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Serum Insulin-like Growth Factor-1 is an Independent Predictor of Prognosis in Patients with Renal Cell Carcinoma

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Obesity is associated with an increased risk of certain cancers, including renal cell carcinoma. A possible mediator of this risk is insulin-like growth factor-1 (IGF-1). The authors evaluated the prognostic information of IGF-1, IGFBP-3, leptin, and prealbumin in sera sampled at diagnosis from 256 consecutive patients with renal cell carcinoma. Insulin-like growth factor-1 and leptin were positively correlated to body mass index (BMI). Insulin-like growth factor-1 and IGFBP-3 did not correlate to tumour stage or grade. Leptin and prealbumin were both inversely related to tumour stage and grade. When survival was analysed in patients with levels above a median of IGF-1, leptin, and prealbumin, prognosis was more favourable, compared with those with lower levels ($p = 0.017$; $p = 0.024$, and $p < 0.0001$, respectively). In a multivariate analysis, tumour stage and serum IGF-1 levels were independent prognostic factors. The results indicate that serum IGF-1 at diagnosis is related to prognosis in renal cell carcinoma.

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Obesity is associated with an elevated risk of certain cancers. The risk of endometrial cancer is increased in obese women, as is the risk of breast cancer in obese postmenopausal women. In men, obesity is linked to an increased risk of colo-rectal and prostate cancer (1). Several reports indicate an increased risk of renal cell carcinoma in overweight persons (2–4). Reasons for an association between overweight and cancer risk may include hyperinsulinaemia, increased exposure to oestrogen or insulin-like growth factors (5), or lower physical activity. Epidemiologic data also indicate that patients with high body mass index (BMI) have an increased risk of dying from cancer, especially in women (4).

Insulin-like growth factor-1 (IGF-1) is a 7.7 kD polypeptide regulated by growth hormone and insulin, and it is mainly synthesized in the liver. It is crucial for embryonic development, and produced throughout life, although serum levels decrease after puberty. Insulin-like growth factor-1 is a potent inhibitor of apoptosis, and elevated serum levels have been associated with increased risk of breast (6), prostate (7), and colon cancer (8). An indicator of a possible causal association between elevated IGF-1 and cancer is the fact that patients with acromegaly have an increased risk of colo-rectal cancer (9).

Among the binding proteins with high affinity for IGF-1, IGFBP-3 is the most abundant in serum. This protein has an opposing effect on IGF-1, partly by binding, but also by direct inhibitory effects on target cells (10, 11).

Leptin is a 16 kD protein hormone mainly produced in adipose tissue and the circulating levels are strongly correlated to body fat mass (12). Leptin also stimulates angiogenesis, and might act as a cytokine (13). In a recent prospective nested case-referent study, Stattin et al. (14) found an increased risk of prostate cancer in individuals with moderately increased plasma leptin. However, in another case-control study in prostate cancer (15), and in in situ carcinoma of the breast (16), serum leptin was not associated with an increased risk of tumour development.

The nutritional status of the patients is crucial for clinical outcome. Prealbumin is a nutritional marker that has a shorter half-life than albumin (17).

Against this background we assumed that IGF-1 and leptin could be related to tumour proliferation and outcome. The aim of this study was to evaluate serum IGF-1,

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IGFBP-3, leptin, and prealbumin in relation to prognosis in patients with renal cell carcinoma.

MATERIAL AND METHODS

Two hundred and fifty-six patients, 144 men and 112 women, were included in the study, from 1982 to 2000. Their median age was 66 (range, 25–86) years. Following clinical investigation including computerized tomography of the abdomen, 239 were operated on with radical nephrectomy, and three with nephrone-sparing surgery. Fourteen patients received palliative treatment with medroxyprogesterone acetate, interferon, or arterial occlusion. Tumour stage was assessed according to TNM (18), and nuclear grading followed the principles of Skinner et al. (19). Sixty-seven patients had stage I, 40 stage II, 60 stage III, and 89 patients stage IV disease. Body mass index (BMI, kg/m^2) was assessed in 184 of the patients at diagnosis. Median BMI was 24.6 (range, 16.6–47.4), without any gender difference.

Following patients' informed consent, sera were collected before initiation of therapy. The samples were obtained before 10 a.m. and stored at $-80^{\circ}C$ until analysis. Serum IGF-1 was analysed after extraction using a radioimmunoassay from Nichols Institute Diagnostics (San Juan Capistrano, CA, USA), and IGFBP-3 using quantitative sandwich immunoassay Quantikine from R&D Systems Inc. (Minneapolis, MN, USA). Leptin was assessed using a commercial radioimmunoassay from Linco (St Charles, MO, USA), and prealbumin by turbidimetry using antibodies from Dakopatt A/S (Denmark). According to the producers, the limits of sensitivity for the IGF-1 and the leptin assays were 22.5 and 0.5 ng/ml, respectively. The inter- and intraassay coefficients of variation (CV) variability for IGF-1 at the serum level 43.9 ng/ml were 21.9% and 19.0%, respectively. Corresponding values at the level 152 ng/ml were 12.1% and 13.5%, respectively. The total CV for IGF-1 at the lower concentration was 29.0%, and 18.2% at the higher concentration. The total CV of IGFBP-3 at the level 30 ng/ml was 8.1% according to the manufacturer. For leptin, total CV:s at levels 2.8 ng/ml and 20.0 ng/ml were 8.3% and 5.7%, respectively. For prealbumin, total CV:s at levels 183 mg/l and 265 mg/l were 1.9% and 1.5%, respectively.

After therapy, the patients were followed up according to clinical routine, with regular clinical examinations. Cause-specific survival curves were calculated from the time of diagnosis according to the Kaplan–Meier method, and evaluated using the log-rank test. In case of death, the cause was based on medical records and death certificates. Data are presented as median values and ranges. For statistical analysis Mann–Whitney and Kruskal–Wallis tests were used. Multivariate analysis was performed according to Cox's proportional hazards model.

RESULTS

As shown in Table 1, serum IGF-1 and IGFBP-3, but not leptin and prealbumin, decreased with age. Furthermore, IGF-1 was slightly higher in men than in women, while the opposite was found for IGFBP-3 and leptin. Serum IGF-1 and leptin were both positively related to BMI. High pretreatment serum IGF-1 levels were associated with high IGFBP-3 and prealbumin ($r = 0.55$, $p < 0.01$, and $r = 0.31$, $p < 0.01$, respectively, Pearson correlation). Stability during storage was assessed by comparing the levels in three groups divided according to the years of sampling (1982–1988, 1989–1995, and 1996–2000). In these three groups the levels of IGF-1 and IGFBP-3 were similar, while leptin and prealbumin was slightly lower in the samples stored for the longest time, compared with those stored for a shorter period (data not shown). A relative increase in the women

Table 1

Serum IGF-1, IGFBP-3, leptin and prealbumin in relation to age, gender and BMI in patients with renal cell carcinoma

	No.	IGF-1 (ng/ml)		p-value[1]	IGFBP-3 (ng/ml)		p-value[1]	Leptin (ng/ml)		p-value[1]	Prealbumin (mg/ml)		p-value[1]
		Median	Range		Median	Range		Median	Range		Median	Range	
Total	256	55.0	23–236		1549	603–4266		8.0	1.0–81.8		247	19–565	
Age (yr)													
<66	136	71.0	23–236	0.0001	1655	635–4266	0.001	8.1	1.0–81.8	NS	250	19–565	0.09
>66	120	46.5	23–184		1453	603–3489		7.9	1.0–59.9		246	28–400	
Gender													
Male	144	60.0	23–236	0.03	1468	603–4266	0.02	5.5	1.0–24.2	0.0001	250	19–565	NS
Female	112	48.5	23–232		1659	746–3489		13.3	1.4–81.8		223	28–440	
BMI													
<24.6	91	51.0	23–162	0.004	1512	603–3489	NS	5.3	1.0–42.4	0.0001	220	32–565	0.09
>24.6	93	70.0	23–236		1632	746–4266		10.5	1.7–81.8		250	55–440	

[1]Mann–Whitney test; NS not significant.

to men ratio from 0.71 to 0.89 was found but no significant differences in age distribution, BMI, tumour stage, or grade between the three groups (data not shown).

No association was observed between IGF-1 or IGFBP-3 and tumour stage or grade (Table 2). However, serum leptin and prealbumin levels were inversely related to tumour stage and grade.

The median follow-up time for patients who were still alive was 61.5 (range, 17–210) months. During the follow-up, 132 patients died as a result of renal cell carcinoma, and 38 as a result of intercurrent diseases. Eighty-six patients were alive at the latest follow-up. Cause-specific survival related to IGF-1 levels is shown in Fig. 1. Patients with IGF-1 levels above the median of 55 ng/ml had a more favourable prognosis compared with those with lower levels ($p = 0.017$). When survival was related to leptin and prealbumin, patients with levels above the median had a better prognosis, compared with those with lower levels ($p = 0.024$, $p < 0.0001$, respectively). No differences in survival were related to IGFBP-3 or BMI (data not shown).

The prognostic value of age, gender, tumour stage and grade, IGF-1, IGFBP-3, leptin, and prealbumin levels was assessed in a multivariate analysis (Table 3). Only tumour stage and serum IGF-1 were identified as independent prognostic factors. Tumour grade had a borderline significance ($p = 0.057$).

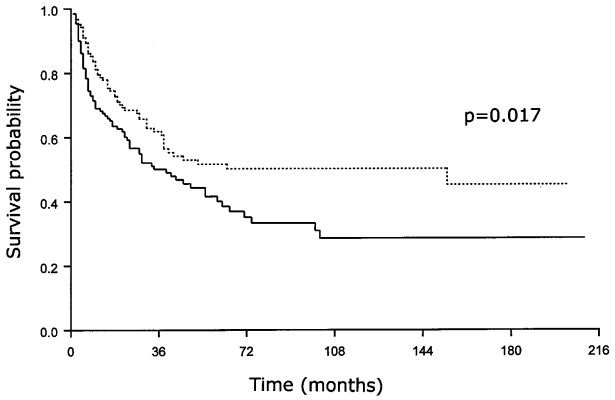

Fig. 1. Cause-specific survival in patients with renal cell carcinoma according to the Kaplan–Meyer method. Serum IGF-1 ≤55 (——) in 132 patients, and >55 ng/ml (·····) in 124 patients.

DISCUSSION

Food intake and physical activity are factors that influence body weight. Insulin-like growth factor-1 and leptin are hormones linked to the regulation of body height and fat mass. In the present study serum IGF-1 was associated with prognosis in renal cell carcinoma, supporting the hypothesis that specific hormones may be of importance for induction and progression of certain types of cancer (5). The relation of IGF-1 to cancer risk has been reviewed extensively and an association between increased IGF-1 and cancer risk has been reported (10, 20). However, the role of IGF-1 in relation to prognosis in patients with cancer has been less studied.

Our results indicate that serum IGF-1 is related to prognosis in renal cell carcinoma. We found no earlier reports concerning the prognostic value of IGF-1 in this disease. However, Vadgama et al. (21), analysed IGF-1 at the time of diagnosis in 130 women with breast cancer, and found that survival was greater in women with plasma IGF-1 <120 ng/ml. Similar results have been presented in myeloma, where patients with serum IGF-1 <13 nM had higher probability of survival, compared with those with higher IGF-1 levels (22). In prostate cancer two studies failed to demonstrate any significant influence of IGF-1 on prognosis (23, 24). In contrast with these results, we found that patients with serum IGF-1 >55 ng/ml had a higher

Table 2

Serum IGF-1, IGFBP-3, leptin, and prealbumin in relation to tumour stage and grade in patients with renal cell carcinoma

	No.	IGF-1 (ng/ml)		p-value[1]	IGFBP-3 (ng/ml)		p-value[1]	Leptin (ng/ml)		p-value[1]	Prealbumin (mg/ml)		p-value[1]
		Median	Range		Median	Range		Median	Range		Median	Range	
Stage													
I	67	54	23–232	NS	1665	659–3523	NS	10.8	1.7–59.9	0.005	280	28–565	0.0001
II	40	70	23–182		1601	807–4197		8.0	1.0–55.1		246	19–384	
III	60	48	23–236		1466	603–3489		5.8	1.1–46.8		212	50–351	
IV	89	55	23–236		1543	635–4266		8.0	1.0–81.8		220	32–440	
Grade													
1	9	49	23–111	NS	1665	1089–3295	NS	11.7	8.6–32.9	0.001	295	159–383	0.0001
2	46	55	23–232		1645	699–3523		10.2	1.7–56.8		272	100–425	
3	129	54	23–236		1581	635–4197		7.3	1.0–81.8		250	19–565	
4	63	68	23–236		1506	603–4266		6.1	1.0–34.4		175	32–350	

[1]Kruskal–Wallis test; NS not significant.

Table 3

Multivariate analysis of prognostic factors in renal cell carcinoma. Median values used as cut-off for age, IGF-1, IGFBP-3, leptin, and prealbumin

Factor		RR	95% CI low–high	p-value
Age (years)	≤66	1.0		
	>66	0.85	0.59–1.24	0.40
Gender	Male	1.0		
	Female	0.88	0.60–1.29	0.51
Stage	I–II	1.0		
	III–IV	8.83	4.91–16.25	<0.0001
Grade	1–2	1.0		
	3–4	2.41	0.97–5.97	0.057
IGF-1 (ng/ml)	≤55	1.0		
	>55	0.62	0.41–0.95	0.028
IGFBP-3 (ng/ml)	≤1549	1.0		
	>1549	1.24	0.82–1.86	0.30
Leptin (ng/ml)	≤median[1]	1.0		
	>median[1]	1.01	0.70–1.46	0.98
Prealbumin (mg/ml)	≤247	1.0		
	>247	0.77	0.52–1.14	0.19

[1]Median for men 5.5, for women 13.3 ng/ml.
RR = relative risk; CI = confidence interval.

survival probability compared with those with lower levels. The reason for these conflicting results is not obvious. Notably, the IGF-1 levels differed between the studies. The median serum IGF-1 in our study was 55.0 ng/ml, compared with a mean value of 111.9 ± 6.6 ng/ml in the breast cancer study (21), and even higher in patients with myeloma or prostate cancer (22–24). This difference may partly be explained by differences in patient age but in the prostate cancer study the median age was similar to that of our patients. Another factor that may influence IGF-1 is weight loss before the time of diagnosis. We have no information concerning possible weight loss before the time of diagnosis, a factor that also may be crucial for prognosis.

Importantly, the levels of prealbumin and BMI seemed normal, and those factors were not independent predictors of survival. Prealbumin is considered an indicator of malnutrition in cancer (17). This assumption is supported by observations in the present study, which demonstrated inverse relations of prealbumin to both tumour stage and grade. Furthermore, in univariate analysis, patients with prealbumin levels above median had a better prognosis, compared with those with lower levels. However, the prognostic information on prealbumin was lost in the multivariate analysis. This observation argues against malnutrition or severe weight loss as a confounding factor in our analyses.

There was no impact of patient weight (BMI) on prognosis in this study. Senie et al. (25), however, found that obesity at diagnosis in breast cancer was related to a lower probability of disease-free survival. In contrast, Daniell (26) demonstrated that obese men with prostate cancer had a better prognosis compared with lean men, probably due to differences in endogenous oestrogen levels. In addition, obese patients had lower risk of recurrence of renal cell carcinoma compared with non-obese patients (27). Disease-free and overall survival was increased in patients with a BMI exceeding 120% of the normal value, in contrast with the findings in the present study.

The present study supports earlier observations on the relation between circulating leptin levels and adipose tissue, here estimated as BMI, and the fact that women have significantly higher serum leptin levels than men (12). No previous study on leptin in renal cell carcinoma has been performed, but in breast cancer, Tessitore et al. (28) showed that serum leptin was significantly higher compared with healthy controls. In our study with a large number of patients an inverse relation between serum leptin and tumour stage and grade was found, as opposed to the results of a limited number of patients with breast cancer, where no relation to stage was found (28). In our study, an inverse relation of serum leptin to tumour grade was demonstrated associated with a decrease in BMI. The results also indicated that patients with low serum leptin levels had a worse prognosis irrespective of BMI. Notably, low leptin levels led to an impaired cell-mediated immunity (29), a factor that might influence prognosis.

A factor that may interfere with our results is the stability of proteins during storage. Our sera were stored at -80°C unthawed between 1 and 18 years before analysis. The stability of IGF-1 and leptin were assessed in a short-term exposure to $+30^{\circ}$C, >120 hours in combination with different anticoagulants, and both hormones were stable (30). We found lower levels of leptin and prealbumin in the group of samples stored for the longest time. The changes of leptin over time may partly be due to the increasing proportion of women, and also a slight increase in BMI ($+8.5\%$).

In summary, our results show inverse relations of serum leptin and prealbumin to tumour stage and grade at diagnosis in patients with renal cell carcinoma. Insulin-like growth factor-1, leptin, and prealbumin were related to prognosis in univariate analysis. However, multivariate analysis showed that only tumour stage and serum IGF-1 were independent predictors of prognosis.

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