Diagnostic Efficiency of HE4 and CYFRA 21-1 in Patients with Lung Cancer

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ABSTRACT

Lung cancer is the leading cause of cancer related deaths. Despite the modern diagnostic and therapeutic advances, 5-year survival rate of all cases of lung cancer does not exceed 15%. Therefore, sensitive tumor biomarkers are needed for the early detection and differential diagnosis of lung cancer. The aim of the study was to evaluate the diagnostic efficiency of HE4 (Human epididymis protein 4) and CYFRA 21-1 in patients with lung cancer. Serum samples were collected from 80 patients; Group 1 consisted of 53 patients with lung cancer and Group 2 consisted of 27 patients as control. HE4 and CYFRA 21.1 levels were measured by chemiluminescent microparticle immunoassay (CMIA). The cut-off limits for HE4 was 70 pmol/L and 2 ng/mL for CYFRA 21-1. Serum mean HE4 levels in Group 1 (94.79±50.56 pmol/L) were significantly higher than that of Group 2 (52.00±21.06 pmol/L), (p< 0.001). CYFRA 21-1 levels in Group 1 and Group 2 were 5.15±7.89 ng/mL and 1.75±2.11 ng/mL, respectively (p= 0.004). The sensitivity rates were 73.5% for HE4 and 50.9% for CYFRA 21-1. Both tumor markers were clearly related to stage with significantly higher ratio of increase in advanced stages (III-IV) than in early stages (I-II), (p= 0.021 for HE4, p=0.003 for CYFRA 21-1). HE4 and CYFRA 21.1 might be used as potential diagnostic markers for lung cancer patients. Especially HE4 may be candidate as a "leading-marker" for the discrimination of lung cancer because of its high sensitivity, positive predictive value and diagnostic accuracy.

Keywords: Human epididymis protein 4, CYFRA 21-1, Tumor marker, Lung Cancer

ÖZET

Akciğer Kanseri Hastalarında HE4 ve CYFRA 21-1'in Tanısal Etkinliği

Akciğer kanseri, kansere bağlı ölüm nedenleri arasında erkekler ve kadınlarda ilk sırada yer almaktadır. Modern tanısal ve tedaviye yönelik gelişmelere rağmen akciğer kanseri olgularında ortalama sağ kalım %15'i geçmemektedir. Bu nedenle akciğer kanserinin erken tanısı ve ayırıcı tanısında duyarlı biyobelirteçlere ihtiyaç duyulmaktadır. Bu çalışmanın amacı, akciğer kanseri hastalarında HE4 ve CYFRA 21-1 biyobelirteçlerinin tanısal etkinliğinin değerlendirilmesidir. Serum örnekleri 80 hastadan toplandı; Grup 1 akciğer kanseri tanısı alan 53 hastadan oluşmakta idi, Grup 2 ise 27 hastadan oluşan kontrol grubu idi. HE4 ve CYFRA 21-1 değerleri kemiluminesan mikropartikül immüm yöntem ile ölçüldü. HE4 için eşik değeri 70 pmol/L, CYFRA 21-1 için ise 2 ng/mL olarak belirlendi. Grup 1 için ortalama HE4 değerleri (94.79±50.56 pmol/L) Grup 2 için ölçülen değerlerden (52.00±21.06 pmol/L) istatistiksel olarak anlamlı ölçüde yüksek bulundu (p< 0.001). Grup 1 ve Grup 2 için ortalama CYFRA 21-1 değerleri sırasıyla 5.15±7.89 ng/mL ve 1.75±2.11 ng/mL olarak bulundu (p= 0.004). HE4 biyobelirtecinin duyarlılığı %73.5, CYFRA 21-1 biyobelirtecinin duyarlılığı ise %50.9 olarak saptandı. Her iki tümör biyobelirteçinin ileri evrelerde (Evre III-IV) artış oranı, erken evrelere (Evre I-II) göre anlamlı derecede yüksek bulundu (HE4 için p=0.021, CYFRA 21-1 için p= 0.003). HE4 ve CYFRA 21-1, akciğer kanseri hastalarının tanısında potansiyel biyobelirteçler olarak kullanılabilir. Özellikle HE4 yüksek duyarlılık, pozitif tahmin değeri ve tanısal etkinliği nedeni ile akciğer kanseri ayırıcı tanısında önemli biyobelirteç olmaya adaydır.

Anahtar Kelimeler: HE 4, CYFRA 21-1, Tümör biyobelirteci, Akciğer kanseri

INTRODUCTION

Lung cancer is the leading cause of cancer related death in men and women. Despite modern diagnostic, staging and therapeutic advances, the 5-year survival rate of all cases diagnosed with lung cancer does not exceed 15%.[1] Surgical resection is the most effective treatment in patients with lung cancer, 5-year survival rate following surgical resection has only been improved in patients with early stages of disease. Thus, research efforts have focused on early detection and intervention at an earlier stage to decrease the high mortality, which implies the significance of diagnostic methods in lung cancer.[2,3]

Bronchoscopic examination is one of the most effective diagnostic tool to provide histological diagnosis in lung cancer patients.[2] Histological diagnosis of lung cancer is sometimes challenging in patients without bronchus involvement especially in peripheral mass lesions, solid and semisolid pulmonary nodules. Therefore some efficient diagnostic methods such as biochemical or immunologic markers are needed to increase the diagnostic yield of lung cancer patients.

Human epididymis protein 4 (HE4) is a 25kD whey acid protein with a 4 disulfide core that is predominantly expressed in epithelial cells of the epididymis, respiratory epithelium of proximal airways and the normal female reproductive tract.[4-8] Recently, it has been shown that elevated serum HE4 levels may be a diagnostic marker for lung, ovarian and endometrial cancer detection.[4,9,10]

CYFRA 21-1 comprises a soluble fragment of cytokeratin 19 with a molecular weight of 30,000 which is expressed by respiratory epithelium cells and has been detected in lung cancer in addition to breast and pancreatic cancer. It has been shown that CYFRA 21-1 reflects tumor mass by correlating with tumor stage, survival, and surgical removal.[11-13] CYFRA 21-1 assay detects cytokeratin-19 fragment in serum by KS 19-1 and BM 19-21 antibodies.[14,15]

The aim of the study was to evaluate the adjunctive diagnostic value of HE4 and CYFRA 21-1 in non-small lung cancer (NSCLC). We also assessed the relationship between the two novel markers both with the stage of the disease and lymphovascular invasion.

Table 1. Patient characteristics

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Group 1 (mean age: 63.39±10.57 years)	
Squamous Cell Carcinoma	26
Adenocarcinoma	27
Group 2 (mean age: 48.14±17.56 years)	
Bronchogenic cyst	4
Pleural effusion	3
Secondary pulmonary neoplasm	3
Pneumonia	3
Tuberculosis granuloma	3
Pulmonary hamartoma	2
Bronchiectasis	2
Pseudotumor	1
Parapneumonic empyema	1
Neurofibroma	1
Intrathoracic neuroblastoma	1
Mesothelioma	1
Chest wall sarcoma	1
Mediastinal lymphoma	1

MATERIALS AND METHODS

Patients and serum samples

Serum samples were collected from 80 patients who were treated in Department of Thoracic Surgery of Guven Hospital between April 2013 and May 2014. The patients were 59 men and 21 women with a mean age of 58.25±15.09 (range: 1-84). Diagnosis was made on the basis of clinical and radiologic features, bronchoscopic findings and preoperative and/or postoperative histological examinations. Patients were classified into two groups. Group 1 consisted of 53 patients with lung cancer. Group 2 consisted of 27 patients with benign lung disease, mediastinal cyst / neoplasm, secondary pulmonary neoplasm, and pleural diseases as control group.

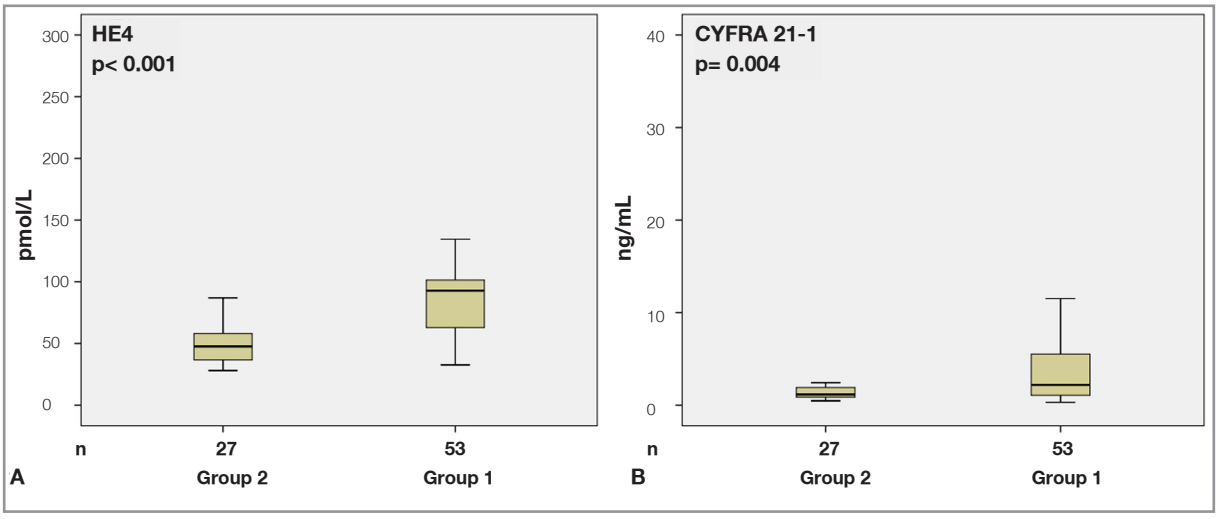

Figure 1. Box-plot graphics of HE4 (A) and CYFRA 21-1(B) in Group 1 and Group 2

In Group 1, there were 45 male and 8 female with a mean age of 63.39±10.57 years (median: 64.00, range: 35-84). Histopathologic diagnosis was squamous cell carcinoma in 26 patients and adenocarcinoma in 27 patients. In group 2, there were 14 male and 13 female with a mean age of 48.14±17.56 years (median:52, range: 1-70). None of these patients had coexisting or previous primary lung, ovarian or endometrial cancer. The diagnoses of Group 1 and Group 2 patients are given in Table 1.

Measurement of HE4 and CYFRA 21-1 levels

All blood samples had been collected preoperatively in serum separator tubes and were centrifuged at 1500g for 10 minutes (Rotanta 460). The serum samples were separated and stored at -80^{0}C. CYFRA 21-1 and HE4 levels were measured by chemiluminescent microparticle immunoassay (CMIA) using the Architect system (Abbott Diagnostics, USA). The cut-off limits for HE4 was 70 pmol/L and 2 ng/mL for CYFRA 21-1.

Statistical Analysis

HE4 and CYFRA 21-1 levels were compared between groups with non-parametric tests (Mann-Whitney test). Receiver operator characteristic (ROC) curves were assessed to reflect the relationship between sensitivity and specificity for HE4 and CYFRA 21-1. The following calculations were made: sensitivity= true-positive/(true-positive + false-negative); specificity= true-negative/(true-negative+false-positive); positive predictive value (PPV) = true-positive/(true-positive + false-positive); negative predictive value (NPV)= True-negative/(true-negative + false-negative); diagnostic accuracy (DA)= true-positive + true-negative/true-positive + false-negative + false-positive + true-negative. Data were expressed as mean ± the standard deviation (SD). A P value less than 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics Version 21.

RESULTS

Serum mean HE4 levels in Group 1 (94.79±50.56 pmol/L) were significantly higher than that of Group 2 (52.00±21.06 pmol/L), (p< 0.001). CYFRA 21-1 levels in the Group 1 and Group 2 were 5.15±7.89 ng/mL and 1.75±2.11 ng/mL, respectively. The difference between the groups was significant (p= 0.004). Box-plot graphics of HE4 and CYFRA 21-1 were given in Figure 1.

When we compared the mean levels of CYFRA 21-1 within Group 1; a significant differ-

Table 2. Correlations of HE4 and CYFRA 21-1 levels between Group 1 and Group 2

	HE4>70 pmol/L n (%)	HE4<70 pmol/L n (%)	CYFRA 21-1>2 ng/mL n (%)	CYFRA 21-1<2 ng/mL n (%)
Group 1	39 (73.6%)	14 (26.4%)	27 (50.9%)	26 (49.1%)
Group 2	4 (14.8%)	23 (85.2%)	5 (18.5%)	22 (81.5%)
p value	p< 0.001		p= 0.011	

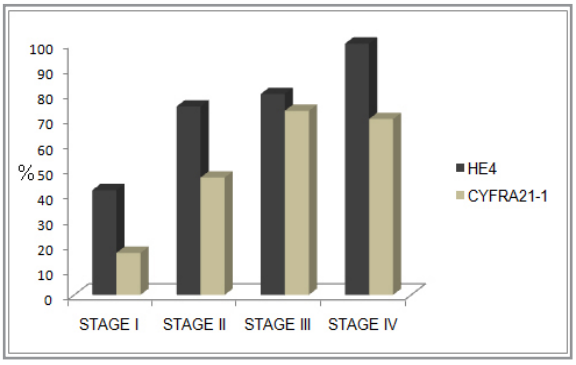

Figure 2. Elevation ratio of HE4 and CYFRA 21-1 in patients with lung cancer, subdivided according to the tumor stage

ence was observed between squamous cell lung cancer (6.91±9.28 ng/mL) and adenocarcinoma (3.46±5.97 ng/mL), (p= 0.028). Similarly, we observed significant difference between the squamous cell lung cancer patients (6.91±9.28 ng/mL) and Group 2 (1.75±2.11 ng/mL), (p= 0.001). However, no significant difference was observed between squamous cell cancer (92.33±51.14 pmol/L) and adenocarcinoma (97.17±50.85 pmol/L) for mean HE4 levels in Group 1 (p= 0.749).

When the cut-off value of HE4 was accepted as 70 pmol/L, elevation of HE4 was observed in 39 patients of Group 1 (73.6%), whereas only 4 patients (14.8%) showed elevated levels of HE4 in Group 2 (p< 0.001). When 2 ng/mL was accepted as the cut-off value for CYFRA 21-1, 50.9% of Group 1 patients and 18.5% of Group 2 patients showed higher levels of CYFRA 21.1 (p= 0.011) as shown in Table 2.

When the levels of HE4 and CYFRA 21-1 were analyzed according to the stages of lung cancer, it was observed that the elevation ratio for both markers increased in parallel to the stages of lung cancer. Figure 2 shows the elevation ratio of HE4 and CYFRA 21-1 in patients with lung cancer, subdivided according to the tumor stages. Although 41.7% (n= 5) of Stage I patients showed elevated HE4 levels, CYFRA 21-1 increase was observed only 16.7% (n= 2) of Stage I patients. Both tumor markers were clearly related to stages with significantly higher ratio of increase in advanced stages (III-IV) than in early stages (I-II) (p= 0.021 for HE4, p= 0.003 for CYFRA 21-1) as given in Table 3.

In Group 1 primary lung cancer patients, we observed that the presence of lymphovascular inva-

Table 3. Elevation ratio of HE4 and CYFRA 21-1 in patients with lung cancer, categorized to early and advanced stages

	HE4>70 pmol/L n (%)	HE4<70 pmol/L n (%)	CYFRA 21-1>2 ng/mL n (%)	CYFRA 21-1<2 ng/mL n (%)
Stages I-II	17 (60.7%)	11 (39.3%)	9 (32.1%)	19 (67.9%)
Stages III-IV	22 (88%)	3 (12%)	18 (72%)	7 (28%)
p value	p= 0.021		p=0.003	

Table 4. Correlations between lymphovascular invasion and tumor markers

	HE4>70 pmol/L n (%)	HE4<70 pmol/L n (%)	CYFRA 21-1>2 ng/mL n (%)	CYFRA 21-1<2 ng/mL n (%)
Lymphovascular invasion (+)	37 (84.1%)	7 (15.9%)	26 (59.1%)	18 (40.9%)
Lymphovascular invasion (-)	2 (22.2%)	7 (77.8%)	1(11.1%)	8 (88.9%)
p value	p= 0.001		p= 0.011	

sion was correlated with both HE4 and CYFRA 21-1 levels. As shown in Table 4, 84.1% of patients with lymphovascular invasion showed HE4 levels higher than 70 pmol/L, whereas 59.1% of patients with lymphovascular invasion showed CYFRA 21-1 levels higher than 2 ng/mL.

Figure 3 shows the ROC curves for evaluating the utility of HE4 and CYFRA 21-1 in the diagnosis of lung cancer. The area under the curve (AUC) for HE4 was 0.824 (95% confidence interval, 0.725-0.922, p< 0.001) and for CYFRA 21-1 was 0.698 (95% confidence interval, 0.580-0.816, p= 0.004), respectively. The AUC for HE4 was definitely higher than CYFRA 21-1.

Table 5 shows the HE4 and CYFRA 21-1 efficiency in the diagnosis of lung cancer as a tumor marker. The sensitivity, specificity, PPV and NPV of HE4 were higher than CYFRA 21-1. HE4 had also higher diagnostic accuracy compared with CYFRA 21-1. Dual marker combination of HE4 and CYFRA 21-1 reached up to a sensitivity of 77%, increased the sensitivity of either marker alone for the detection of lung cancer.

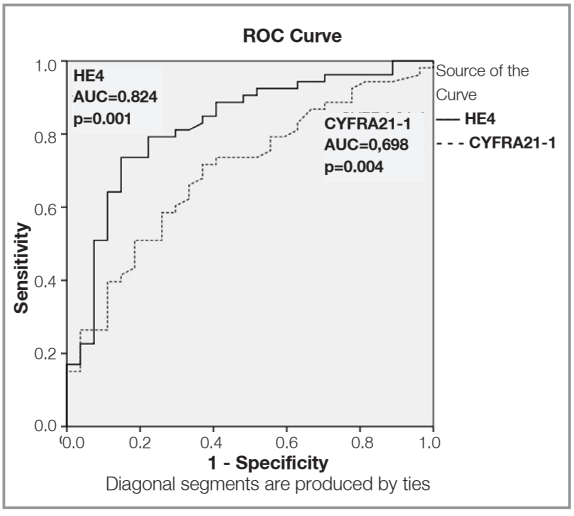

Figure 3. ROC curves for HE4 and CYFRA 21-1

DISCUSSION

The prognosis of lung cancer has improved over the last 30 years due to new diagnostic tools such as endobronchial ultrasonography and PET-CT. Limited therapeutic progress has been achieved with multimodal treatment concepts of locally advanced non-small cell lung cancer (NSCLC). However, the prognosis in metastatic NSCLC is still pretty poor. Today, surgery is the only therapeutic option to cure a NSCLC patient. Even with a successful surgery in patients with early stages, the 5-year survival rates are 50-70%.[15-18] Due to the lack of diagnostic tools for early detection of lung cancer, the vast majority of patients are diagnosed when they have an advanced stage of lung cancer. Therefore, sensitive and useful tumor biomarkers are needed

Table 5. Sensitivity, specificity, PPV, NPV and diagnostic accuracy for HE4, CYFRA 21-1

	HE4	CYFRA21-1
Sensitivity (%)	73.5	50.9
Specificity (%)	85	81.4
PPV	0.90	0.84
NPV	0.62	0.45
Diagnostic accuracy	0.77	0.61

for the early detection and differential diagnosis of lung cancer. Recently, diagnostic efficiency of HE4 and CYFRA 21-1 in patients with lung cancer has been described in few articles.[4,14,15,19-22]

Hertlein et al.[4] reported significantly higher HE4 values for lung cancer (median: 77.3 pmol/L for female, 89.2 pmol/L for male) compared with healthy controls (40.4 pmol/L for female, 26.2 pmol/L for male). For benign lung diseases, they also indicated median HE4 values as 44.4 pmol/l and 57.1 pmol/L in women and men, respectively. The difference was significant only in male group when compared with the healthy controls. In our study, we observed significantly higher HE4 ($p< 0.001$) and CYFRA 21-1 ($p= 0.004$) levels in primary lung cancer patients compared to control group. Hertlein et al.[4] also showed significantly higher AUC values for HE4 in lung cancer than benign diseases both in men (0.689) and women (0.847). Likewise, AUC values were reported as 0.825 by Yamashita[22] and 0.988 by Iwahori.[19] In our study, AUC was 0.824 for HE4, which is very close to previous reports.

Liu et al.[20] measured significantly higher HE4 levels in lung cancer patients with a sensitivity of 67.4% and specificity of 86%. They also observed significantly higher HE4 levels at advanced stages (Stage I-II vs. Stage III-IV, $p= 0.02$), and higher levels of serum HE4 ($\geq$ 83.90 pmol/l) were significantly correlated with an unfavorable 3-year survival rate for patients with NSCLC ($p< 0.05$). In our study, rates of sensitivity and specificity were 73.5% and 85% for HE4, respectively. Even the specificity rates were almost similar; our sensitivity was higher than Liu's study. Additionally, when we compared early stages (Stage I-II) versus advanced stages (Stage III-IV), we observed significantly elevated HE4 and CYFRA 21-1 levels at advanced stages compared to early stages as shown in Table 3 ($p= 0.021$ for HE4, $p= 0.003$ for CYFRA 21-1), similar to Liu et al. According to our results, increase in HE4 was observed in 41.7% of Stage I lung cancer patients, whereas CYFRA 21-1 was elevated only in 16.7% of Stage I patients, showing that HE4 was a better marker to discriminate malignancy even at Stage I.

Heuvel et al.[11] have compared CYFRA 21-1 and CEA in NSCLC and shown that CYFRA 21-1 increased in 63% and CEA in 52% of NSCLC patients. They reported that AUC was 0.92 (0.89-0.96) for CYFRA 21-1. The increase in CYFRA 21-1 was observed in 56% adenocarcinoma and 71% of squamous cell carcinoma whereas CEA was elevated in 75% of adenocarcinoma and 20% of squamous cell carcinoma. In our study, CYFRA 21-1 increased in 50.9% of lung cancer patients and the AUC for CYFRA 21-1 was 0.698 (0.580-0.816). If we analyze the data according to the histological type, elevation of CYFRA 21-1 was observed in 37% of adenocarcinoma and 65.4% of squamous cell carcinoma patients. We observed significant difference between Group 1 and Group 2 for CYFRA 21-1 positivity ($p= 0.011$), likewise there was a significant difference between Group 2 and squamous cell lung cancer patients ($p= 0.001$).

Some recent studies have reported that both HE4 and CYFRA 21-1 are potential prognostic factors for lung cancer.[15,19-22] Lymphovascular space invasion (LVI) is an established negative prognostic factor in lung cancer. LVI is associated with an increased risk of regional lymph node involvement and also it is an adverse prognostic factor for the development of distant metastases and long-term survival.[23] Therefore, we evaluated the correlation between LVI positivity with HE4 and CYFRA 21-1. As given in Table 5, we observed a strong correlation between LVI positivity and HE4 (84.1%, $p= 0.001$), also with CYFRA 21-1 (59.1%, $p= 0.011$) in our study.

In conclusion, both HE4 and CYFRA 21.1 are potential diagnostic markers for lung cancer patients. Especially HE4 may be a candidate as a "leading-marker" for the discrimination of lung cancer because of its high sensitivity, PPV and diagnostic accuracy. It seems that CYFRA 21-1 can be a valuable marker, especially for squamous cell lung cancer. Dual marker combination of HE4 and CYFRA 21-1 increased the sensitivity of either marker alone for the detection of lung cancer. In addition, both markers may be used to predict prognosis, detection of recurrences and monitor treatment response.

REFERENCES

1. Boring CC, Squires TS, Tong T. Cancer Statistics. CA Cancer J Clin 42: 19-38,1992.
2. Muley T, Fetz TH, Dienemann H, et al. Tumor volume and tumor marker index based on CYFRA 21-1 and CEA are strong prognostic factors in operated early stage NSCLC. Lung Cancer 60: 408-415, 2008.
3. Dikmen E, Kara M, Dikmen G, et al. Detection of telomerase activity in bronchial lavage as an adjunct to cytological diagnosis in lung cancer. Eur J Cardiothorac Surg. 23: 194-199, 2003.
4. Herthlein L, Stieber P, Kirschenhofer A, et al. Human Epididymis protein 4(HE4) in benign and malignant diseases. Clin Chem Lab Med 50: 2181-2188, 2012.
5. Kalapotharakos G, Asciutto C, Henic E, et al. High preoperative blood levels of HE4 predicts poor prognosis in patients with ovarian cancer. J Ovarian Res 5: 20, 2012.
6. Moore RG, Miller MC, Eklund EE, et al. Serum levels of the ovarian cancer biomarker HE4 are decreased in pregnancy and increase with age. Am J Obstet Gynecol 206: 349.e1-7, 2012.
7. Moore RG, Miller MC, Steinhoff MM, et al. Serum HE4 levels are less frequently elevated than CA125 in women with benign gynecologic disorders. Am J Obstet Gynecol 206: 351. e1-8, 2012.
8. Bolstad N, Øijordsbakken M, Nustad K, Bjerner J. Human epididymis protein 4 reference limits and natural variation in a Nordic reference population. Tumour Biol 33: 141-148, 2012.
9. Moore RG, McMeekin DS, Brown AK, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol 112: 40-46, 2009.
10. Li J, Dowdy S, Tipton T, Podratz K, et al. HE4 as a biomarker for ovarian and endometrial cancer management. Expert Rev Mol Diagn 9: 555-566, 2009.
11. Van den Heuvel MM, Korse CM, Bonfrei JMG, Baas P. Non-invasive diagnosis of pleural malignancies: The role of tumor markers. Lung Cancer 59: 350-354, 2008.
12. Muley T, Fetz TH, Dienemann H, et al. Tumor volume and tumor marker index based on CYFRA 21-1 and CEA are strong prognostic factors in operated early stage NSCLC. Lung Cancer 60: 408-415, 2008.
13. Vollmer RT, Govindan R, Graziano SL, et al. Serum CYFRA 21-1 in Advanced Stage Non-Small Cell Lung Cancer. Clin Cancer Res 9: 1728-1733, 2003.
14. Wieskopf B, Demangeat C, Purohit A, et al. Cyfra 21-1 as a biologic marker of non-small cell lung cancer. Evaluation of sensitivity, specificity, and prognostic role. Chest 108: 163-169, 1995.
15. Pujol JL, Grenier J, Parrat E, et al. Cytokeratins as serum markers in lung cancer: a comparison of CYFRA 21-1 and TPS. Am J Respir Crit Care Med 154: 725-733, 1996.
16. Hotta K, Fujiwara Y, Kiura K, et al. Relationship between response and survival in more than 50,000 patients with advanced non-small cell lung cancer treated with systemic chemotherapy in 143 phase III trials. J Thorac Oncol 2: 402-407, 2007.
17. Pfannschmidt J, Muley T, Bulzebruck H, et al. Prognostic assessment after surgical resection for non-small cell lung cancer: experiences in 2083 patients. Lung Cancer 55: 371-377, 2007.
18. Koike T, Tsuchiya R, Goya T, et al. Prognostic factors in 3315 completely resected cases of clinical stage I non-small cell lung cancer in Japan. J Thorac Oncol 2: 408-413, 2007.
19. Iwahori K, Suzuki H, Kishi Y, et al. Serum HE4 as a diagnostic and prognostic marker for lung cancer. Tumour Biol 33: 1141-1149, 2012.
20. Liu W, Yang J, Chi PD, et al. Evaluating the clinical significance of serum HE4 levels in lung cancer and pulmonary tuberculosis. Int J Tuberc Lung Dis 17: 1346-1353, 2013.
21. Yamashita S, Tokuishi K, Hashimoto T, et al. Prognostic significance of HE4 expression in pulmonary adenocarcinoma. Tumour Biol 32: 265-271, 2011.
22. Yamashita S, Tokuishi K, Moroga T, et al. Serum level of HE4 is closely associated with pulmonary adenocarcinoma progression. Tumour Biol 33: 2365-2370, 2012.
23. Higgins KA, Chino JP, Ready N, et al. Lymphovascular invasion in non-small-cell lung cancer: implications for staging and adjuvant therapy. J Thorac Oncol 7: 1141-1147, 2012.

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