Null Results in Brief

No Association between Serum Insulin-Like Growth Factor (IGF)-I, IGF-Binding Protein-3, and Lung Cancer Risk

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Introduction

Insulin-like growth factor (IGF)-I is a circulating hormone and tissue growth factor, which regulates cell growth, differentiation, and apoptosis (1). IGF-I function is modulated in part by IGF-binding protein-3 (IGFBP-3), which makes IGF-I unable to bind cell membrane surface IGF-I receptors (1). Circulating IGF-I levels are associated with energy-related factors [i.e., positive associations with weight and height and inverse associations with physical activity (2)]. Higher IGF-I levels have also been associated with an increased risk of lung (3) and other cancers (4), although three prospective studies observed null associations with respect to lung cancer risk (5-7). Because aberrant cellular growth and differentiation may play a significant role during multistage carcinogenesis, we evaluated whether IGF-I and IGFBP-3 are associated positively and inversely (respectively) with the risk of lung cancer in a nested case-control study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort. We also evaluated effect modification by energy-related factors, disease stage, and follow-up time.

Materials and Methods

A prospective case-control study was conducted within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (8). The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study included 29,133 male smokers, ages 50 to 69 years, in Finland. Subjects were provided α-tocopherol and/or β-carotene supplements or placebo for 5 to 8 years. The study was approved by the institutional review board of the National Cancer Institute and the National Public Health Institute of Finland, and written informed consent was obtained from all participants (8). Lung cancer cases occurring from at least 5 years following baseline blood collection through December 1997 were identified from the Finnish Cancer Registry, which provides ~100% case ascertainment. The medical records of the cases were reviewed by study physicians to confirm the lung cancer diagnosis and to stage the extent of the cancer. A random sample of the lung cancer cases (n = 200) was drawn from those cases free of any cancer at the start of the follow-up of this study. Controls (n = 400) were randomly selected among all eligible cohort members alive without a cancer diagnosis as of 5 years of follow-up as the comparison subcohort. Baseline serum samples were analyzed for IGF-I and IGFBP-3 by ELISA (Diagnostic Systems Laboratory, Webster, TX) as described previously (2). The intrabatch and interbatch coefficients of variation were 5.23% and 4.57% for IGF-I and 4.18% and 6.17% for IGFBP-3, respectively.

Generalized linear models adjusted for age as a continuous variable were used to estimate means and SDs by case-control status. Unconditional logistic regression was used to calculate odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for lung cancer in relation to quartiles of IGF-I and/or IGFBP-3. The final multivariate models shown include those factors that changed the estimated effect by ≥10%. Factors found not to confound the IGF associations included the following: intakes of total calories, carbohydrate, protein, total fat, and alcohol; height, weight, and body mass index (BMI; kg/m²); physical activity; asbestos exposure; number of cigarettes smoked daily; history of bronchial asthma, lung emphysema, chronic bronchitis, or diabetes; urban residence; and education. Tests for trends were conducted using the median values for IGF-I and IGFBP-3 quartiles. To test interactions on a multiplicative scale, a cross-product term of the ordinal score for each quartile of IGF-I and IGFBP-3 and energy-related factors was included in multivariate models. To test for potential heterogeneity by time to diagnosis of lung cancer or disease stage, stratified analyses of these clinical variables were done.

Results

Serum IGF-I and IGFBP-3 distributions among controls were comparable with those observed in other published studies (3, 5-7, 9). Both IGF-I and IGFBP-3 were slightly higher in controls than cases (Table 1). Among controls, the serum IGF-I level was closely correlated with the IGFBP-3 level (r = 0.69; P < 0.01). Cases weighed less, were leaner, and smoked more compared with controls.

As shown in Table 2, IGF-I and/or IGFBP-3 were inversely associated with lung cancer risk in the age- and intervention-adjusted model. However, with additional adjustment for BMI and years of smoking, the associations no longer reached statistical significance. Simultaneous adjustment for IGF-I and
IGFBP-3 did not alter the risk estimates, and categorization of serum IGF-I and IGFBP-3 as tertiles or quintiles resulted in similar, nonsignificant associations (data not shown). We further investigated whether associations were modified by the energy-related factors, such as height, BMI, physical activity, and total energy intake. There was little evidence for interaction (data not shown). Finally, there was little or no heterogeneity of risk with categories of time since serum collection, we endeavored to avoid the potential influence of subclinical cancer on IGF-I and IGFBP-3 serum concentrations. However, our finding that no evidence of effect modification by disease stage or follow-up time also makes this unlikely.

In summary, we did not find evidence for etiologic associations between circulating IGF-I or IGFBP-3 levels and lung cancer risk, and no effect modification by anthropometric factors, disease stage, or follow-up time was observed.

Table 2. Age- and multivariate-adjusted ORs of lung cancer by quartiles of baseline serum IGF-I, IGFBP-3, and IGF-I/IGFBP-3 molar ratio, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
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<td>0.97 (0.89-1.07)</td>
<td>0.99 (0.91-1.09)</td>
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<td>Fully adjusted OR (95% CI) + additionally IGFBP-3 adjusted‡</td>
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*Cut points were based on equal distribution among control subjects.
†Unconditional logistic regression, adjusted for age, intervention arm, BMI, years of smoking, and IGFBP-3.
‡Unconditional logistic regression, adjusted for age, intervention arm, BMI, years of smoking, and IGF-I.
References

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