Plasma Levels of Insulin-Like Growth Factor-I and Lung Cancer Risk: a Case–Control Analysis

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Background: **Insulin-like growth factors (IGFs), in particular IGF-I and IGF-II, strongly stimulate the proliferation of a variety of cancer cells, including those from lung cancer. To examine the possible causal role of IGFs in lung cancer development, we compared plasma levels of IGF-I, IGF-II, and an IGF-binding protein (IGFBP-3) in patients with newly diagnosed lung cancer and in control subjects.** ***Methods:*** **From an ongoing hospital-based, case–control study, we selected 204 consecutive patients with histologically confirmed, primary lung cancer and 218 control subjects who were matched to the case patients by age, sex, race, and smoking status. IGF-I, IGF-II, and IGFBP-3 plasma levels were measured by enzyme-linked immunosorbent assay and then divided into quartiles, based on their distribution in the control subjects. Associations between the IGF variables and lung cancer risk were estimated by use of odds ratios (ORs). Reported *P* values are two-sided.** ***Results:*** **IGF and IGFBP-3 levels were positively correlated (all *r*>.27; all *P*<.001). High plasma levels of IGF-I were associated with an increased risk of lung cancer (OR = 2.06; 95% confidence interval [CI] = 1.19–3.56; *P* = .01), and this association was dose dependent in both univariate and multivariate analyses. Plasma IGFBP-3 showed no association with lung cancer risk unless adjusted for IGF-I level; when both of these variables were analyzed together, high plasma levels of IGFBP-3 were associated with reduced risk of lung cancer (OR = 0.48; 95% CI = 0.25–0.92; *P* = .03). IGF-II was not associated with lung cancer risk.** ***Conclusions:*** **Plasma levels of IGF-I are higher and plasma levels of IGFBP-3 are lower in patients with lung cancer than in control subjects. If these findings can be confirmed in prospective studies, measuring levels of IGF-I and IGFBP-3 in blood may prove useful in assessing lung cancer risk. [J Natl Cancer Inst 1999;91:151–6]**

Cancer cells exhibit numerous abnormal cellular activities—involving cell differentiation, transformation, proliferation, and apoptosis—that are maintained and controlled by a large number of peptide growth factors. Among the growth factors, insulin-like growth factors (IGFs) play a crucial role in regulating cell proliferation and differentiation. IGFs including IGF-I and IGF-II are peptide hormones with strong mitogenic effects on both normal and cancerous cells, including lung cancer cells *(1,2)*. In addition to stimulating cell proliferation, IGFs also suppress cellular apoptotic pathways to facilitate cell growth *(3,4)*. The actions of IGFs on cell proliferation and apoptosis are mediated via a specific cell-membrane receptor, insulin-like growth factor-I receptor (IGF-IR), which has been shown to be involved in cell transformation *(5)* and which contains tyrosine kinase activity. Binding of IGFs to this receptor activates the tyrosine kinase and initiates ras- and PI3 kinase-related signal transduction pathways *(6)*.

The interaction between IGFs and IGF-IR is regulated by the IGF-binding proteins (IGFBPs). Six IGFBPs (IGFBP-1 to IGFBP-6) with high affinity for IGFs have been identified and characterized *(2)*. The binding proteins normally inhibit the action of IGFs by blocking the binding of IGFs to their receptor; however, under certain circumstances, they can enhance IGF action by protecting IGFs from degradation *(7–9)*. The dual regulatory effects of the IGFBPs are further modulated by many factors including the IGFBP proteases, which include prostate-specific antigen (PSA) and cathepsin D *(2,10,11)*. Cell culture studies indicate that the antiproliferative effects of retinoic acid (a metabolite of vitamin A) and of wild-type p53 protein are mediated through increased expression of IGFBP-3, which in

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See ''Notes'' following ''References.''

turn inhibits the mitogenic effect of IGFs on cell proliferation *(12–15).*

Cell culture experiments *(16–19)* have demonstrated that most lung cancer cell lines (small-cell and non-small-cell) are able to express IGFs and their binding proteins. Although IGFs are known to be potent mitogens for lung cancer cells and are present in lung tissue, evidence that IGFs can influence the development of lung cancer remains unknown. To examine the hypothesis that IGFs and their major binding protein in plasma play a causal role in lung cancer, we compared plasma levels of IGF-I, IGF-II, and IGFBP-3 in patients with newly diagnosed lung cancers and in age-, sex-, race-, and smoking status-matched control subjects.

MATERIALS AND METHODS

Study Population

The patients and control subjects were selected consecutively from an ongoing case–control study of lung cancer conducted in the Department of Epidemiology at The University of Texas M. D. Anderson Cancer Center. The study subjects were described in detail elsewhere *(20).* Briefly, the case subjects were consecutive patients with lung cancer registered in the Departments of Thoracic Surgery and Thoracic Medical Oncology at The University of Texas M. D. Anderson Cancer Center. These patients were newly diagnosed with histologically confirmed primary lung cancer. However, histologic rereview is not completed. They had been referred for diagnosis or definitive treatment and had received no previous radiotherapy or chemotherapy. After the patients were informed about the study and agreed to sign an informed consent form for participation, an in-person interview with the use of a structured questionnaire was scheduled.

The control subjects were identified from a control-pool database established from registrants of a large, private, multispecialty health care provider, Kelsey-Seybold Clinic, which involves a health maintenance organization, managed care, and fee-for-service patients in the Houston metropolitan area. There are more than 40 000 individuals enrolled in our potential control database. Control subjects were frequency matched to the case patients by sex, age (within 5 years), and ethnicity (white, black, or Hispanic), with a 1 : 1 ratio. Each randomly selected control subject was contacted by telephone to confirm his or her willingness to participate, and an appointment was scheduled at a Kelsey-Seybold Clinic site convenient to the participant. If the person refused to participate or was deemed ineligible, another potential control subject was selected. Since the study is ongoing and control subject selection is not conducted concurrently with case patient accrual, perfect 1 : 1 matching has not yet been achieved. Furthermore, some subjects did not have sufficient plasma specimens available for the study. Therefore, there are some discrepancies among the matching variables between case patients and control subjects. We adjusted these differences in our data analysis. There are no differences in consent rates between case patients and control subjects. The study was approved by the Institutional Review Boards at The University of Texas M. D. Anderson Cancer Center and the Kelsey-Seybold Foundation.

Specimen Collection

After the interview, 10-mL blood specimens were drawn from each participant through venipuncture. The blood was collected in a heparinized tube and transported immediately to the laboratory, where the specimens were separated and processed. The plasma was collected after centrifugation of the blood at 1500 rpm for 10 minutes at room temperature and was stored at −80 °C. To assess the degradation of IGF-I and IGFBP-3 in stored plasma, a previous study compared levels of IGF-I and IGFBP-3 in stored heparinized plasma and in fresh specimens. No difference was found between the two types of specimen *(21).*

Measurements of IGFs and IGFBP-3

Three commercially available immunoassay kits (DSL, Webster, TX) were used in the study to determine the plasma levels of IGF-I, IGF-II, and IGFBP-3 through enzyme-linked immunosorbent assay. Cross-reaction of the antibodies with other members of the IGF family is not detected at physiologic concentrations, according to the manufacturer. The intra-assay and inter-assay precision is between 4.5%–8.6% and 3.3%–6.8% of the coefficient of variation, respectively, for the IGF-I assay; between 3.4%–6.7% and 5.9%–7.9% for the IGF-II assay; and between 7.3%–9.6% and 8.2%–11.4% for the IGFBP-3 assay.

The assays were performed following the instructions of the manufacturer (DSL) and without knowledge of case–control status. To separate IGFs from their binding proteins, we mixed plasma specimens with acid–ethanol extraction buffer before measurement. The extraction procedure has been evaluated, and the efficiency of the extraction was identical to that for acid-column chromatography. For IGFBP-3, the specimens were diluted 100-fold in an assay buffer before the test. To assess the impact of freeze–thaw cycles on the values of IGF-I, IGF-II, and IGFBP-3 in heparinized plasma, we measured each of 10 plasma specimens once per freeze–thaw cycle for five cycles. Levels of IGF-I, IGF-II, and IGFBP-3 in plasma remained constant over these freeze–thaw cycles.

Statistical Analysis

The correlations among the three growth factors were examined by use of the Spearman correlation coefficient. The distributions of the studied variables between the case patients and control subjects were compared by use of the χ^2 test for categorical data and the two-sample Student's *t* test for numerical data. All *P* values were two-sided. Associations were considered statistically significant at $P<.05$. Since the distributions of IGF-I and IGFBP-3 in the population were positively skewed, the levels of IGFs and IGFBP-3 were analyzed categorically on the basis of their quartile distribution in the control group (Table 1). To assess the strength of the association between lung cancer risk and the growth factors, we calculated the odds ratio (OR) and its 95% confidence interval (CI) with the use of unconditional logistic regression analysis *(22).* The logistic regression model was developed as both univariate and multivariate models. In the multivariate analysis, the following variables were included in the model: sex, age, ethnicity (white, black, or Hispanic), cigarette smoking status (never, former, or current), body mass index (BMI = kg of body weight/m^2 of height), and family history of any cancer (yes or no in their first-degree relatives). The interactions between IGF-I and IGF-II and between IGFs and IGFBP-3 were also examined in the logistic regression model by use of the product of the two given variables.

Table 1. Levels of IGF-I, IGF-II, and IGFBP-3 in case patients with lung cancer and in control subjects*

Variable	Case patients (n = 204)†	Control subjects (n = 218)†
IGF-I, ng/mL		
Mean (95% CI)	166.3 (156.1–176.5)	143.4 (135.5–151.3)
Minimum value	40.9	27.7
1st quartile	113.4	98.4
2nd quartile	151.4	136.1
3rd quartile	204.9	177.5
Maximum value	420.0	376.8
IGF-II, ng/mL		
Mean (95% CI)	595.9 (575.0–616.8)	588.7 (567.6–609.8)
Minimum value	71.3	37.9
1st quartile	308.7	250.2
2nd quartile	587.1	593.6
3rd quartile	695.4	683.7
Maximum value	1072.8	1042.5
IGFBP-3, μg/mL		
Mean (95% CI)	37.0 (35.7–38.3)	37.6 (36.3–38.9)
Minimum value	15.6	14.4
1st quartile	30.0	31.3
2nd quartile	37.4	37.4
3rd quartile	43.3	44.4
Maximum value	69.7	60.7

*IGF-I = insulin-like growth factor-I; IGF-II = insulin-like growth factor-II; IGFBP-3 = insulin-like growth factor-binding protein-3; 95% CI = 95% confidence interval.

†Since the study is ongoing, we have not yet achieved perfect 1:1 matching. Furthermore, plasma samples were not available for all study subjects.

RESULTS

As expected, plasma IGF-I and IGF-II levels were correlated ($r = .27$; $P<.001$), and both IGFs were even more closely correlated with IGFBP-3 ($r = 0.51$ and $P<.001$ for IGF-I; $r = .63$ and $P<.001$ for IGF-II). The mean and quartile values of IGF-I, IGF-II, and IGFBP-3 in the 204 patients and 218 control subjects are shown in Table 1. The mean and median levels of IGF-I were 16% and 11% higher, respectively, in case patients than in control subjects; however, for IGF-II and IGFBP-3, there was little difference in the means or medians between the case patients and control subjects.

Table 2 summarizes the categorical distributions of the three IGF variables together with other variables measured in the two study populations. Because the control subjects were selected to match the patients on sex, age, race, and cigarette smoking status, no statistically significant differences were observed between the two groups for these variables. The BMI was slightly higher in the control subjects than in the patients, and the difference was statistically significant ($P = .03$). Patients in the highest fourth quartile of IGF-I level made up 36.3% of the total, compared with 24.8% of control subjects ($P = .04$). For IGF-II and IGFBP-3, there were no differences between patients and control subjects in the quartile distributions.

Table 2. Associations of lung cancer with IGF-I, IGF-II, IGFBP-3, and other variables*

Variable	Case patients (n = 204)†		Control subjects (n = 218)†		P‡
Age, y, mean (95% CI)	62	(60.6–63.4)	63	(61.8–64.2)	.27
BMI, mean (95% CI)	26.1	(25.5–26.8)	27.2	(26.5–27.9)	.03
Sex, No. (%)					
Male	108	(52.9)	116	(53.2)	
Female	96	(47.1)	102	(46.8)	.96
Cigarette smoking status, No. (%)					
Never smoker	20	(9.8)	20	(9.2)	
Former smoker	92	(45.1)	120	(55.0)	
Current smoker	92	(45.1)	78	(35.8)	.11
Race, No. (%)					
White	151	(74.0)	181	(83.0)	
Hispanic	27	(13.2)	20	(9.2)	
Black	26	(12.8)	17	(7.8)	.08
IGF-I, No. (%)					
1st quartile	36	(17.6)	54	(24.8)	
2nd quartile	42	(20.6)	55	(25.2)	
3rd quartile	52	(25.5)	55	(25.2)	
4th quartile	74	(36.3)	54	(24.8)	.04
IGF-II, No. (%)					
1st quartile	50	(24.5)	54	(24.8)	
2nd quartile	57	(27.9)	55	(25.2)	
3rd quartile	42	(20.6)	54	(24.8)	
4th quartile	55	(27.0)	55	(25.2)	.75
IGFBP-3, No. (%)					
1st quartile	59	(28.9)	55	(25.2)	
2nd quartile	42	(20.6)	54	(24.8)	
3rd quartile	59	(28.9)	53	(24.3)	
4th quartile	44	(21.6)	56	(25.7)	.40

*IGF-I = insulin-like growth factor-I; IGF-II = insulin-like growth factor-II; IGFBP-3 = insulin-like growth factor-binding protein-3; 95% CI = 95% confidence interval; BMI = body mass index (body weight in kg/height in m^2).

†Since the study is ongoing, we have not yet achieved perfect 1:1 matching. Furthermore, plasma samples were not available for all study subjects.

‡All P values are two-sided, and associations are considered statistically significant at $P<.05$.

In our logistic regression analysis, the risk of lung cancer was positively associated with the level of IGF-I in plasma, and the trend was statistically significant ($P = .01$) (Table 3). The OR was 2.06 (95% CI = 1.19–3.56) for the highest quartile of IGF-I compared with the lowest ($P = .01$) (Table 3). This pattern persisted when other variables including age, sex, race, cigarette smoking status, BMI, and family history of any cancer were adjusted in the regression model (Table 4). Because IGFBP-3 regulates the action of IGF-I and because plasma levels of IGFBP-3 and IGF-I are correlated, we also evaluated the association between IGF-I and the disease risk while we adjusted for IGFBP-3 levels. With inclusion of IGFBP-3 in the logistic model, we observed a more substantial increase in the risk of lung cancer associated with IGF-I. The ORs were 2.75 (95% CI = 1.37–5.53) for the fourth quartile and 1.96 (95% CI = 1.02–3.80) for the third quartile compared with the first (lowest) quartile, and both ORs were statistically significant ($P = .004$ and $P = .04$, respectively). However, the interaction term between IGF-I and IGFBP-3 was not significant in the logistic model (data not shown).

Adjusting IGFBP-3 in the model not only enhanced the strength of the association between IGF-I and lung cancer but also demonstrated a potential protective effect of this binding protein. IGFBP-3 levels in plasma did not appear to be associated with risk of lung cancer when this variable was analyzed either in the contingency table (Table 2) or in the logistic regression with the univariate model (Table 3) or the multivariate model without including IGF-I (Table 4). When IGF-I was included in the logistic model, the results suggested that the risk of lung cancer could be reduced by more than 50% for those individuals with the highest quartile of IGFBP-3 levels as compared with those with the lowest quartile (OR = 0.48; 95% CI = 0.25–0.92; $P = .03$). However, there was no clear dose–response relationship for IGFBP-3.

The distribution of the case patients and control subjects

Table 3. Odds ratios of risk of lung cancer for IGF-I, IGF-II, and IGFBP-3 in univariate analysis*,†

Variable	OR	95% CI	P‡
IGF-I			
1st quartile	1.00	Referent	
2nd quartile	1.15	0.64–2.05	.65
3rd quartile	1.42	0.80–2.50	.23
4th quartile	2.06	1.19–3.56	.01
Test for trend: $P = .01$			
IGF-II			
1st quartile	1.00	Referent	
2nd quartile	1.12	0.66–1.91	.68
3rd quartile	0.74	0.43–1.27	.27
4th quartile	1.33	0.77–2.31	.31
Test for trend: $P = .97$			
IGFBP-3			
1st quartile	1.00	Referent	
2nd quartile	0.73	0.42–1.25	.25
3rd quartile	1.04	0.62–1.75	.89
4th quartile	0.73	0.43–1.26	.26
Test for trend: $P = .50$			

*IGF-I = insulin-like growth factor-I; IGF-II = insulin-like growth factor-II; IGFBP-3 = insulin-like growth factor-binding protein-3; OR = odds ratio; 95% CI = 95% confidence interval.

†In univariate analysis, only one variable was included in the model.

‡All P values are two-sided, and associations are considered statistically significant at $P<.05$.

Table 4. Odds ratios of risk of lung cancer for IGF-I and IGFBP-3 in multivariate analysis*,†

Variable	OR	95% CI	P‡
IGF-I without IGFBP-3			
1st quartile	1.00	Referent	
2nd quartile	1.15	0.62–2.11	.66
3rd quartile	1.56	0.85–2.87	.15
4th quartile	2.00	1.10–3.65	.02
Test for trend: $P = .01$			
IGF-I including IGFBP-3			
1st quartile	1.00	Referent	
2nd quartile	1.34	0.71–2.53	.37
3rd quartile	1.96	1.02–3.80	.04
4th quartile	2.75	1.37–5.53	.004
Test for trend: $P = .002$			
IGFBP-3 without IGF-I			
1st quartile	1.00	Referent	
2nd quartile	0.65	0.37–1.15	.14
3rd quartile	0.98	0.57–1.68	.94
4th quartile	0.76	0.44–1.34	.34
Test for trend: $P = .63$			
IGFBP-3 including IGF-I			
1st quartile	1.00	Referent	
2nd quartile	0.56	0.31–1.02	.06
3rd quartile	0.68	0.37–1.24	.21
4th quartile	0.48	0.25–0.92	.03
Test for trend: $P = .05$§			

*IGF-I = insulin-like growth factor-I; IGFBP-3 = insulin-like growth factor-binding protein-3; OR = odds ratio; 95% CI = 95% confidence interval.

†In multivariate analysis, adjustment was made for age, sex, race, cigarette smoking status, body mass index (body weight in kg/height in m^2), and family history of any cancer.

‡All *P* values are two-sided, and associations are considered statistically significant at $P<.05$.

§Exact $P = .049$.

within the four categories of IGF-II did not differ ($P = .75$, Table 2). In the logistic regression analysis, the risk of lung cancer was modestly elevated in the highest quartile compared with the lowest quartile of IGF-II, but the difference was not statistically significant (OR = 1.33; 95% CI = 0.77–2.31; $P = .31$, Table 3). When we adjusted for IGF-I and IGFBP-3 and their interactions in the model, we found no significant association between IGF-II and disease risk (data not shown).

There was no association between cigarette smoking status (never, former, or current smoker) and levels of IGFs and IGFBP-3 among the control subjects (data not shown). We also examined pack-years of smoking, duration of smoking, and the total number of cigarettes smoked in relation to plasma levels of IGF-I, IGF-II, and IGFBP-3. None of the correlations analyzed were shown to be significant (data not shown), suggesting that levels of IGFs and IGFBP-3 in plasma were not influenced by cigarette smoking.

DISCUSSION

In this case–control study, we found that higher plasma levels of IGF-I were associated with an increased risk of lung cancer and that the association remained statistically significant when we adjusted for the variables of age, sex, race, cigarette smoking status, BMI, and family history of any cancer in the analysis. In addition, the study demonstrated a dose–response relationship between the risk of lung cancer and levels of IGF-I. The association became stronger when we adjusted for IGFBP-3 in the analysis. The study also indicated that IGFBP-3 was associated with a reduced risk of the disease, but this effect was seen only when we adjusted for IGF-I in the analysis. In the univariate analysis, IGFBP-3 did not show any statistically significant association with the risk of lung cancer. Despite its close correlation with IGF-I and IGFBP-3 in plasma, IGF-II was not associated with risk when analyzed individually or after adjustment was made for IGF-I, IGFBP-3, or other variables.

Recently, two prospective studies reported higher plasma levels of IGF-I in association with increased risks of prostate cancer in men *(21)* and of breast cancer in premenopausal women *(23)*. We were impressed with the striking similarities between these studies and our own, although three different types of cancers were investigated and our study was a retrospective analysis. There was a substantial association between IGF-I levels in plasma and risks of all three cancers. All three studies consistently showed a strong, dose–response relationship between increased risks of these cancers and elevated levels of IGF-I. The effect of IGF-I tended to be more significant when adjustment was made for levels of IGFBP-3 in the analyses. For prostate and lung cancers, IGFBP-3 also showed some protective effects; however, by itself, IGFBP-3 did not demonstrate such an effect. Also, for both prostate and lung cancers, no association was found for IGF-II.

The consistency of the findings for IGF-I prompts us to speculate that IGF-I either may have a carcinogenic effect or may be a powerful growth promoter and that circulating IGF-I levels may serve as a biomarker for assessing lung cancer risk. It may also be possible that an increased plasma IGF-I level is part of the phenotype of certain types of cancer that require IGF-I to maintain their high rate of proliferation and growth. Results from cell culture studies and animal experiments have suggested that IGF-I is a potent mitogen for a variety of cancer cells, including breast, prostate, lung, colon, and liver cells *(1,24–26)*. IGF-I increases DNA synthesis and up-regulates the expression of cyclin D1, thereby accelerating the cell cycle from G_1 to S phase *(27)*. While stimulating cell proliferation, IGF-I also shuts down the apoptotic pathway *(3,4)*. Because the actions of IGF-I are mediated through the IGF-IR, removing the receptor from the cell membrane could abolish its mitogenic and apoptotic effects *(2,28,29)*. In addition, IGF-IR is involved in cell transformation, and interruption of IGF-IR expression on the cell membrane blocks cell transformation induced by a tumor virus or an oncogene product *(28)*.

The interaction between IGF-I and IGF-IR is regulated by the IGFBPs. In the univariate analysis, of two of the studies cited above, this protein failed to show any association with the risk of prostate or lung cancer. However, when analyzed together with IGF-I, IGFBP-3 appeared to be associated with a reduced risk of both prostate and lung cancers, but the binding protein also appeared to enhance the associations between risk of these cancers and plasma IGF-I level. These observations in epidemiologic studies are compatible with the results from *in vitro* and *in vivo* studies, demonstrating that IGFBP-3 suppresses the mitogenic and apoptotic effects of IGF-I on cancer cells. This suppression is explained by the fact that IGFBP-3 prevents the interaction between IGF-I and IGF-IR because of IGF-I's higher binding affinity for the binding protein than for the receptor. Recent experiments *(30)* also suggest that IGFBP-3 may inhibit cell growth independently of IGF-I.

The relationship between IGF-I and IGFBP-3 in lung cancer may shed light on the action of two antiproliferative molecules

whose effects have been studied in lung cancer, retinoic acid and p53. Mutation of the p53 tumor suppressor gene (also known as TP53) has been linked to the development of many cancers, including lung cancer *(31)*. One of the main functions of the p53 protein is to slow down cell division—which allows cells to repair DNA damage or to initiate apoptosis if the damage is irreversible. The suppression of cell division by p53 is speculated to be mediated through IGFBP-3, because wild-type p53 protein is shown to increase IGFBP-3 expression. IGFBP-3 subsequently suppresses the mitogenic effect of IGF-I, which results in the inhibition of cell proliferation *(13)*. The possible link between IGF-I and p53 is further supported by an observation that the function of p53 protein is suppressed by IGF-I. As a transcription factor, p53 protein must be intranuclear to exert its action. When cells undergo division induced by IGF-I, p53 protein is expelled from the nucleus *(32)*. In addition, p53 protein down-regulates the expression of IGF-IR *(15)*. The growth of bladder tumors induced by *p*-cresidine in p53-deficient transgenic mice was suppressed by decreasing serum levels of IGF-I through diet restriction, and restoring IGF-I levels in serum resulted in resumption of tumor growth and progression *(33)*. This study also indicated that tumor growth control by IGF-I was related to IGF-I's mitogenic and anti-apoptotic effects.

Cell culture studies *(12,14,34)* have found that retinoic acid stimulated the production of IGFBP-3, which in turn inhibited the action of IGF-I. Findings from our study support such a relationship between IGF-I and IGFBP-3 and, furthermore, indicate that monitoring changes in IGFBP-3 and IGF-I levels in the blood may help to evaluate the effectiveness of vitamin supplements as chemopreventive agents.

In our study, the BMI was lower in the case subjects than in the control subjects, and the difference was statistically significant ($P = .03$). However, this difference should not have any impact on the association between IGF-I and lung cancer risk, because the ORs did not show substantial changes when we adjusted for BMI in the analysis. Furthermore, no correlation between IGF-I and BMI has been observed in previous studies *(19,35,36)*. Because this is a case–control study, findings from our study need to be further confirmed by prospective cohort studies. Nevertheless, similarities between our study and two cohort studies on different cancer sites lend support to our speculation that IGF-I may be involved in the disease's development. If our observations can be confirmed in prospective studies, the measurement of plasma levels of IGF-I and IGFBP-3 will have potential utility in assessing lung cancer risk and/or in monitoring the effectiveness of chemoprevention interventions.

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NOTES

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