METABOLISM CLINICAL AND EXPERIMENTAL 60 (2011) 1100–1106

available at www.sciencedirect.com

ScienceDirect

www.metabolismjournal.com

Insulin resistance: an independent risk factor for lung cancer?

Eleni Th. Petridou[a,*], *Theodoros N. Sergentanis*[a], *Constantine N. Antonopoulos*[a], *Nick Dessypris*[a], *Ioannis L. Matsoukis*[a], *Konstantinos Aronis*[b], *Anna Efremidis*[c], *Constantinos Syrigos*[d], *Christos S. Mantzoros*[b,e]

[a] *Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, 115 27 Athens, Greece*
[b] *Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*
[c] *2nd Pathology Oncology Clinic, Saint-Savvas Anticancer Hospital, Athens, Greece*
[d] *Oncology Unit, 3rd Department of Internal Medicine, Sotiria General Hospital, Athens University Medical School, Athens, Greece*
[e] *VA Boston Healthcare System, Harvard Medical School, Boston, MA, USA*

ARTICLE INFO

Article history:
Received 21 September 2010
Accepted 8 December 2010

ABSTRACT

Insulin resistance is closely associated with numerous metabolic disorders. Although studies have supported the importance of insulin resistance in carcinogenesis, the existing data have not established its relevance in the context of lung cancer. The aim of the present case-control study was to evaluate the association between insulin resistance and lung cancer after adjusting for possible confounders. Homeostasis model assessment of insulin resistance (HOMA-IR) and serum leptin and adiponectin levels were determined in 81 lung cancer cases and 162 age- and sex-matched controls; anthropometric and lifestyle variables were recorded. Mean HOMA-IR in the cases was more than 2-fold higher compared with the mean value of controls ($P < .001$). Among controls, HOMA-IR correlated positively with serum leptin ($r = 0.16$; $P = .04$), body mass index ($r = 0.43$; $P = .0001$), and waist-to-hip ratio ($r = 0.21$; $P = .01$) but negatively with serum adiponectin ($r = –0.29$; $P = .0002$). As expected, smoking was associated with an approximately 10-fold increase in lung cancer risk in multiple logistic regression models. A positive association between HOMA-IR, treated as continuous variable, and lung cancer (odds ratio [OR] = 1.52, 95% confidence interval [CI]: 1.16-1.99, $P = .002$, model 1) was demonstrated, which persisted after adjustment for somatometric and lifestyle variables (OR = 2.36, 95% CI: 1.00-5.55, $P = .05$, model 2). When serum adiponectin was also taken into account, the association seemed fairly robust (OR = 2.58, 95% CI: 1.11-6.01, $P = .03$, model 3); on the contrary, when serum leptin was added, the association remained positive, but lost its statistical significance (OR = 1.76, 95% CI: 0.78-3.98, $P = .17$, model 4). In the fully adjusted model, HOMA-IR was still positively, but only marginally, associated with lung cancer risk (OR = 2.02, 95% CI: 0.88-4.65, $P = .10$, model 5). Insulin resistance may represent a meaningful risk factor for lung cancer.

Author contributions: ETP conceived the idea of the study, drafted the manuscript, and takes responsibility for the integrity of the data as well as for the accuracy of the data analysis; TNS and CNA drafted the manuscript and interpreted the results; ND performed statistical analysis and contributed to drafting the manuscript; ILM and KA revised critically the manuscript for important intellectual content; AE and CS contributed to the subject recruitment and revised critically the manuscript for important intellectual content; CSM conceived the idea, performed the serum measurements, and contributed to the discussion of results.

* *Corresponding author*. Tel.: +30 210 7462187; fax: +30 210 7462105.
E-mail address: epetrid@med.uoa.gr (E.T. Petridou).

0026-0495/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2010.12.002

1. Introduction

Insulin resistance is a condition with increased prevalence and significance in the context of obesity, metabolic syndrome, nonalcoholic fatty liver disease, type 2 diabetes mellitus [1,2], and malignancy [3,4]. Recent large cohort studies including the National Health and Nutrition Examination Survey III in the United States [5] and the Heart Disease and Diabetes Risk Indicators in a Screened Cohort in the United Kingdom [6] have independently pointed to insulin resistance as a risk factor for overall cancer mortality. Similarly, diabetes mellitus seems to correlate with overall cancer mortality [7,8]. Studies remain conflicting regarding the link between diabetes and lung cancer specifically, as positive [9], null [10-12], or even inverse [13] associations have been reported. In addition, the National Health and Nutrition Examination Survey III reported that the exclusion of lung cancer cases reinforced the interplay between insulin resistance and cancer mortality [5], as lung cancer is a malignancy typically not associated with obesity [14].

Long after the establishment of the clear-cut association between smoking and lung cancer, the latter is currently viewed as an entity integrating occupational, lifestyle, dietary, and genetic risk factors [15]. Among inherent risk factors, attention has recently shifted to adipocytokines, such as leptin and adiponectin, with intriguing results. Leptin, a 16-kd protein hormone, is mainly synthesized by adipose tissue and is involved in the physiologic process of food intake, energy expenditure [16], and immune regulation [17,18]; despite conflicting results [19], elevated serum levels of leptin seem to represent a meaningful risk factor for lung cancer [20] due to direct growth-promoting [21] or indirect actions. On the other hand, adiponectin, an adipocyte-secreted 247–amino acid protein acting as an endogenous insulin sensitizer [22], has not yielded promising results in terms of conferring any lung cancer risk [19,23]. Nevertheless, the expression of adiponectin receptors in lung cancer tissue, as well as the

Table 1 – Distribution of 81 lung cancer cases and 162 age- and sex- matched controls by anthropometric/demographic/lifestyle variables and mean (SD) values of HOMA-IR, leptin, and adiponectin

Variable	Cases		Controls		P value
	n	%	n	%	
Age (y)					Matched variable
<55	14	17.3	28	17.3	
55-64	26	32.1	50	30.9	
65-74	21	25.9	43	26.5	
75+	20	24.7	41	25.3	
Sex					Matched variable
Male	68	84.0	136	84.0	
Female	13	16.0	26	16.0	
Education (y)					.04[a]
Uneducated/primary (<6)	41	50.6	67	41.4	
Elementary (6-8)	13	16.1	19	11.7	
Intermediate (9-11)	10	12.3	22	13.6	
High school (12)	11	13.6	31	19.1	
College/university (12+)	6	7.4	23	14.2	
Smoking (cigarettes smoked daily × years smoking)					.0001[a]
0	2	2.5	65	40.1	
1-649	12	14.8	42	25.9	
650-1399	23	28.4	36	22.2	
1400+	44	54.3	19	11.8	
Daily coffee consumption					.005[b]
Yes	77	95.1	133	82.1	
No	4	4.9	29	17.9	
Alcohol consumption (glasses/mo)					.001[b]
0	14	17.3	24	14.8	
1-60	42	51.8	118	72.8	
61+	25	30.9	20	12.4	
	Mean	SD	Mean	SD	P value
HOMA-IR	10.8	16.67	4.1	3.70	.0006
Leptin (ng/mL)	9.4	9.98	8.1	7.23	.31
Adiponectin (μg/mL)	10.5	3.58	9.7	3.24	.09
BMI (kg/m^2)	25.7	3.90	28.2	3.86	.0001
WHR (%)	97.0	8.91	96.2	8.46	.53
Weight change (kg)	-2.9	4.11	0.1	2.35	.0001
Smoking (cigarettes smoked daily × years smoking)	1556.0	877.14	600.7	877.90	.0001

[a] P value derived from χ^2 for trend.
[b] P value derived from χ^2 for contrast.

Table 2 – Pearson correlation coefficient (*P* values) of HOMA-IR, age, serum leptin, serum adiponectin, and somatometric variables among 162 controls

	Age	Leptin	Adiponectin	BMI	WHR
HOMA-IR	−0.02 (.80)	0.16 (.04)	−0.29 (.0002)	0.43 (.0001)	0.21 (.01)
Age		0.07 (.37)	0.14 (.07)	−0.14 (.07)	−0.04 (.60)
Leptin			0.15 (.06)	0.41 (.0001)	−0.14 (.08)
Adiponectin				−0.16 (.05)	−0.26 (.001)
BMI					0.24 (.002)

emergence of lower serum adiponectin levels in advanced lung cancer cases, is a dipole potentially implicating adiponectin in lung carcinogenesis [23].

Adipocytokines and insulin resistance seem to be mutually intertwined within a complex network of interactions. Specifically, insulin resistance indices were shown to be negatively associated with serum adiponectin levels in healthy [24] and diabetic [25] populations, in line with the insulin-sensitizing properties of adiponectin. On the contrary, elevated serum leptin [26] or elevated leptin-to-adiponectin ratio seems to directly correlate with insulin resistance [27]. Given the interrelationships among insulin resistance, obesity, leptin, and adiponectin, the possibility for mutual confounding needs to be considered.

Thus, the optimal examination of insulin resistance in the context of lung cancer risk necessitates the simultaneous, careful evaluation of its meaningful counterparts, that is, obesity and serum leptin and adiponectin levels. In light of the above, the present case-control study aims to evaluate the association between lung cancer and insulin resistance, adjusting for a variety of confounders, including body mass index (BMI), weight loss, and serum adipocytokine levels.

2. Methods

The study comprised 85 patients who were admitted to 3 major general hospitals in Athens from February 2002 to June 2005 with a histologically confirmed diagnosis of lung cancer. Patients who reported any other cancer type before enrolment were excluded. For each case, 2 apparently healthy controls

Table 3 – Logistic regression–derived ORs and 95% CIs for HOMA-IR controlling for study covariates

Variable	Category or increment	ORs [a] (95% CIs)	ORs [b] (95% CIs)	ORs [c] (95% CIs)	ORs [d] (95% CIs)	ORs [e] (95% CIs)
		P value	*P* value	*P* value	*P* value	*P* value
HOMA-IR	1 SD among controls	1.52 (1.16-1.99) .002	2.36 (1.00-5.55) .05	2.58 (1.11-6.01) .03	1.76 (0.78-3.98) .17	2.02 (0.88-4.65) .10
BMI	≥2 kg/m^2		0.53 (0.32-0.86) .01	0.58 (0.35-0.98) .04	0.46 (0.27-0.80) .006	0.49 (0.27-0.90) .02
Weight change	≤1 kg		0.67 (0.53-0.85) .001	0.67 (0.53-0.86) .002	0.66 (0.49-0.87) .004	0.66 (0.49-0.90) .008
WHR	1 Quintile more		0.81 (0.50-1.33) .41	0.85 (0.52-1.38) .5	0.89 (0.53-1.51) .67	0.92 (0.54-1.56) .75
Education	1 Level more		0.67 (0.40-1.11) .12	0.58 (0.33-1.04) .07	0.66 (0.38-1.16) .15	0.57 (0.30-1.07) .08
Coffee consumption	Yes vs no		0.55 (0.06-5.26) .61	0.58 (0.05-6.52) .66	0.52 (0.05-5.92) .60	0.49 (0.04-6.86) .60
Smoking	1 Quartile more		9.50 (2.77-32.62) .001	9.78 (2.60-36.84) .001	10.12 (2.69-38.11) .001	11.89 (2.50-56.53) .002
Alcohol	0 vs 1-60 glasses/mo		1.98 (0.30-13.27) .48	2.00 (0.26-15.41) .51	2.35 (0.28-19.63) .43	3.05 (0.28-33.77) .36
	61+ vs 1-60 glasses/mo		2.20 (0.52-9.43) .29	3.36 (0.62-18.19) .16	2.59 (0.57-11.75) .22	4.89 (0.74-32.23) .10
Adiponectin	1 SD among controls			1.84 (0.82-4.12) .14		2.00 (0.80-4.97) .14
Leptin	1 SD among controls				1.50 (0.95-2.38) .08	1.54 (0.95-2.51) .08

[a] Model 1: unadjusted OR for HOMA-IR.
[b] Model 2: OR for mutually adjusted HOMA-IR, BMI, weight change during the last 2 months, WHR, education, coffee consumption, smoking, and alcohol.
[c] Model 3: OR for mutually adjusted HOMA-IR, BMI, weight change during the last 2 months, WHR, education, coffee consumption, smoking, alcohol, and adiponectin.
[d] Model 4: OR for mutually adjusted HOMA-IR, BMI, weight change during the last 2 months, WHR, education, coffee consumption, smoking, alcohol, and leptin.
[e] Model 5: OR for mutually adjusted HOMA-IR, BMI, weight change during the last 2 months, WHR, education, coffee consumption, smoking, alcohol, adiponectin, and leptin.

matched for sex and age (±5 years) who presented for routine health screening examinations were consecutively enrolled in the study. In the end, 81 cases and 162 controls participated in this study, the majority of whom resided in the Greater Athens area. For all participants, fasting blood samples were obtained. Further details on exclusion criteria for controls, interview of cases and controls, as well as blood sampling are provided in the Supplementary Online Appendix.

The blood sample levels of serum glucose, leptin, and adiponectin were collected and blindly analyzed in the same laboratory batch by the same technician, as previously described [20,23]. Average preservation time was similar for cases and controls. All determination of human insulin levels were measured via radioimmunoassay (Millipore, Billerica, MA) with an interassay coefficient of variation of 2.9% to 6.0%, an intraassay coefficient of variation of 2.2% to 4.4%, and a sensitivity of 2 μU/mL. Thereafter, insulin resistance was estimated by calculating homeostasis model assessment of insulin resistance (HOMA-IR) based on the equation HOMA-IR = insulin (in microunits per liter) * glucose (in milligrams per deciliter)/405 [28]. The study protocol was approved by the University of Athens Medical School Ethics Committee and conformed to the Helsinki Declaration of 1975, and all participants provided informed consent.

Descriptive statistics (mean, standard deviation [SD]) of the anthropometric and lifestyle variables, serum hormones, as well as for HOMA-IR were calculated for cases and controls. Subsequently, we calculated the Pearson correlation coefficient of HOMA-IR with the serum hormones and the somatometric variables among controls. In addition, to study the possible association of HOMA-IR with lung cancer, the data were modeled through multiple conditional logistic regression analyses using case-control status as the outcome variable and HOMA-IR (in increments of 1 SD of the index among controls) as the main predictor variable of interest. Previously described potential confounders [23], namely, BMI at the time of diagnosis (in 2-kg/m^2 increments), body weight loss in the 2 months before diagnosis (1 kg less), waist-to-hip ratio (WHR) (in quintiles), education (1 level more), coffee consumption (yes vs no), smoking (quartiles of cigarette-years of smoking), and alcohol consumption (0 vs 1-60 glasses per month and 61+ vs 1-60 glasses per month) were also included in the analysis. The effect of serum adiponectin (in increments of 1 SD among controls) and serum leptin (in increments of 1 SD among controls) was additionally tested. In addition, the association of HOMA-IR, especially with non–small cell lung cancer (NSCLC) (which represented the majority of cases), was also examined by conducting unconditional logistic regression analysis, controlling for age and sex. The possible variation of HOMA-IR with the advancement of disease among cases was examined using logistic regression analysis also controlling for age, sex, education, smoking, BMI, WHR, and weight change during the last 2 months. The SAS (Cary, NC) statistical package was used.

3. Results

Table 1 presents the distribution of anthropometric, lifestyle, and sociodemographic data, as well as HOMA-IR and serum adiponectin and leptin hormonal levels, in cases and controls. These data serve mostly descriptive purposes and are not directly interpretable because of mutual confounding. With respect to possible confounders, results of this study are consistent with the findings of a previous study [23]. Concerning HOMA-IR, the mean value of cases was more than 2-fold higher compared with the mean value of controls ($P < .001$).

Table 2 shows the correlation of HOMA-IR among controls with age, serum leptin, serum adiponectin, BMI, and WHR. The HOMA-IR was statistically significantly and positively correlated with serum leptin ($P = .04$), BMI ($P = .0001$), and WHR ($P = .01$), whereas it was also significantly but negatively correlated with serum adiponectin ($P = .0002$).

Results derived from multiple logistic regression models (odds ratios [ORs] and 95% confidence intervals [CIs]) are shown in Table 3. An increased risk for lung cancer emerged with higher HOMA-IR (OR = 1.52, 95% CI: 1.16-1.99, $P = .002$, model 1). Adjustment for somatometric variables (BMI, weight change during the last 2 months, and WHR) and sociodemographic and lifestyle variables (education, coffee consumption, smoking, and alcohol consumption) did not alter the positive association between HOMA-IR and lung cancer (OR = 2.36, 95% CI: 1.00-5.55, $P = .05$, model 2). When serum adiponectin, which was found to be inversely correlated to HOMA-IR, was also taken into account, the magnitude of the association of HOMA-IR with lung cancer increased and remained statistically significant (OR = 2.58, 95% CI: 1.11-6.01, $P = .03$, model 3). On the contrary, when serum leptin was added into the model, the association of HOMA-IR and lung cancer remained positive, but of no statistical significance (OR = 1.76, 95% CI: 0.78-3.98, $P = .17$, model 4). In the fully adjusted model, where both serum leptin and serum adiponectin were included, the effect of HOMA-IR was once again positive, but marginal (OR = 2.02, 95% CI: 0.88-4.65, $P = .10$,

Table 4 – Mean values and SDs of HOMA-IR among 81 lung cancer cases, by disease stage (upper panel), along with unconditional multiple logistic regression–derived OR and 95% CI among cases with advanced vs limited disease (lower panel)

Variable	HOMA-IR	
	Mean (SD)	P value
Limited: n = 7	3.73 (1.87)	.18[a]
NSCLC stage I: n = 3	3.69 (1.76)	
SCLC: n = 4	3.77 (2.22)	
Advanced: n = 74	11.42 (17.29)	
NSCLC stage IIIa: n = 6	15.18 (18.54)	
NSCLC stage IIIb: n = 15	16.22 (19.12)	
NSCLC stage IV: n = 39	8.59 (15.93)	
SCLC: n = 14	12.53 (18.79)	
Multiple logistic regression–derived OR		
	OR (95% CI)	P value
HOMA-IR (increment of 1 SD among controls)	2.86 (0.81-10.14)	.10[b]

[a] P value derived from Wilcoxon 2-sided test comparing limited vs advanced disease.
[b] Controlling for age, sex, education, smoking, BMI, WHR, and weight change during the last 2 months.

model 5). No significant interactions between HOMA-IR and BMI, adiponectin, or leptin were observed.

In the subset analysis of NSCLC cases, the results of the first 3 models were similar to the findings of the analysis regarding all lung cancer cases (model 1: OR = 1.51, 95% CI: 1.16-1.97, P = .002; model 2: OR = 1.77, 95% CI: 1.16-2.68, P = .01; model 3: OR = 2.44, 95% CI: 1.43-4.16, P = .001). The introduction of serum leptin in the models did not potentially affect the association of HOMA-IR with NSCLC (model 4: OR = 1.52, 95% CI: 1.00-2.32, P = .05; model 5: OR = 2.15, 95% CI: 1.21-3.81, P = .01). No significant interactions between HOMA-IR and BMI, adiponectin, or leptin in the subset analysis were observed.

Table 4 presents HOMA-IR values in 81 lung cancer cases by disease stage. There was an indication that HOMA-IR was associated with advanced lung cancer disease, as advanced cases exhibited nearly 4-fold higher values. This observation was confirmed by unconditional multiple logistic regression (OR = 2.86, 95% CI: 0.81-10.14, P = .10), also controlling for age, sex, education, smoking, BMI, WHR, and weight change during the last 2 months. Concerning HOMA-IR, no statistically significant differences between small cell lung cancer (SCLC) cases and NSCLC cases were observed. Regarding meaningful interactions between covariates, we have examined the possible interaction of HOMA-IR with education, smoking, and adiponectin; all of them were not statistically significant (data not shown).

4. Discussion

Insulin resistance, quantified by means of HOMA-IR, emerged as a meaningful factor pointing to elevated lung cancer risk in this case-control study. The association between insulin resistance and lung cancer risk was robust enough to persist during adjustment for a wide variety of somatometric and lifestyle covariates. These variables may confound the effect of the former because elevated BMI [1,29], smoking [30], and alcohol consumption [31] may well correlate with insulin resistance. Specifically, the association between insulin resistance and lung cancer seems to be independent of all these confounders, as evidenced by the sizeable effect size (OR = 2.36) in the respective model.

This finding is in contrast to the findings of 2 cohort studies that had failed to demonstrate the relevance of insulin resistance in the context of lung cancer [5,6]. In this study, the effect of insulin resistance was rather strong and remained significant after adjustment for adiponectin (OR = 2.58), but essentially lost its statistical significance when adjusted for serum leptin levels. This could have been anticipated to a certain extent, as adiponectin per se was not a major predictor of lung cancer risk in previous studies [19,23]; accordingly, the HOMA-IR–adiponectin interaction [32] was not statistically significant. The observed loss of significance during adjustment for serum leptin may entail both a statistical and physiologic aspect. From a statistical perspective, these data need to be replicated in the context of a larger study, which would provide increased power because the effect size for insulin resistance in this study was sizeable (OR = 1.76 or 2.02 in the fully adjusted model). From a physiologic point of view, leptin and insulin resistance are closely associated [33]. Insulin induces leptin expression in adipose tissue [34,35]. Leptin reflects the amount of adipose tissue/fat mass. Because increased fat mass leads to both increased leptin levels and insulin resistance, it is possible that the attenuation of the statistical association when adjusting for leptin may simply reflect the potential confounding effect of fat mass.

Elevated insulin levels, which are an indispensable constituent of insulin resistance, may potentially exhibit cancer-promoting effects through various molecular mechanisms. Insulin may potentiate the activity of insulin-like growth factor–I (IGF-I) either via direct up-regulation [36] or indirectly through the down-regulation of IGF-binding protein–1 [37]. In turn, IGF-I represents a potent growth-promoting factor for lung cancer, although the specific relevance of its serum levels remains to be elucidated [38]. Moreover, insulin is one of the major stimulants of the Ras signaling pathway, promoting the farnesylation of p21Ras that subsequently can be activated by a host of growth-promoting signals [39]; noticeably, the Ras pathway is of pivotal importance in lung carcinogenesis [40]. Additional mechanisms, such as stimulation of local angiogenesis [41] or direct growth promotion via insulin receptors present on lung cancer cells [42], cannot be excluded.

Because case-control studies do not prove causality, it is also possible that lung cancer may also lead to insulin resistance [43]. A variety of mechanisms have been proposed to explain this observation, including the induction of cachexia-related interleukin-6 [44]. Interestingly, the numerically 4-fold higher values of HOMA-IR observed in the advanced lung cancer cases of our study (compared with limited lung cancer cases) may well be in accordance with the notion of lung cancer eliciting insulin resistance along with its progression.

A finding of this study that merits commenting pertains to the nearly 10-fold increased lung cancer risk associated with smoking. This finding may well be in line with existing knowledge [45,46] but seems worth highlighting, as further supporting the validity of the study. Of note, the effect of smoking on subjects from the same ethnic background appears fairly distinct when compared with other common cancer types, like prostate cancer [47]. Smoking may emerge as a multipotent factor, as it may have an effect on adipocytokines, such as leptin [48] and IGF-1 [49], the latter possibly exhibiting higher levels in insulin resistance. In any case, potential confounding has been eliminated using mutual adjustment at the multivariate analysis; importantly, the interaction between HOMA-IR and smoking did not prove to be statistically significant. Taken as a whole, the effect of insulin resistance, considerably weaker than the extremely sizeable one conferred by smoking, seemed robust enough to emerge in our setting; future studies should take care not to miss a relatively weaker signal in the presence of a strong risk factor.

This case-control study provides evidence for the potential association between insulin resistance and lung cancer. Although insulin resistance is a widely investigated topic, various definitions have appeared in the literature. The Adult Treatment Panel III has adopted impaired fasting glucose (>110 mg/dL) as an indicator of insulin resistance for the clinical identification of the metabolic syndrome [50]. Serum insulin [5,51], C-peptide [5,52], or clusters of biomarkers [6] have also been implemented as tangible indices for insulin resistance. The present study has adopted the use of HOMA-IR, which conceptually integrates fasting serum glucose as

well as serum insulin and exhibits considerable advantages, such as the compensation for basal glucose levels and its straightforward physiologic basis [53]. Moreover, the simultaneous evaluation of insulin resistance and obesity, serum leptin levels, and serum adiponectin levels allows for the simultaneous study of the role of potential confounders in lung cancer development.

Limitations of this case-control study include the small number of SCLC cases that did not allow the performance of subgroup analyses, so as to identify any diverging results according to lung cancer subtypes. In addition, the relatively small number of limited lung cancer cases may have hampered the statistical power of tests aiming to assess the differences between limited and advanced lung cancer. Furthermore, the association of HOMA-IR with lung cancer should probably be evaluated in terms of additional possible confounders, such as cachexia index, fat mass index, markers of inflammation, and dietary factors including the Mediterranean diet because the latter has been linked with adipocytokines [54,55] and cancer in general. We used weight changes as a surrogate marker of cachexia in adjusted models. Moreover, information about passive smoking has not been available in this study. Finally, it should be disclosed that 2 studies have been performed on the pool of our lung cancer patients and controls, one examining serum adiponectin levels and adiponectin receptors [23] and another examining serum leptin [20]; importantly, none of them had addressed or examined insulin resistance, which is examined herein for the first time.

In conclusion, this case-control study points to insulin resistance as a risk factor for lung cancer. Insulin resistance and elevated serum leptin levels are interrelated and may function at an orchestrated manner to promote carcinogenesis in the lung. Nevertheless, the generation of insulin resistance by lung cancer may not be ruled out. In any case, this study points to the relevance of insulin resistance in a cancer type that is traditionally viewed as obesity independent; this may imply that adipocytokines and insulin resistance may mediate cancer-related functions fairly distinct from their body weight–related aspects. It should be acknowledged, however, that more extensive prospective studies are needed to conclusively establish insulin resistance in the causation of lung cancer.

Supplementary materials related to this article can be found online at doi:10.1016/j.metabol.2010.12.002.

REFERENCES

[1] Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet 2010;375: 2267-77.

[2] Tritos NA, Mantzoros CS. Clinical review 97: syndromes of severe insulin resistance. J Clin Endocrinol Metab 1998;83: 3025-30.

[3] Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control 1996;7: 605-625.

[4] Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11:1531-43.

[5] Parekh N, Lin Y, Hayes RB, Albu JB, Lu-Yao GL. Longitudinal associations of blood markers of insulin and glucose metabolism and cancer mortality in the third National Health and Nutrition Examination Survey. Cancer Causes Control 2010;21:631-42.

[6] Loh WJ, North BV, Johnston DG, Godsland IF. Insulin resistance-related biomarker clustering and subclinical inflammation as predictors of cancer mortality during 21.5 years of follow-up. Cancer Causes Control 2010;21: 709-718.

[7] Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004;159:1160-7.

[8] Oba S, Nagata C, Nakamura K, Takatsuka N, Shimizu H. Self-reported diabetes mellitus and risk of mortality from all causes, cardiovascular disease, and cancer in Takayama: a population-based prospective cohort study in Japan. J Epidemiol 2008;18:197-203.

[9] Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. Eur J Cancer Prev 2007;16:83-9.

[10] Hall GC, Roberts CM, Boulis M, Mo J, MacRae KD. Diabetes and the risk of lung cancer. Diabetes Care 2005;28:590-4.

[11] Ehrlich SF, Quesenberry Jr CP, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care 2010;33:55-60.

[12] Rousseau MC, Parent ME, Pollak MN, Siemiatycki J. Diabetes mellitus and cancer risk in a population-based case-control study among men from Montreal, Canada. Int J Cancer 2006;118:2105-9.

[13] Batty GD, Shipley MJ, Marmot M, Smith GD. Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. Cancer Causes Control 2004;15:873-81.

[14] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348: 1625-38.

[15] Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non–small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-94.

[16] Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 2007;8:21-34.

[17] Matarese G, Moschos S, Mantzoros CS. Leptin in immunology. J Immunol 2005;174:3137-42.

[18] Mantzoros CS, Flier JS. Editorial: leptin as a therapeutic agent—trials and tribulations. J Clin Endocrinol Metab 2000;85:4000-2.

[19] Karapanagiotou EM, Tsochatzis EA, Dilana KD, Tourkantonis I, Gratsias I, Syrigos KN. The significance of leptin, adiponectin, and resistin serum levels in non–small cell lung cancer (NSCLC). Lung Cancer 2008;61:391-7.

[20] Terzidis A, Sergentanis TN, Antonopoulos G, et al. Elevated serum leptin levels: a risk factor for non–small-cell lung cancer? Oncology 2009;76:19-25.

[21] Tsuchiya T, Shimizu H, Horie T, Mori M. Expression of leptin receptor in lung: leptin as a growth factor. Eur J Pharmacol 1999;365:273-9.

[22] Brennan AM, Mantzoros CS. Leptin and adiponectin: their role in diabetes. Curr Diab Rep 2007;7:1-2.

[23] Petridou ET, Mitsiades N, Gialamas S, et al. Circulating adiponectin levels and expression of adiponectin receptors in relation to lung cancer: two case-control studies. Oncology 2007;73:261-9.

[24] Matsubara M, Katayose S, Maruoka S. Decreased plasma adiponectin concentrations in nondiabetic women with

elevated homeostasis model assessment ratios. Eur J Endocrinol 2003;148:343-50.
[25] Bajaj M, Suraamornkul S, Piper P, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab 2004;89:200-6.
[26] Wauters M, Considine RV, Yudkin JS, Peiffer F, De Leeuw I, Van Gaal LF. Leptin levels in type 2 diabetes: associations with measures of insulin resistance and insulin secretion. Horm Metab Res 2003;35:92-6.
[27] Oda N, Imamura S, Fujita T, et al. The ratio of leptin to adiponectin can be used as an index of insulin resistance. Metabolism 2008;57:268-73.
[28] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412-9.
[29] Marsland AL, McCaffery JM, Muldoon MF, Manuck SB. Systemic inflammation and the metabolic syndrome among middle-aged community volunteers. Metabolism 2010;59: 1801-8.
[30] Bergman BC, Perreault L, Hunerdosse DM, Koehler MC, Samek AM, Eckel RH. Intramuscular lipid metabolism in the insulin resistance of smoking. Diabetes 2009;58: 2220-7.
[31] Ishizaka N, Ishizaka Y, Toda E, Yamakado M, Koike K, Nagai R. Association between gamma-glutamyltransferase levels and insulin resistance according to alcohol consumption and number of cigarettes smoked. J Atheroscler Thromb 2010;17: 476-85.
[32] Park JT, Yoo TH, Chang TI, et al. Insulin resistance and lower plasma adiponectin increase malignancy risk in nondiabetic continuous ambulatory peritoneal dialysis patients. Metabolism 2010.
[33] Ceddia RB, Koistinen HA, Zierath JR, Sweeney G. Analysis of paradoxical observations on the association between leptin and insulin resistance. FASEB J 2002;16:1163-76.
[34] Saladin R, De Vos P, Guerre-Millo M, et al. Transient increase in obese gene expression after food intake or insulin administration. Nature 1995;377:527-9.
[35] Leroy P, Dessolin S, Villageois P, et al. Expression of ob gene in adipose cells. Regulation by insulin. J Biol Chem 1996;271: 2365-8.
[36] Phillips LS, Harp JB, Goldstein S, Klein J, Pao CI. Regulation and action of insulin-like growth factors at the cellular level. Proc Nutr Soc 1990;49:451-8.
[37] Snyder DK, Clemmons DR. Insulin-dependent regulation of insulin-like growth factor-binding protein–1. J Clin Endocrinol Metab 1990;71:1632-6.
[38] Kim WY, Jin Q, Oh SH, et al. Elevated epithelial insulin-like growth factor expression is a risk factor for lung cancer development. Cancer Res 2009;69:7439-48.
[39] Goalstone ML, Draznin B. What does insulin do to Ras? Cell Signal 1998;10:297-301.
[40] Mascaux C, Iannino N, Martin B, et al. The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. Br J Cancer 2005;92:131-9.
[41] Rensing KL, Houttuijn Bloemendaal FM, Weijers EM, et al. Could recombinant insulin compounds contribute to adenocarcinoma progression by stimulating local angiogenesis? Diabetologia 2010;53:966-70.
[42] Zhang H, Fagan DH, Zeng X, Freeman KT, Sachdev D, Yee D. Inhibition of cancer cell proliferation and metastasis by insulin receptor downregulation. Oncogene 2010;29:2517-27.
[43] Rohdenburg GL, Bernhard A, Krehbiel O. Sugar tolerance in cancer. JAMA 1919;72:1528-30.
[44] Makino T, Noguchi Y, Yoshikawa T, Doi C, Nomura K. Circulating interleukin 6 concentrations and insulin resistance in patients with cancer. Br J Surg 1998;85:1658-62.
[45] Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J 1950;2:739-48.
[46] Boffetta P, Jayaprakash V, Yang P, et al. Tobacco smoking as a risk factor of bronchioloalveolar carcinoma of the lung: pooled analysis of seven case-control studies in the International Lung Cancer Consortium (ILCCO). Cancer Causes Control 2010.
[47] Hsieh CC, Thanos A, Mitropoulos D, Deliveliotis C, Mantzoros CS, Trichopoulos D. Risk factors for prostate cancer: a case-control study in Greece. Int J Cancer 1999;80:699-703.
[48] Mantzoros CS, Liolios AD, Tritos NA, et al. Circulating insulin concentrations, smoking, and alcohol intake are important independent predictors of leptin in young healthy men. Obes Res 1998;6:179-86.
[49] Kaklamani VG, Linos A, Kaklamani E, Markaki I, Mantzoros C. Age, sex, and smoking are predictors of circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3. J Clin Oncol 1999;17:813-7.
[50] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
[51] Mack R, Skurnick B, Sterling-Jean Y, Pedra-Nobre M, Bigg D. Fasting insulin levels as a measure of insulin resistance in American blacks. J Med 2003;34:31-8.
[52] Bonser AM, Garcia-Webb P. C-peptide measurement: methods and clinical utility. Crit Rev Clin Lab Sci 1984;19: 297-352.
[53] Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-95.
[54] Mantzoros CS, Williams CJ, Manson JE, Meigs JB, Hu FB. Adherence to the Mediterranean dietary pattern is positively associated with plasma adiponectin concentrations in diabetic women. Am J Clin Nutr 2006;84:328-35.
[55] Qi L, van Dam RM, Liu S, Franz M, Mantzoros C, Hu FB. Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. Diabetes Care 2006;29: 207-11.