from 1975-1994. Poisson regression was used to analyze the associations between active smoking and household passive smoke exposure and pancreatic cancer risk. RESULTS: Current active smoking was associated with a two-fold increased risk of pancreatic cancer in both cohorts. Among never-smokers in each cohort, exposure to household passive smoke was not associated with an increased risk of pancreatic cancer, although the confidence limits were wide due to a small number of cases. CONCLUSIONS: This study further documents the approximate doubling of pancreatic cancer risk in current active smokers. Our results also indicate that household passive smoke exposure is not associated with pancreatic cancer risk, although our risk estimates lacked precision.

Gammon, M. D., S. M. Eng, et al. "Environmental tobacco smoke and breast cancer incidence." Environ Res. 2004 Oct;96(2):176-85.

To evaluate whether environmental tobacco smoke (ETS) influences breast cancer incidence, data from a population-based case-control study were analyzed. Respondents with available ETS information assessed by in-person questionnaires included 1356 newly diagnosed cases and 1383 controls. Relative to nonsmokers who reported no residential ETS exposure throughout the life course, the odds ratios (OR) for breast cancer were not

substantially elevated in relation to ETS exposure, active smoking, or a joint measure of active and passive smoking (OR, 1.15, 95% CI, 0.90, 1.48). An increased OR, however, was noted among nonsmokers who lived with a smoking spouse for over 27 years (2.10, 95% CI, 1.47, 3.02), although no dose-response was evident. Also, among women with hormone-receptor-positive tumors only, the OR for both active and passive smoking was increased (1.42 for ER+ PR+, 95% CI, 1.00, 2.00). Our data suggest that if there is an effect for ETS on breast cancer, that effect is restricted to selected subgroups of women, such as those with long-term exposure from a smoking spouse.

Goldkorn, T., S. Filosto, et al. "Lung injury and lung cancer caused by cigarette smoke-induced oxidative stress: Molecular mechanisms and therapeutic opportunities involving the ceramide-generating machinery and epidermal growth factor receptor." Antioxid Redox Signal. 2014 Nov 20;21(15):2149-74. doi: 10.1089/ars.2013.5469. Epub 2014 Jul 1.

Chronic obstructive pulmonary disease (COPD) and lung cancer are frequently caused by tobacco smoking. However, these diseases present opposite phenotypes involving redox signaling at the cellular level. While COPD is characterized by excessive airway epithelial cell death and lung injury, lung cancer is caused by uncontrolled epithelial cell proliferation. Notably, epidemiological studies have demonstrated that lung cancer incidence is significantly higher in patients who have preexisting emphysema/lung injury. However, the molecular link and common cell signaling events underlying lung injury diseases and lung cancer are poorly understood. This review focuses on studies of molecular mechanism(s) underlying smoking-related lung injury (COPD) and lung cancer. Specifically, the role of the ceramide-generating machinery during cigarette smoke-induced oxidative stress leading to both apoptosis and proliferation of lung epithelial cells is emphasized. Over recent years, it has been established that ceramide is a sphingolipid playing a major role in lung epithelia structure/function leading to lung injury in chronic pulmonary diseases. However, new and unexpected findings draw attention to its potential role in lung development, cell proliferation, and tumorigenesis. To address this dichotomy in detail, evidence is presented regarding several protein targets, including Src, p38 mitogen-activated protein kinase, and neutral sphingomyelinase 2, the major sphingomyelinase that controls ceramide generation during oxidative stress. Furthermore, their roles are presented not only in apoptosis and lung injury but also in enhancing cell proliferation, lung cancer development, and resistance to epidermal growth factor receptor-targeted therapy for treating lung cancer.

Gomez Raposo, C., J. De Castro Carpeno, et al. "[Causes of lung cancer: smoking, environmental tobacco smoke exposure, occupational and environmental exposures and genetic predisposition]." Med Clin (Barc). 2007 Mar 17;128(10):390-6.

Every year, in Spain 18,000 new cases of lung cancer (LC) are diagnosed. Approximately, 80-90% LC in men and women are directly attributable to tobacco abuse. Cigarette smoke contains over 300 chemicals, 40 of which are known to be potent carcinogens. In the last decade, as in Spain, prevalence of smoking in women has generally increased in the European Union. LC risk can be substantially reduced after smoking cessation, yet never reaches baseline. On the other hand, environmental tobacco smoke exposure (passive smoking) in nonsmokers appears to have a significantly increased risk of LC. An updated of etiology factors of LC, risk related to duration as well as intensity of smoking, relationship between environmental tobacco smoke exposure and LC risk, genetic predisposition and a variety of occupational and environmental exposures implicated as potential risk factors for the development of LC will be reviewed here.

Gonzalez-Avila, G., J. Delgado, et al. "Differences in plasma MMPs and TIMPs protein expression and chemotherapy response in patients with tobacco- or wood-smoke-induced lung cancer." Respiration. 2013;85(4):281-8. doi: 10.1159/000336559. Epub 2012 Mar 22.

BACKGROUND: One of the risk factors associated with lung cancer in never-smoker patients is wood smoke exposure (WS). However, information about its clinical and molecular characteristics remains scant. OBJECTIVE: This was to analyze--in plasma from patients with tobacco- or wood-smoke-induced lung cancer--whether the enzymatic activity and concentration of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) differ, and to determine whether there was a correlation between these indicators of the metastatic potential and the first-line chemotherapy response. METHODS: Patients were classified according to lung cancer associated with: the smoking of tobacco (T), WS and where no association with a known risk factor (N) could be established. The gelatinase activity of plasma MMP was analyzed by radiolabeled substrate degradation and zymography assay. Protein expression of MMPs and TIMPs was evaluated by Western blot densitometry analysis. RESULTS: The 26.9% WS patients had a better response to therapy in

comparison with the T group (OR = 4.9, 95% CI = 1.25-20.15; p = 0.019). The lowest gelatinase activity was observed in WS subjects, in comparison with T and N subjects (96.7 +/- 15.9, 182.9 +/- 31.5 and 163.3 +/- 22.7 microg of degraded gelatin/mg of incubated plasma protein, respectively; p < 0.025); this enzymatic activity corresponded to MMP-2. The highest MMP-2, MMP-9, MT1-MMP and TIMP-1 plasma levels were observed in T subjects. CONCLUSION: Tobacco and wood smoke have different effects on MMP and TIMP synthesis and gelatinase activity, directly influencing lung cancer metastatic potential and chemotherapy response.

Hahn, F. F., A. P. Gigliotti, et al. "A review of the histopathology of cigarette smoke-induced lung cancer in rats and mice." Int J Toxicol. 2007 Jul-Aug;26(4):307-13.

In the past several years an increased number of lung tumors has been reported in laboratory studies of rats and mice after lifetime exposure to mainstream cigarette smoke. Proliferative epithelial lesions are present in the lungs of both species and are apparent antecedent lesions to benign and malignant tumors. Both species have alveolar epithelia hyperplasia, alveolar adenomas, and alveolar carcinomas. The incidence of all three are more in the rats. In addition, mice also have bronchiolar epithelial hyperplasia and bronchial papillomas not found in rats. Rats have a low incidence of squamous cyst that is not found in mice. Lung tumors in rats and mice are found at the end of the life span and rarely metastasize. The characteristics of the lung tumors, and the proliferative changes associated with the tumors, are important in helping understand the mechanisms of lung cancer induction. These studies in rats and mice allow new approaches to the study of cigarette smoke-induced changes in the lung.

Hasnis, E., A. Z. Reznick, et al. "Synergistic effect of cigarette smoke and saliva on lymphocytes--the mediatory role of volatile aldehydes and redox active iron and the possible implications for oral cancer." Int J Biochem Cell Biol. 2004 May;36(5):826-39.

Oral squamous cell carcinoma (SCC) is most induced by exposure of the oral epithelial cells to tobacco products such as cigarette smoke. This exposure always occurs in the presence of saliva and presumably is induced by free radicals. To explore the effects of CS on cells in the presence of saliva, we used peripheral blood lymphocytes (PBL) and exposed them to CS, alone or in the presence of saliva. We discovered that after 80min, exposure of the lymphocytes to CS alone resulted in a time-dependent cellular loss with a survival rate of 56%, while following lymphocyte exposure to CS in the presence of saliva, less than 15% of the cells survived. This was accompanied by concomitant accumulation of cellular protein carbonyls which could be protected by the exogenous addition of uric acid or glutathione, but not by the addition of ascorbate (Asc), N-acetyl-l-cystein (NAC) or desferal (DES). Exposure of the lymphocytes to aldehydes present in CS, such as acrolein and croton-aldehyde, also resulted in the elevation of protein carbonyls, which was ameliorated primarily by the addition of glutathione. However, lymphocyte exposure to acroline in the presence of saliva did not show the same synergism in cell death observed as when the lymphocytes were exposed to CS and saliva. Thus, we postulated the existence of another mechanism and examined the role of redox active iron as an additional explanation for this synergism. In fact, it was found that in the presence of saliva and ascorbate there was a marked decrease in the lymphocyte survival rate; this was reversed by the addition of the iron chelator desferal. In light of these results, a comprehensive mechanism for the induction of oral cancer by cigarette smoke is suggested, stressing the role of a pivotal player in the process leading to oral cancer which has never been previously considered in this regard - the saliva.

Hecht, S. S., S. E. Murphy, et al. "Tobacco smoke biomarkers and cancer risk among male smokers in the Shanghai cohort study." Cancer Lett. 2013 Jun 28;334(1):34-8. doi: 10.1016/j.canlet.2012.07.016. Epub 2012 Jul 20.

Metabolites of tobacco smoke constituents can be quantified in urine and other body fluids providing a realistic measure of carcinogen and toxicant dose in a smoker. Many previous studies have demonstrated that these metabolites - referred to as biomarkers in this paper - are related to tobacco smoke exposure. The studies reviewed here were designed to answer another question: are these substances also biomarkers of cancer risk? Using a prospective study design comparing biomarker levels in cancer cases and controls, all of whom were smokers, the results demonstrate that several of these biomarkers - total cotinine, total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), r-1-,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT), and total N'-nitrosonornicotine (NNN) - are biomarkers of cancer risk. Therefore, these biomarkers have the potential to become part of a cancer risk prediction algorithm for smokers.

Hershkovich, O., J. Oliva, et al. "Lethal synergistic effect of cigarette smoke and saliva in an in vitro model: does saliva have a role in the development of oral cancer?" Eur J Cancer. 2004 Jul;40(11):1760-7.

Exposure of oral mucosal cells to cigarette smoke induces oral cancer, presumably via the injurious effect of free radicals. To explore the effects of cigarette smoke on cells in the presence of saliva, we used peripheral blood lymphocytes (PBL) and exposed them to cigarette smoke, alone or in the presence of saliva. After 80 min exposure to cigarette smoke alone, a time-dependent cellular loss and survival rate of 52% was observed. By contrast, following the exposure of the lymphocytes to cigarette smoke in the presence of saliva, less than 20% of the cells survived. Saliva secreted from the submandibular/sublingual (Sm/Sl) glands was highly cytotoxic, while saliva secreted from the parotid glands was only moderately cytotoxic. Redox active iron ions in saliva and aldehydes in cigarette smoke were shown to play the major injurious roles in this synergistic phenomenon. The salivary-borne redox active iron ions participate in Fenton and Haber-Weiss reactions to transform low-reactive free radicals, which originate from cigarette smoke into highly-reactive .OH(-)-free radicals. In light of these results, a comprehensive mechanism for the induction of oral cancer by cigarette smoke is suggested where saliva may be a pivotal player.

Hooker, C. M., L. Gallicchio, et al. "A prospective cohort study of rectal cancer risk in relation to active cigarette smoking and passive smoke exposure." Ann Epidemiol. 2008 Jan;18(1):28-35. Epub 2007 Sep 27.

PURPOSE: The present investigation prospectively examined active cigarette smoking and household passive smoke exposure and the risk of developing rectal cancer. METHODS: Cigarette smoking data were collected on all household members during two private censuses in Washington County, Maryland. These two cohorts were followed up, one cohort from 1963-1978 and the other from 1975-1994 for first-time diagnoses of rectal cancer. We identified 148 and 169 rectal cancer cases in the 1963 and 1975 cohorts, respectively. Relative risks were estimated by means of Poisson regression models. RESULTS: In men, the adjusted relative risks (aRR) and 95% confidence intervals (CI) for the association between current smoking and rectal cancer were 3.1 (1.2-7.8) in the 1963 cohort and 1.8 (0.9-3.7) in the 1975 cohort; the corresponding aRRs in women were 0.9 (0.5-1.8) and 1.6 (0.9-3.8) in the 1963 and 1975 cohorts, respectively. In nonsmokers, household passive smoke exposure was strongly associated with rectal cancer among men in the 1963 cohort (aRR = 5.8; 1.8-18.4) but not the 1975 cohort (aRR = 1.1; 0.2-5.0). In women, household passive exposure was not strongly associated with rectal cancer in either cohort. CONCLUSIONS: The results of our study suggest that active cigarette smoking may contribute to rectal cancer risk, but inconsistencies in the findings preclude drawing strong, clear-cut inferences.

Hutt, J. A., B. R. Vuillemenot, et al. "Life-span inhalation exposure to mainstream cigarette smoke induces lung cancer in B6C3F1 mice through genetic and epigenetic pathways." Carcinogenesis. 2005 Nov;26(11):1999-2009. Epub 2005 Jun 8.

Although cigarette smoke has been epidemiologically associated with lung cancer in humans for many years, animal models of cigarette smoke-induced lung cancer have been lacking. This study demonstrated that life time whole body exposures of female B6C3F1 mice to mainstream cigarette smoke at 250 mg total particulate matter/m(3) for 6 h per day, 5 days a week induces marked increases in the incidence of focal alveolar hyperplasias, pulmonary adenomas, papillomas and adenocarcinomas. Cigarette smoke-exposed mice (n = 330) had a 10-fold increase in the incidence of hyperplastic lesions, and a 4.6-fold (adenomas and papillomas), 7.25-fold (adenocarcinomas) and 5-fold (metastatic pulmonary adenocarcinomas) increase in primary lung neoplasms compared with sham-exposed mice (n = 326). Activating point mutations in codon 12 of the K-ras gene were identified at a similar rate in tumors from sham-exposed mice (47%) and cigarette smoke-exposed mice (60%). The percentages of transversion and transition mutations were similar in both the groups. Hypermethylation of the death associated protein (DAP)-kinase and retinoic acid receptor (RAR)-beta gene promoters was detected in tumors from both sham- and cigarette smoke-exposed mice, with a tendency towards increased frequency of RAR-beta methylation in the tumors from the cigarette smoke-exposed mice. These results emphasize the importance of the activation of K-ras and silencing of DAP-kinase and RAR-beta in lung cancer development, and confirm the relevance of this mouse model for studying lung tumorigenesis.

Huynh, T. P., V. Mah, et al. "Na,K-ATPase is a target of cigarette smoke and reduced expression predicts poor patient outcome of smokers with lung cancer." Am J Physiol Lung Cell Mol Physiol. 2012 Jun 1;302(11):L1150-8. doi: 10.1152/ajplung.00384.2010. Epub 2012 Feb 17.

Diminished Na,K-ATPase expression has been reported in several carcinomas and has been linked to tumor progression. However, few studies have determined whether Na,K-ATPase function and expression are altered in lung malignancies. Because cigarette smoke (CS) is a major factor underlying lung carcinogenesis and progression, we investigated whether CS affects Na,K-ATPase activity and expression in lung cell lines. Cells exposed to CS in

vitro showed a reduction of Na,K-ATPase activity. We detected the presence of reactive oxygen species (ROS) in cells exposed to CS before Na,K-ATPase inhibition, and neutralization of ROS restored Na,K-ATPase activity. We further determined whether Na,K-ATPase expression correlated with increasing grades of lung adenocarcinoma and survival of patients with smoking history. Immunohistochemical analysis of lung adenocarcinoma tissues revealed reduced Na,K-ATPase expression with increasing tumor grade. Using tissue microarray containing lung adenocarcinomas of patients with known smoking status, we found that high expression of Na,K-ATPase correlated with better survival. For the first time, these data demonstrate that CS is associated with loss of Na,K-ATPase function and expression in lung carcinogenesis, which might contribute to disease progression.

Johnson, K. C., A. B. Miller, et al. "Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009)." Tob Control. 2011 Jan;20(1):e2. doi: 10.1136/tc.2010.035931. Epub 2010 Dec 8.

Four authoritative reviews of active smoking and breast cancer have been published since 2000, but only one considered data after 2002 and conclusions varied. Three reviews of secondhand smoke (SHS) and breast cancer (2004-2006) each came to different conclusions. With 30 new studies since 2002, further review was deemed desirable. An Expert Panel was convened by four Canadian agencies, the Ontario Tobacco Research Unit, the Public Health Agency of Canada, Physicians for a Smoke-Free Canada and the Canadian Partnership Against Cancer to comprehensively examine the weight of evidence from epidemiological and toxicological studies and understanding of biological mechanisms regarding the relationship between tobacco smoke and breast cancer. This article summarises the panel's full report (http://www.otru.org/pdf/special/expert_panel_tobacco_breast_cancer.pdf). There are 20 known or suspected mammary carcinogens in tobacco smoke, and recognised biological mechanisms that explain how exposure to these carcinogens could lead to breast cancer. Results from the nine cohort studies reporting exposure metrics more detailed than ever/never and ex/current smoker show that early age of smoking commencement, higher pack-years and longer duration of smoking increase breast cancer risk 15% to 40%. Three meta-analyses report 35% to 50% increases in breast cancer risk for long-term smokers with N-acetyltransferase 2 gene (NAT2) slow acetylation genotypes. The active smoking evidence bolsters support for three meta-analyses that each reported about a 65% increase in premenopausal breast cancer risk among never smokers exposed to SHS. The Panel concluded that: 1) the association between active smoking and breast cancer is consistent with causality and 2) the association between SHS and breast cancer among younger, primarily premenopausal women who have never smoked is consistent with causality.

Kalabus, J. L., Q. Cheng, et al. "Induction of carbonyl reductase 1 (CBR1) expression in human lung tissues and lung cancer cells by the cigarette smoke constituent benzo[a]pyrene." Toxicol Lett. 2012 Jun 20;211(3):266-73. doi: 10.1016/j.toxlet.2012.04.006. Epub 2012 Apr 15.

Carbonyl reductase 1 (CBR1) reduces various xenobiotic carbonyl substrates to corresponding alcohol metabolites. Here we demonstrated that benzo[a]pyrene (B[a]P), a potent pro-carcinogen and predominant polycyclic aromatic hydrocarbon (PAH) compound in cigarette smoke and air pollutants, upregulates CBR1 gene expression in vitro and in vivo, and that a proximal xenobiotic response element (XRE) motif ((-)(1)(2)(2)XRE) mediates the induction effect of B[a]P. First, we observed 46% and 50% increases in CBR1 mRNA and CBR1 protein levels, respectively, in human lung tissue samples from smokers compared to never-smokers. Second, we detected 3.0-fold ($p<0.0001$) induction of CBR1 mRNA and 1.5-fold ($p<0.01$) induction of CBR1 protein levels in cells of the human lung cancer cell line A549 incubated with 2.5 muM B[a]P for 24h. Third, results from experiments with CBR1 promoter constructs indicated that a proximal XRE motif (-)(1)(2)(2)XRE) mediates induction of reporter activity in response to B[a]P. Furthermore, we detected enhanced nuclear translocation of aryl hydrocarbon receptor (AhR) following B[a]P exposure in A549 cells. Finally, we demonstrated increased binding of specific protein complexes to (-)(1)(2)(2)XRE in nuclear extracts from B[a]P-treated cells and the presence of the AhR/Arnt complex in the specific nuclear protein (-)(1)(2)(2)XRE complexes.

Karagueuzian, H. S., C. White, et al. "Cigarette smoke radioactivity and lung cancer risk." Nicotine Tob Res. 2012 Jan;14(1):79-90. doi: 10.1093/ntr/ntr145. Epub 2011 Sep 27.

INTRODUCTION: To determine the tobacco industry's policy and action with respect to radioactive polonium 210 ((210)Po) in cigarette smoke and to assess the long-term risk of lung cancer caused by alpha particle deposits in the lungs of regular smokers. METHODS: Analysis of major tobacco industries' internal secret documents on cigarette radioactivity made available online by the Master Settlement

Agreement in 1998. RESULTS: The documents show that the industry was well aware of the presence of a radioactive substance in tobacco as early as 1959. Furthermore, the industry was not only cognizant of the potential "cancerous growth" in the lungs of regular smokers but also did quantitative radiobiological calculations to estimate the long-term (25 years) lung radiation absorption dose (rad) of ionizing alpha particles emitted from the cigarette smoke. Our own calculations of lung rad of alpha particles match closely the rad estimated by the industry. According to the Environmental Protection Agency, the industry's and our estimate of long-term lung rad of alpha particles causes 120-138 lung cancer deaths per year per 1,000 regular smokers. Acid wash was discovered in 1980 to be highly effectively in removing (210)Po from the tobacco leaves; however, the industry avoided its use for concerns that acid media would ionize nicotine converting it into a poorly absorbable form into the brain of smokers thus depriving them of the much sought after instant "nicotine kick" sensation. CONCLUSIONS: The evidence of lung cancer risk caused by cigarette smoke radioactivity is compelling enough to warrant its removal.

Kispert, S., J. Marentette, et al. "Cigarette smoke induces cell motility via platelet-activating factor accumulation in breast cancer cells: a potential mechanism for metastatic disease." Physiol Rep. 2015 Mar;3(3). pii: e12318. doi: 10.14814/phy2.12318. Epub 2015 Mar 22.

Most cancer deaths are a result of metastasis rather than the primary tumor. Although cigarette smoking has been determined as a risk factor for several cancers, its role in metastasis has not been studied in detail. We propose that cigarette smoking contributes to metastatic disease via inhibition of breast cancer cell platelet-activating factor acetylhydrolase (PAF-AH), resulting in PAF accumulation and a subsequent increase in cell motility. We studied several breast cell lines, including immortalized mammary epithelial cells (MCF-10A), luminal A hormone positive MCF-7, basal-like triple negative MDA-MB-468, and claudin-low triple-negative highly metastatic MDA-MB-231 breast tumor cells. We exposed cells to cigarette smoke extract (CSE) for up to 48 h. CSE inhibited PAF-AH activity, increased PAF accumulation, and increased cell motility in MDA-MB-231 metastatic triple negative breast cancer cells. The calcium-independent phospholipase A2 (iPLA2) inhibitor, (S) bromoenol lactone ((S)-BEL) was used to prevent the accumulation of PAF and further prevented the increase in cell motility seen previously when cells were exposed to CSE. Thus, iPLA2 or PAF may represent a therapeutic target to manage metastatic disease, particularly in triple-negative breast cancer patients who smoke.

Klosky, J. L., V. L. Tyc, et al. "Establishing the predictive validity of intentions to smoke among preadolescents and adolescents surviving cancer." J Clin Oncol. 2010 Jan 20;28(3):431-6. doi: 10.1200/JCO.2008.21.7232. Epub 2009 Dec 14.

PURPOSE: A significant proportion of adults surviving childhood cancer are smokers. Although these estimated rates of smoking are slightly lower than those in the US population, they remain alarmingly high for this high-risk group. The purpose of this study was to examine the predictive validity of adolescent self-reported smoking intentions for later smoking among childhood cancer survivors. PATIENTS AND METHODS: Baseline tobacco intentions were collected from 119 nonsmoking cancer survivors, age 10 to 18 years, who participated in a tobacco-based clinical trial during the late 1990s. Follow-up smoking status was systematically collected annually up to 10 years postintervention (median follow-up, 6.0 years; interquartile range, 3.0 to 6.9 years) as part of clinical survivorship care. RESULTS: Twenty-seven participants (22.7%) subsequently initiated tobacco use within 5 years of study enrollment. The 5-year cumulative incidence was 29.8% +/- 6.0% for those who were susceptible to smoking compared with 12.8% +/- 5.4% for those who were committed never smokers (P = .022). Past use (P < .001) and having friends who smoked (P = .038) were also associated (univariate model) with tobacco initiation, and there was a trend for an association for older adolescents (P = .073). Every unit increase on the intentions scale was associated with a 17% increase in the risk for tobacco initiation (P = .002) after adjusting for age group and past tobacco use in a multivariable model. CONCLUSION: Because early intentions to smoke are predictive of later tobacco use, survivors as young as 10 years of age who waver in their commitment to remain tobacco abstinent should be targeted for tobacco prevention interventions.

Klosky, J. L., V. L. Tyc, et al. "Predictors of non-participation in a randomized intervention trial to reduce environmental tobacco smoke (ETS) exposure in pediatric cancer patients." Pediatr Blood Cancer. 2009 May;52(5):644-9. doi: 10.1002/pbc.21946.

BACKGROUND: Exposure to environmental tobacco smoke (ETS) is associated with the development of serious health consequences in children with cancer due to preexisting disease and treatment-related vulnerabilities. The purpose of the current investigation was to identify predictors of non-

participation in a randomized intervention trial to reduce ETS exposure among pediatric cancer patients. METHODS: One hundred fifty-three families of pediatric cancer patients met study eligibility criteria. Parents of 117 (76%) patients agreed to study participation, whereas 36 (24%) parents declined (non-participants). Data were collected with respect to participant sociodemographic, medical, and treatment-related characteristics. RESULTS: Univariate analyses indicated that families whose primary caregivers were females or smokers were more likely to be non-participants in the ETS reduction trial (P = 0.045 and P = 0.009, respectively). Medical features that significantly associated with study non-participation included CNS tumor diagnosis (P = 0.030), no history of chemotherapy (P = 0.012), history of surgery prior to study recruitment (P = 0.036), and having future radiation therapy planned post study recruitment (P = 0.009). Multivariable logistic regression modeling revealed that study non-participation was associated with the primary caregiver being a smoker (OR = 6.48, P = 0.002) or female (OR = 8.56, P = 0.023), and patient CNS tumor diagnosis (OR = 4.63, P = 0.021). CONCLUSIONS: Although a large percentage of eligible participants enrolled in the ETS reduction trial, findings suggest that future recruitment strategies of families should be tailored to parental smoking status and gender, as well as child diagnosis and treatment.

Krayzler, E. and R. M. Nagler "Carbonyl levels and survival rates in oral cancer cells exposed to cigarette smoke." Anticancer Res. 2015 Apr;35(4):1961-5.

BACKGROUND: Cigarette smoke (CS) is the main inducer of oral cancer, increasing prevalence 4-7 times. MATERIALS AND METHODS: We examined SCC-25 and SCC-15 suitability for studying CS effects on oral cancer cells, measuring carbonyl levels for free radical-mediated CS effect on survival and time/CS dependence. RESULTS: Protein oxidation increased significantly during CS exposure. At all time points, carbonyl levels increased six-fold ($p<0.001$) in both cell lines. Cell viability decrease was time-dependent. Longer CS exposure led to higher cell mortality. At 120 min, SCC-25 cell survival reduction was 43.7%, ($p<0.01$). Propidium iodide (PI) assay results matched the Trypan blue assay showing a time-dependent cell viability decrease following CS exposure. At 120 min, cell survival reduction was 37% ($p<0.05$). CONCLUSION: Cell death is mediated by CS free radicals with pathological process occurring first. Oral cancer cell models SCC-25 and SCC-15 are suitable for studying CS-induced free radical-related damage, potentially leading to the pathogenesis of oral cancer.

Krishnan, V. G., P. J. Ebert, et al. "Whole-genome sequencing of asian lung cancers: second-hand smoke unlikely to be responsible for higher incidence of lung cancer among Asian never-smokers." Cancer Res. 2014 Nov 1;74(21):6071-81. doi: 10.1158/0008-5472.CAN-13-3195. Epub 2014 Sep 4.

Asian nonsmoking populations have a higher incidence of lung cancer compared with their European counterparts. There is a long-standing hypothesis that the increase of lung cancer in Asian never-smokers is due to environmental factors such as second-hand smoke. We analyzed whole-genome sequencing of 30 Asian lung cancers. Unsupervised clustering of mutational signatures separated the patients into two categories of either all the never-smokers or all the smokers or ex-smokers. In addition, nearly one third of the ex-smokers and smokers classified with the never-smoker-like cluster. The somatic variant profiles of Asian lung cancers were similar to that of European origin with G.C>T.A being predominant in smokers. We found EGFR and TP53 to be the most frequently mutated genes with mutations in 50% and 27% of individuals, respectively. Among the 16 never-smokers, 69% had an EGFR mutation compared with 29% of 14 smokers/ex-smokers. Asian never-smokers had lung cancer signatures distinct from the smoker signature and their mutation profiles were similar to European never-smokers. The profiles of Asian and European smokers are also similar. Taken together, these results suggested that the same mutational mechanisms underlie the etiology for both ethnic groups. Thus, the high incidence of lung cancer in Asian never-smokers seems unlikely to be due to second-hand smoke or other carcinogens that cause oxidative DNA damage, implying that routine EGFR testing is warranted in the Asian population regardless of smoking status.

Kurmi, O. P., P. H. Arya, et al. "Lung cancer risk and solid fuel smoke exposure: a systematic review and meta-analysis." Eur Respir J. 2012 Nov;40(5):1228-37. doi: 10.1183/09031936.00099511. Epub 2012 May 31.

The aim of this systematic review was to quantify the impact of biomass fuel and coal use on lung cancer and to explore reasons for heterogeneity in the reported effect sizes. A systematic review of primary studies reporting the relationship between solid fuel use and lung cancer was carried out, based on pre-defined criteria. Studies that dealt with confounding factors were used in the meta-analysis. Fuel types, smoking, country, cancer cell type and sex were considered in sub-group analyses. Publication bias and heterogeneity were estimated. The pooled effect estimate for coal smoke as a lung carcinogen (OR 1.82, 95% CI 1.60-2.06) was greater than that

from biomass smoke (OR 1.50, 95% CI 1.17-1.94). The risk of lung cancer from solid fuel use was greater in females (OR 1.81, 95% CI 1.54-2.12) compared to males (OR 1.16, 95% CI 0.79-1.69). The pooled effect estimates were 2.33 (95% CI 1.72-3.17) for adenocarcinoma, 3.58 (1.58-8.12) for squamous cell carcinoma and 1.57 (1.38-1.80) for tumours of unspecified cell type. These findings suggest that in-home burning of both coal and biomass is consistently associated with an increased risk of lung cancer.

Kwon, Y. M., J. H. Park, et al. "Different susceptibility of increased DNMT1 expression by exposure to tobacco smoke according to histology in primary non-small cell lung cancer." J Cancer Res Clin Oncol. 2007 Apr;133(4):219-26. Epub 2006 Oct 20.

PURPOSE: DNA methyltransferase 1 (DNMT1) is known to play an important role in the development of cancers. However, the underlying mechanisms responsible for the altered expression of DNMT1 in non-small cell lung cancers (NSCLCs) remain to be elucidated. METHODS: We investigated the relationships of mRNA expression levels of DNMT1 to the altered expression of retinoblastoma (Rb) and p53 and to the clinicopathological variables in 153 NSCLCs. The expression of DNMT1 was determined by quantitative real-time PCR, and the altered expressions of p53 and Rb were assessed by immunohistochemistry. RESULTS: The increased expression of DNMT1 was found in 47 (31%) of 153 NSCLC patients examined. The prevalence of increased DNMT1 expression was significantly different between adenocarcinoma and squamous cell carcinoma (42% vs. 19%, respectively; P = 0.004). Patients who had smoked more than 65 packyears showed a 4.17 times [95% confidence interval (CI) = 1.17-69.49; P = 0.007] higher risk of increased DNMT1 expression compared to those who had smoked less than 45 packyears in adenocarcinoma. The expressions of Rb and p53 proteins were not associated with the increased expression of DNMT1 in 153 NSCLCs (P = 0.18 and 0.54, respectively). CONCLUSIONS: The present study suggests that the susceptibility of increased DNMT1 expression by exposure to tobacco smoke may be different according to histologic subtypes in NSCLC.

Lacko, M., H. M. Roelofs, et al. "Genetic polymorphisms in the tobacco smoke carcinogens detoxifying enzyme UGT1A7 and the risk of head and neck cancer." Head Neck. 2009 Oct;31(10):1274-81. doi: 10.1002/hed.21090.

BACKGROUND: UGT1A7 is an enzyme involved in the metabolism of (pre)carcinogens present in tobacco smoke. We investigated whether genetic polymorphisms in UGT1A7, with predicted altered enzyme activity, may have a risk-modifying effect on head and neck carcinogenesis. METHODS: Blood samples from 427 patients with oral, pharyngeal, and laryngeal carcinoma and 420 healthy control subjects were investigated for UGT1A7 polymorphisms. Based on these polymorphisms, patients and controls were divided according to predicted enzyme activity (low, intermediate, high). RESULTS: Logistic regression analysis showed a significant increased distribution of predicted high activity UGT1A7 polymorphisms among the patients (OR:1.44; 95% CI: 1.07-1.93). Stratified analyses demonstrated that high activity UGT1A7 polymorphisms were even more significantly present in patients with laryngeal cancer, older patients, heavy smokers, and heavy drinkers when compared with the control subjects. CONCLUSIONS: Predicted high activity UGT1A7 polymorphisms were significantly associated with an increased risk of head and neck cancer.

Lash, T. L., B. D. Bradbury, et al. "A case-only analysis of the interaction between N-acetyltransferase 2 haplotypes and tobacco smoke in breast cancer etiology." Breast Cancer Res. 2005;7(3):R385-93. Epub 2005 Mar 21.

INTRODUCTION: N-acetyltransferase 2 is a polymorphic enzyme in humans. Women who possess homozygous polymorphic alleles have a slower rate of metabolic activation of aryl aromatic amines, one of the constituents of tobacco smoke that has been identified as carcinogenic. We hypothesized that women with breast cancer who were slow acetylators would be at increased risk of breast cancer associated with active and passive exposure to tobacco smoke. METHODS: We used a case-only study design to evaluate departure from multiplicativity between acetylation status and smoking status. We extracted DNA from buccal cell samples collected from 502 women with incident primary breast cancer and assigned acetylation status by genotyping ten single-nucleotide polymorphisms. Information on tobacco use and breast cancer risk factors was obtained by structured interviews. RESULTS: We observed no substantial departure from multiplicativity between acetylation status and history of ever having been an active smoking (adjusted odds ratio estimate of departure from multiplicativity = 0.9, 95% confidence interval 0.5 to 1.7) or ever having had passive residential exposure to tobacco smoke (adjusted odds ratio = 0.7, 95% confidence interval 0.4 to 1.5). The estimates for departure from multiplicativity between acetylation status and various measures of intensity, duration, and timing of active and passive tobacco exposure lacked consistency and were generally not

supportive of the idea of a gene-environment interaction. CONCLUSION: In this, the largest case-only study to evaluate the interaction between acetylation status and active or passive exposure to tobacco smoke, we found little evidence to support the idea of a departure from multiplicativity.

Leistikow, B. "Lung cancer rates as an index of tobacco smoke exposures: validation against black male approximate non-lung cancer death rates, 1969-2000." Prev Med. 2004 May;38(5):511-5.

BACKGROUND: Researchers use lung cancer death rates (rates) as an index of the cumulative burdens of smoking. That index lacks direct validation and calibration. So this study directly validates and calibrates that index against annual approximately non-lung (all-sites minus lung and stomach) rates from 1969 to 2000 in United States black men, then estimates their cancer death rate smoking-attributable fractions (SAFs). METHODS: This study uses linear regression, age-adjusted rates from http://www.seer.cancer.gov/canques, and the formula SAF = (1- ((rate in the unexposed) / (rate in the exposed))). Estimated rates in the unexposed range between the 1969 rate and the rate predicted for a population with no smoking-attributable lung cancers. Stomach and lung cancer rate SAFs were based on published cohort studies. RESULTS: Lung cancer death rates predicted 98% and 97% of the variances in approximately non-lung cancer death rates throughout their 1969-1990 34% rise and subsequent declines, respectively (each $P < 0.0001$). The findings suggest that the SAF of the all-sites cancer death rate in black men peaked at 66% in 1990. CONCLUSIONS: Lung cancer death rates were a good index of smoke exposure for predicting approximately non-lung cancer death rates in black men. Smoking may cause most premature cancer deaths in black men.

Leistikow, B. N., M. Chen, et al. "Tobacco smoke overload and ethnic, state, gender, and temporal cancer mortality disparities in Asian-Americans and Pacific Islander-Americans." Prev Med. 2006 Jun;42(6):430-4. Epub 2006 Mar 24.

BACKGROUND: Asians and Pacific Islanders (APIs) are important populations nationally and globally. So we assessed cumulative tobacco smoke overexposure (smoke overload)/cancer mortality associations across states, ethnicities, years, and genders among API-Americans. METHODS: Death rates were adjusted to the 2000 United States age standard, lung cancer death rates used as a smoke overload bio-index, and lung/non-lung cancer death rate linear regressions run. Cancer death rate smoking-attributable fractions (SAFs) are equal to 1--estimated unexposed rate/observed rate. RESULTS: The two lowest smoke overload and non-lung cancer death rates were in South Asian (Indo)-Californian females and males. The highest were in Korean-Californian males. Non-lung cancer death rates were tightly and steeply associated with smoke overload across ethnicity, state, year, or gender. Cancer death rate smoking-attributable fractions ranged from 0 in female and 6% in male Indo-Californians, to 39% in female and 57% in male API-Americans in 2002, to 71% in Korean-Californian and 69% in API Hawaiian males. DISCUSSION: Many API American cancer death rate disparities across genders, ethnicities, states, or years can be explained by smoke overload disparities. Tobacco control may greatly reduce cancer death rates and disparities among API-Americans and, likely, others.

Leistikow, B. N., Z. Kabir, et al. "Male tobacco smoke load and non-lung cancer mortality associations in Massachusetts." BMC Cancer. 2008 Nov 24;8:341. doi: 10.1186/1471-2407-8-341.

BACKGROUND: Different methods exist to estimate smoking attributable cancer mortality rates (Peto and Ezzati methods, as examples). However, the smoking attributable estimates using these methods cannot be generalized to all population sub-groups. A simpler method has recently been developed that can be adapted and applied to different population sub-groups. This study assessed cumulative tobacco smoke damage (smoke load)/non-lung cancer mortality associations across time from 1979 to 2003 among all Massachusetts males and ages 30-74 years, using this novel methodology. METHODS: Annual lung cancer death rates were used as smoke load bio-indices, and age-adjusted lung/all other (non-lung) cancer death rates were analyzed with linear regression approach. Non-lung cancer death rates include all cancer deaths excluding lung. Smoking-attributable-fractions (SAFs) for the latest period (year 2003) were estimated as: 1-(estimated unexposed cancer death rate/observed rate). RESULTS: Male lung and non-lung cancer death rates have declined steadily since 1992. Lung and non-lung cancer death rates were tightly and steeply associated across years. The slopes of the associations analyzed were 1.69 (95% confidence interval (CI) 1.35-2.04, $r = 0.90$), and 1.36 (CI 1.14-1.58, $r = 0.94$) without detected autocorrelation (Durbin-Watson statistic = 1.8). The lung/non-lung cancer death rate associations suggest that all-sites cancer death rate SAFs in year 2003 were 73% (Sensitivity Range [SR] 61-82%) for all ages and 74% (SR 61-82%) for ages 30-74 years. CONCLUSION: The strong lung/non-lung cancer death rate associations suggest that tobacco smoke load may be responsible for most prematurely fatal cancers at both lung and non-lung sites. The present

method estimates are greater than the earlier estimates. Therefore, tobacco control may reduce cancer death rates more than previously noted.

Lemjabbar-Alaoui, H., V. Dasari, et al. "Wnt and Hedgehog are critical mediators of cigarette smoke-induced lung cancer." PLoS One. 2006 Dec 20;1:e93.

BACKGROUND: Lung cancer is the leading cause of cancer death in the world, and greater than 90% of lung cancers are cigarette smoke-related. Current treatment options are inadequate, because the molecular basis of cigarette-induced lung cancer is poorly understood. METHODOLOGY/PRINCIPAL FINDINGS: Here, we show that human primary or immortalized bronchial epithelial cells exposed to cigarette smoke for eight days in culture rapidly proliferate, show anchorage-independent growth, and form tumors in nude mice. Using this model of the early stages of smoke-induced tumorigenesis, we examined the molecular changes leading to lung cancer. We observed that the embryonic signaling pathways mediated by Hedgehog and Wnt are activated by smoke. Pharmacological inhibition of these pathways blocked the transformed phenotype. CONCLUSIONS/SIGNIFICANCE: These experiments provide a model in which the early stages of smoke-induced tumorigenesis can be elicited, and should permit us to identify molecular changes driving this process. Results obtained so far indicate that smoke-induced lung tumors are driven by activation of two embryonic regulatory pathways, Hedgehog (Hh) and Wnt. Based on the current and emerging availability of drugs to inhibit Hh and Wnt signaling, it is possible that an understanding of the role of Hh and Wnt in lung cancer pathogenesis will lead to the development of new therapies.

Lilla, C., E. Verla-Tebit, et al. "Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption." Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):99-107.

N-Acetyltransferases 1 and 2 (NAT1 and NAT2), both being highly polymorphic, are involved in the metabolism of aromatic and heterocyclic aromatic amines present in cigarette smoke and red meat cooked by high-temperature cooking techniques. We investigated the effect of differences in acetylation capacity, determined by NAT1 and NAT2 genotypes, on colorectal cancer risk associated with exposure to tobacco smoke or red meat consumption. In this population-based case-control study in Germany, 505 patients with incident colorectal cancer and 604 age- and sex-matched control individuals with genotyping data and detailed risk factor information were included. Genotyping of NAT1 and NAT2 genetic polymorphisms was done using a fluorescence-based melting curve analysis method. The association between genotypes, environmental exposures, and colorectal cancer risk was estimated using multivariate logistic regression. Colorectal cancer risk associated with active smoking was elevated after accumulation of 30(+) pack-years of smoking [odds ratio (OR), 1.4; 95% confidence interval (95% CI), 0.9-2.2] but not significantly modified by either NAT1 or NAT2 genotype. Exposure to environmental tobacco smoke was associated with an increased risk for colorectal cancer only among NAT2 fast acetylators (OR, 2.6; 95% CI, 1.1-5.9 for exposure in childhood and adulthood). Frequent consumption of red meat significantly increased colorectal cancer risk for the group comprising all NAT2 fast acetylators or carriers of the NAT1*10 allele (OR, 2.6; 95% CI, 1.1-6.1) but not among those with "slow" NAT1 and NAT2 genotypes. Our findings indicate that NAT1 and NAT2 genotypes may contribute jointly to individual susceptibility and that heterocyclic aromatic amines may play an important role in colorectal cancer associated with red meat and possibly also exposure to environmental tobacco smoke.

Martey, C. A., S. J. Pollock, et al. "Cigarette smoke induces cyclooxygenase-2 and microsomal prostaglandin E2 synthase in human lung fibroblasts: implications for lung inflammation and cancer." Am J Physiol Lung Cell Mol Physiol. 2004 Nov;287(5):L981-91. Epub 2004 Jul 2.

Cigarette smoking can lead to many human pathologies including cardiovascular and respiratory disease. Recent studies have defined a role for fibroblasts in the development of colon cancer. Moreover, fibroblasts are now thought of as key "sentinel" cells that initiate inflammation by releasing proinflammatory mediators including prostaglandins (PGs). Pathological overexpression of cyclooxygenase-2 (COX-2) and excess eicosanoid production are found in the early stages of carcinogenesis. By promoting chronic inflammation, COX-2 and eicosanoid production may actually cause a predisposition to malignancy. Furthermore, the associated inflammation induced by production of these mediators is central to the pathogenesis of chronic obstructive pulmonary disease. Little is known of the responses of normal lung fibroblasts to cigarette smoke, despite their abundance. We report herein that normal human lung fibroblasts, when exposed to cigarette smoke extract, induce COX-2 with concurrent synthesis of prostaglandin E2 (PGE2). The mechanisms by which cigarette-derived toxicants lead to increased COX-2 levels and PGE2 synthesis include increases in steady-state COX-2 mRNA levels (approximately four- to fivefold), phosphorylation of

ERK1/2, and nuclear translocation of the p50 and p65 subunits of the transcription factor NF-kappaB, which are important elements in COX-2 expression. Furthermore, there was a dramatic 25-fold increase in microsomal prostaglandin E synthase, the key enzyme involved in the production of PGE2. We propose that normal human lung fibroblasts, when exposed to cigarette smoke constituents, elicit COX-2 expression with consequent prostaglandin synthesis, thus creating a proinflammatory environment. This chronic inflammatory state may act as one of the first steps towards epithelial transformation.

McBride, C. M., K. I. Pollak, et al. "Distress and motivation for smoking cessation among lung cancer patients' relatives who smoke." J Cancer Educ. 2003 Fall;18(3):150-6.

BACKGROUND: Heightened distress at the time of a loved one's lung cancer diagnosis may motivate relatives to quit smoking or could undermine cessation. METHODS: Relatives of new lung cancer patients at Duke were surveyed by telephone to assess diagnosis-related depression, distress, and motivation for smoking cessation. RESULTS: Relatives who reported above average avoidant and intrusive thinking patterns, depressive symptoms or worry were more likely to report that the patient's diagnosis increased their intentions to quit than the less distressed. CONCLUSIONS: Interventions are needed that encourage smoking cessation as a strategy for adaptively coping with a loved ones' lung cancer diagnosis.

Miller, D. P., I. De Vivo, et al. "Association between self-reported environmental tobacco smoke exposure and lung cancer: modification by GSTP1 polymorphism." Int J Cancer. 2003 May 10;104(6):758-63.

Environmental Tobacco Smoke (ETS) exposure has been associated with lung cancer risk. ETS is composed of emissions from cigarette smoke and contains a higher concentration of tobacco smoke carcinogens than mainstream smoke. Polymorphisms in genes that metabolize tobacco smoke carcinogens have been studied as effect modifiers of the association between active smoking and lung cancer risk. GSTP1 is a polymorphic gene that encodes for GST pi, a detoxification enzyme and has a high expression in the lung. We investigated the association between ETS and lung cancer risk and the modification of this association by the GSTP1 polymorphism. Using a case-control design, individuals were genotyped for GSTP1 using PCR-RFLP techniques. All analyses were carried out using multiple logistic regression. The association between ETS exposure and lung cancer risk was evaluated in different strata based on smoking habits to evaluate the consistency of results. The effect of the GSTP1 polymorphisms on lung cancer risk was evaluated by considering the joint effect of having both an ETS exposure and the GSTP1 GG genotype compared to the absence of ETS exposure and the GSTP1 AA genotype as a reference group as well as doing stratified analysis by genotype. ETS exposure was associated consistently with higher lung cancer risk in all the strata considered. The adjusted odds ratios (AOR) evaluating the association between ETS and lung cancer risk for the different strata were: nonsmokers (Cases/Controls 66/413; AOR = 1.38; 95% CI = 0.78-2.43), ex-smokers (Cases/Controls 560/527; AOR = 1.66; 95% CI = 1.22-2.25), current smokers (Cases/Controls 415/219; AOR = 1.56; 95% CI = 1.00-2.41). The AORs for ex-smokers and light smoking subgroups were: ex-smokers who quit for 19 years or more (Cases/Controls 144/244; AOR = 2.64; 95% CI = 1.55-4.50), ex-smokers who quit for 10-19 years (Cases/Controls 141/128; AOR = 1.16; 95% CI = 0.66-2.04), ex-smokers who quit for 10 years or less (Cases/Controls 247/122; AOR = 1.45; 95% CI = 0.83-2.55) and participants who had <15 packyears and nonsmokers combined (Cases/Controls 143/640; AOR = 1.52; 95% CI = 1.02-2.28). Among those with the GSTP1 GG genotype the ETS-lung cancer risk association was greater than those with the GSTP1 AA genotype: nonsmokers (GSTP1 GG AOR = 7.84; 95% CI = 0.80-76.68; GSTP1 AA AOR = 1.15; 95% CI = 0.46-2.90), ex-smokers (GSTP1 GG AOR = 2.32; 95% CI = 0.90-5.96; GSTP1 AA AOR = 2.15; 95% CI = 1.34-3.44), current smokers (GSTP1 GG AOR = 1.75; 95% CI = 0.42-7.32; GSTP1 AA AOR = 1.32; 95% CI = 0.67-2.58) and participants who had <15 packyears and nonsmokers (GSTP1 GG AOR = 1.93; 95% CI = 0.54-6.97; GSTP1 AA AOR = 1.58; 95% CI = 0.83-3.01). We found that ETS exposure is associated with higher lung cancer risk. Furthermore, the presence of the GSTP1 GG genotype appears to enhance the magnitude of the association between ETS exposure and lung cancer. Larger studies will be needed to confirm these preliminary findings.

Moktar, A., R. Singh, et al. "Cigarette smoke condensate-induced oxidative DNA damage and its removal in human cervical cancer cells." Int J Oncol. 2011 Oct;39(4):941-7. doi: 10.3892/ijo.2011.1106. Epub 2011 Jun 29.

Exposure to cigarette smoke is well documented to increase oxidative stress and could account for higher risk of cervical cancer in smokers. Cervical pre-cancerous lesions that are initiated by human papillomavirus (HPV) infection generally regress in the absence of known risk factors such as smoking. 8-oxodeoxyguanosine (8-oxodG) is a highly

mutagenic oxidative DNA lesion that is formed by the oxidation of deoxyguanosine. In the present study, we examined: a) the effect of cigarette smoke condensate (CSC) on 8-oxodG formation in and its removal from HPV-transfected (ECT1/E6 E7), HPV-positive (CaSki) and HPV-negative (C33A) human cervical cancer cells, and b) the cell cycle progression and apoptosis in CSC-treated ECT1/E6 E7 cells. CSC induced 8-oxodG in a dose- (p=0.03) and time (p=0.002)-dependent fashion in ECT1/E6 E7 cells as determined by flow cytometry. A 2.4-fold higher level of 8-oxodG was observed in HPV-positive compared with HPV-negative cells. However, 8-oxodG lesions were almost completely removed 72 h post-exposure in all cell lines as determined by ImageStream analysis. This observation correlates with the 2- and 5-fold increase in the p53 levels in ECT1/E6 E7 and CaSki cells with no significant change in C33A cells. We conclude that: a) cigarette smoke constituents induce oxidative stress with higher burden in HPV-positive cervical cancer cells and b) the significant increase observed in p53 levels in wild-type cervical cells (ECT1/E6 E7 and CaSki) may be attributed to the p53-dependent DNA repair pathway while a p53-independent pathway in C33A cells cannot be ruled out.

Momi, N., M. P. Ponnusamy, et al. "Nicotine/cigarette smoke promotes metastasis of pancreatic cancer through alpha7nAChR-mediated MUC4 upregulation." Oncogene. 2013 Mar 14;32(11):1384-95. doi: 10.1038/onc.2012.163. Epub 2012 May 21.

Despite evidence that long-term smoking is the leading risk factor for pancreatic malignancies, the underlying mechanism(s) for cigarette-smoke (CS)-induced pancreatic cancer (PC) pathogenesis has not been well established. Our previous studies revealed an aberrant expression of the MUC4 mucin in PC as compared with the normal pancreas, and its association with cancer progression and metastasis. Interestingly, here we explore a potential link between MUC4 expression and smoking-mediated PC pathogenesis and report that both cigarette smoke extract and nicotine, which is the major component of CS, significantly upregulates MUC4 in PC cells. This nicotine-mediated MUC4 overexpression was via the alpha7 subunit of nicotinic acetylcholine receptor (nAChR) stimulation and subsequent activation of the JAK2/STAT3 downstream signaling cascade in cooperation with the MEK/ERK1/2 pathway; this effect was blocked by the alpha7nAChR antagonists, alpha-bungarotoxin and mecamylamine, and by specific siRNA-mediated STAT3 inhibition. In addition, we demonstrated that nicotine-mediated MUC4 upregulation promotes the PC cell migration through the activation of the downstream effectors, such as HER2, c-Src and FAK; this effect was attenuated by shRNA-mediated MUC4 abrogation, further implying that these nicotine-mediated pathological effects on PC cells are MUC4 dependent. Furthermore, the in vivo studies showed a marked increase in the mean pancreatic tumor weight (low dose (100 mg/m(3) total suspended particulate (TSP)), P=0.014; high dose (247 mg/m(3) TSP), P=0.02) and significant tumor metastasis to various distant organs in the CS-exposed mice, orthotopically implanted with luciferase-transfected PC cells, as compared with the sham controls. Moreover, the CS-exposed mice had elevated levels of serum cotinine (low dose, 155.88+/-35.96 ng/ml; high dose, 216.25+/-29.95 ng/ml) and increased MUC4, alpha7nAChR and pSTAT3 expression in the pancreatic tumor tissues. Altogether, our findings revealed for the first time that CS upregulates the MUC4 mucin in PC via the alpha7nAChR/JAK2/STAT3 downstream signaling cascade, thereby promoting metastasis of PC.

Murin, S., K. E. Pinkerton, et al. "The effect of cigarette smoke exposure on pulmonary metastatic disease in a murine model of metastatic breast cancer." Chest. 2004 Apr;125(4):1467-71.

INTRODUCTION: Women who smoke have a higher rate of fatal breast cancer than nonsmoking women. An association between smoking and pulmonary metastases from breast cancer has been suggested by epidemiologic studies. STUDY OBJECTIVES: To examine the relationship between exposure to cigarette smoke and pulmonary metastasis in a murine model of metastatic mammary cancer. STUDY DESIGN: Prospective, randomized study. SETTING: Animal research laboratory. EXPERIMENTAL SUBJECTS: Female sexually mature BALB/cAnN mice. INTERVENTIONS: Mice were randomly divided into experimental and control groups. Experimental animals were exposed to cigarette smoke in specialized exposure chambers, at concentrations chosen to approximate active cigarette smoking. Control animals were exposed to filtered air. One week after the initiation of exposures, mouse mammary tumor cells (tumor cell line 4526) were injected into the tail veins of experimental animals at one of three concentrations (50,000, 100,000, or 150,000 cells per 100 micro L). Three weeks later, the mice were killed, and pulmonary metastases were counted and measured. RESULTS: The mean metastatic burden in the lungs was consistently greater for smoke-exposed animals at each concentration of cells injected (at 50,000 cells per 100 micro L, 9.8 vs 4.8 micro m(3), respectively [p < 0.01]; at 100,000 cells per 100 micro L, 34.5 vs 17.4 micro m(3), respectively [p < 0.10]; and at 150,000 cells per 100 micro L, 54.0 vs 31.5 micro m(3), respectively [p <

0.05]). This was largely attributable to a significant increase in the number of metastatic nodules per animal (at 50,000 cells per 100 micro L, 8.7 vs 4.8, respectively [p < 0.001]; at 100,000 cells per 100 micro L, 24.3 vs 14.0, respectively [p > 0.10]; and at 150,000 cells per 100 micro L, 42.0 vs 20.1, respectively [p < 0.02]) rather than to a change in nodule size. CONCLUSIONS: Cigarette smoke exposure is associated with an increase in the total pulmonary metastatic burden in this murine model of metastatic mammary cell cancer. This study provides experimental support for an adverse effect of smoking on the metastatic process and suggests a possible mechanism for smokers' increased breast cancer mortality.

Nagler, R., O. Ben-Izhak, et al. "Oral cancer, cigarette smoke and mitochondrial 18kDa translocator protein (TSPO) - In vitro, in vivo, salivary analysis." Biochim Biophys Acta. 2010 May;1802(5):454-61. doi: 10.1016/j.bbadis.2010.01.008. Epub 2010 Jan 18.

Oral cancer features high rates of mortality and morbidity, and is in dire need for new approaches. In the present study we analyzed 18 kDa translocator protein (TSPO) expression in oral (tongue) cancer tumors by immunohistochemistry. We also assayed TSPO binding in human tongue cancer cell lines and in the cellular fraction of saliva from tongue cancer patients, heavy cigarette smokers, and non-smoking healthy people as controls. Concurrently, TSPO protein levels, cell viability, mitochondrial membrane potential (Deltapsi(m)), and general protein levels were analyzed. TSPO expression could be significantly enhanced in oral cancer tumors, compared to unaffected adjacent tissue. We also found that five-year survival probability dropped from 65% in patients with TSPO negative tumors to 7% in patients with highly expressed TSPO (p<0.001). TSPO binding capacity was also pronounced in the human oral cancer cell lines SCC-25 and SCC-15 (3133+/-643 fmol/mg protein and 6956+/-549 fmol/mg protein, respectively). Binding decreased by 56% and 72%, in the SCC-25 and SCC-15 cell lines, respectively (p<0.05) following CS exposure in cell culture. In the cellular fraction of saliva of heavy smokers TSPO binding was lower than in non-smokers (by 53%, p<0.05). Also the cellular fraction of saliva exposed to CS in vitro showed decreased TSPO binding compared to unexposed saliva (by 30%, p<0.001). Interestingly, oral cancer patients also displayed significantly lower TSPO binding in the cellular fraction of saliva compared to healthy controls (by 40%, p<0.01). Our results suggest that low TSPO binding found in the cellular fraction of saliva may depend on genetic background as well as result from exposure to CS. We suggest that this may be related to a predisposition for occurrence of oral cancer.

Nagler, R., S. Cohen, et al. "Penicillamine as a potent protector against injurious effects of cigarette smoke in aerodigestive tract cancer." Oncology. 2010;78(1):12-9. doi: 10.1159/000287967. Epub 2010 Feb 24.

BACKGROUND: Cigarette smoke (CS) is the major risk factor for aerodigestive tract cancers such as lung and oral cancers. METHODS: In in vitro models of lung and oral cancers, we found D-penicillamine (PenA) to be a most potent protector against CS, both in the absence and presence of saliva (a highly pro-oxidative condition). RESULTS: The survival rate of lung cancer cells and oral cancer cells was reduced by CS in the absence of saliva by 39-45% (p < 0.01) and by 55-60% (p < 0.01) in the presence of saliva. The addition of 5 mM PenA to cell medium prior to CS exposure limited cell loss to 22-25% only (p < 0.01). Similarly, the iron chelator desferal protected the cells only in the presence of saliva. PenA also protected against a CS-induced increase in carbonyls (oxidized proteins) and decrease in p53 levels (in the presence of saliva) and mitochondrial membrane potential (a hallmark of CS-induced apoptotic cell death). Malfunctioning p53 often characterizes carcinogenesis of CS-induced cancers. CONCLUSIONS: Redox-active iron and copper in pleural fluid and saliva, upon encounter with CS, may be responsible for this carcinogenesis, mediated via alteration of p53 function. Chelation of redox-active metals may be an efficient tool for prevention of CS-induced lung and oral cancers. The superiority of PenA results from its copper-chelating action as well as its antialdehyde and anti-inflammatory capabilities.

Nagler, R. H., E. Puleo, et al. "Internet use among childhood and young adult cancer survivors who smoke: implications for cessation interventions." Cancer Causes Control. 2012 Apr;23(4):647-52. doi: 10.1007/s10552-012-9926-9. Epub 2012 Feb 28.

OBJECTIVE: To identify patterns of Internet use among childhood and young adult cancer survivors who smoke. METHODS: Baseline assessment data were collected from 2005 to 2008 for the Partnership for Health-2 (PFH-2) study, a web-based smoking cessation intervention for childhood and young adult cancer survivors. Participants were surveyed about their Internet access and use. Sociodemographic, clinical, and psychosocial data also were collected. RESULTS: Internet access and use was widespread among PFH-2 participants. However, older, less-educated, and female survivors reported less frequent Internet use, even when they had access to the Internet at home and/or at work.

These associations were significant in multivariable analyses. CONCLUSIONS: Although the digital divide is narrowing, Internet use and engagement remains socially patterned. web-based prevention interventions are a promising method of reaching this geographically dispersed, high-risk population, but certain subgroups-particularly older and lower socioeconomic status survivors-might be missed by this approach.

Nagler, R. H., E. Puleo, et al. "Health media use among childhood and young adult cancer survivors who smoke." Support Care Cancer. 2014 Sep;22(9):2497-507. doi: 10.1007/s00520-014-2236-x. Epub 2014 Apr 13.

PURPOSE: Promoting healthy behaviors may reduce the risk of co-morbidities among childhood and young adult (CYA) cancer survivors. Although behavioral interventions are one way to encourage such activities, there is increasing evidence that health media use-particularly health information seeking-also may influence health knowledge, beliefs, and behaviors. The current study explores patterns of health media use among survivors of CYA cancer. Our focus is on survivors who smoke and thus are at even greater risk of co-morbidities. METHODS: We analyzed data from the Partnership for Health-2 study, a web-based smoking cessation intervention, to examine the prevalence of and factors associated with health media use (N = 329). RESULTS: Nearly two thirds (65.3 %) of CYA survivors who smoke reported infrequent or no online health information seeking. Many reported never reading health sections of newspapers or general magazines (46.2 %) or watching health segments on local television news (32.3 %). Factors associated with health media use include education and employment, cancer-related distress, and smoking quit attempts. CONCLUSIONS: Health information engagement is low among CYA survivors who smoke, particularly active seeking of health information online. Population subgroups differ in their media use patterns; some of these differences reflect communication inequalities, which have the potential to exacerbate health disparities. Clinicians have an opportunity to guide CYA survivors towards useful and reliable information sources. This guidance could help survivors fulfill their unmet information and support needs and may be particularly important for less educated survivors and other underserved populations.

Nicholson, J. S., V. L. Tyc, et al. "Parental psychosocial predictors of secondhand smoke exposure (SHSe) for children with cancer." J Child Health Care. 2012 Sep;16(3):211-23. doi: 10.1177/1367493511426422. Epub 2012 Feb 3.

Children with cancer are at greater risk for the negative consequences of secondhand smoke exposure, making the identification of predictors of exposure critical. The current study investigated the impact of parents' psychosocial variables (perceived stress and vulnerability, self-efficacy), as well as health-related and demographic variables, on children's current exposure levels. Data were from 135 families whose children (M = 8.6 years old) lived with a smoker and were being treated for cancer. Self-efficacy was the consistent significant psychosocial predictor of exposure and the time since a child's diagnosis was indicative of lower exposure when limiting the sample to only smoking parents (n = 95). Both predictors of exposure have implications on motivation for behavioral change and may be suggestive of a teachable moment. Interventions may profit from tailoring programs to families based on these predictors of exposure, in particular for tobacco-based interventions for parents of medically compromised children, such as children with cancer.

Novy, D. M., C. Lam, et al. "Distinguishing features of cancer patients who smoke: pain, symptom burden, and risk for opioid misuse." J Pain. 2012 Nov;13(11):1058-67. doi: 10.1016/j.jpain.2012.07.012. Epub 2012 Sep 24.

Although many cancer patients who have pain are smokers, the extent of their symptom burden and risk for opioid misuse are not well understood. In this study we analyzed records of patients being treated for cancer pain, 94 of whom were smokers and 392 of whom were nonsmokers, to determine smoking status group differences. Smokers had significantly higher pain intensity, fatigue, depression, and anxiety than nonsmokers (independent samples t-tests P < .002). Smokers were at higher risk for opioid misuse based on the short form of the Screener and Opioid Assessment for Patients with Pain (SOAPP). Specifically, smokers had more frequent problems with mood swings, taking medications other than how they are prescribed, a history of illegal drug use, and a history of legal problems (chi-square tests P </= .002). Changes in pain and opioid use were examined in a subset of patients (146 nonsmokers and 46 smokers) who were receiving opioid therapy on at least 2 of the 3 data time points (consult, follow-up 1 month after consult, follow-up 6 to 9 months after consult). Results based on multilevel linear modeling showed that over a period of approximately 6 months, smokers continued to report significantly higher pain than nonsmokers. Both smokers and nonsmokers reported a significant decline in pain across the 6-month period; the rate of decline did not differ across smokers and nonsmokers. No significant difference over time was found in opioid use between smokers and nonsmokers.

These findings will guide subsequent studies and inform clinical practice, particularly the relevancy of smoking cessation. PERSPECTIVE: This article describes pain, symptom burden, and risk for opioid misuse among cancer patients with pain across smoking status. Smoking appears to be a potential mechanism for having an increased pain and symptom burden and risk for opioid misuse. This improved understanding of cancer pain will inform clinical practice.

Ortega-Garcia, J. A., M. Martin, et al. "Transgenerational tobacco smoke exposure and childhood cancer: an observational study." J Paediatr Child Health. 2010 Jun;46(6):291-5. doi: 10.1111/j.1440-1754.2010.01710.x. Epub 2010 Apr 16.

AIM: Although tobacco smoke is an established risk factor for adult cancer, studies of the association between parental smoking and childhood cancer have produced inconsistent results. To investigate the transgenerational relationship between pre-natal and post-natal tobacco smoke exposure from the grandmother's pregnancies until after the post-natal period and childhood cancer. METHODS: Exposure to tobacco smoke was recorded for three generations. Data were collected through personal interviews using the paediatric environmental history, and were compared among 128 children with cancer and 128 matched controls. The contingency tables and a logistic multivariable regression model were used to control for possible confounding factors. RESULTS: Smoke exposure during oogenesis (maternal grandmother smokers)--odds ratio (OR) 2.2 (95% confidence interval (CI) 1.1-4.9)--and during the mother' pregnancies--OR 1.8 (95% CI 1.1-3.3)--were significantly associated with an increased risk of childhood cancer. CONCLUSIONS: Tobacco smoke exposure during the grandmother's and mother's pregnancies increase the risk of cancer in the descendants. The results suggest that the biological plausibility of the association between parental smoking and paediatric cancer can be explained by the large latency period of paediatric carcinogenesis.

Pan, H., J. Califano, et al. "Loss of heterozygosity patterns provide fingerprints for genetic heterogeneity in multistep cancer progression of tobacco smoke-induced non-small cell lung cancer." Cancer Res. 2005 Mar 1;65(5):1664-9.

Dilution end point loss of heterozygosity (LOH) analysis, a novel approach for the analysis of LOH, was used to evaluate allelic losses with the use of 21 highly polymorphic microsatellite markers at nine chromosomal sites most frequently affected in smoking-related non-small cell lung cancers. Allelotyping was done for bronchial epithelial cells and matching blood samples from 23 former and current smokers and six nonsmokers as well as in 33 adenocarcinomas and 25 squamous cell carcinomas (SCC) and corresponding matching blood from smokers. Major conclusions from these studies are as follows: (a) LOH at chromosomal sites 8p, 9p, 11q, and 13q ($P > 0.05$, Fisher's exact test) are targeted at the early stages, whereas LOH at 1p, 5q, 17p, and 18q ($P < 0.05$, Fisher's exact test) occur at the later stages of non-small cell lung cancer progression; (b) LOH at 1p, 3p, 5q, 8p, 9p, 11q, 13q, 17p, and 18q occurs in over 45% of the tobacco smokers with SCC and adenocarcinoma; (c) compared with bronchial epithelial cells from smokers, there is a significantly higher degree of LOH at 1p, 5q, and 18q in adenocarcinoma and at 1p, 3p, and 17p in SCC ($P < 0.05$, Fisher's exact test). We propose that lung cancer progression induced by tobacco smoke occurs in a series of target gene inactivations/activations in defined modules of a global network. The gatekeeper module consists of multiple alternate target genes, which is inclusive of but not limited to genes localized to chromosomal loci 8p, 9p, 11q, and 13q.

Park, H. Y., B. Leistikow, et al. "Smoke load/cancer death rate associations in Korea females, 1985-2004." Prev Med. 2007 Oct;45(4):309-12. Epub 2007 Jul 10.

BACKGROUND: Korea female death rates from many cancers have risen rapidly since 1985. The sources of those cancer death epidemics are unclear but may be related to rising cumulative tobacco smoke damage (smoke load). We assessed Korea female smoke load/cancer death rate associations from 1985 to 2004. METHODS: Lung cancer rates were used as a smoke load bio-index. Subtracting lung, stomach, and uterine corpus cancer death World age standard rates (rates) from all-sites rates gave us non-lung-stomach-uterine corpus (NLSUc) rates. Lung/NLSUc linear regressions were run, adjusted for autocorrelation. Estimated, lower, and upper bound smoking-attributable fractions (SAFs) were calculated using the formula SAF=1-{(unexposeds' cancer death rate)/(observed rate)}, based on the linear regression and respective best, upper, and lower bound estimated lung, stomach, and uterine cancer death rates in the unexposed. RESULTS: Lung cancer death rates (smoke load) can explain 88% of the variance in NLSUc rates from 1985 to 2004 after adjusting for autocorrelation. The estimated Korea female all-sites cancer death rate SAF in 2004 was 43% (sensitivity range 29-56%). CONCLUSIONS: Smoke load, probably from tobacco given the epidemic time course, may cause a large cancer death burden in Korea females despite their very low self-reported prevalence of smoking.

Parsons, S. K. and D. K. Mayer "Cancer-related health policy: beyond the smoke and mirrors." Semin Oncol Nurs. 2002 Nov;18(4):241-51.

OBJECTIVE: To review the process of cancer-related health policy in the US. DATA SOURCES: Professional journals, texts, government and organization newsletters, and Internet websites. CONCLUSIONS: Health care and cancer-related health policy has been fraught with contention and ambiguity. Special interest groups of all sizes and causes interface with the legislative process to influence outcome at every level of policy development, implementation, and evaluation. Cancer-related health policy is formulated and actualized being influenced by competing interests, needs, and resources, which is an inherently political process. IMPLICATIONS FOR NURSING PRACTICE: A more complete understanding of this process will aid oncology nurses to participate more fully and more effectively in helping reduce the burden of cancer.

Pate Capps, N., A. Stewart, et al. "The interplay between secondhand cigarette smoke, genetics, and cervical cancer: a review of the literature." Biol Res Nurs. 2009 Apr;10(4):392-9. doi: 10.1177/1099800408330849. Epub 2009 Feb 26.

Research has suggested a link between smoking and cervical cancer; however, little data are available on secondhand smoke (SHS) exposure and cervical cancer risk. This article reviews the literature on the links among smoking, SHS exposure and cervical cancer. The review was based on a search of electronic databases. The research reviewed clearly showed that smoking increases cervical cancer risk through myriad mechanisms that interact with genetics and the pathologic processes leading to cervical cancer. However, less is understood about the role of SHS in cervical cancer. With new technology enabling scientists to examine how genomic structure responds to environmental stimuli, more information should be forthcoming on links between SHS exposure, biomarkers, and genetic changes involved in the development of cervical cancer.

Peck, K. R., V. L. Tyc, et al. "Reduction of Secondhand Smoke Exposure in the Cars of Children With Cancer." J Pediatr Oncol Nurs. 2015 Feb 3. pii: 1043454214563755.

This study examined whether an intervention designed to reduce secondhand smoke exposure (SHSe) among children being treated for cancer had effects in the specific setting of a motor vehicle. The parents or guardians (n = 71) of children being treated for cancer were randomized to either a behavioral secondhand smoke (SHS) reduction program or a standard care control group. Parental reports of SHSe were collected over the course of 12 months. Younger children were exposed at baseline more than their older counterparts. The greatest initial declines in car exposure were observed among children </=5 years old in the intervention group compared with same-aged peers in the control group. After the 3-month time point, the control group showed greater reductions in car exposure in comparison with the intervention group. Interventions that teach parents strategies to manage their smoking while driving in their personal vehicles may produce even greater reductions in child exposure and should be developed. Based on the age-specific results reported here, future studies should account for effects of child age and use setting-specific measures of SHS.

Peppone, L. J., M. C. Mahoney, et al. "Colorectal cancer occurs earlier in those exposed to tobacco smoke: implications for screening." J Cancer Res Clin Oncol. 2008 Jul;134(7):743-51. doi: 10.1007/s00432-007-0332-8. Epub 2008 Feb 9.

BACKGROUND: Colorectal cancer (CRC) is the third most common cancer in the USA. While various lifestyle factors have been shown to alter the risk for colorectal cancer, recommendations for the early detection of CRC are based only on age and family history. METHODS: This case-only study examined the age at diagnosis of colorectal cancer in subjects exposed to tobacco smoke. Subjects included all patients who attended RPCI between 1957 and 1997, diagnosed with colorectal cancer, and completed an epidemiologic questionnaire. Adjusted linear regression models were calculated for the various smoking exposures. RESULTS: Of the 3,540 cases of colorectal cancer, current smokers demonstrated the youngest age of CRC onset (never: 64.2 vs. current: 57.4, $P < 0.001$) compared to never smokers, followed by recent former smokers. Among never smokers, individuals with past second-hand smoke exposure were diagnosed at a significantly younger age compared to the unexposed. CONCLUSION: This study found that individuals with heavy, long-term tobacco smoke exposure were significantly younger at the time of CRC diagnosis compared to lifelong never smokers. The implication of this finding is that screening for colorectal cancer, which is recommended to begin at age 50 years for persons at average risk should be initiated 5-10 years earlier for persons with a significant lifetime history of exposure to tobacco smoke.

Peppone, L. J., K. M. Piazza, et al. "Associations between adult and childhood secondhand smoke exposures and fecundity and fetal loss among women

who visited a cancer hospital." Tob Control. 2009 Apr;18(2):115-20. doi: 10.1136/tc.2008.027961. Epub 2008 Nov 27.

BACKGROUND: A large percentage of the population continues to be exposed to secondhand smoke (SHS). Although studies have consistently linked active smoking to various pregnancy outcomes, results from the few studies examining SHS exposure and pregnancy difficulties have been inconsistent. METHODS: Approximately 4800 women who presented to Roswell Park Cancer Institute between 1982 and 1998 and reported being pregnant at least once were queried about their childhood and adult exposures to SHS using a standardised questionnaire. Women were asked to report on selected prenatal pregnancy outcomes (fetal loss and difficulty becoming pregnant). RESULTS: Approximately 11.3% of women reported difficulty becoming pregnant, while 32% reported a fetal loss or 12.4% reported multiple fetal losses. 40% reported any prenatal pregnancy difficulty (fetal loss and/or difficulty becoming pregnant). SHS exposures from their parents were associated with difficulty becoming pregnant (OR = 1.27, 95% CI 1.03 to 1.56) and lasting >1 year (OR = 1.34, 95% CI 1.12 to 1.60). Exposure to SHS in both at home during childhood and at the time of survey completion was also associated with fetal loss (OR = 1.39, 95% CI 1.17 to 1.66) and multiple fetal losses (OR = 1.62, 95% CI 1.25 to 2.11). Increasing current daily hours of SHS exposure as an adult was related to the occurrence of both multiple fetal loss and reduced fecundity (p(trend) < 0.05). CONCLUSIONS: Reports of exposures to SHS during childhood and as an adult were associated with increased odds for prenatal pregnancy difficulties. These findings underscore the public health perspective that all people, especially women in their reproductive years, should be fully protected from tobacco smoke.

Peppone, L. J., M. E. Reid, et al. "The effect of secondhand smoke exposure on the association between active cigarette smoking and colorectal cancer." Cancer Causes Control. 2010 Aug;21(8):1247-55. doi: 10.1007/s10552-010-9552-3. Epub 2010 Apr 8.

BACKGROUND: Studies published prior to 1980 failed to find an association between smoking and colorectal cancer, while subsequent studies reported an association after accounting for a three to four decade initiation period. The aims of this study were to determine the effect of accounting for secondhand smoke (SHS) exposure on the association between smoking and colorectal cancer and to determine the association between SHS and colorectal cancer. METHODS: Approximately 1,200 colorectal cancer cases treated at Roswell Park Cancer Institute between 1982 and 1998 were matched to 2,400 malignancy-free controls. The effect of accounting for SHS exposure was determined by comparing the odds ratios (OR) for each smoking variable in the overall sample and then for those who reported no current SHS exposure. RESULTS: A small, significant increase in colorectal cancer odds was noted for heavy, long-term smoking males when not accounting for SHS exposure (>45 PY: OR = 1.34; 95% CI 1.04-1.72). OR increased when the analyses were restricted to individuals reporting no current SHS exposure (>45 PY: OR = 2.40; 95% CI 1.36-4.23). CONCLUSIONS: Accounting for SHS exposure resulted in a substantial increase in the odds of colorectal cancer for all smoking variables in this study. Future studies should account for SHS exposure when examining the association between smoking and colorectal cancer.

Pimhanam, C., S. Sangrajrang, et al. "Tobacco smoke exposure and breast cancer risk in Thai urban females." Asian Pac J Cancer Prev. 2014;15(17):7407-11.

The incidence of urban female breast cancer has been continuously increasing over the past decade with unknown etiology. One hypothesis for this increase is carcinogen exposure from tobacco. Therefore, the objective of this study was to investigate the risk of urban female breast cancer from tobacco smoke exposure. The matched case control study was conducted among Thai females, aged 17-76 years and living in Bangkok or its surrounding areas. A total of 444 pairs of cases and controls were recruited from the Thai National Cancer Institute. Cases were newly diagnosed and histologically confirmed as breast cancer while controls were selected from healthy women who visited a patient, matched by age +/- 5 years. After obtaining informed consent, tobacco smoke exposure data and information on other potential risk factors were collected by interview. The analysis was performed by conditional logistic regression, and presented with odds ratio (ORs) and 95% confidence intervals(CI). From all subjects, 3.8% of cases and 3.4% of controls were active smokers while 11.0% of cases and 6.1% of controls were passive smokers. The highest to lowest sources of passive tobacco smoke were from spouses (40.8%), the workplace (36.8%) and public areas (26.3%), respectively. After adjusting for other potential risk factors or confounders, females with frequent low-dose passive smoke exposure (</= 7 hours per week) from a spouse or workplace had adjusted odds ratio 3.77 (95%CI=1.11-12.82) and 4.02 (95%CI=1.04-15.50) higher risk of breast cancer compared with non-smokers, respectively. However, this study did not find any association of breast cancer

risk in high dose passive tobacco smoke exposure, or a dose response relationship in cumulative passive tobacco smoke exposure per week, or in the active smoker group. In conclusion, passive smoke exposure may be one important risk factor of urban female breast cancer, particularly, from a spouse or workplace. This risk factor highlights the importance of avoiding tobacco smoke exposure as a key measure for breast cancer prevention and control.

Pope, C. A., 3rd, R. T. Burnett, et al. "Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships." Environ Health Perspect. 2011 Nov;119(11):1616-21. doi: 10.1289/ehp.1103639. Epub 2011 Jul 19.

BACKGROUND: Lung cancer and cardiovascular disease (CVD) mortality risks increase with smoking, secondhand smoke (SHS), and exposure to fine particulate matter < 2.5 mum in diameter (PM(2).(5)) from ambient air pollution. Recent research indicates that the exposure-response relationship for CVD is nonlinear, with a steep increase in risk at low exposures and flattening out at higher exposures. Comparable estimates of the exposure-response relationship for lung cancer are required for disease burden estimates and related public health policy assessments. OBJECTIVES: We compared exposure-response relationships of PM(2).(5) with lung cancer and cardiovascular mortality and considered the implications of the observed differences for efforts to estimate the disease burden of PM2.5. METHODS: Prospective cohort data for 1.2 million adults were collected by the American Cancer Society as part of the Cancer Prevention Study II. We estimated relative risks (RRs) for increments of cigarette smoking, adjusting for various individual risk factors. RRs were plotted against estimated daily dose of PM(2).(5) from smoking along with comparison estimates for ambient air pollution and SHS. RESULTS: For lung cancer mortality, excess risk rose nearly linearly, reaching maximum RRs > 40 among long-term heavy smokers. Excess risks for CVD mortality increased steeply at low exposure levels and leveled off at higher exposures, reaching RRs of approximately 2-3 for cigarette smoking. CONCLUSIONS: The exposure-response relationship associated with PM(2).(5) is qualitatively different for lung cancer versus cardiovascular mortality. At low exposure levels, cardiovascular deaths are projected to account for most of the burden of disease, whereas at high levels of PM(2).(5), lung cancer becomes proportionately more important.

Pulliero, A., Y. Wu, et al. "Nanoparticles increase the efficacy of cancer chemopreventive agents in cells exposed to cigarette smoke condensate." Carcinogenesis. 2015 Mar;36(3):368-77. doi: 10.1093/carcin/bgv008. Epub 2015 Feb 3.

Lung cancer is a leading cause of death in developed countries. Although smoking cessation is a primary strategy for preventing lung cancer, former smokers remain at high risk of cancer. Accordingly, there is a need to increase the efficacy of lung cancer prevention. Poor bioavailability is the main factor limiting the efficacy of chemopreventive agents. The aim of this study was to increase the efficacy of cancer chemopreventive agents by using lipid nanoparticles (NPs) as a carrier. This study evaluated the ability of lipid NPs to modify the pharmacodynamics of chemopreventive agents including N-acetyl-L-cysteine, phenethyl isothiocyanate and resveratrol (RES). The chemopreventive efficacy of these drugs was determined by evaluating their abilities to counteract cytotoxic damage (DNA fragmentation) induced by cigarette smoke condensate (CSC) and to activate protective apoptosis (annexin-V cytofluorimetric staining) in bronchial epithelial cells both in vitro and in ex vivo experiment in mice. NPs decreased the toxicity of RES and increased its ability to counteract CSC cytotoxicity. NPs significantly increased the ability of phenethyl isothiocyanate to attenuate CSC-induced DNA fragmentation at the highest tested dose. In contrast, this potentiating effect was observed at all tested doses of RES, NPs dramatically increasing RES-induced apoptosis in CSC-treated cells. These results provide evidence that NPs are highly effective at increasing the efficacy of lipophilic drugs (RES) but are not effective towards hydrophilic agents (N-acetyl-L-cysteine), which already possess remarkable bioavailability. Intermediate effects were observed for phenethyl isothiocyanate. These findings are relevant to the identification of cancer chemopreventive agents that would benefit from lipid NP delivery.

Ramirez, N., M. Z. Ozel, et al. "Exposure to nitrosamines in thirdhand tobacco smoke increases cancer risk in non-smokers." Environ Int. 2014 Oct;71:139-47. doi: 10.1016/j.envint.2014.06.012. Epub 2014 Jul 16.

In addition to passive inhalation, non-smokers, and especially children, are exposed to residual tobacco smoke gases and particles that are deposited to surfaces and dust, known as thirdhand smoke (THS). However, until now the potential cancer risks of this pathway of exposure have been highly uncertain and not considered in public health policy. In this study, we estimate for the first time the potential cancer risk by age group through non-dietary

ingestion and dermal exposure to carcinogen N-nitrosamines and tobacco-specific nitrosamines (TSNAs) measured in house dust samples. Using a highly sensitive and selective analytical approach we have determined the presence of nicotine, eight N-nitrosamines and five tobacco-specific nitrosamines in forty-six settled dust samples from homes occupied by both smokers and non-smokers. Using observations of house dust composition, we have estimated the cancer risk by applying the most recent official toxicological information. Calculated cancer risks through exposure to the observed levels of TSNAs at an early life stage (1 to 6years old) exceeded the upper-bound risk recommended by the USEPA in 77% of smokers' and 64% of non-smokers' homes. The maximum risk from exposure to all nitrosamines measured in a smoker occupied home was one excess cancer case per one thousand population exposed. The results presented here highlight the potentially severe long-term consequences of THS exposure, particularly to children, and give strong evidence of its potential health risk and, therefore, they should be considered when developing future environmental and health policies.

Ramroth, H., A. Dietz, et al. "Environmental tobacco smoke and laryngeal cancer: results from a population-based case-control study." Eur Arch Otorhinolaryngol. 2008 Nov;265(11):1367-71. doi: 10.1007/s00405-008-0651-7. Epub 2008 Apr 1.

Information is lacking on environmental tobacco smoke (ETS) and the risk of laryngeal cancer. We performed a population-based case-control study conducted in Germany, with 257 cases and 769 controls. ETS exposure was assessed from spouse/partner, working history and childhood. The odds ratio (OR) for ETS exposure (binary) in all individuals was 1.2 (95% CI 0.77-1.8), controlled for active smoking, alcohol consumption and education. For the continuous variable of lifetime exposure hours to spouse/partner, we found an OR of 1.2 (95% CI 1.0-1.4) for lifelong exposure of 20,000 h. Since laryngeal cancer is relatively rare and since most cases are (ex-)smokers, studies with sufficient power to investigate the effect of ETS in nonsmokers are difficult to perform. Our findings are in line with the hypothesis that ETS increases the risk of laryngeal cancer. Meta-analyses based on subgroups of nonsmokers from earlier studies are warranted to confirm our findings.

Ratovitski, E. A. "LKB1/PEA3/DeltaNp63 pathway regulates PTGS-2 (COX-2) transcription in lung cancer cells upon cigarette smoke exposure." Oxid Med Cell Longev. 2010 Sep-Oct;3(5):317-24. Epub 2010 Sep 1.

This is the first study to show that cigarette smoking induced the LKB1/PEA3/DeltaNp63-dependent transcriptional regulation of inflammatory molecules, such as COX-2/PTGS-2. Using mainstream smoke extract (MSE) and sidestream smoke extract (SSE) as modeling tools for primary and second-hand smoking, we found that both MSE and SSE down regulated protein levels for LKB1, while up regulated protein levels for PEA3 and COX-2 in a dose-dependent manner. Using the endogenous ChIP analysis, we further found that the C/EBPbeta, NF-kB, NF-Y (CHOP), PEA3 (ETS), and DeltaNp63 proteins bound to the specific area (-550 to -130) of the COX-2 promoter, while forming multiple protein complexes in lung cancer cells exposed to MSE and SSE. Our results define a novel link between various transcription factors occupying the COX-2 promoter and cellular response to cigarette smoke exposure bringing a new component, DeltaNp63alpha, showing a critical role for cooperation between various chromatin components in regulation of COX-2 expression and, therefore strengthening the central role of inflammatory process in tumorigenesis of epithelial cells, especially after cigarette smoke exposure (both primary and second-hand.

Richardson, C. G., L. L. Struik, et al. "Initial impact of tailored web-based messages about cigarette smoke and breast cancer risk on boys' and girls' risk perceptions and information seeking: randomized controlled trial." JMIR Res Protoc. 2013 Dec 10;2(2):e53. doi: 10.2196/resprot.2858.

BACKGROUND: Recent evidence indicates a causal link between both active smoking and secondhand smoke (SHS) exposure and breast cancer (BC). OBJECTIVE: The objective of the present study was to evaluate the initial reactions of girls and boys to tailored Web-based messages that describe the relationship between SHS and BC, using a parallel, single-blinded cluster randomized controlled trial. METHODS: This trial was nested within a cycle of an ongoing longitudinal study of 1498 students from 74 secondary schools. Self-reported assessments were used to evaluate the impact of study messages on participants' risk perception and interest in obtaining additional information after participants were randomized by schools to control or intervention groups. The intervention group received a tailored visual message (based on gender and Aboriginal status) about BC and tobacco smoke. The control group received a standard visual message about smoking and cancer. RESULTS: SHS exposure was identified as a BC risk factor by 380/1488 (25.54%) participants, during the preintervention analysis. Compared to the female participants in the control group (491/839, 58.5%), girls who received the

intervention (339/649, 52.2%) were 14% more likely to agree that exposure to SHS increased their BC risk (relative risk [RR] 1.14, 95% CI 1.07-1.21). Nonsmoking girls who received the intervention were 14% more likely to agree that starting smoking would increase their BC risk (RR 1.14, 95% CI 1.07-1.21). Compared to the male participants in control group (348/839, 41.5%), boys who received the intervention (310/649, 47.8%) were 10% more likely to agree that girls' exposure to SHS increased their BC risk (RR 1.10, 95% CI 1.02-1.18). Compared to controls, girls who received the intervention were 52% more likely to request additional information about SHS and BC (RR 1.52, 95% CI 1.12-2.06). CONCLUSIONS: Brief gender-sensitive messages delivered via the Internet have the potential to increase awareness and to stimulate information seeking about the risk for BC associated with SHS.

Robles, A. I., P. Yang, et al. "A DRD1 polymorphism predisposes to lung cancer among those exposed to secondhand smoke during childhood." Cancer Prev Res (Phila). 2014 Dec;7(12):1210-8. doi: 10.1158/1940-6207.CAPR-14-0158. Epub 2014 Oct 3.

Lung cancer has a familial component which suggests a genetic contribution to its etiology. Given the strong evidence linking smoking with lung cancer, we studied miRNA-related loci in genes associated with smoking behavior. CHRNA, CHRNB gene families, CYP2A6, and DRD1 (dopamine receptor D1) were mined for SNPs that fell within the seed region of miRNA binding sites and then tested for associations with risk in a three-stage validation approach. A 3'UTR (untranslated region) SNP in DRD1 was associated with a lower risk of lung cancer among individuals exposed to secondhand smoke during childhood [OR, 0.69; 95% confidence interval (CI), 0.60-0.79; P < 0.0001]. This relationship was evident in both ever (OR, 0.74; 95% CI, 0.62-0.88; P = 0.001) and never smokers (OR, 0.61; 95% CI, 0.47-0.79; P < 0.0001), European American (OR, 0.65; 95% CI, 0.53-0.80; P < 0.0001), and African American (OR, 0.73; 95% CI, 0.62-0.88; P = 0.001) populations. Although much remains undefined about the long-term risks associated with exposure to secondhand smoke and heterogeneity between individuals in regard to their susceptibility to the effects of secondhand smoke, our data show an interaction between an SNP in the 3'UTR of DRD1 and exposure to secondhand smoke during childhood. Further work is needed to explore the mechanistic underpinnings of this SNP and the nature of the interaction between DRD1 and exposure to secondhand smoke during childhood.

Rollison, D. E., R. C. Brownson, et al. "Case-control study of tobacco smoke exposure and breast cancer risk in Delaware." BMC Cancer. 2008 Jun 2;8:157. doi: 10.1186/1471-2407-8-157.

BACKGROUND: Tobacco smoke exposure may be associated with increased breast cancer risk, although the evidence supporting the association is inconclusive. We conducted a case-control study in Delaware, incorporating detailed exposure assessment for active and secondhand smoke at home and in the workplace. METHODS: Primary invasive breast cancer cases diagnosed among female Delaware residents, ages 40-79, in 2000-2002 were identified through the Delaware cancer registry (n = 287). Delaware drivers license and Health Care Finance Administration records were used to select age frequency-matched controls for women <65 and > or = 65, respectively. Detailed information on tobacco smoke exposure was obtained through telephone interviews. RESULTS: A statistically significant increased risk of breast cancer was observed for ever having smoked cigarettes (odds ratio = 1.43, 95% confidence interval = 1.03-1.99). However, there was no evidence of a dose-response relationship between breast cancer risk and total years smoked, cigarettes per day, or pack-years. Neither residential nor workplace secondhand smoke exposure was associated with breast cancer. Recalculations of active smoking risks using a purely unexposed reference group of women who were not exposed to active or secondhand smoking did not indicate increased risks of breast cancer. CONCLUSION: These findings do not support an association between smoking and breast cancer.

Sagiv, S. K., M. M. Gaudet, et al. "Active and passive cigarette smoke and breast cancer survival." Ann Epidemiol. 2007 May;17(5):385-93. Epub 2007 Mar 28.

PURPOSE: The association between active and passive cigarette smoking before breast cancer diagnosis and survival was investigated among a cohort of invasive breast cancer cases (n = 1273) participating in a population-based case-control study. METHODS: Participants diagnosed with a first primary breast cancer between August 1, 1996, and July 31, 1997, were followed-up until December 31, 2002, for all-cause mortality (n = 188 deaths), including breast cancer-specific mortality (n = 111), as reported to the National Death Index. RESULTS: In Cox models, the adjusted hazards ratios (HRs) for all-cause mortality were slightly higher among current and former active smokers, compared with never smokers (HR, 1.23; 95% confidence interval [95% CI], 0.83-1.84) and 1.19 (95% CI, 0.85-1.66), respectively). No association was found between

active or passive smoking and breast cancer-specific mortality. All-cause and breast cancer-specific mortality was higher among active smokers who were postmenopausal (HR, 1.64; 95% CI, 1.03-2.60 and HR, 1.45; 95% CI, 0.78-2.70, respectively) or obese at diagnosis (HR, 2.10; 95% CI, 1.03-4.27 and HR, 1.97; 95% CI, 0.89-4.36, respectively). Associations between smoking and all-cause and breast cancer-specific mortality did not differ by cancer treatment. CONCLUSIONS: These data do not provide strong evidence for an association between smoking and all-cause or breast cancer-specific mortality, although smokers who are postmenopausal or obese at diagnosis may be at higher risk.

Salem, A. F., M. S. Al-Zoubi, et al. "Cigarette smoke metabolically promotes cancer, via autophagy and premature aging in the host stromal microenvironment." Cell Cycle. 2013 Mar 1;12(5):818-25. doi: 10.4161/cc.23722. Epub 2013 Feb 6.

Cigarette smoke has been directly implicated in the disease pathogenesis of a plethora of different human cancer subtypes, including breast cancers. The prevailing view is that cigarette smoke acts as a mutagen and DNA damaging agent in normal epithelial cells, driving tumor initiation. However, its potential negative metabolic effects on the normal stromal microenvironment have been largely ignored. Here, we propose a new mechanism by which carcinogen-rich cigarette smoke may promote cancer growth, by metabolically "fertilizing" the host microenvironment. More specifically, we show that cigarette smoke exposure is indeed sufficient to drive the onset of the cancer-associated fibroblast phenotype via the induction of DNA damage, autophagy and mitophagy in the tumor stroma. In turn, cigarette smoke exposure induces premature aging and mitochondrial dysfunction in stromal fibroblasts, leading to the secretion of high-energy mitochondrial fuels, such as L-lactate and ketone bodies. Hence, cigarette smoke induces catabolism in the local microenvironment, directly fueling oxidative mitochondrial metabolism (OXPHOS) in neighboring epithelial cancer cells, actively promoting anabolic tumor growth. Remarkably, these autophagic-senescent fibroblasts increased breast cancer tumor growth in vivo by up to 4-fold. Importantly, we show that cigarette smoke-induced metabolic reprogramming of the fibroblastic stroma occurs independently of tumor neo-angiogenesis. We discuss the possible implications of our current findings for the prevention of aging-associated human diseases and, especially, common epithelial cancers, as we show that cigarette smoke can systemically accelerate aging in the host microenvironment. Finally, our current findings are consistent with the idea that cigarette smoke induces the "reverse Warburg effect," thereby fueling "two-compartment tumor metabolism" and oxidative mitochondrial metabolism in epithelial cancer cells.

Samanic, C., M. Kogevinas, et al. "Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender." Cancer Epidemiol Biomarkers Prev. 2006 Jul;15(7):1348-54.

We examined the effects of dose, type of tobacco, cessation, inhalation, and environmental tobacco smoke exposure on bladder cancer risk among 1,219 patients with newly diagnosed bladder cancer and 1,271 controls recruited from 18 hospitals in Spain. We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between bladder cancer risk and various characteristics of cigarette smoking. Current smokers (men: OR, 7.4; 95% CI, 5.3-10.4; women: OR, 5.1; 95% CI, 1.6-16.4) and former smokers (men: OR, 3.8; 95% CI, 2.8-5.3; women: OR, 1.8; 95% CI, 0.5-7.2) had significantly increased risks of bladder cancer compared with nonsmokers. We observed a significant positive trend in risk with increasing duration and amount smoked. After adjustment for duration, risk was only 40% higher in smokers of black tobacco than that in smokers of blond tobacco (OR, 1.4; 95% CI, 0.98-2.0). Compared with risk in current smokers, a significant inverse trend in risk with increasing time since quitting smoking blond tobacco was observed (> or =20 years cessation: OR, 0.2; 95% CI, 0.1-0.9). No trend in risk with cessation of smoking black tobacco was apparent. Compared with men who inhaled into the mouth, risk increased for men who inhaled into the throat (OR, 1.7; 95% CI, 1.1-2.6) and chest (OR, 1.5; 95% CI, 1.1-2.1). Cumulative occupational exposure to environmental tobacco smoke seemed to confer increased risk among female nonsmokers but not among male nonsmokers. After eliminating the effect of cigarette smoking on bladder cancer risk in our study population, the male-to-female incidence ratio decreased from 8.2 to 1.7, suggesting that nearly the entire male excess of bladder cancer observed in Spain is explained by cigarette smoking rather than occupational/environmental exposures to other bladder carcinogens.

Schwartz, J., J. L. Bottorff, et al. "Effect of web-based messages on girls' knowledge and risk perceptions related to cigarette smoke and breast cancer: 6-month follow-up of a randomized controlled trial." JMIR Res Protoc. 2014 Sep 30;3(3):e53. doi: 10.2196/resprot.3282.

BACKGROUND: Evidence indicating an association between cigarette smoke exposure and an increase in breast cancer risk highlights the need for health messages that aim to prevent smoking initiation and reduce secondhand smoke (SHS) exposure among adolescent girls. OBJECTIVE: This study aimed to evaluate the efficacy of targeted gender-sensitive, breast cancer-specific, Web-based messages about the increased risk of breast cancer associated with cigarette smoke exposure. Outcomes assessed 6 months postmessage delivery included nonsmoking adolescent girls' knowledge of the link between cigarette smoke exposure and breast cancer, perceptions of breast cancer risk associated with cigarette smoke, smoking behavior and intentions, and stage of change related to avoidance of secondhand smoke. METHODS: A prospective randomized controlled trial was used to compare standard (control) messages with targeted gender- and Aboriginal status-sensitive, breast cancer-specific (intervention) messages. Messages were delivered online to 618 nonsmoking girls, aged 13 to 15 years, clustered in 74 Canadian secondary schools. RESULTS: Compared with the control group, girls in the intervention group were significantly more likely to report that breast cancer is an illness caused by cigarette smoke (adjusted relative risk [ARR] 1.33, 95% CI 1.05-1.68) and to agree that exposure to SHS increases their risk of breast cancer (ARR 1.10, 95% CI 1.02-1.20). No significant effects were observed for a change in smoking status, intention to try smoking, or stage of change related to avoidance of SHS.

Siegel, M. and M. Skeer "Exposure to secondhand smoke and excess lung cancer mortality risk among workers in the "5 B's": bars, bowling alleys, billiard halls, betting establishments, and bingo parlours." Tob Control. 2003 Sep;12(3):333-8.

OBJECTIVE: To review existing data on exposure to secondhand smoke in bars, bowling alleys, billiard halls, betting establishments, and bingo parlours (the "5 B's") as assessed by ambient nicotine air concentration measurements and to estimate the excess lung cancer mortality risk associated with this exposure. DATA SOURCES: Using the Medline, Toxline, and Toxnet databases, the internet, and bibliographies of relevant articles, we identified studies that reported measurements of ambient nicotine concentrations in the 5 B's. STUDY SELECTION: Studies were included if they reported a mean concentration of ambient nicotine measured in at least one of the 5 B's. DATA EXTRACTION: We calculated a weighted average of nicotine concentrations in each of the 5 B's. We then estimated the working lifetime excess lung cancer mortality risk associated with this exposure, as well as with exposure at the upper and lower limits of the range of mean exposures reported in all of the studies in each establishment category. DATA SYNTHESIS: Nicotine concentrations in the 5 B's were 2.4 to 18.5 times higher than in offices or residences, and 1.5 to 11.7 times higher than in restaurants. At these exposure levels, estimated working lifetime excess lung cancer mortality risk from secondhand smoke exposure for workers in the 5 B's is between 1.0-4.1/1000, which greatly exceeds the typical de manifestis risk level of 0.3/1000. CONCLUSIONS: Workers in the 5 B's have high levels of occupational exposure to secondhand smoke and must be included in workplace smoking regulations.

Sobus, S. L. and G. W. Warren "The biologic effects of cigarette smoke on cancer cells." Cancer. 2014 Dec 1;120(23):3617-26. doi: 10.1002/cncr.28904. Epub 2014 Jul 9.

Smoking is one of the largest preventable risk factors for developing cancer, and continued smoking by cancer patients is associated with increased toxicity, recurrence, risk of second primary cancer, and mortality. Cigarette smoke (CS) contains thousands of chemicals, including many known carcinogens. The carcinogenic effects of CS are well established, but relatively little work has been done to evaluate the effects of CS on cancer cells. In this review of the literature, the authors demonstrate that CS induces a more malignant tumor phenotype by increasing proliferation, migration, invasion, and angiogenesis and by activating prosurvival cellular pathways. Significant work is needed to understand the biologic effect of CS on cancer biology, including the development of model systems and the identification of critical biologic mediators of CS-induced changes in cancer cell physiology.

Spitz, M. R., I. P. Gorlov, et al. "Variants in inflammation genes are implicated in risk of lung cancer in never smokers exposed to second-hand smoke." Cancer Discov. 2011 Oct;1(5):420-9. doi: 10.1158/2159-8290.CD-11-0080. Epub 2011 Aug 25.

Lung cancer in lifetime never smokers is distinct from that in smokers, but the role of separate or overlapping carcinogenic pathways has not been explored. We therefore evaluated a comprehensive panel of 11,737 single-nucleotide polymorphisms (SNP) in inflammatory-pathway genes in a discovery phase (451 lung cancer cases, 508 controls from Texas). SNPs that were significant were evaluated in a second external population (303 cases, 311 controls from the Mayo Clinic). An intronic SNP in the ACVR1B gene, rs12809597, was replicated with significance and restricted to those reporting adult exposure to environmental tobacco smoke. Another

promising candidate was an SNP in NR4A1, although the replication OR did not achieve statistical significance.

Stampfli, M. R. and G. P. Anderson "How cigarette smoke skews immune responses to promote infection, lung disease and cancer." Nat Rev Immunol. 2009 May;9(5):377-84. doi: 10.1038/nri2530.

A complex and multilayered immune defence system protects the host against harmful agents and maintains tissue homeostasis. Cigarette smoke exposure markedly impacts the immune system, compromising the host's ability to mount appropriate immune and inflammatory responses and contributing to smoking-related pathologies. These adverse effects on the immune system not only occur in active smokers, but also in those exposed to smoke passively in contaminated environments, and may persist for decades after exposure has ended.

Steinetz, B. G., T. Gordon, et al. "The parity-related protection against breast cancer is compromised by cigarette smoke during rat pregnancy: observations on tumorigenesis and immunological defenses of the neonate." Carcinogenesis. 2006 Jun;27(6):1146-52. Epub 2006 Feb 12.

Early pregnancy is a powerful negative risk factor for breast cancer (BCa) in women. Pregnancy also protects rats against induction of BCa by carcinogens such as N-methyl-N-nitrosourea (MNU), making the parous rat a useful model for studying this phenomenon. Smoking during early pregnancy may lead to an increased risk of BCa in later life, possibly attributable to carcinogens in cigarette smoke (CS), or to reversal of the parity-related protection against BCa. To investigate these possibilities, 50-day-old timed first-pregnancy rats were exposed to standardized mainstream CS (particle concentration = 50 mg/m3) or to filtered air (FA) 4 h/day, Day 2-20 of gestation. Age-matched virgin rats were similarly exposed to CS or FA. At age 100 days, the CS or FA-exposed, parous and virgin rats were injected s.c. with MNU (50 mg/kg body wt), or with MNU vehicle. Mammary tumors (MTs) first appeared in virgin rats 9 weeks post-MNU injection. While no MTs were detected in FA-exposed parous rats until 18 weeks post-MNU, MTs appeared in the CS-exposed parous rats as early as 10 wks ($P < 0.02$). As no MTs developed in CS-exposed rats not injected with MNU, CS did not act as a direct mammary carcinogen. Serum prolactin concentration on Day 19 of pregnancy in CS-exposed dams was reduced by 50% compared with FA-exposed dams ($P < 0.005$). CS exposure during a pregnancy may thus 'deprotect' rats, enhancing their vulnerability to MNU-induced BCa.

Steliga, M. A. and C. M. Dresler "Epidemiology of lung cancer: smoking, secondhand smoke, and genetics." Surg Oncol Clin N Am. 2011 Oct;20(4):605-18. doi: 10.1016/j.soc.2011.07.003.

The link between smoking and development of lung cancer has been demonstrated, not only for smokers but also for those exposed to secondhand smoke. Despite the obvious carcinogenic effects of tobacco smoking, not all smokers develop lung cancer, and conversely some nonsmokers can develop lung cancer in the absence of other environmental risk factors. A multitude of genetic factors are beginning to be explored that interact with environmental exposure to alter the risk of developing this deadly disease. By more fully appreciating the complex interrelationship between genetics and other risks the development of lung cancer can be more completely understood.

Strohsnitter, W. C., K. L. Noller, et al. "Breast cancer incidence in women prenatally exposed to maternal cigarette smoke." Epidemiology. 2005 May;16(3):342-5.

BACKGROUND: Clinical studies show that maternal cigarette smoking reduces pregnancy estrogen levels. Women prenatally exposed to maternal cigarette smoke may, therefore, have a lower breast cancer risk because the fetal mammary gland's exposure to maternal estrogen is decreased. Associations between prenatal maternal cigarette smoke exposure and breast cancer, however, have not been observed in previous case-control studies that relied on exposure assessment after the onset of cancer. At the start of this study, cigarette smoking history was obtained directly from the mother. METHODS: The National Cooperative DES Adenosis project was a follow-up study of health outcomes in women prenatally exposed to diethylstilbestrol (DES). At the start of the study, women's mothers provided information about cigarette smoking habits during the time they were pregnant with the study participant. In the current study, the breast cancer rates are compared among 4031 women who were or were not prenatally exposed to maternal cigarette smoke. The resultant relative rate (RR) is adjusted for potential confounding by other breast cancer risk factors using Poisson regression modeling.

Sundar, I. K., M. Z. Nevid, et al. "Cigarette smoke induces distinct histone modifications in lung cells: implications for the pathogenesis of COPD and lung cancer." J Proteome Res. 2014 Feb 7;13(2):982-96. doi: 10.1021/pr400998n. Epub 2013 Dec 13.

Cigarette smoke (CS)-mediated oxidative stress induces several signaling cascades, including kinases, which results in chromatin modifications

(histone acetylation/deacetylation and histone methylation/demethylation). We have previously reported that CS induces chromatin remodeling in pro-inflammatory gene promoters; however, the underlying site-specific histone marks formed in histones H3 and H4 during CS exposure in lungs in vivo and in lung cells in vitro, which can either drive gene expression or repression, are not known. We hypothesize that CS exposure in mouse and human bronchial epithelial cells (H292) can cause site-specific posttranslational histone modifications (PTMs) that may play an important role in the pathogenesis of CS-induced chronic lung diseases. We used a bottom-up mass spectrometry approach to identify some potentially novel histone marks, including acetylation, monomethylation, and dimethylation, in specific lysine and arginine residues of histones H3 and H4 in mouse lungs and H292 cells. We found that CS-induced distinct posttranslational histone modification patterns in histone H3 and histone H4 in lung cells, which may be considered as usable biomarkers for CS-induced chronic lung diseases. These identified histone marks (histone H3 and histone H4) may play an important role in the epigenetic state during the pathogenesis of smoking-induced chronic lung diseases, such as chronic obstructive pulmonary disease and lung cancer.

Tam, K. W., W. Zhang, et al. "CDKN2A/p16 inactivation mechanisms and their relationship to smoke exposure and molecular features in non-small-cell lung cancer." J Thorac Oncol. 2013 Nov;8(11):1378-88. doi: 10.1097/JTO.0b013e3182a46c0c.

INTRODUCTION: CDKN2A (p16) inactivation is common in lung cancer and occurs via homozygous deletions, methylation of promoter region, or point mutations. Although p16 promoter methylation has been linked to KRAS mutation and smoking, the associations between p16 inactivation mechanisms and other common genetic mutations and smoking status are still controversial or unknown. METHODS: We determined all three p16 inactivation mechanisms with the use of multiple methodologies for genomic status, methylation, RNA, and protein expression, and correlated them with EGFR, KRAS, STK11 mutations and smoking status in 40 cell lines and 45 tumor samples of primary non-small-cell lung carcinoma. We also performed meta-analyses to investigate the impact of smoke exposure on p16 inactivation. RESULTS: p16 inactivation was the major mechanism of RB pathway perturbation in non-small-cell lung carcinoma, with homozygous deletion being the most frequent method, followed by methylation and the rarer point mutations. Inactivating mechanisms were tightly correlated with loss of mRNA and protein expression. p16 inactivation occurred at comparable frequencies regardless of mutational status of EGFR, KRAS, and STK11, however, the major inactivation mechanism of p16 varied. p16 methylation was linked to KRAS mutation but was mutually exclusive with EGFR mutation. Cell lines and tumor samples demonstrated similar results. Our meta-analyses confirmed a modest positive association between p16 promoter methylation and smoking. CONCLUSION: Our results confirm that all the inactivation mechanisms are truly associated with loss of gene product and identify specific associations between p16 inactivation mechanisms and other genetic changes and smoking status.

Theis, R. P., S. M. Dolwick Grieb, et al. "Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study." BMC Cancer. 2008 Dec 24;8:387. doi: 10.1186/1471-2407-8-387.

BACKGROUND: Kidney and renal pelvis cancers account for 4% of all new cancer cases in the United States, among which 85% are renal cell carcinomas (RCC). While cigarette smoking is an established risk factor for RCC, little is known about the contribution of environmental tobacco smoke (ETS) to RCC incidence. This study assesses the role of smoking and ETS on RCC incidence using a population-based case-control design in Florida and Georgia. METHODS: Incident cases (n = 335) were identified from hospital records and the Florida cancer registry, and population controls (n = 337) frequency-matched by age (+/- 5 years), gender, and race were identified through random-digit dialing. In-person interviews assessed smoking history and lifetime exposure to ETS at home, work, and public spaces. Home ETS was measured in both years and hours of exposure. Odds ratios and 95% confidence intervals were calculated using logistic regression, controlled for age, gender, race, and BMI. RESULTS: Cases were more likely to have smoked 20 or more pack-years, compared with never-smokers (OR: 1.35, 95% CI: 0.93 - 1.95). A protective effect was found for smoking cessation, beginning with 11-20 years of cessation (OR: 0.39, 95% CI: 0.18-0.85) and ending with 51 or more years of cessation (OR: 0.11, 95% CI: 0.03-0.39) in comparison with those having quit for 1-10 years. Among never-smokers, cases were more likely to report home ETS exposure of greater than 20 years, compared with those never exposed to home ETS (OR: 2.18; 95% CI: 1.14-4.18). Home ETS associations were comparable when measured in lifetime hours of exposure, with cases more likely to report 30,000 or more hours of home ETS exposure (OR: 2.37; 95% CI: 1.20-4.69).

Tommasi, S., A. Zheng, et al. "Exposure of mice to secondhand smoke elicits both transient and long-lasting transcriptional changes in cancer-related functional networks." Int J Cancer. 2015 May 15;136(10):2253-63. doi: 10.1002/ijc.29284. Epub 2014 Nov 6.

Secondhand smoke (SHS) has long been linked to lung cancer and other diseases in nonsmokers. Yet, the underlying mechanisms of SHS carcinogenicity in nonsmokers remain to be elucidated. We investigated the immediate and long-lasting effects of SHS exposure on gene expression in mice in vivo. We exposed mice whole body to SHS for 5 h/day, 5 days/week for 4 months in exposure chambers of a microprocessor-controlled smoking machine. Subsequently, we performed microarray gene expression profiling, genome-wide, to construct the pulmonary transcriptome of SHS-exposed mice, immediately after discontinuation of exposure (T0) and following 1-month (T1) and 7-month (T2) recoveries in clean air. Sub-chronic exposure of mice to SHS elicited a robust transcriptomic response, including both reversible and irreversible changes in gene expression. There were 674 differentially expressed transcripts immediately after treatment (T0), of which the majority were involved in xenobiotic metabolism, signaling, and innate immune response. Reduced, yet, substantial numbers of differentially expressed transcripts were detectable in mice after cessation of SHS-exposure (254 transcripts at T1 and 30 transcripts at T2). Top biofunctional networks disrupted in SHS-exposed mice, even after termination of exposure, were implicated in cancer, respiratory disease, and inflammatory disease. Our data show that exposure of mice to SHS induces both transient and long-lasting changes in gene expression, which impact cancer-related functional networks. The pattern of transcriptional changes in SHS-exposed mice may provide clues on the underlying mechanisms of lung tumorigenesis in nonsmokers. Our findings underscore the importance of eliminating SHS from environments where nonsmokers are unavoidably exposed to this carcinogen.

Toyooka, S., R. Maruyama, et al. "Smoke exposure, histologic type and geography-related differences in the methylation profiles of non-small cell lung cancer." Int J Cancer. 2003 Jan 10;103(2):153-60.

Aberrant methylation of several known or putative tumor suppressor genes occurs frequently during the pathogenesis of lung cancers. There are major smoke exposure, histology, geography and gender-related changes in non-small cell lung cancer (NSCLC). We investigated smoking-related, histologic, geographic and gender differences in the methylation profiles of resected NSCLCs. We examined 514 cases of NSCLC and 84 corresponding nonmalignant lung tissues from 4 countries (USA, Australia, Japan and Taiwan) for the methylation status of 7 genes known to be frequently methylated in lung cancers [p16, RASSF1A (RAS association domain family 1), APC, RARbeta, CDH13, MGMT and GSTP1]. Multivariate analyses were used for data analysis. Adenocarcinoma was the major histologic type in women and never smokers; analyses that involved smoke exposure and gender were limited to this histology. Our major findings are a) methylation status of any single gene was largely independent of methylation status of other genes; b) the rates of methylation of p16 and APC and the mean Methylation Index (MI), a reflection of the overall methylation status, were significantly higher in ever smokers than in never smokers; c) the mean MI of tumors arising in former smokers was significantly lower than the mean of current smokers; d) the methylation rates of APC, CDH13 and RARbeta were significantly higher in adenocarcinomas than in squamous cell carcinomas; e) methylation rates of MGMT and GSTP1 were significantly higher in the USA and Australian cases than in those from Japan and Taiwan; and (f) no significant gender-related differences in methylation patterns were noted. Our findings demonstrate important smoke exposure, histologic type and geography-related differences in the methylation profiles of NSCLC tumors.

Tranah, G. J., E. A. Holly, et al. "Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer: a population-based study in the San Francisco Bay Area." BMC Cancer. 2011 Apr 15;11:138. doi: 10.1186/1471-2407-11-138.

BACKGROUND: To examine the influence of cigarette, cigar and pipe smoking, cessation of cigarette smoking and passive smoke exposure on the risk of pancreatic cancer. METHODS: Exposure data were collected during in-person interviews in a population-based case-control study of pancreatic cancer (N = 532 cases, N = 1701 controls) in the San Francisco Bay Area. Odds ratios (ORs) were adjusted for potential confounders. RESULTS: The adjusted odds ratio (OR) of pancreatic cancer among current smokers was 1.9 (95% confidence interval (CI), 1.4-2.7). A significant, positive trend in risk with increasing pack-years of smoking was observed (P-trend <0.0001). Compared with participants who continued to smoke, former smokers had no statistically significant elevation in risk of pancreatic cancer 10 years after smoking cessation, with risk reduced to that of never smokers regardless of prior smoking intensity. Both men and women experienced similar increased risk of pancreatic cancer with increasing smoking duration. Cigar and pipe smoking

and exposure to passive smoke were not associated with pancreatic cancer.

Troy, J. D., J. R. Grandis, et al. "Childhood passive smoke exposure is associated with adult head and neck cancer." Cancer Epidemiol. 2013 Aug;37(4):417-23. doi: 10.1016/j.canep.2013.03.011. Epub 2013 Apr 22.

INTRODUCTION: Passive smoke is carcinogenic but its association with head and neck squamous cell carcinoma (HNSCC) is uncertain. METHODS: We conducted a case-control study of childhood passive smoke exposure (CPSE) and HNSCC in 858 cases and 806 frequency-matched controls using an interviewer-administered questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with logistic regression controlling for adult smoking in the total study population, and in never-smokers only (184 cases and 415 controls). CPSE was also studied in oropharyngeal separately from other HNSCC using polytomous logistic regression. RESULTS: CPSE was associated with HNSCC (OR, 1.28; 95% CI, 1.01-1.63) after controlling for adult smoking and other factors. This association was similar in magnitude, although not statistically significant, among subjects who never smoked as adults (OR, 1.19, 95% CI, 0.80-1.76). CPSE was associated more strongly with oropharyngeal cancer (a HNSCC subtype commonly associated with human papillomavirus (HPV) infection) than with HNSCC at non-oropharyngeal sites (OR, 2.02; 95% CI, 1.01-4.06, N=52 cases vs. OR, 1.04; 95% CI, 0.68-1.60, N=132 cases; P-for-heterogeneity=0.08). CONCLUSIONS: Data from this large US-based case control study suggest a role for CPSE in HNSCC etiology.

Tyc, V. L., Q. Huang, et al. "Intervention to reduce secondhand smoke exposure among children with cancer: a controlled trial." Psychooncology. 2013 May;22(5):1104-11. doi: 10.1002/pon.3117. Epub 2012 Jun 8.

OBJECTIVE: This randomized controlled trial tested the efficacy of parent-based behavioral counseling for reducing secondhand smoke exposure (SHSe) among children with cancer. It also examined predictors of smoking and SHSe outcomes. METHODS: Participants were 135 parents or guardians of nonsmoking children with cancer, <18 years, at least 30 days postdiagnosis, and living with at least one adult smoker. Parents were randomized to either a standard care control group or an intervention consisting of six counseling sessions delivered over 3 months. Parent-reported smoking and child SHSe levels were obtained at baseline, 3, 6, 9, and 12 months. Children provided urine samples for cotinine analyses. RESULTS: Reductions in parent-reported smoking and exposure were observed in both the intervention and control conditions. There was a significantly greater reduction in parent-reported smoking and child SHSe at 3 months for the intervention group compared with the control group. Child SHSe was significantly lower at 12 months relative to baseline in both groups. Children's cotinine levels did not show significant change over time in either group. Exposure outcomes were influenced by the number of smokers at home, smoking status of the parent participating in the trial, and the child's environment (home versus hospital) the day before the assessment. CONCLUSIONS: Children's SHSe can be reduced by advising parents to protect their child from SHSe, combined with routine reporting of their child's exposure and cotinine testing, when delivered in the context of the pediatric cancer setting. More intensive interventions may be required to achieve greater reductions in SHSe.

Tyc, V. L., J. Klosky, et al. "Parent-reported environmental tobacco smoke exposure among preadolescents and adolescents treated for cancer." Psychooncology. 2004 Aug;13(8):537-46.

Exposure to environmental tobacco smoke (ETS) poses serious health risks for children with cancer. Parental smoke is a primary source of exposure for these children. Parent smoking behaviors and parent-reported ETS exposure among children treated for cancer were examined in this study. In addition, reports of ETS exposure among children with cancer who currently smoked or who had smoked in the past were compared to those of children with cancer who never smoked. Written questionnaires about smoking behaviors and ETS exposure were administered to 47 smoking parents of youngsters diagnosed with cancer, 10-18 years of age (57.4% male, 78.7% Caucasian). Child reports of smoking status were also obtained. Results indicated that children with cancer are exposed to ETS from a number of sources and settings, as reported by their parents. Current or previous child smokers had greater ETS exposure than non-smoking children. Older children and Caucasian children also had greater ETS exposure. Level of ETS exposure did not differ based on the child's treatment status. Interventions that teach parents to protect their youngster from ETS exposure have potential for reducing adverse health outcomes in this vulnerable population.

Tyc, V. L., L. Throckmorton-Belzer, et al. "Smoking among parents of pediatric cancer patients and children's exposure to environmental tobacco smoke." J Child Health Care. 2004 Dec;8(4):288-300.

For 303 children newly diagnosed with cancer, we investigated the prevalence of parental smoking and examined patients' respiratory or pulmonary symptoms according to household smoking status. Results indicated that approximately 45 percent of patients came from households with at least one current parent smoker and 20 percent of current non-smoking parents reported past tobacco use. There was a trend for more patients from smoking households to experience respiratory problems than patients from non-smoking households (p = .068). In conclusion, many patients are at risk for parental smoke exposure and associated health problems if they are continually exposed during therapy. Clinician-delivered interventions to reduce environmental smoke exposure are clearly warranted.

Vaid, M. and S. K. Katiyar "Grape seed proanthocyanidins inhibit cigarette smoke condensate-induced lung cancer cell migration through inhibition of NADPH oxidase and reduction in the binding of p22(phox) and p47(phox) proteins." Mol Carcinog. 2015 Jun;54 Suppl 1:E61-71. doi: 10.1002/mc.22173. Epub 2014 May 5.

Cigarette smoking is the major cause of lung cancer. It is therefore important to develop effective strategies that target molecular abnormalities induced by cigarette smoke condensate (CSC). Cigarette smoking increases oxidative stress particularly via activation of NADPH oxidase (NOX), a key source of superoxide anion production. Here, we report that grape seed proanthocyanidins (GSPs) exert an inhibitory effect on the CSC-induced migration of non-small cell lung cancer (NSCLC) cells (A549, H460, and H1299). Using an in vitro invasion assay, we found that treatment of NSCLC cells with CSC increased NSCLC cell migration by enhancing NOX mediated-oxidative stress. Treatment of NSCLC cells with GSPs inhibited the CSC-induced cell migration through reduction in oxidative stress levels and a reduction in the epithelial-to-mesenchymal transition. To identify the molecular targets of GSPs, we examined the effects of GSPs on CSC-induced alterations in the levels of key NOX components, namely p22(phox) and p47(phox) proteins, using A549 cells. We also determined the effect of GSPs on CSC-induced interaction/binding between these proteins, which is a key event in NOX activation. We found that treatment of A549 cells with GSPs not only inhibited the CSC-induced increase in the expression levels of p22(phox) and p47(phox) , but also reduced the binding of p22(phox) to p47(phox) proteins. This new insight into the anti-lung cancer cell migration activity of GSPs could serve as a basis for development of improved chemopreventive or therapeutic strategies for lung cancer.

Valera, P., S. H. Cook, et al. ""They are not taking cigarettes from me . . . I'm going to smoke my cigarettes until the day I die. I don't care if I get cancer": smoking behaviors of men under community supervision in New York City." Nicotine Tob Res. 2014 Jun;16(6):800-6. doi: 10.1093/ntr/ntt280. Epub 2014 Jan 30.

INTRODUCTION: Cigarette smoking declined from 42.4% in 1965 to 19.3% in 2010 among the general population, but it remains the leading cause of preventable death and illness in the United States, especially among high-risk populations, including those with criminal justice involvement. METHODS: A mixed-methods approach was used to investigate the smoking behaviors of men under parole or probation. Phase I focused on qualitative data of 30 semi-structured interviews of men who were recently released from a state prison and/or jail. Phase II analyzed quantitative data resulting from a study that examined smoking characteristics and treatment approaches of 259 participants, 197 of whom were cigarette smokers. RESULTS: The survey participants' age of tobacco initiation ranged from 7 to 45 years of age. Participants smoked between 1 and 40 cigarettes per day; the mean number of cigarettes smoked per day was 10.37. Men released from prison used cigarettes for more years on average than men released from jail (t[194] = -2.22, p < .05). A linear regression procedure revealed that the influence of friends and family significantly predicted smoking behavior (beta = .25, p < .0001).

Vardavas, C. I., I. Mpouloukaki, et al. "Second hand smoke exposure and excess heart disease and lung cancer mortality among hospital staff in Crete, Greece: a case study." Int J Environ Res Public Health. 2008 Sep;5(3):125-9.

Exposure to secondhand smoke (SHS) is a serious threat to public health, and a significant cause of lung cancer and heart disease among non-smokers. Even though Greek hospitals have been declared smoke free since 2002, smoking is still evident. Keeping the above into account, the aim of this study was to quantify the levels of exposure to environmental tobacco smoke and to estimate the attributed lifetime excess heart disease and lung cancer deaths per 1000 of the hospital staff, in a large Greek public hospital. Environmental airborne respirable suspended particles (RSP) of PM2.5 were performed and the personnel's excess mortality risk was estimated using risk prediction formulas. Excluding the intensive care unit and the operating theatres, all wards and clinics were polluted with environmental tobacco smoke. Mean SHS-RSP measurements ranged from 11 to 1461 microg/m3

depending on the area. Open wards averaged 84 microg/m3 and the managing wards averaged 164 microg/m3 thus giving an excess lung cancer and heart disease of 1.12 (range 0.23-1.88) and 11.2 (range 2.3-18.8) personnel in wards and 2.35 (range 0.55-12.2) and 23.5 (range 5.5-122) of the managing staff per 1000 over a 40-year lifespan, respectively. Conclusively, SHS exposure in hospitals in Greece is prevalent and taking into account the excess heart disease and lung cancer mortality risk as also the immediate adverse health effects of SHS exposure, it is clear that proper implementation and enforcement of the legislation that bans smoking in hospitals is imperative to protect the health of patients and staff alike.

Veglia, F., P. Vineis, et al. "Occupational exposures, environmental tobacco smoke, and lung cancer." Epidemiology. 2007 Nov;18(6):769-75.

BACKGROUND: There is uncertainty regarding the association of occupational exposures with lung cancer. We have studied the association between 52 high-risk job titles and lung cancer incidence in a large prospective study, with more than 200,000 participants followed for more than 6 years and 809 incident cases of lung cancer. METHODS: Hazard ratios and 95% confidence intervals were computed by the Cox proportional-hazard regression model, adjusting for country, age, sex, social class, diet, physical activity, and smoking habits. We used a CAREX-based job-exposure matrix to infer exposure to lung carcinogens. False-positive report probability was calculated as a measure of potentially false-positive results. RESULTS: Eighteen occupations, mainly related with agriculture, constructions, and metal processing, were associated with increased risk. In addition, incidence tended to increase with the number of hazardous jobs reported. When the occupations were classified according to the presumed exposure to specific carcinogenic agents, the hazard ratios were 1.5 (95% confidence interval = 1.2-1.9) for asbestos, 1.4 (1.1-1.8) for heavy metals, 1.4 (1.1-1.8) for polycyclic aromatic hydrocarbons, and 1.6 (1.2-2.1) for work-related environmental tobacco smoke. The estimated population attributable risk for employment in at least 1 at-risk job was 16% in men and 12% in women.

Verla-Tebit, E., C. Lilla, et al. "Exposure to environmental tobacco smoke and the risk of colorectal cancer in a case-control study from Germany." Eur J Cancer Prev. 2009 Feb;18(1):9-12. doi: 10.1097/CEJ.0b013e3282f0c06c.

In a population-based case-control study in Germany, 540 incident cases of colorectal cancer (CRC) aged > or =30 years and 614 controls were recruited from January 2003 to June 2004. Information on risk factors of CRC and lifetime history of active smoking and exposure to environmental tobacco smoke (ETS) was obtained by personal interviews. This analysis is limited to never smokers (252 cases and 292 controls). Associations were assessed using conditional logistic regression models adjusting for potential confounders. We found no evidence of an increased risk of CRC following exposure to ETS overall, in childhood or at work. For spousal exposure, we, however, found a significant risk increase for women currently exposed (OR: 3.54; 95% CI: 1.03-12.15) and for women exposed to >23 pack-years of spousal smoking (OR: 3.02; 95% CI: 0.99-9.28). Our findings do not indicate a major impact of ETS on CRC risk but suggest that risk may be increased following spousal exposure.

Villeneuve, P. J., K. C. Johnson, et al. "Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study." Can J Public Health. 2004 Jan-Feb;95(1):32-7.

BACKGROUND: Despite the fact that tobacco is a well-recognized risk factor for pancreatic cancer, no study has yet reported on the association between environmental tobacco smoke (ETS) and this malignancy. We investigated the relationship between pancreatic cancer and childhood and adult exposure to ETS using a case-control study design. METHODS: Our study population consisted of 583 pancreatic cancer cases and 4,813 population-based controls that were identified within 8 Canadian provinces between 1994 and 1997. Mail-out questionnaires were used to collect risk factor information and a lifetime residential and occupational history of exposure to ETS. RESULTS: Among never smokers, those who were exposed to ETS both as a child and as an adult had an odds ratio of 1.21 (95% CI=0.60-2.44) relative to those with no exposure. For active smoking, when the referent group consisted of never smokers who had not been regularly exposed to ETS, the risk increases were more pronounced with an increased number of years of smoking, cigarette pack-years, years since quit smoking, and average number of cigarettes smoked daily. CONCLUSIONS: Overall, our results are suggestive of a weak association between pancreatic cancer and ETS. Perhaps more importantly, they suggest that ETS smoking exposures may confound the risk of pancreatic cancer associated with active smoking measures commonly used in epidemiologic studies.

Vineis, P., L. Airoldi, et al. "Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and

never smokers in the EPIC prospective study." BMJ. 2005 Feb 5;330(7486):277. Epub 2005 Jan 28.

OBJECTIVES: To investigate the association between environmental tobacco smoke, plasma cotinine concentration, and respiratory cancer or death. DESIGN: Nested case-control study within the European prospective investigation into cancer and nutrition (EPIC). PARTICIPANTS: 303,020 people from the EPIC cohort (total 500,000) who had never smoked or who had stopped smoking for at least 10 years, 123,479 of whom provided information on exposure to environmental tobacco smoke. Cases were people who developed respiratory cancers or died from respiratory conditions. Controls were matched for sex, age (plus or minus 5 years), smoking status, country of recruitment, and time elapsed since recruitment. MAIN OUTCOME MEASURES: Newly diagnosed cancer of lung, pharynx, and larynx; deaths from chronic obstructive pulmonary disease or emphysema. Plasma cotinine concentration was measured in 1574 people. RESULTS: Over seven years of follow up, 97 people had newly diagnosed lung cancer, 20 had upper respiratory cancers (pharynx, larynx), and 14 died from chronic obstructive pulmonary disease or emphysema. In the whole cohort exposure to environmental tobacco smoke was associated with increased risks (hazard ratio 1.30, 95% confidence interval 0.87 to 1.95, for all respiratory diseases; 1.34, 0.85 to 2.13, for lung cancer alone). Higher results were found in the nested case-control study (odds ratio 1.70, 1.02 to 2.82, for respiratory diseases; 1.76, 0.96 to 3.23, for lung cancer alone). Odds ratios were consistently higher in former smokers than in those who had never smoked; the association was limited to exposure related to work.

Vogelsang, M., J. D. Paccez, et al. "Aberrant methylation of the MSH3 promoter and distal enhancer in esophageal cancer patients exposed to first-hand tobacco smoke." J Cancer Res Clin Oncol. 2014 Nov;140(11):1825-33. doi: 10.1007/s00432-014-1736-x. Epub 2014 Jun 17.

PURPOSE: Polymorphisms in MSH3 gene confer risk of esophageal cancer when in combination with tobacco smoke exposure. The purpose of this study was to investigate the methylation status of MSH3 gene in esophageal cancer patients in order to further elucidate possible role of MSH3 in esophageal tumorigenesis. METHODS: We applied nested methylation-specific polymerase chain reaction to investigate the methylation status of the MSH3 promoter in tumors and matching adjacent normal-looking tissues of 84 esophageal cancer patients from a high-risk South African population. The Cancer Genome Atlas data were used to examine DNA methylation profiles at 17 CpG sites located in the MSH3 locus. RESULTS: Overall, promoter methylation was detected in 91.9 % of tumors, which was significantly higher compared to 76.0 % in adjacent normal-looking esophageal tissues (P = 0.008). When samples were grouped according to different demographics (including age, gender and ethnicity) and smoking status of patients, methylation frequencies were found to be significantly higher in tumor tissues of Black subjects (P = 0.024), patients of 55-65 years of age (P = 0.032), males (P = 0.037) and tobacco smokers (P = 0.015). Furthermore, methylation of the MSH3 promoter was significantly more frequent in tumor samples from smokers compared to tumor samples from non-smokers [odds ratio (OR) = 31.9, P = 0.031]. The TCGA data confirmed significantly higher DNA methylation level at the MSH3 promoter region in tumors (P = 0.0024). In addition, we found evidence of an aberrantly methylated putative MSH3-associated distal enhancer element. CONCLUSION: Our results suggest that methylation of MSH3 together with exposure to tobacco smoke is involved in esophageal carcinogenesis. Due to the active role of the MSH3 protein in modulating chemosensitivity of cells, methylation of MSH3 should further be examined in association with the outcome of esophageal cancer treatment using anticancer drugs.

Vrieling, A., H. B. Bueno-de-Mesquita, et al. "Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition." Int J Cancer. 2010 May 15;126(10):2394-403. doi: 10.1002/ijc.24907.

Cigarette smoking is an established risk factor for pancreatic cancer. However, prospective data for most European countries are lacking, and epidemiologic studies on exposure to environmental tobacco smoke (ETS) in relation to pancreatic cancer risk are scarce. We examined the association of cigarette smoking and exposure to ETS with pancreatic cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). This analysis was based on 465,910 participants, including 524 first incident pancreatic cancer cases diagnosed after a median follow-up of 8.9 years. Estimates of risk were obtained by Cox proportional hazard models and adjusted for weight, height, and history of diabetes mellitus. An increased risk of pancreatic cancer was found for current cigarette smokers compared with never smokers (HR = 1.71, 95% CI = 1.36-2.15), and risk increased with greater intensity and pack-years. Former cigarette smokers who quit for less than 5 years were at increased risk of pancreatic cancer (HR = 1.78, 95%

CI = 1.23-2.56), but risk was comparable to never smokers after quitting for 5 years or more. Pancreatic cancer risk was increased among never smokers daily exposed to ETS (for many hours) during childhood (HR = 2.61, 95% CI = 0.96-7.10) and exposed to ETS at home and/or work (HR = 1.54, 95% CI = 1.00-2.39). These results suggest that both active cigarette smoking, as well as exposure to ETS, is associated with increased risk of pancreatic cancer and that risk is reduced to levels of never smokers within 5 years of quitting.

Wadhwa, S. K., T. G. Kazi, et al. "Case-control study of male cancer patients exposed to arsenic-contaminated drinking water and tobacco smoke with relation to non-exposed cancer patients." Hum Exp Toxicol. 2011 Dec;30(12):2013-22. doi: 10.1177/0960327111408154. Epub 2011 May 9.

The investigated data indicated that inorganic arsenic in drinking water is associated with increased mortality from different types of cancers. In the present study, biological samples (blood and scalp hair) of male subjects having lung and bladder cancers and non-cancerous subjects belonging to arsenic (As)-exposed area of southern parts of Pakistan were analysed for As contents. The As levels in drinking water of understudy area showed that sections of understudy population are exposed to arsenic concentrations, which was 3-15-fold higher than the permissible level (<10 mug/L). For comparative purposes the biological samples of matched male cancer patient, as referent patients belonging to big city (Hyderabad) who had used municipal treated water with low arsenic levels <10 mug/L, were also collected. The exposed cancer patients have 2-3-fold higher level of As in both biological samples compared to non-exposed case-matched cancerous male subjects. This study is compelling evidence in support of positive associations between arsenic-contaminated water, food and cigarette with different types of risks of cancer.

Winiarczyk, B., G. Namyslowski, et al. "[The concentration of the chosen smoke toxicity biomarkers among smokers suffering from larynx cancer]." Otolaryngol Pol. 2007;61(1):39-46.

INTRODUCTION: An incidence of laryngeal cancer is strongly connected with exposure to tobacco smoke containing dozens of carcinogens. Genotoxic agents such as polycyclic aromatic hydrocarbons present in tobacco smoke are responsible for lesions of structure DNA and formation of DNA adducts by metabolically activated intermediates. Detecting the presence of DNA adducts in human tissues is therefore, a tool for studies of cancer. An evidence demonstrates that DNA adducts are useful markers of carcinogen exposure. The aim of this work was estimation of relationship between cigarette smoke exposure, determined as urinary cotinine and urinary 1-hydroxypyrene concentration, and number of aromatic-DNA adducts in blood lymphocytes. MATERIAL AND METHODS: The study group consisted of 60 men at the age of 45 up to 65 years - 20 healthy non-smokers, 20 healthy current smokers and 20 current smokers with primary larynx cancer, which was classified histopathologically as squamous cell carcinoma. The cotinine and 1-hydroxypyrene were determined in the urine with high performance liquid chromatography. Analysis of DNA adducts was performed by the 32P - postlabelling method. RESULTS: Urinary cotinine concentration in healthy smokers and cancer subjects in comparison with non-smokers was significant higher than in non-smokers, respectively, 29- and 31-fold higher but differences between healthy and sicks smokers were insignificant. Concentration of 1-hydroxypyrene in urine of healthy and cancer subjects was significantly higher (9- and 10-fold higher, respectively) compared with non-smokers. The highest level of aromatic-DNA adducts was found in lympfocytes of healthy smokers but differences between number of adducts in healthy smokers compared with non-smokers (+35%) and cancer subjects (+7,1%) were insignificant.

Witschi, H. "Tobacco smoke-induced lung cancer in animals--a challenge to toxicology (?)." Int J Toxicol. 2007 Jul-Aug;26(4):339-44.

Tobacco smoke is a known human carcinogen that primarily produces malignant lesions in the respiratory tract, although it also affects multiple other sites. A reliable and practical animal model of tobacco smoke-induced lung cancer would be helpful for in studies of product modification and chemoprevention. Over the years, many attempts to reproduce lung cancer in experimental animals exposed to tobacco smoke have been made, most often with negative or only marginally positive results. In hamsters, malignant lesions have been produced in the larynx, but not in the deeper lung. Female rats and female B6C3F1 mice, when exposed over lifetime to tobacco smoke, develop tumors in the nasal passages and also in the lung. Contrary to what is seen in human lung cancers, most rodent tumors are located peripherally and only about half of them show frank malignant features. Distant metastases are extremely rare. Male and female strain A mice exposed to 5 months to tobacco smoke and then kept for another 4 months in air respond to tobacco smoke with increased lung tumor multiplicities. However, the increase over background levels is comparatively small, making it difficult to detect significant differences when the effects of chemopreventive

agents are evaluated. On the other hand, biomarkers of exposure and of effect as well as evaluation of putative carcinogenic mechanisms in rats and mice exposed to tobacco smoke allow detection of early events and their modification by different smoke types or chemopreventive agents. The challenge will be to make such data broadly acceptable and accepted in lieu of having to do more and more long term studies involving larger and larger number of animals.

Wittel, U. A., N. Momi, et al. "The pathobiological impact of cigarette smoke on pancreatic cancer development (review)." Int J Oncol. 2012 Jul;41(1):5-14. doi: 10.3892/ijo.2012.1414. Epub 2012 Mar 23.

Despite extensive efforts, pancreatic cancer remains incurable. Most risk factors, such as genetic disposition, metabolic diseases or chronic pancreatitis cannot be influenced. By contrast, cigarette smoking, an important risk factor for pancreatic cancer, can be controlled. Despite the epidemiological evidence of the detrimental effects of cigarette smoking with regard to pancreatic cancer development and its unique property of being influenceable, our understanding of cigarette smoke-induced pancreatic carcinogenesis is limited. Current data on cigarette smoke-induced pancreatic carcinogenesis indicate multifactorial events that are triggered by nicotine, which is the major pharmacologically active constituent of tobacco smoke. In addition to nicotine, a vast number of carcinogens have the potential to reach the pancreatic gland, where they are metabolized, in some instances to even more toxic compounds. These metabolic events are not restricted to pancreatic ductal cells. Several studies show that acinar cells are also greatly affected. Furthermore, pancreatic cancer progenitor cells do not only derive from the ductal epithelial lineage, but also from acinar cells. This sheds new light on cigarette smoke-induced acinar cell damage. On this background, our objective is to outline a multifactorial model of tobacco smoke-induced pancreatic carcinogenesis.

Word, B., L. E. Lyn-Cook, Jr., et al. "Cigarette smoke condensate induces differential expression and promoter methylation profiles of critical genes involved in lung cancer in NL-20 lung cells in vitro: short-term and chronic exposure." Int J Toxicol. 2013 Jan-Feb;32(1):23-31. doi: 10.1177/1091581812465902. Epub 2012 Nov 21.

Establishing early diagnostic markers of harm is critical for effective prevention programs and regulation of tobacco products. This study examined effects of cigarette smoke condensate (CSC) on expression and promoter methylation profile of critical genes (DAPK, ECAD, MGMT, and RASSF1A) involved in lung cancer development in different human lung cell lines. NL-20 cells were treated with 0.1-100 mug/ml of CSC for 24 to 72 hrs for short-term exposures. DAPK expression or methylation status was not significantly affected. However, CSC treatment resulted in changes in expression and promoter methylation profile of ECAD, MGMT, and RASSF1A. For chronic studies, cells were exposed to 1 or 10 mug/ml CSC up to 28 days. Cells showed morphological changes associated with transformation and changes in invasion capacities and global methylation status. This study provides critical data suggesting that epigenetic changes could serve as an early biomarker of harm due to exposure to cigarette smoke.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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