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Circulating adiponectin levels in relation to melanoma: A case–control study

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ABSTRACT

Aim: Melanoma, a malignancy with steadily increasing prevalence, has been associated not only with sun exposure but also with phenotypic characteristics including obesity. Adiponectin, an adipocyte secreted endogenous insulin sensitizer, has been found to play a protective role in several obesity related cancers but has not yet been studied in relation to melanoma. We investigated the association of circulating adiponectin levels with melanoma in Greece, a country with rather low incidence of the disease and high annual sunshine levels.

Methods: In the context of a case–control study, we studied over a 22-month period 55 patients with incident, histologically confirmed melanoma cases and 165 healthy controls matched for gender and age.

Results: After controlling for the possible confounding effect of education, body mass index and waist-to-hip ratio in multiple logistic regression analyses, sun sensitive skin type was significantly and positively associated with melanoma risk (OR: 2.48, 95% Confidence Interval: 1.22–5.10, *p*: 0.01). On the contrary, there was a sizeable, though non-significant, inverse association of serum adiponectin levels with the disease (OR: 0.75, 95% Confidence Interval: 0.52–1.10, *p*: 0.14).

Conclusion: A protective role of adiponectin in the development of melanoma cannot be excluded given the presented empirical evidence (25% reduction per one SD of adiponectin) and the direct anti-neoplastic features of the hormone. The results are intriguing enough to point to the need for further investigation.

1. Introduction

The incidence of malignant melanoma in Caucasians has been steadily increasing during the last decades; only in Europe, ~59,000 individuals are annually diagnosed with melanoma, while 15,000 die of this disease.[1] A 'sensitive' skin phototype (fair skin, tendency to burn, inability to tan) and intermittent sun exposure, a prominent mole pattern, presence of dysplastic nevi, a family history of melanoma and immunosuppression are considered established risk

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factors.[2,3] Diet and alcohol intake have also been implicated as risk factors for melanoma in several[4–13] but not all studies[8,13–15], whereas recent accumulating evidence supports a role for obesity in the aetiology of melanoma in several races and populations.[16–19]

Adiponectin, an adipocyte secreted endogenous insulin sensitizer, the circulating levels of which are inversely associated with obesity, has been found to play a protective role for several types of malignancies,[20,21] notably those related to obesity. Importantly, no previous study has explored whether adiponectin is associated with melanoma. In this study, we investigate the association of adiponectin levels with melanoma in Greece, a country with a rather low incidence of melanoma,[22] despite ample sunshine.

2. Patients and methods

During a 22-month period (March 2002 to December 2003), 60 incident cases of histologically confirmed malignant melanoma (cutaneous in 85% of the cases) were referred to and were recruited in the study at the Oncology Department of Laikon, Hospital, one of the four major university tertiary medical centres in Athens, Greece. This center covers the entire Athens metropolitan area and evaluates for treatment (adjuvant therapy or chemotherapy) subjects with higher than stage I melanoma who are referred by primary, secondary or other tertiary care centers. Five patients refused to participate (participation rate: 92%). The patients were staged using the final version of the American Joint Committee on Cancer (AJCC) staging system for melanoma.[23] Among the 55 melanoma patients, 8 cases (14.5%) had stage II disease, 5 (9.1%) stage IIa, 6 (10.9%) stage IIb, 27 (49.1%) stage III and 9 (16.4%) stage IV disease. All cases were defined as sporadic melanomas, whereas none had a history of familial melanoma or of any other type of cancer.

For each melanoma patient, three eligible controls (a total of 165), matched for gender, age (±5 years) and place of residence, were also enrolled in the study as previously described.[24] More specifically, controls were recruited among residents of the Athens metropolitan area participating in routine health screening examinations. Controls had a negative self reported medical history for cancer (including skin cancer), hepatic disease, major hormonal or a hematological disorders, asthma, autoimmune disease, HIV infection, advanced heart failure, chronic kidney failure, recent myocardial infarction, stroke, acute pancreatitis or bone fracture and normal complete blood count and electrolytes. The study protocol was approved by the University of Athens Medical School Ethics Committee and the study design and performance were in accordance with the Helsinki Declaration of 1975, and the participants provided informed consent.

Each case and the three matched controls were interviewed by one of four trained interviewers. The interview lasted for about 30 min and information pertaining to sociodemographic, anthropometric, lifestyle and medical history variables was obtained. Recorded characteristics included eye colour (blue or green, brown or black) and skin sensitivity to sun exposure (also referred to as skin type). Two categories of skin sensitivity were used: the first comprising I and II (very fair skin, always/easy burns, never/difficult tans) and the second III and IV (moderately sun sensitive and barely sun sensitive) Fitzpatrick's phototypes.[25] Anthropometric variables were measured by the trained interviewers, namely height, with subjects wearing no shoes; waist and hip circumference, with subjects wearing no clothes. The reported weight two-month prior to diagnosis was also recorded. Blood samples were taken from all cases and controls (no later than 9 a.m.) for determination of hormonal measurements. All coded samples were centrifuged and stored at −70 °C with a similar average preservation time for cases and controls, although adiponectin levels are not altered by storage time.[26] The samples, blinded as to case–control status, were air shipped with dry ice in one batch to Beth Israel Deaconess Medical Center, in Boston USA. Serum adiponectin levels were measured utilizing a radioimmunoassay procedure with a sensitivity of 2 ng/ml as previously described.[24]

For the statistical analysis, representative values (mean, SD, and percentiles) of the anthropometric variables and serum adiponectin levels were calculated among cases and controls. To study the association of adiponectin with melanoma, we modelled the data through multiple conditional logistic regression analysis using case–control as the outcome variable and adiponectin (in increments of one standard deviation of the hormone among controls) as predictor variable, controlling for a series of possible confounders, namely: skin type (two categories), eye colour (two categories), education (in five categories, ordered) and body mass index (BMI) before

Table 1 – Distribution of 55 cases of melanoma and 165 age- and gender-matched controls by demographic and phenotypic variables

Variable	Cases		Controls		p-value
	N	%	N	%	
Age					Matched variable
<40 years	14	25.5	34	20.6	
40–49	10	18.2	36	21.8	
50–59	10	18.2	32	19.4	
60–69	14	25.5	40	24.3	
70+	7	12.6	23	13.9	
Gender					Matched variable
Male	32	58.2	96	58.2	
Female	23	41.8	69	41.8	
Education					0.21*
<6 years	3	5.5	14	8.5	
6–8	11	20.0	36	21.8	
9–11	11	20.0	34	20.6	
12	11	20.0	43	26.1	
12+	19	34.5	38	23.0	
Skin type					0.002**
Sun sensitive	23	41.8	34	20.6	
Other	32	58.2	131	79.4	
Eye colour					0.06**
Blue/green	20	36.4	39	23.6	
Brown/black	35	63.6	126	76.4	

* p-value derived from χ^2 for trend.
** p-value derived from χ^2 for contrast.

diagnosis (in 2 kg/m^2 increments) or alternatively, waist-to-hip ratio (in quintiles, ordered). The SAS statistical package was used in the analyses.[27]

3. Results

In Table 1, we present data on demographic and phenotypic variables for melanoma patients and their gender- and age-matched controls. These data serve mostly descriptive purposes and are not directly interpretable because of mutual confounding. The figures are in line, however, with established risk characteristics of melanoma with patients having more frequently a sun sensitive phototype and a weaker association with lighter eye colour, compared to controls.

Table 2 shows the representative values of somatometric variables and serum adiponectin levels by case–control status. There were no statistically significant differences between cases and controls for any of the unadjusted mean values of the anthropometric variables used in this study (height, weight, BMI, waist circumference and waist-to-hip ratio) apart from one measure of subcutaneous fat, namely hip circumference, which was higher among cases. Unadjusted mean serum adiponectin levels were not different between cases and controls. Again, these results may not be directly interpretable because of the possibility of mutual confounding.

Pearson correlation coefficients were then calculated (Table 3) in order to examine the associations of serum adipo-

Table 2 – Representative values of the somatometric variables and adiponectin levels by case–control status (*p*-value derived from *t*-tests)

Variable	N	Minimum value	25%	Median	75%	Maximum value	Standard deviation	Mean	*p*-value
Height (cm)									0.25
Cases	55	147	165	170	175	190	9.20	169.6	
Controls	165	145	160	169	175	190	9.50	168.0	
Weight (kg)									0.56
Cases	55	58	67	78	87	109	13.48	78.3	
Controls	165	46	66	75	87	150	15.88	76.9	
BMI (kg/m^2)									0.99
Cases	55	20.2	25.3	26.8	29.4	37.1	3.75	27.2	
Controls	165	18.0	24.5	26.7	29.7	43.8	4.52	27.2	
Waist circumference (cm)									0.42
Cases	55	71	91	96	102	117	10.36	96.3	
Controls	165	64	88	94	103	148	13.71	94.8	
Hip circumference (cm)									0.01
Cases	55	87	102	109	112	133	8.00	107.4	
Controls	165	68	98	103	110	140	11.05	104.0	
Waist/hip ratio (%)									0.32
Cases	55	64.6	85.0	92.1	95.8	108.9	8.94	89.8	
Controls	165	64.8	84.3	92.9	97.6	138.2	10.62	91.4	
Adiponectin (μg/ml)									0.42
Cases	55	2.7	7.6	9.6	12.3	21.8	3.87	10.1	
Controls	165	0.2	8.2	10.2	13.3	22.5	3.46	10.5	

Table 3 – Pearson correlation coefficients (*p*-values) between age, somatometric variables and adiponectin levels among the 165 controls

Variable	Height	Weight	BMI	Waist circumference	Hip circumference	waist-to-hip ratio	Adiponectin
Age	−0.30 (0.0001)	0.02 (0.83)	0.25 (0.001)	0.27 (0.0005)	0.16 (0.04)	0.22 (0.004)	0.04 (0.59)
Height		0.59 (0.0001)	0.04 (0.63)	0.32 (0.0001)	0.09 (0.25)	0.29 (0.0001)	−0.32 (0.0001)
Weight			0.82 (0.0001)	0.81 (0.0001)	0.60 (0.0001)	0.44 (0.0001)	−0.34 (0.0001)
BMI				0.79 (0.0001)	0.69 (0.0001)	0.34 (0.0001)	−0.19 (0.01)
Waist circumference					0.63 (0.0001)	0.66 (0.0001)	−0.32 (0.0001)
Hip circumference						−0.15 (0.05)	−0.10 (0.20)
waist-to-hip ratio							−0.31 (0.0001)

Table 4 – Conditional logistic regression-derived odd ratios (ORs) and 95% confidence intervals (95% CIs) for melanoma by circulating adiponectin levels and by somatometric and demographic variables

Variable	Category or increment	*p*-value					
		ORs[a] (95% CIs)	ORs[b] (95% CIs)	ORs[c] (95% CIs)	ORs[d] (95% CIs)	ORs[e] (95% CIs)	ORs[f] (95% CIs)
Education	1 level more	1.19 (0.92–1.54) 0.18			1.27 (0.96–1.69) 0.10	1.25 (0.95–1.65) 0.12	1.30 (0.97–1.73) 0.08
Skin type	Sun sensitive versus other	2.84 (1.44–5.61) 0.003			2.50 (1.22–5.10) 0.01	2.48 (1.22–5.10) 0.01	2.43 (1.19–4.97) 0.01
Eye colour	Blue/green versus brown/black	1.96 (0.98–3.92) 0.06			1.70 (0.81–3.58) 0.16	1.70 (0.81–3.57) 0.16	1.70 (0.81–3.58) 0.16
BMI	2 kg/m^2	1.10 (0.82–1.47) 0.55	1.08 (0.80–1.45) 0.62		1.13 (0.82–1.55) 0.47		1.16 (0.84–1.61) 0.37
Waist/hip ratio	20% more	0.85 (0.64–1.12) 0.25		0.83 (0.62–1.10) 0.19		0.83 (0.62–1.12) 0.23	0.82 (0.61–1.10) 0.19
Adiponectin	1 SD among controls	0.85 (0.60–1.20) 0.36	0.86 (0.61–1.22) 0.39	0.82 (0.57–1.17) 0.27	0.79 (0.54–1.15) 0.22	0.75 (0.52–1.10) 0.14 0.14	0.76 (0.52–1.12) 0.16

a Unadjusted odds ratio for education, skin type, eye colour, BMI, waist-to-hip ratio and adiponectin.
b Odds ratio for mutually adjusted BMI and adiponectin.
c Odds ratio for mutually adjusted waist-to-hip ratio and adiponectin.
d Odds ratio for mutually adjusted education, skin type, eye colour, BMI and adiponectin.
e Odds ratio for mutually adjusted education, skin type, eye colour, waist-to-hip ratio and adiponectin.
f Odds ratio for mutually adjusted education, skin type, eye colour, BMI, waist-to-hip ratio and adiponectin.

nectin with somatometric variables as well as age among healthy controls. Adiponectin was negatively correlated with obesity, especially central obesity, as expected.[28]

Subsequently, multiple logistic regression analyses were performed and the odds ratios for melanoma for each increment of adiponectin, corresponding to one standard deviation among controls, were determined (Table 4). Odds ratios were also derived from additional models controlling for either BMI as an indicator of overall obesity or for waist-to-hip ratio as the main indicator for central obesity. The inverse association between serum adiponectin and melanoma (crude OR: 0.85) was not statistically significant (p-value = 0.36). Further adjustment for BMI only (model 2) (OR = 0.86, p-value = 0.39), as well as for potential confounders, including BMI, education and phototype related variables (model 4), did not essentially alter the results (OR = 0.79, p-value = 0.22). The associations of the other variables with melanoma in this model were in line with those initially presented in the descriptive tables, with regards to sensitive phototypes, whereas the associations with light eye colour, education and BMI were weaker and statistically non-significant. When waist-to-hip ratio, instead of BMI, was included in the model along with adiponectin (model 3), the association of adiponectin with melanoma retained its magnitude (OR = 0.82, p-value = 0.27) and became somewhat more suggestive when the remaining potential confounders were also adjusted for (model 5) (OR = 0.75, p-value = 0.14). Finally no essential changes were observed when all potential confounding variables, including both BMI and waist to hip ratio as well as education and phototype were also adjusted (model 6) (OR = 0.76, p-value = 0.16).

4. Discussion

This case–control study confirms the previously reported positive association of sensitive skin type and light eye colour with melanoma risk in a population exposed rather constantly to high annual sunshine levels. Overall, no association of melanoma with indices of obesity was found in this dataset, but an inverse association with circulating levels of the adipocyte secreted hormone, adiponectin, could not be excluded.

The association of sun exposure with melanoma has been well established in epidemiological studies with the risk being higher in individuals with 'sensitive' skin phototype, especially among those who have sustained intermittent sun exposure. The relatively low proportion of individuals with sensitive skin types among those residing in countries of the Mediterranean basin, such as Greece, along with a climate offering constant daily sunshine may provide some explanation regarding the rather low incidence of melanoma in this part of the world.[22,29]

Sun exposure, however, is not the only risk factor for developing melanoma; several recent studies have explored the association of the disease with somatometric variables.[11,12,16] It remains unclear, however, whether obesity per se or an obesity derived factor is associated with risk for melanoma. Alternatively, the increased risk for melanoma might be simply due to increased body surface area which accompanies obesity in both men and women.[9,16,30] Thus, potential explanations for the reported association of obesity with melanoma would include either an increased total number of melanocytes that can undergo malignant transformation,[31] and/or a potential role for growth hormone/growth factors and/or other endocrine factors in carcinogenesis.[32]

Following several reports on other obesity associated malignancies,[20,21] we aimed to study the role of a novel adipocyte-secreted protein, adiponectin, which has gained much attention as a marker of insulin resistance and related conditions, including diabetes and cardiovascular disease.[33] Notably, adiponectin is one of the most abundant serum proteins, with plasma levels in healthy humans in the microgram per ml range (≈10 μg/ml).[28] Although its role has not been definitively established, accumulating evidence suggests that adiponectin regulates insulin sensitivity. Adiponectin-knockout mice develop glucose intolerance and insulin resistance, while adiponectin treatment improves insulin resistance, lipid and vascular abnormalities.[34] Studies in humans and non-human primates have shown a strong inverse correlation of adiponectin levels with fasting glucose, insulin and insulin resistance, independently of BMI.[35]

Circulating adiponectin levels are also decreased in several cancers associated with obesity and insulin resistance.[21] Several epidemiological studies show an inverse association between adiponectin levels and risk for endometrial,[21,36] breast,[37,38] prostate,[39,40] gastric,[41] renal cancer[24] and colorectal cancer.[26] It is also possible that, in addition to its insulin-sensitising role, adiponectin may also regulate cell proliferation and specific signalling pathways directly in cancer cells. Studies *in vivo* showed that intratumoral administration of adiponectin to mice resulted in the suppression of a fibrosarcoma tumour[42] and exogenous adiponectin suppressed the growth of myelomonocytic leukaemia cells.[43] Two recent in vitro studies found that adiponectin suppressed cell growth in the MDA-MB-231[44] and MCF-7[45] breast cancer cell lines and inhibited proliferation of an androgen dependent (LNCaP-FGC) as well as two androgen independent (DU145 and PC-3) prostate cancer cell lines,[46] providing further support for a direct anti-tumourigenetic effect of the hormone.[47]

This is the first study to explore the role of adiponectin, a hormone with apparent anti-tumour properties, in melanoma development. The well-established strong association with reported sun exposure was also found herein with principal proxies of exposure used in this investigation. Standardised questionnaires were used by trained interviewers in order to minimize the risk of interviewer bias, whereas public health messages regarding prevention of melanoma are unlikely to have generated recall bias given the nature of the main examined variables. The relatively small study size may have prevented the observed association of adiponectin levels with melanoma to nominally reach statistical significance, whereas the exclusion, by design, of stage I melanomas might hinder generalizability of the results to less severe melanoma cases.

In conclusion, we present evidence that adiponectin may have a protective role in the development of melanoma; not withstanding the lack of statistical significance, the apparent sizeable association (25% reduction per one SD of adiponectin) points to the need for further investigation.

Conflict of interest statement

All authors state that there is no conflict of interest related to this research paper.

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