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Could serum Raftlin and GPER-1levels be new biomarkers for early detection of non-small cell lung cancer?

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Abstract

Background Lung cancer is the leading cause of cancer-related deaths worldwide. Therefore, the search for new biomarkers continues in order to diagnose lung cancer at an early stage. In this study, we investigated blood levels of G-protein associated membrane estrogen receptor (GPER)-1 and Raftlin as markers of early-stage in lung cancer.

Methods Lung cancer cases admitted to our hospital between 2016 and 2018 were included in our study. GPER-1 and Raftlin levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) in blood samples taken from patients diagnosed with lung cancer and healthy volunteers.

Results There were 64 cases in total, 32 cases in lung cancer group and 32 cases in control group. We evluated GPER-1 levels for each group. GPER-1 level was 2.54 (IQR: 1.08–5.78) ng/mL in the lung cancer group and 5 (IQR: 2.69–7.99) ng/mL in the control group. ROC analysis value for GPER-1, (AUC) was 0.66 ($p < 0.01$). Raftlin levels were 4.5 (IQR: 3.3-11.52) ng/mL in control group and 7.77 (IQR: 6.24–9.85) ng/mL in lung cancer group. ROC analysis value for Raftlin, (AUC) was 0.629($P = 0.09$).

Conclusions In our study, there was no statistically significant difference between our groups in terms of Raftlin values. Therefore, it was thought that Raftlin could not be a specific marker in the diagnosis of lung cancer. GPER-1 was found to be lower in the lung cancer group than in healthy individuals. Therefore, it was thought that GPER-1 could be evaluated as a diagnostic marker in lung cancer. However, we think that more definitive results can be obtained by determining the tissue and expression level of GPER in lung cancer with further studies.

Keywords GPER-1, Raftlin, Non-small cell lung cancer, Serum biomarkers, New tumor markers

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Introduction

Lung cancer (LC) is one of the main causes of cancer-related death today. The majority of LC cases consist of non-small cell lung cancer (NSCLC) [1]. Five-year survival rates in lung cancer patients are closely related to the stage of the cancer [2]. Therefore, patients in the risk group must be diagnosed early so that they can be treated early. Histological subtypes affect survival in lung cancer. Histological diversity may vary depending on the etiology of the cancer. While adenocarcinoma often develops as a sequela of previous infection, both squamous and adeno cancer can develop due to smoking, which is the most common etiological factor. However, some patients may develop lung cancer even if they do not have a history of smoking. This condition is more common in female patients. Additionally, the risk of lung adenocarcinoma is significantly higher in women than in men [3]. This condition is thought to be closely related to estrogen, and according to a recent study, breast cancer patients using antiestrogens have a lower risk of dying from lung cancer. Similarly, it has been reported that the risk of lung cancer is significantly lower in women receiving antiestrogen therapy [4]. Although it is known that estrogen accelerates the maturation of healthy lung tissue, it is unclear how it affects the development and spread of lung cancer [5, 6]. Some studies suggest that estrogen causes cancer development by affecting cell cycle, proliferation and apoptosis [7, 8]. Estrogen also triggers additional cellular response mechanisms with the help of a different receptor known as G-protein-associated membrane estrogen receptor GPER-1 [8]. GPER-1 was first discovered in breast cancer tissue in 1996 [9]. High levels of GPER-1 expression have been observed in estrogen-negative breast cancer cells. Therefore, GPER-1 plays an important role in cancer biology through an estrogen receptor-independent pathway.

Raftlin, the major lipid raft protein, was first described in B cells. Raftlin is responsible for regulating antigen receptor signaling in B cells. It plays a crucial role in autoimmune and inflammatory processes [10]. Insulin-like growth factor (IGF), phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt), which are regulated by lipid raft proteins and are important signaling pathways for the cell, are very important for the proliferation of cancer cells [11]. Some studies have suggested that these signaling mechanisms are disrupted in cancer cells. For example, it has been shown that Akt expression increases in lung cancer. Additionally, lipid rafts play an important role in cancer metastasis through CD44 receptors [12].

Currently, no marker has been identified that can be screened with routine blood tests in the early diagnosis of lung cancer. We thought that blood levels of GPER-1 and Raftlin, which play a role in many important mechanisms in cancer development, may differ between lung cancer patients and healthy individuals and may be markers for early diagnosis. Therefore, in this study, we aimed to evaluate GPER-1 and Raftlin levels in the blood of healthy individuals and lung cancer patients.

Material and method

Our study included 32 cases of lung cancer who applied to our hospital between 2016 and 2018, and a control group of 32 healthy volunteers. Stage of lung cancer was $T_1N_0M_0$ in all cases. Lung cancer 8th staging system recommended by the "International Association for the Study of Lung Cancer (IASLC)" was used. All individuals included in the study were informed and consent forms were obtained. Patients with histologically proven diagnosis of lung cancer and diagnosed with non-small cell lung cancer were included in our study. Fiberoptic bronchoscopy was used for the histological diagnosis of 17 cases and transthoracic fine needle aspiration biopsy was used for the diagnosis of 15 cases. The cases were divided into two subgroups as adenocarcinoma and squamous cell carcinoma. Lung cancer subtypes were divided equally, with 16 cases from lung adenocarcinoma and 16 cases from squamous cell carcinoma.

Inclusion and exclusion criteria

Patients who had undergone surgery for lung cancer, received chemotherapy or radiotherapy were not included in the study. In addition, those with pituitary adenoma, ovarian or adrenal tumor, adrenal hyperplasia, polycystic ovary syndrome (PCOS), rheumatoid arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease and vasculitis were excluded from the study. In addition, individuals who smoked two week before the blood sample in both groups were excluded from the study.

Collection and analysis of samples

Venous blood samples of patients were collected in gel-separator blood tubes (Becton Dickinson, New Jersey, USA). Blood tubes were centrifuged at 3500 rpm for 10 min after blood clotting to obtain serum. Serum samples were stored at -80 °C until analysis. Among the samples, the longest stored sample was 20 months, and the shortest stored sample was kept in the freezer for one week.

According to the instructions provided by the manufacturer, the levels of RAFTLİN (SunRedBio Technology Co, catalog number: 201-12-6471, Shanghai, China) and GPER-1 (Cloud-Clone Corp., SEG045Hu, Houston, TX, USA) were assessed using sandwich ELISA immunoenzymatic assays.The detection range of Raftlin was 0.5–70 ng/ml. The within- and total-run coefficient of variation (CV) values were < 12%. GPER-1 assay range was 0.3–20 ng/ml. The within- and total-run CV values were < 10%

Table 1 Demographic characteristics of the cases

	Lung cancer group	Control group	*P* value
Age (year)*	58.66 ± 7.48	57.63 ± 6.49	0,29[a]
Female (n,%)	11 (39.1%)	14 (43.8%)	0,60[b]
Male (n,%)	21(60.9%)	18 (56.2%)	

*mean ± standard deviation, n: number

Independent sample U Test[a], Chi-Square Tests[b]

and < 12%, respectively. Estradiol levels were analyzed by the electrochemiluminescence method (ECLIA) on the Cobas 6000 (Roche Diagnostics, Germany) device. Blood samples from lung cancer patients and healthy participants were tested for GPER-1 and Raftlin levels. Relationships between lung cancer and serum levels were investigated.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) and MedCalc 14 (MedCalc Software, Ostend, Belgium). Shapiro-Wilk's test was used to assess the assumption of normality. Continuous variables were presented with mean ± standard deviation or (in the case of non-normal distribution) median (interquartile range (IQR)). Categorical variables were summarized as counts (percentages). Comparisons of numeric variables between groups were carried out using independent samples t test/Mann-Whitney U test, whichever was appropriate. Association between two categorical variables was examined by Chi-square test. Receiver operator characteristic curves (ROC) analysis was used to determine AUC, sensitivity, specificity and cut-off values. All statistical analyses were carried out with 5% significance and a two-sided p-value < 0.05 was considered as statistically significant. A power analysis was conducted using G*Power version 3.1.9.4. Test family was selected as "t tests", the statistical test was selected as "Means: Difference between two independent means (two groups)" and total sample size was calculated as 52 (n1 = 26, n2 = 26) for $\alpha = 0.05$ and effect size = 0.80. To increase the power of our study we studied with a sample of size 64 (n1 = 32, n2 = 32).

Results

Demographic characteristics

There were 64 cases in total, 32 cases in the lung cancer group and 32 cases in the control group. There were 21(60,9%) male and 11 (39,1%) female cases in the lung cancer group, and 18 (56,2%) male and 14 (43,8%) female cases in the control group. The mean age was 58.66 ± 7.48 years in the lung cancer group, and 57.63 ± 6.49 years in the control group. There was no statistically significant difference between lung cancer and control groups in terms of age and gender. The demographic values of the cases are shown in Table 1.

The ages of 11 female patients in the lung cancer group ranged from 48 to 78 years, with a mean age of 60 years. The age of 14 female patients in the control group ranged from 41 to 71 years, with a mean age of 58 years. Except for the 41-year-old female case in the control group, all cases were in menopause. While the median estrogen level in female patients in the lung cancer group was 27.05 (IQR: 0.08–30.1) pg/ml, the median estrogen level in the control group was 25.60 (IQR: 12.11-31) pg/ml There was no statistically significant difference between the two groups in terms of estrogen levels ($p = 0.17$). The distribution of the parameters by gender is shown in Table 2.

When the Raftlin and GPER-1 values were evaluated in terms of men and women, no statistically significant difference was found (Raftlin $p = 0.67$, GPER-1 $p = 0.06$). No significant difference was found between lung cancer subtypes in terms of Raftlin and GPER-1 values ($p = 0.61$, $p = 0.38$, respectively).

GPER-1 values

Each group's GPER-1 levels were assessed. Median GPER-1 level was 2.54 (IQR: 1.08–5.78) ng/mL in the lung cancer group and 5 (IQR: 2.69–7.99) ng/mL in the control group. The difference between the GPER-1 levels between the lung cancer and control groups was found to be statistically significant ($p = 0.02$).The distribution of GPER-1 levels in lung cancer and control groups is shown in Fig. 1. An ROC analysis was performed for GPER-1 values and the area under the curve (AUC) was 0.66 ($p < 0.01$) (Fig. 2). Sensitivity and specificity values were 46.88 (95% CI:29.1–65.3) and 84.37 (95%CI: 67.2–94.7), respectively. Cut-off value for GPER-1 was obtained as

Table 2 Distribution of parameters by gender

	Lung Cancer Group			Control Group		
	Male Median (IQR)	Female Median (IQR)	*P** value	Male Median (IQR)	Female Median (IQR)	*P** value
GPER-1 (ng/mL)	2.39 (1.08–3.45)	2.86 (1.92–5.78)	0.46	4.75 (2.69–6.23)	5.25 (3.91–7.99)	0.12
Raftlin (ng/mL)	8.59 (7.68–9.85)	7.25 (6.24–8.19)	0.36	5.41 (4.1-11.52)	3.59 (3.3–8.76)	0.17
Estrogen (pg/ml)	19.56 (11.48–22.53)	27.05 (0.08–30.1)	0.09	21.68 (10.48–33.44)	25.60 (12.11-31)	0.21

*Indipendent sample Mann Whitney-U Test

IQR: Interquartile range

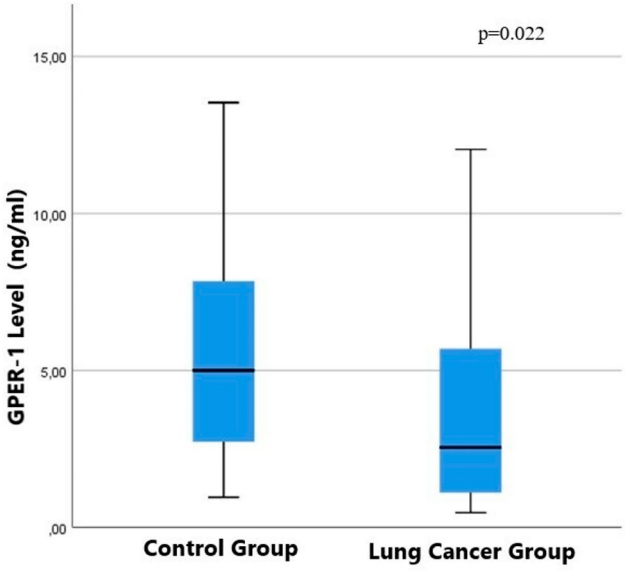

Fig. 1 Box-plot of the GPER-1 values of the lung cancer and the control group

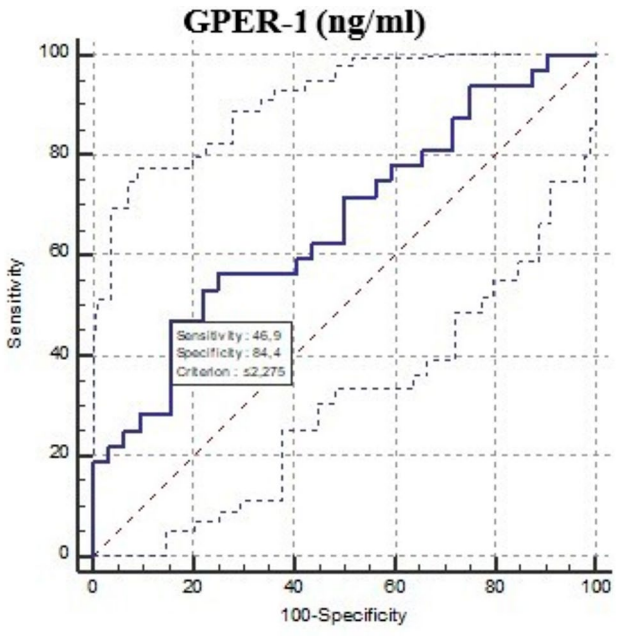

Fig. 2 ROC curve of GPER-1

2.28 ng/mL. In the ROC analysis, serum GPER-1 levels were found to be statistically significant for lung cancer ($p = 0.01$).

Raftlin values

Raftlin levels were 4.5 (IQR: 3.3-11.52) ng/mL in the control group and 7.77 (IQR: 6.24–9.85) ng/mL in the lung cancer group. When lung cancer and control groups were compared in terms of Raftlin level, it was not statistically significant ($p > 0.05$). When ROC analysis was performed for Raftlin level, AUC = 0.62, $P = 0.09$. Cut-off value was not calculated since the P value was not statistically significant.

Table 3 Distribution of parameters between groups

	Raftlin (ng/mL)	GPER-1 (ng/mL)
	Median (IQR)	**Median (IQR)**
Control Group	4.5 (3.3-11.52)	5 (2.69–7.99)
Lung Cancer Group	7.77 (6.24–9.85)	2.54 (1.08–5.78)
P value*	0.07	0.02

*Indipendent sample Mann Whitney-U Test

IQR: Interquartile range

Raftlin, GPER-1 levels of the lung cancer and the control group were shown in Table 3.

Discussion

In this study, apart from radiological and histological diagnosis methods in lung cancer, it was investigated whether early diagnosis could be made by taking blood samples from the patients. Raftlin and GPER-1 levels were evaluated as biomarkers for diagnosis. The levels of Raftlin and GPER-1 were assessed using sandwich ELISA immunoenzymatic assays. GPER-1 level was found to be lower in patients with lung cancer than in healthy individuals, and the difference was statistically significant. Raftlin values were similar in both groups. It was thought that low GPER-1 level might be a marker for lung cancer.

Lung cancer is the most common cancer in men. It is the most common type of cancer in women after breast and colorectal cancers. Lung cancer is the second most common cause of cancer-related death in women after breast cancer. Histologically, the incidence of lung adenocarcinoma has increased more rapidly than squamous cell carcinoma, especially in women, and has become the most common type of lung cancer in both sexes [3]. Smoking and air pollution are accepted as major risk factors for lung cancer [3]. In some studies, it has been reported that viral infections are involved in the etiology of lung cancer.

Despite all current treatment strategies, 5-year survival rates in advanced lung cancer are below 5% [13]. The diagnosis of lung cancer in the early stage is usually made incidentally during radiological examinations performed for different reasons. Even if radiological screening programs are planned for the diagnosis of early stage lung cancer, it is not very possible to apply them in clinical practice. Therefore, the search for new biomarkers for early diagnosis in lung cancer continues. Blood sampling for biomarkers is the first choice because it is easy and reliable. Also biomarkers to look for in the blood provide an overview of the entire patient body, including metastatic disease. Although various biomarkers have been identified, there is no definitive biomarker in terms of early diagnosis and treatment response in lung cancer. In

some studies, the effects of blood levels of sex hormones on lung cancer were investigated. High estrogen levels in women make them more susceptible to the cancer-causing effects of tobacco. In addition, estrogen can act directly as a carcinogen by altering cell proliferation [14]. Researchers have looked at how male sex hormones may contribute to lung cancer, and they have found that the androgen receptor (AR), which is primarily expressed in male patients' pneumocytes and lung epithelium, is involved in the disease's etiology [14]. ERα and ERβ, which are estrogen receptors (ER), belong to the nuclear steroid hormone receptor family and induce estrogen-dependent gene transactivation. However, the existence of receptors showing pregenomic estrogen activity has been the subject of debate. It has been accepted that the most likely receptor to fulfill this task is G protein-coupled ER (GPER)-1. Several studies have shown that estrogen pregenomic signaling in ER-negative, GPER-1-positive cells is mediated by GPER-1. GPER-1 stimulates adenylate cyclase and triggers its release. A number of tissues, including the neurological, reproductive, digestive, and muscular systems, have been identified to have GPER-1 [15]. It has been shown to be highly present in breast, endometrial and thyroid cancers [16–18]. In the examinations performed in urinary system cancers, it has been shown that GPER-1 acts independently of the estrogen receptor in cancer cells. According to these studies, ER and GPER-1 use different signaling mechanisms. The fact that some ER antagonists serve as GPER-1 agonists supports these studies. Although GPER-1 uses signaling pathways similar to estrogen receptors on the cell membrane, immunohistochemical analyzes have shown that GPER-1 is found intracellularly in breast carcinoma. GPER-1 expression in breast cancers has been associated with poor clinical progression [19]. In addition, high levels of GPER-1 protein expression in breast cancer specimens are also associated with increased tumor size and metastasis.

Compared to healthy lung bronchial epithelial cells, GPER-1 is greater in non-small cell lung cancer cells. GPER-1 level increases due to high ERβ expression in lung cancer [20]. ERβ levels expressed in primary lung tumors are approximately twice the ERα levels [20]. GPER-1 induces matrix metalloproteinases in lung cancer cell and metastasis is seen at a higher rate in lung cancer cells with high GPER-1 expression [21–23]. Although GPER-1 is elevated in lung cancer and is considered a poor prognostic factor, the precise role of GPER-1, its intracellular location, and its role in mediating estrogen function are controversial. Shen et al. showed that GPER-1 promoted the formation of non-small cell lung cancer using the NATCH1 signaling pathway [24]. Liu et al. showed that GPER-1 responds to estrogen stimulation and leads to tumor formation in non-small cell lung cancer and causes tumor proliferation [25]. Also, in the same study, they showed that G15, which inhibits GPER-1, blocked the tumor. In some studies, it is mentioned that the increase in GPER-1 level is a defense against tumoral tissue. Krakstad et al. showed in their study that low GPER-1 levels are associated with poor prognosis in ERα-positive endometrial cancers [26]. In our study, the lung cancer group's GPER-1 level was lower than that of the control group. It was statistically significant that the two groups differed from one another. According to this result of our study, low GPER-1 level was accepted as a risk factor for lung cancer. Contrary to the general literature, we think that high GEPER-1 level has a protective effect in malignant patients.

Lipid rafts contain high levels of cholesterol and glycosphingolipids. They exist in the cell as a special structure of the plasma membrane.The phospholipid side chains in the lipid raft have more saturated fatty acids and less fluid cholesterol. The lipid raft's physical characteristics enable it to function as a signaling platform that binds crucial elements together and promotes their interaction.It has been reported that cancer cells show high levels of membrane lipid rafts and cholesterol [27]. This is very important for cancer cells, and high concentrations of lipid rafts may serve different signaling in these cells. In addition, lipid rafts harbor many adhesion molecules in cancer cells [28]. The epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor that plays an important role in cell growth and proliferation and is closely related to signal transduction of lipid rafts [28]. It is known that EGFR mutations play an important role in the formation of lung cancer. Irwin et al. showed that EGFRs on lipid rafts are highly effective in the development of resistance to tyrosine kinase inhibitors and showed that cancer patients become sensitive to gefitinib when cholesterol levels in lipid rafts are lowered [29]. Similarly Gupta et al. showed in their study that CD 133, an oncogenic stem cell marker, is located on lipid rafts and is very important in developing drug resistance in cancer cells [30]. Therefore, lipid rafts have become very effective target points in cancer treatments. Additionally Raftlin associated Urokinase-type plasminogen activator surface receptor (uPAR) is found in excess in many malignant epithelial tumors [31]. For these reasons, we thought that Raftlin, which contains a very important signaling mechanism in cancer cells, may differ in blood levels in lung cancer patients compared to the normal population. However, in our study, there was no statistically significant difference between the lung cancer group and the control group. According to our study, Raftlin seems far from being a new biomarker in lung cancer.

Our study has several limitations as follows; relatively small sample size, being a single-center study, GPER-1 and Raftlin levels being affected by many factors. In

addition, the lack of comparative studies with other tumoral diseases is the limiting factor of our study.

In conclusion, still one of the most prevalent cancers in the world, lung cancer has a relatively high fatality rate. Because of late symptoms in many patients, early diagnosis of lung cancer occurs at very low rates. For this reason, studies on early diagnosis of lung cancer continue. The search for new biomarkers for the early detection of lung cancer, especially in people with risk factors, continues.

According to the results of our study, we could not detect a significant difference between the normal population and the lung cancer group in terms of Raftlin level, and we decided that it would not be an appropriate biomarker for the diagnosis of lung cancer.

In our study, it was shown that the GPER-1 level was lower in lung cancer compared to the normal population, and it could be used as a marker in lung cancer. We think that the cut-off value for GPER-1 that we obtained in our study will be very helpful in the early diagnosis of lung cancer and in the follow-up of its prognosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-024-03296-4.

Supplementary Material 1

Supplementary Material 2

Author contributions

A E: wrote the main manuscript text B G: reviewed the manuscript H E: wrote the main manuscript text G T Ç: prepared figures H F S: reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. This study was conducted with formal and written approval from the Institutional Ethics Committee of the University of Zonguldak Bülent Ecevit University (06/06/2018, protocol number: 2018-150-06/06). The study was performed according to the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants gave written consent for inclusion and were fully anonymized.

Competing interests

The authors declare no competing interests.

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