ORIGINAL ARTICLE

Inflammatory Gene Polymorphisms in Lung Cancer Susceptibility

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ABSTRACT

Introduction: Chronic inflammation has been implicated in carcinogenesis, with increasing evidence of its role in lung cancer. We aimed to evaluate the role of genetic polymorphisms in inflammation-related genes in the risk for development of lung cancer.

Methods: A nested case-control study design was used, and 625 cases and 625 well-matched controls were selected from participants in the β-Carotene and Retinol Efficacy Trial, which is a large, prospective lung cancer chemoprevention trial. The association between lung cancer incidence and survival and 23 polymorphisms descriptive of 11 inflammation-related genes (interferon gamma gene [*IFNG*], interleukin 10 gene [*IL10*], interleukin 1 alpha gene [*IL1A*], interleukin 1 beta gene [*IL1B*], interleukin 2 gene [*IL2*], interleukin 4 receptor gene [*IL4R*], interleukin 4 gene [*IL4*], interleukin 6 gene [*IL6*], prostaglandin-endoperoxide synthase 2 gene [*PTGS2*] (also known as *COX2*), transforming growth factor beta 1 gene [*TGFB1*], and tumor necrosis factor alpha gene [*TNFA*]) was evaluated.

Results: Of the 23 polymorphisms, two were associated with risk for lung cancer. Compared with individuals with the wild-type (CC) variant, individuals carrying the minor allele variants of the *IL-1β-511*C>T promoter polymorphism (rs16944) (CT and TT) had decreased odds of lung cancer (OR = 0.74, [95% confidence interval (CI): 0.58–0.94] and OR = 0.71 [95% CI: 0.50–1.01], respectively, $p = 0.03$). Similar results were observed for the *IL-1β-1464* C>G promoter polymorphism (rs1143623), with presence of the minor variants CG and CC having decreased odds of lung cancer (OR = 0.75 [95% CI: 0.59–0.95] and OR = 0.69 [95% CI: 0.46–1.03], respectively, $p = 0.03$). Survival was not influenced by genotype.

Conclusions: This study provides further evidence that *IL1B* promoter polymorphisms may modulate the risk for development of lung cancer.

Keywords: Lung cancer; Polymorphism; Genetics; Cytokines; Inflammation

Introduction

Lung cancer is the leading cause of cancer mortality worldwide, with 155,870 deaths predicted in the United States in 2017.[1] Although the vast majority of lung cancer cases occur in the setting of tobacco use, lung cancer develops in less than 20% of smokers.[2] To explain these observations, a genetic basis for susceptibility to the carcinogenic effects of tobacco smoke has been postulated. Candidate genetic polymorphisms include genes involved in the metabolism and activation of the carcinogens in tobacco smoke, DNA repair, and cell cycle regulation.[3,4] Genome-wide association studies have demonstrated that single nucleotide polymorphisms (SNPs) located within the 15q25 region

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encoding for subunits of the nicotinic acetylcholine receptor are significantly associated with risk for lung cancer.[5,6]

Several lines of evidence support the hypothesis that persons with chronic inflammatory conditions, such as chronic obstructive pulmonary disease[7] or asthma,[8] have an increased risk for development of lung cancer, even when exposure to tobacco smoke is taken into account. Asbestos and cigarette smoke may exert some of their carcinogenic effects in the lung through chronic inflammation,[9] as tobacco use has been associated with higher levels of inflammatory cytokines and inflammatory cells.[10] Other evidence indicates that among persons with lung cancer, a proinflammatory state may lead to worse prognosis. This hypothesis is supported by the finding that patients with lung cancer with increased numbers of intratumoral macrophages had shorter relapse-free survival than do patients with low intratumoral macrophage density.[11] In addition, the total degree of systemic inflammation, as measured by C-reactive protein and albumin levels, has been found to be a powerful prognostic indicator in patients with lung cancer.[12]

The role of chronic infections in the etiology of hepatocellular carcinoma, gastric cancer, and cervical cancer is well established and is postulated to be mediated through the inflammatory response.[13] In humans, the role of inflammatory gene polymorphisms has been investigated in a variety of tumors, including gastric, liver, breast, ovarian, prostate, pancreas, skin, colon, and hematologic malignancies. Gene families studied have included interleukin 1 alpha (*IL1A*), interleukin 1 beta (*IL1B*), interleukin 1 receptor antagonist (*IL1RN*), interleukin 2 (*IL2*), interleukin 4 (*IL4*), interleukin 6 (*IL6*), interleukin 8 (*IL8*), interleukin 10 (*IL10*), tumor necrosis factor alpha (*TNFA*), lymphotoxin alpha (*LTA*), prostaglandin-endoperoxide synthase 2 (*PTGS2*) (also cyclooxygenase 2 [also known as *COX2*]), interferon gamma [*IFNG*], Toll like receptor 4 (*TLR4*), and others.[14,15] Inflammatory gene families have been studied most extensively in gastric cancer, where the results have been variable. Initial studies suggested that the proinflammatory alleles *IL-1β-31T* and *IL-1RN*2* increased effective interleukin-1 (IL-1) levels and inhibited gastric acid secretion, thereby increasing risk of noncardia gastric cancer.[16,17] These polymorphisms, in addition to polymorphisms in *TNFA* and *IL10*, were found to increase noncardia gastric cancer risk.[16] Further studies, however, have indicated that whereas *IL1B* and *IL-1RN* SNPs and haplotypes may be associated with atrophic gastritis, there is no association with gastric cancer.[18,19] Furthermore, results vary significantly depending on the population being studied, with variability most pronounced between white and Asian populations.[20]

Various studies have begun to understand the role of inflammatory genes in the pathogenesis of lung cancer. Measured free levels of circulating IL-17A, IL-17F, IL-22, IL-23, and tumor necrosis factor-α have been demonstrated to be significantly increased in patients with NSCLC compared with in healthy controls.[21] Research has focused on the role of SNPs within the *IL1B* gene and the *IL1RN* gene, similarly to prior studies in gastric cancer. Studies have demonstrated an increased risk of lung cancer as well as COPD among individuals carrying a -31T>C (rs1143627), -511C>T (rs16944), -3893A>G (rs12621220), or -1464 C>G (rs1143623) mutation.[22–25] Furthermore, studies have demonstrated haplotype linkage disequilibrium between the aforementioned *IL1B* SNPs and *IL1RN* variable number tandem repeats (VNTRs) with association between certain haplotypes and increased risk of lung cancer.[22–24,26] The success of checkpoint inhibitors in NSCLC has underscored the importance of immune regulations in the development and progression of lung cancer.[27]

Given these observations linking inflammatory gene SNPs and haplotypes with lung cancer risk, we tested the hypothesis that variation in the form of single-nucleotide polymorphisms (SNPs) in additional genes involved in the inflammatory response influences lung cancer risk and prognosis.

Materials and Methods

Subjects

Participants in this study were enrolled in the β-Carotene and Retinol Efficacy Trial (CARET), which is a large, randomized, multicenter trial that examined the effect of β-carotene and retinol versus placebo in a population at high risk for development of lung cancer.[28] Participants in CARET included heavy smokers who were age 50 to 69 years at the time of entry into the study, had a smoking history of 20 or more pack-years, and were either current smokers or had quit within the previous 6 years. As part of the study, genomic DNA was prospectively collected and banked from more than 12,000 subjects out of a total of 18,314 enrolled subjects. The Fred Hutchinson Cancer Research Center Institutional Review Board granted approval for the original intervention study, DNA collection, and use of the samples and data for the current study.

Criteria for the current study included (1) a diagnosis of lung cancer (both SCLC and NSCLC were included), (2) availability of a dried blood spot as source of DNA, and (3) availability of a matched control from the CARET data set. A matched, nested case-control design was used to minimize bias from population stratification. Demographic and exposure data on this population are well