



Cancer Research Center Hotline

Etiologic Research on Lung Cancer in Hawaii: The Roles of Smoking, Phytochemicals and Metabolic Genes

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Lung cancer is the most common malignancy worldwide and is the leading cause of cancer death in North America and in Hawaii. It is estimated that 90% of lung cancer deaths in the U.S. are caused by smoking. Risk has been shown to increase in relation to both smoking intensity and duration, and a person who smoked one pack per day for 30 years is estimated to have a lung cancer risk ten- to twenty-fold greater than that of a life-long non-smoker. Smoking cessation leads to a reduction in the risk of lung cancer, but not significantly before the fifth year and risk, possibly, never quite returns to the background level of a life-long non-smoker. The major increase in cigarette consumption starting in the 1910s has resulted in a sharp rise in lung cancer occurrence between the 1930s and 1980s. Rates in Hawaii have now peaked in males but are still increasing in females. Even though smoking rates have decreased, this disease will remain an important source of mortality in the future due to the large number of former smokers in our population. In the past fifty years, we have also seen a shift in the pathologic presentation of lung cancer in Hawaii, as in other parts of the US. The frequency of adenocarcinoma has markedly increased, whereas that of squamous cell carcinoma has proportionally decreased, presumably as a result of changes in cigarette composition and smoking behavior. Survival from lung cancer has remained extremely poor with a five-year survival rate of 12-15%.

Incidence rates for lung cancer show marked differences among ethnic groups in Hawaii, with the rates for Hawaiians and Caucasians being two- to three-fold higher than those for the Asian groups. The etiologic research undertaken on this malignancy at the Cancer Research Center of Hawaii has been aimed at elucidating these ethnic differences, with the goal of advancing our understanding of the disease. Because there seemed to be a poor correlation between lifelong smoking patterns and lung cancer incidence among the main ethnic groups in our population, efforts first focused on exploring other possible risk factors and, in particular, diet. Faculty of the Center's Epidemiology Program were among the first to report that intake of lipids may increase lung cancer risk and that a variety of constituents in fruits and vegetables may be protective.¹

³ At a time when most studies focused on beta-carotene only, we showed that additional carotenoids (especially, lutein and alpha-carotene) may decrease risk.⁴ More recently, we also showed that certain flavonoids (quercetin in onions and apples, and naringin from grapefruit) may also be protective.⁵ Because recent large clinical trials testing the ability of beta-carotene to prevent lung cancer have shown no beneficial effect (and even a detrimental effect in high risk smokers), the potential preventive effects of other

plant constituents ("phytochemicals") are currently receiving renewed research interest.

The detailed information collected from a large number of patients in Hawaii allowed us to examine the relationship between smoking and lung cancer in the main ethnic groups. After taking into account patterns of smoking (intensity, duration, type of cigarettes, depth of inhalation, etc.), we found that the overall lung cancer risk associated with cigarette smoking was 120% greater for Hawaiians and 50% greater for Caucasians than for Japanese.⁶ As a possible explanation for these differences, we turned our attention to the possibility that the ability to activate or detoxify carcinogens from tobacco smoke varies among ethnic groups. Many chemical carcinogens need first to be transformed into reactive intermediates that are capable of binding to DNA, potentially starting the carcinogenic process. Considerable variation exists among individuals in the activity of the enzymes responsible for the activation and detoxification of tobacco carcinogens (e.g., cytochrome P450 enzymes, glutathione-S-transferases). At least part of this variability is often due to minor inherited genetic variation [e.g., single nucleotide polymorphism (SNPs)] that affects the transcription of the gene or function of the protein. Thus, we have been investigating whether genetic variants in the genes coding for these enzymes occur with different frequencies among the ethnic groups, whether they can be shown to affect enzyme activity and whether they are associated with risk of lung cancer. We are also studying the effects of various dietary factors on these enzymatic pathways in relation to lung cancer risk.

For example, we recently showed that a polymorphism in the *CYP1A1* gene was directly associated with lung squamous cell carcinoma and that a polymorphism in the *CYP2E1* gene was inversely associated with lung adenocarcinoma, pointing to different etiologies for these tumors.⁷ We also showed that the frequencies of these polymorphisms vary markedly among ethnic groups and that they both result in a change in enzyme activity.^{8,9} The inducibility of cytochrome P4501A1 (which bioactivates polycyclic hydrocarbons) was found to be increased in subjects with the variant *CYP1A1* allele. The activity of cytochrome P4502E1 (capable of activating nitrosamines) was reduced for subjects with the *CYP2E1* variant allele. Examining the detailed dietary information collected on the subjects, we found that the protective effect of onion intake against lung cancer differed according to the *CYP1A1* genotype of the subjects, suggesting that the known inhibiting effect of the flavonoid quercetin (present in large quantities in onions) on *CYP1A1* may be an important protective mechanism.⁵ Studies using various biomarkers of exposure, genetic susceptibility and early biological effects have been initiated to confirm these relationships. In particular, we are currently recruiting smokers for feeding studies in which the effects of specific vegetables and fruits on carcinogen activation are being tested.

Other polymorphisms found to be associated with lung cancer in our population include variants in "metabolic genes" (glutathione-S-transferase, myeloperoxidase, NADPH-quinone-oxidoreductase, 8-oxoguanine glycosylase) and oncogenes (*H-ras*), suggesting a role for specific agents and/or mechanisms in the etiology of this disease. Hawaii's multiethnic population is a unique resource for such studies as the ethnic groups have retained different cancer risk patterns and different frequencies for many of these genetic poly-

morphisms. This allows for valuable comparisons and a gain in statistical power.

Each year, lung cancer kills about one million individuals worldwide, including about 400 in Hawaii. Avoidance of all tobacco smoking is a clear priority in preventing the disease and public health strategies have been largely successful in gradually changing smoking behaviors. However, additional approaches are needed for strongly addicted smokers who are unable to quit, and for ex-smokers since they remain for many years at significantly increased risk. Progress in our understanding of the biological processes involved in nicotine addiction and lung carcinogenesis is leading to the identification of genetic susceptibility markers for smoking and/or lung cancer, as well as markers of early disease. Such new markers might allow the identification of high risk individuals for specifically designed interventions. Moreover, a number of nutritional or pharmaceutical agents are known to block carcinogen activation, enhance detoxification or inhibit downstream carcinogenic events in experimental models. They may lead to nutritional or chemoprevention approaches that may be useful for the prevention of lung cancer and the many other malignancies that have been related to smoking. Our goal is to continue to contribute new knowledge in these areas. However, further tobacco control and improved cessation strategies are likely to remain the key component in the prevention of lung cancer.

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