

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 $\geq 10\%$. 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/m^2); 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

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Table 1. Age-adjusted baseline characteristics of case and control participants, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

Characteristic	Mean (SD)		P*
	Cases (N = 200)	Controls (N = 400)	
Age (y)	59.5 ± 72.1	56.4 ± 100.0	
IGF-I (ng/mL)	137.2 ± 52.3	145.5 ± 52.0	0.07
IGFBP-3 (ng/mL)	2,228 ± 650	2,369 ± 640	0.01
Height (cm)	173.4 ± 5.7	173.7 ± 6.0	0.62
Weight (kg)	76.7 ± 14.1	80.0 ± 14.0	<0.01
BMI (kg/m ²)	25.5 ± 2.8	26.5 ± 4.0	<0.01
Smoking history			
No. cigarette/d	23.8 ± 8.5	20.1 ± 8.0	<0.01
Years of smoking	38.4 ± 7.1	35.8 ± 6.0	<0.01
Asbestos exposure (%)	3.3	4.4	
Daily dietary intake			
Total energy (kcal)	2,840 ± 863	2,823 ± 840	0.82
Carbohydrate (g)	297.8 ± 49.5	305.3 ± 48.0	0.08
Protein (g)	102.9 ± 15.6	103.5 ± 14.0	0.63
Saturated fat (g)	54.9 ± 14.1	53.4 ± 14.0	0.22
Education	19.0	21.2	0.54
(% >elementary school)			
Intervention	49.1	54.2	0.26
(% α-tocopherol supplement)			
Intervention	52.8	52.1	0.88
(% β-carotene supplement)			

*P for case-control difference.

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 to lung cancer diagnosis [relative risk for highest quartile of IGF-I, 0.87 (5.0-7.8 years) versus 0.76 (7.8-11.7 years); median cutoff] and disease stage [relative risk for highest quartile of IGF-I, 0.82 (stages I and II) versus 0.71 (stages III and IV)].

Discussion

Our data do not support the hypothesis that IGF-I or IGFBP-3 is etiologically associated with lung cancer among smokers, confirming three previous studies. In fact, small inverse associations were suggested but were not statistically significant. Three recent prospective case-control studies reported no association between circulating IGF-I and IGFBP-3 and lung cancer risk, although nonsignificant inverse associations were also observed by these (5-7). By contrast, the study of Spitz et al. (9) showed a positive association for IGFBP-3 in heavy smokers and asbestos-exposed men. Our study size and power were comparable with the existing studies (3, 5-7, 9) and had sufficient power to detect moderate positive associations if they existed.

There are several explanations for the lack of an association between IGF-I or IGFBP-3 and lung cancer. One possibility is that IGFs are energy-metabolism and growth-related peptides, whereas lung cancer has not generally been positively associated with energy-related factors. Although it is possible that smoking may affect energy metabolism and appetite among smokers (10), we did not find that these energy-related factors modified the IGF-lung cancer association among smokers. Another explanation is that growth factor-related risk may be overshadowed by strong carcinogenic exposure and hazard of smoking. This would be consistent with the null associations observed for IGFs in other smoking-related cancers (2, 5-7, 11). Finally, findings of null associations with prospective studies (5-7), including our study, and findings of a positive association with a hospital-based case-control study (3) leave open the possibility that IGFs may be tumor markers [i.e., IGF levels may increase with tumor growth as a result of alterations in growth factor expression in (lung) tumor tissue (12)]. In particular, by excluding cases diagnosed within 5 years of 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

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
IGF-I					
Cases/controls	79/99	35/100	48/100	38/101	
Range (ng/mL)*	44.77-113.07	113.08-138.34	138.35-174.07	174.08-348.26	
Age- and intervention-adjusted OR (95% CI)	1.00 (referent)	0.43 (0.26-0.72)	0.67 (0.42-1.08)	0.57 (0.35-0.94)	0.06
Fully adjusted OR (95% CI) [†]	1.00 (referent)	0.51 (0.30-1.02)	0.76 (0.46-1.24)	0.69 (0.41-1.15)	0.26
Fully adjusted OR (95% CI) + additionally IGFBP-3 adjusted [‡]	1.00 (referent)	0.53 (0.31-1.08)	0.79 (0.45-1.39)	0.76 (0.39-1.49)	0.53
IGFBP-3					
Cases/controls	77/100	47/100	48/100	28/100	
Range (ng/mL)*	714-1,952	1,953-2,330	2,331-2,827	2,828-5,164	
Age- and intervention-adjusted OR (95% CI)	1.00 (referent)	0.66 (0.41-1.06)	0.78 (0.49-1.27)	0.50 (0.29-0.85)	0.02
Fully adjusted OR (95% CI) [†]	1.00 (referent)	0.69 (0.43-1.12)	0.97 (0.59-1.60)	0.64 (0.36-1.13)	0.24
Fully adjusted OR (95% CI) + additionally IGF-I adjusted [§]	1.00 (referent)	0.82 (0.48-1.38)	1.11 (0.61-2.02)	0.71 (0.35-1.47)	0.48
IGF-I/IGFBP-3 molar ratio					
Cases/controls	49/99	40/101	67/99	44/101	
Range*	0.08-0.19	0.19-0.22	0.23-0.25	0.26-0.46	
Age- and intervention-adjusted OR (95% CI)	1.00 (referent)	0.72 (0.43-1.22)	1.25 (0.77-2.03)	0.79 (0.47-1.33)	0.75
Fully adjusted OR (95% CI) [†]	1.00 (referent)	0.71 (0.41-1.23)	1.30 (0.79-2.14)	0.80 (0.47-1.36)	0.81

*Cut points were based on equal distribution among control subjects.

[†]Unconditional logistic regression, adjusted for age, intervention arm, BMI, and years of smoking.

[‡]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.

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