Observational Study

Medicine®

OPEN

Serum REG Iα as a potential novel biomarker in cancer

An observational study

Yumin Zhang, MD[a,b], Xuelu Yuan, MM[c], Xiangyun Zhu, MD[a,b], Qian Wang, BS[d], Xuebing Yu, BS[d], Qiong Wei, MD[a,b,*], Ling Li, MD[a,b,*]

Abstract

The regulation of the gene-regenerating family member 1 alpha (REG Iα) played important roles in cancer cell biology. However, the correlation between its gene product serum REG Iα and cancer has not been evaluated. In this observational study, 130 hospitalized patients from the department of internal medicine in Zhongda Hospital Southeast University were included and assigned to cancer or noncancer groups. History, clinical, and laboratory data were obtained. Serum REG Iα levels and alanine aminotransferase were found significantly higher in patients with cancer ($P < .001$ and $P < .05$ respectively). Logistic regression analysis indicated that REG Iα was an independent risk factor for cancer ($P < .001$). The area under the curve of REG Iα was 0.764 and the optimal cut-off point of REG Iα was 46.97 ng/mL. Besides, the cancer patients with metastasis had significantly higher serum REG Iα levels than those in nonmetastasis cancer group ($P < .05$). In conclusion, serum REG Iα was significantly elevated in patients with cancer, and it might be a potential biomarker in predicting cancer occurrence and development.

Abbreviations: ALP = alanine aminotransferase, BMI = body mass index, ELISA = enzyme-linked immunosorbent assay, FE-1 = fecal elastase-1, FINS = fasting insulin, FPG = fasting plasma glucose, GGT = gamma glutamyl transferase, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, REG Iα = regenerating family member 1 alpha, TC = total cholesterol, UA = uric acid.

Keywords: breast cancer, cancer biomarker, gastrointestinal cancer, pulmonary cancer, serum REG Iα

1. Introduction

In the global world, cancer has been widely recognized as a big threat as its increasing incidences and heavy economic burden.[1] Therefore, the early diagnosis and treatment of cancer have been the focus of current clinical work. Cancer biomarker referred to a kind of substance existing or secreted in cancer cells, which could predict the occurrence and development of cancer and monitor the response of cancer to treatment, including tumor antigen, hormone, glycoprotein, enzyme and iso-enzyme, oncogene, and so on. With the development of molecular biology technology, cancer biomarkers' detection played an important role in the screening, early diagnosis, and treatment of various cancer.

Regenerating family member 1 alpha (REG Iα), also termed as lithostathine-1-alpha and pancreatic stone protein have been found independently in the field of pancreatitis and diabetes, although the 2 proteins have been subsequently proved identical.[2] It was a type I subclass member of the regenerating protein family which was grouped into 4 subclasses, types I, II, III, and IV based on the primary structures of the proteins.

Under healthy conditions REG Iα was expressed at low levels in the pancreas,[3] and its normal serum levels varied between 10 and 15 ng/mL. Upon local or systemic extra-pancreatic inflammation, REG Iα was strongly elevated. Previous studies showed that diseases such as chronic obstructive pulmonary disease,[4] sepsis,[5] ventilator-associated pneumonia,[6] renal dysfunction in pregnant women,[7] diabetes,[8,9] and diabetic kidney disease[10] were all associated with the increase of serum REG Iα levels. In normal tissues apart from the pancreas, REG Iα gene was not expressed or lowly expressed. However under cancer condition such as in gastric cancers,[11] breast cancers,[12] colon cancers,[13] esophageal cancers,[14] lung cancers,[15] liver cancers,[16] and bladder cancers,[17] REG Iα showed high expression and its abnormal expression had high correlations with the prognosis of cancers. But until now, whether serum REG Iα had the same correlations with cancer still remained unknown.

Editor: Yoshihiro Shidoji.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was supported by the Natural Science Foundation of Jiangsu Province (BK20170700) and the National Natural Science Foundation of China (81900773).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, Medical School, [b] Pancreatic Research Institute, Southeast University, Nanjing, [c] Department of Endocrinology, Yixing NO. 2 People's Hospital, Wuxi, [d] Department of Endocrinology, Changzhou Jintan District People's Hospital, Changzhou, PR China.

[*] Correspondence: Qiong Wei, Southeast University Zhongda Hospital, nanjing, jiangsu China (e-mail: weiqiong_seu@163.com); Ling Li, Southeast University Zhongda Hospital, nanjing, jiangsu China (e-mail: li-ling76@hotmail.com).

How to cite this article: Zhang Y, Yuan X, Zhu X, Wang Q, Yu X, Wei Q, Li L. Serum REG Iα as a potential novel biomarker in cancer: An observational study. Medicine 2020;99:38(e22281).

Received: 4 May 2020 / Received in final form: 30 July 2020 / Accepted: 20 August 2020

http://dx.doi.org/10.1097/MD.0000000000022281

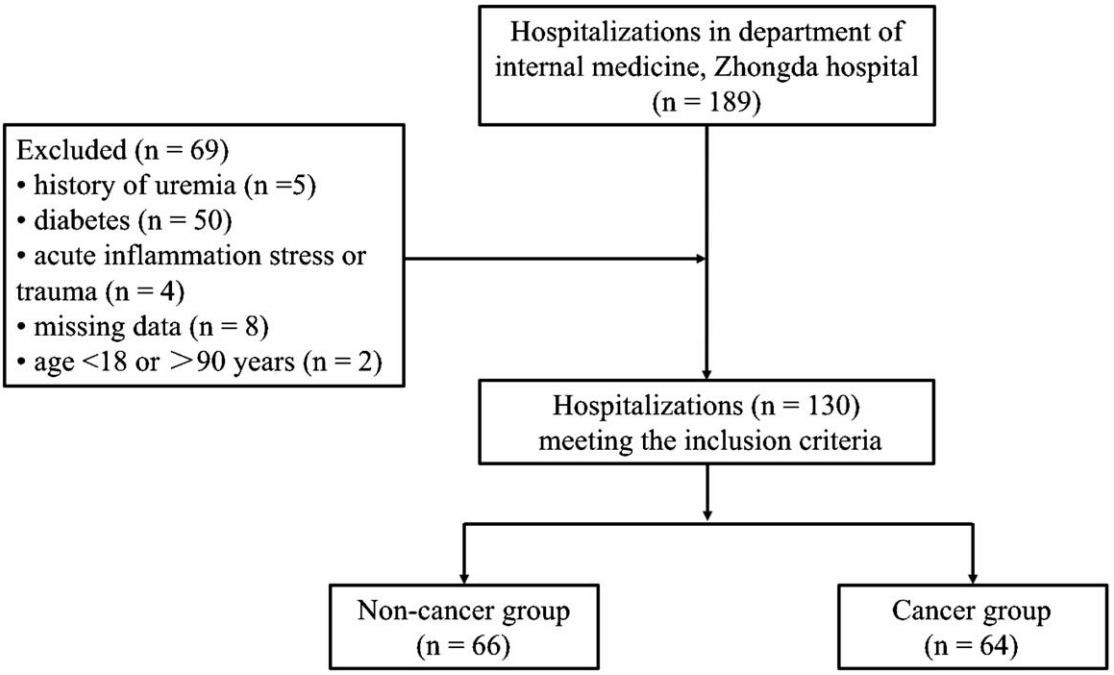

Figure 1. Flow chart of the study.

Previous study from our group had demonstrated the elevated serum REG Iα changes in type 2 diabetes[9] and pregnancy.[7] In this study, we continued to investigate possible changes of serum REG Iα in patients with cancer.

2. Materials and methods

2.1. Study design and population

This observational and cross-sectional study of 130 hospitalized patients was conducted at Zhongda Hospital, Southeast University, Nanjing in China as shown in Figure 1. Written informed consents were obtained from all patients. These study protocols were approved by the ethics committee of Zhongda Hospital, Southeast University, and experimental methods were performed strictly in accordance with the approved guidelines. The patients were recruited consecutively from the Department of Internal Medicine from March to July 2017. Patients were eligible for the study if they were 18 to 90 years of age. Exclusion criteria included history of uremia, diabetes, acute inflammation, stress, or trauma. The patients with missing clinical data would also be excluded.

2.2. Clinical baseline examinations

We collected information on sex, age, history of present illness, previous history, and family history. Weight and height measured without shoes were gathered. Body mass index (BMI) was calculated by weight in kilogram dividing by the square of height in meters. Serum samples for fasting concentrations were drawn in the morning after an overnight fast. Fasting plasma glucose (FPG), triglyceride, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), lactic dehydrogenase were determined by an oxidase method, and fasting insulin (FINS) was determined by radioimmunoassay. Feces samples were reserved to measure fecal elastase-1 (FE-1) toward test kit (Schebo-Biotech, Giessen, Germany).

2.3. REG Iα enzyme-linked immunosorbent assay (ELISA)

Serum REG Iα level was determined as previously described using an isoform-specific ELISA.[18] The serum collected from patients was incubated in plates precoated with guinea pig antihuman recombinant REG Iα antibody. After washing, rabbit anti-REG Iα was incubated and detected by phosphatase-coupled anti-rabbit IgG. The reaction of the phosphatase with a substrate was determined on a multiplate reader (Dynatech), and subjects' serum REG Iα levels were compared with standard amounts of recombinant human REG Iα protein. The detection limit was <0.1 ng/mL, and the interplate variance was $<10\%$.

2.4. Statistical analysis

All statistical analyses were conducted using SPSS version 25.0. Continuous variables were descripted as mean ± standard error if they were followed by normal distribution and median (25% quartile, 75% quartile) if they were skewed. Categorical variables were reported as count and percentage. Spearman correlation and partial correlation were used to assess the connections among REG Iα and clinical indicators. Logistic regression model was used to analyze the influencing factors of cancer incidence. Nonparametric test was conducted to quest the differences in cancer group and noncancer group. And we subsequently divided the cancer group into different subgroups according to the cancer

Table 1

Baseline characteristics of the subjects.

	All (n = 130)	Noncancer (n = 66)	Cancer (n = 64)
Sex (female/male)	56/74	28/38	28/36
Age (y)	58.54 ± 1.06	56.95 ± 1.77	60.17 ± 1.07
Hypertension, n (%)	169 (12.3)	31 (48.44)	30 (46.88)
CAD, n (%)	13 (10.0)	10 (15.63)	6 (9.38)
CI, n (%)	64 (49.2)	9 (14.06)	4 (6.25)
Current smoking, n (%)	13 (10.0)	6 (9.38)	7 (10.94)
Systolic BP (mm Hg)	128.94 ± 1.45	130.97 ± 2.11	127.47 ± 2.01
Diastolic BP (mm Hg)	75.92 ± 0.90	74.91 ± 1.32	76.98 ± 1.27
BMI (kg/m^2)	23.74 ± 0.31	23.81 ± 0.39	23.56 ± 0.48
FPG (mmol/L)	6.24 (4.96,6.31)	6.10 (4.93,6.23)	6.11 (5.03,6.43)
FINS (pmol/L)	57.61 (33.08,80.51)	41.47 (28.22,80.42)	42.24 (34.74,80.51)
UA (umol/L)	306.58 ± 7.04	297.48 ± 9.15	315.41 ± 10.88
Triglycerides (mg/L)	1.63 (0.95,2.00)	1.48 (1.02,1.74)	1.59 (0.89,2.17)
TC (mg/L)	4.72 (4.00,5.33)	4.48 (4.16,5.38)	4.87 (3.68,5.23)
LDL-C (mmol/L)	2.77 ± 0.08	2.63 ± 0.13	2.88 ± 0.10
HDL-C (mmol/L)	1.21 (1.02,1.33)	1.18 (0.94,1.42)	1.23 (1.02,1.33)
BUN (mg/L)	5.73 ± 0.4	5.14 ± 0.23	6.34 ± 0.78
Creatinine (umol/L)	75.67 ± 1.72	73.63 ± 1.64	77.88 ± 3.09
ALT (U/L)	26.72 ± 1.37	29.17 ± 1.94	24.20 ± 1.93
AST (U/L)	24.79 ± 1.17	23.29 ± 0.83	26.34 ± 2.21
ALP (U/L)	91.82 (66.75,106.00)	82.48 (69.00,117.00)	101.47 (61.60,101.50)*
GGT (U/L)	38.12 (18.00,38.50)	34.57 (20.00,45.00)	41.78 (16.00,34.00)
LDH (U/L)	207.70 (171.75,223.25)	199.02 (164.25,229.00)	216.66 (173.50,220.00)
FE-1 (ug/g)	582.11 ± 18.39	607.16 ± 23.7	555.92 ± 28.7
REG Iα (ng/mL)	46.45 ± 3.66	32.93 ± 1.52	60.60 ± 6.87†

ALP = alkaline phosphatase, ALT = alanine aminotransferaerase, AST = aspartate aminotransferase, BMI = body mass index, BP = blood pressure, BUN = blood urea nitrogen, CAD = coronary artery disease, FE-1 = fecal elastase-1, FINS = fasting insulin, FPG = fasting plasma glucose, GGT = gamma glutamyl transferase, HDL-C = high-density lipoprotein-cholesterol, LDH = lactic dehydrogenase, LDL-C = low-density lipoprotein-cholesterol, TC = total cholesterol, UA = uric acid.

* Statically significant P value $< .05$.

† Statistically significant P value $< .01$.

type, nonparametric test was conducted to quest the differences in one specific cancer group and noncancer group. All tests were 2-sided and $P \leq .05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics of cancer group and noncancer group

In total 130 patients were included in the study and subsequently divided into 2 groups that were listed in Table 1. Compared with the control group, the cancer group had no significant differences in sex, age, chronic disease history including hypertension, coronary artery disease, cerebral infarction, and smoking habits. The systolic blood pressure, diastolic blood pressure, BMI, and metabolic indicators such as FPG, FINS, UA, triglyceride, TC, HDL-C, LDL-C were also comparable between the cancer group and control group. We also compared the kidney function between 2 groups and found no differences. The patients from cancer group had significantly higher levels of liver function indicator ALP when compared with noncancer group ($P < .05$). Of note, the REG Iα levels of the 2 groups were quite different, and showed significant difference ($P < .001$). As serum REG Iα was an exocrine product of pancreas which were easily influenced by the exocrine pancreatic dysfunction, we test the FE-1 levels which was a recognized noninvasive and stable marker in testing exocrine function of pancreas.[19] And we found that there was no significant difference in FE-1 levels.

3.2. Relationships of serum REG Iα levels and cancer

Considering the significant differences in the value distribution of REG Iα between cancer group and noncancer group, we did a correction analysis and found REG Iα level was positively correlated to cancer incidence ($P < .001$) as shown in Supplement Table 1, http://links.lww.com/MD/E878. And after adjustment of the possible influencing factors Age, Systolic blood pressure, TC, blood urea nitrogen, Creatinine, GGT, ALP, and FE-1, REG Iα still remained correlated to cancer incidence in partial correlation ($P < .01$). We also did a logistic regression analysis to find the relationship of REG-1α and cancer. The results showed that REG Iα was independent risk factors for patients with cancer (Table 2). We further classified the cancer type in cancer group, the results showed that the number of patients with gastrointestinal cancer, pulmonary cancer, breast cancer constituted the top 3 (Fig. 2A). We compared the REG Iα levels in these subgroups to control group. And the results showed that the REG Iα levels were significantly higher in these 3 subgroups than control group (Fig. 2B). As the gene expression of REG Iα in biopsy samples was

Table 2

Logistic regression analyses of independent factors associated with cancer incidence.

	β	*SE*	*Wald*χ^2	*P*	OR	95% CI
REG Iα	0.09	0.022	16.386	<.001	1.094	1.043–1.106

REG Iα = regenerating family member 1 alpha.

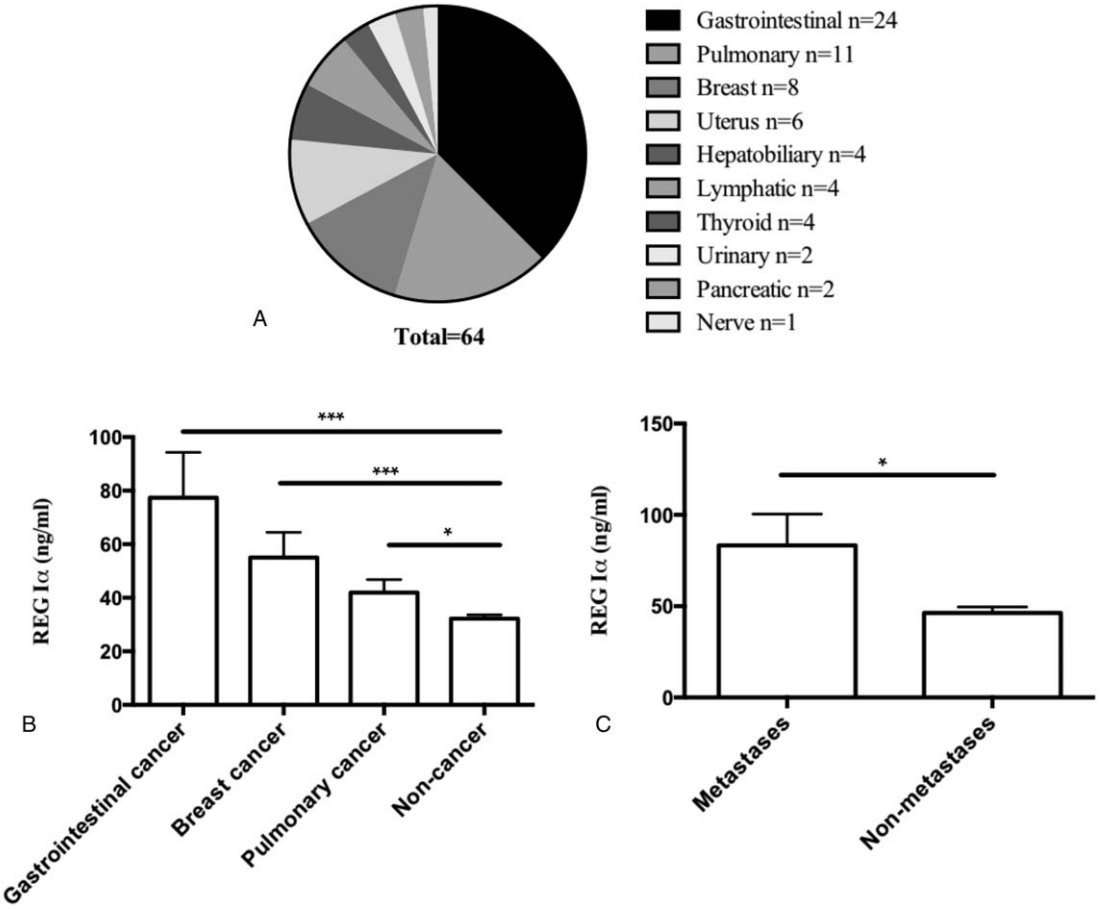

Figure 2. Serum REG-1α levels change in different cancers and cancer stage. A, Composition of the cancer types in cancer group. B, The serum REG-1α levels in gastrointestinal cancer, pulmonary cancer, breast cancer, and noncancer group. C, The serum REG-1α levels in metastasis and nonmetastasis cancer group. $^{*}P < .05$, $^{***}P < .001$. REG Iα = regenerating family member 1 alpha.

once reported as a prognostic indicator in cancer, we divided the patients into cancer group into 2 groups: metastasis and nonmetastasis and compared the serum REG Iα levels between 2 groups. The metastasis group had significantly higher REG Iα levels than nonmetastasis group (Fig. 2C).

3.3. The diagnostic value of REG-1α in cancer

We used a ROC curve to evaluate the diagnostic value for predicting cancer (Fig. 3). The area under the curve values of REG Iα was 0.792, which had a significant diagnostic value with $P < .001$. Furthermore, ROC analysis revealed that the optimal cut-off point of REG Iα was 46.97 ng/mL in predicting cancer (Youden index = 0.47, sensitivity, 62.5%; specificity, 87.5%).

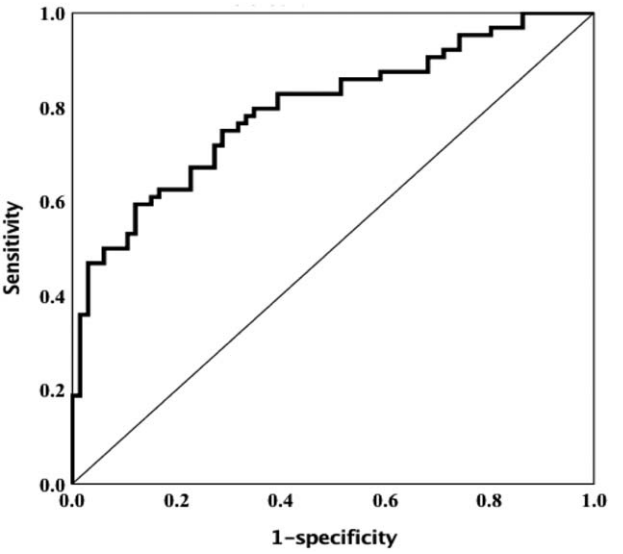

Figure 3. ROC curve analysis.

4. Discussion

Previous studies have reported that the abnormal expression of REG Iα gene played an important role in many kinds of cancers. For example, REG Iα was highly expressed in gastrointestinal cancer cells tumors.[20,21] And the prognosis of patients with gastric tumors with high expression of REG Iα was poor. For colorectal cancer, the expression of REG Iα was reported to be

upregulated[22] and might be closely linked to the pathogenesis, invasion, lymph node metastasis, and chemo-resistance of colorectal cancer.[13] Barrett esophagus is a precancerous lesion of esophageal cancer, and the rapid proliferation of cells is an important factor leading to deterioration of the disease. Chinuki et al showed that the positive expression of REG Iα in Barrett esophagus was 18% (48/266), especially in squamous metaplasia[23] which linked the expression of REG Iα to the occurrence of esophageal cancer. For breast cancer[15] and small-cell lung cancer,[12] REG Iα did not express in normal cells, but was highly expressed in cancer cells. And its high expression could also be used as a prognostic indicator for both cancers. In bladder cancer, Geng et al[17] found downregulation of REG Iα expression could reduce tumor growth, migration, invasion, and angiogenesis. For hepatocellular carcinoma, Yuan et al[16] found the expression of REG Iα leads to more advanced prognosis. In general, the existence of expression or overexpression of REG Iα gene was closely related to multiple cancers.

The serum REG Iα protein was the gene product of REG Iα. Similar to the gene expression pattern in cancer, our study found that serum REG Iα levels were significantly higher in cancer group than noncancer group. We also compared the REG Iα levels in gastrointestinal, pulmonary, and breast cancers, and found the differences exist significantly. These findings supported the serum REG Iα could be cancer biomarker especially when the tissue biopsy was not unavailable. Besides, as the supplement of REG Iα has been proven benefits in diabetic blood glucose control,[24,25] we believed that adoption of REG Iα might be a consideration of anticancer therapy in the future, which however requires more experiments.

At present, it is still not very clear how REG Iα participates in the pathogenesis of cancer. Sanchez et al[26] studied the relationship between REG Iα and the differentiation of pancreatic acinar cells, and they found that the overexpression of REG Iα was very important to maintain the phenotype of acinar cells, while when the inhibition of REG Iα expression could lead to acinar cells expressing β cells, ductal cells, and cancer cell markers. Wang et al found that there was no REG Iα expression in normal hepatocytes. When the liver was damaged and regenerated, the expression of REG Iα in bile duct cells increased, suggesting that REG Iα played an important role in liver regeneration. Fukuhara et al[11] reported that REG Iα was the main factor affecting the proliferation of gastric progenitor cells, and played a role in the repair of gastric tissue by promoting the growth of gastric cells. In addition, REG Iα could protect cells and resist apoptosis. In the process of gastric cancer, REG Iα played a key role in antiapoptosis through STAT3 signaling pathway.[27] Malka et al[28] reported that when adding REG Iα, the apoptosis induced by the TNF-α in AR42J cells was significantly reduced. In our study, we found that the serum REG Iα was significantly elevated in the cancer with metastases, when compared with those cancer patients in relevantly early stage. It might be because the cell regeneration and apoptosis in the late stage of cancer were severer. Thus, we concluded that the serum REG Iα not only could be used as an early biomarker in cancer, but also be used as a prognosis predictor.

As the serum REG Iα levels could be affected by many factors in the body, it was very important to exclude the possible confounding factors. As in our previous study, we have reported that serum REG Iα was highly correlated with diabetes and renal function in pregnant woman, thus we excluded the patients with diabetes and severe kidney problems. We also excluded the patients within acute inflammation, stress, or trauma which was also previously reported affecting serum REG Iα.[29] As there were still many factors affecting serum REG Iα which we had presented in Supplement Table 1, http://links.lww.com/MD/E878, a relatively detailed correction should be taken into consideration when adopting serum REG Iα as cancer biomarker in the future.

5. Conclusions

In summary, in this study we found the serum REG Iα was specifically elevated in patients with cancer and the only independent risk factors for cancer incidence among many clinical indicators, which meant REG Iα was a potential cancer biomarker. And serum REG Iα increased in cancer with metastasis than in the cancer without metastasis, which hinted its value in screening prognosis. However, this study had several limitations. First, the etiopathogenesis of various kinds of cancer was different, and the increase of serum REG Iα could be induced by only one or several specific cancers. Thus, we need more analysis in one specific type of cancer to see its changes. Secondly, the findings are limited to cross-sectional assessment. We need more follow-up researches to prove if the relationship between REG Iα and cancer was an epiphenomenon or causal.

Author contributions

YZ, XY, and XZ conducted the study. YZ, QW, and LL drafted the manuscript. QW, LL, XZ, QW, and XY participated in the design of the study. YZ and XY performed statistical analyses. All of the authors read and approved the final manuscript

References

[1] Fitzmaurice C, Abate D, Abbasi N, et al. Global Burden of Disease Cancer CollaborationGlobal, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol 2019; 5:1749–68.

[2] Watanabe T, Yonekura H, Terazono K, et al. Complete nucleotide sequence of human reg gene and its expression in normal and tumoral tissues. The reg protein, pancreatic stone protein, and pancreatic thread protein are one and the same product of the gene. J Biol Chem 1990;265:7432–9.

[3] Sanchez D, Figarella C, Marchand-Pinatel S, et al. Preferential expression of reg I beta gene in human adult pancreas. Biochem Biophys Res Commun 2001;284:729–37.

[4] Scherr A, Graf R, Bain M, et al. Pancreatic stone protein predicts positive sputum bacteriology in exacerbations of COPD. Chest 2013;143:379–87.

[5] Llewelyn MJ, Berger M, Gregory M, et al. Sepsis biomarkers in unselected patients on admission to intensive or high-dependency care. Crit Care 2013;17:R60.

[6] Boeck L, Graf R, Eggimann P, et al. Pancreatic stone protein: a marker of organ failure and outcome in ventilator-associated pneumonia. Chest 2011;140:925–32.

[7] Zhu X, Dong B, Reding T, et al. Association of serum PSP/REG Ialpha with renal function in pregnant women. Biomed Res Int 2019; 2019:6970890.

[8] Bacon S, Kyithar MP, Schmid J, et al. Serum levels of pancreatic stone protein (PSP)/reg1A as an indicator of beta-cell apoptosis suggest an increased apoptosis rate in hepatocyte nuclear factor 1 alpha (HNF1A-MODY) carriers from the third decade of life onward. BMC Endocr Disord 2012;12:13.

[9] Yang J, Li L, Raptis D, et al. Pancreatic stone protein/regenerating protein (PSP/reg): a novel secreted protein up-regulated in type 2 diabetes mellitus. Endocrine 2015;48:856–62.

[10] Zhu H, Zhu X, Lin H, et al. Association of Serum PSP/REG Iα with Renal Function in Type 2 Diabetes Mellitus. J Diabetes Res 2020;2020: 9787839.

[11] Fukuhara H, Kadowaki Y, Ose T, et al. In vivo evidence for the role of RegI in gastric regeneration: transgenic overexpression of RegI accelerates the healing of experimental gastric ulcers. Lab Invest 2010;90:556–65.
[12] Sasaki Y, Minamiya Y, Takahashi N, et al. REG1A expression is an independent factor predictive of poor prognosis in patients with breast cancer. Ann Surg Oncol 2008;15:3244–51.
[13] Wang Y, Liu X, Liu J, et al. Knockdown of REG Ialpha enhances the sensitivity to 5-fluorouracil of colorectal cancer cells via Cyclin D1/CDK4 pathway and BAX/BCL-2 pathways. Cancer Biother Radiopharm 2019;34:362–70.
[14] Usami S, Motoyama S, Koyota S, et al. Regenerating gene I regulates interleukin-6 production in squamous esophageal cancer cells. Biochem Biophys Res Commun 2010;392:4–8.
[15] Minamiya Y, Kawai H, Saito H, et al. REG1A expression is an independent factor predictive of poor prognosis in patients with non-small cell lung cancer. Lung Cancer 2008;60:98–104.
[16] Yuan RH, Jeng YM, Chen HL, et al. Opposite roles of human pancreatitis-associated protein and REG1A expression in hepatocellular carcinoma: association of pancreatitis-associated protein expression with low-stage hepatocellular carcinoma, beta-catenin mutation, and favorable prognosis. Clin Cancer Res 2005;11:2568–75.
[17] Geng J, Fan J, Wang Q, et al. Decreased REG1alpha expression suppresses growth, invasion and angiogenesis of bladder cancer. Eur J Surg Oncol 2017;43:837–46.
[18] Keel M, Härter L, Reding T, et al. Pancreatic stone protein is highly increased during posttraumatic sepsis and activates neutrophil granulocytes. Crit Care Med 2009;37:1642–8.
[19] Löser C, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut 1996;39:580–6.
[20] Yamagishi H, Fukui H, Sekikawa A, et al. Expression profile of REG family proteins REG Ialpha and REG IV in advanced gastric cancer: comparison with mucin phenotype and prognostic markers. Mod Pathol 2009;22:906–13.
[21] Yamauchi A, Takahashi I, Takasawa S, et al. Thiazolidinediones inhibit REG Ialpha gene transcription in gastrointestinal cancer cells. Biochem Biophys Res Commun 2009;379:743–8.
[22] Zheng HC, Sugawara A, Okamoto H, et al. Expression profile of the REG gene family in colorectal carcinoma. J Histochem Cytochem 2011;59:106–15.
[23] Chinuki D, Amano Y, Ishihara S, et al. REG Ialpha protein expression in Barrett's esophagus. J Gastroenterol Hepatol 2008;23:296–302.
[24] Watanabe T, Yonemura Y, Yonekura H, et al. Pancreatic beta-cell replication and amelioration of surgical diabetes by Reg protein. Proc Natl Acad Sci U S A 1994;91:3589–92.
[25] Viterbo D, Callender GE, DiMaio T, et al. Administration of anti-Reg I and anti-PAPII antibodies worsens pancreatitis. JOP 2009;10:15–23.
[26] Sanchez D, Mueller CM, Zenilman ME. Pancreatic regenerating gene I and acinar cell differentiation: influence on cellular lineage. Pancreas 2009;38:572–7.
[27] Sekikawa A, Fukui H, Fujii S, et al. REG Ialpha protein mediates an anti-apoptotic effect of STAT3 signaling in gastric cancer cells. Carcinogenesis 2008;29:76–83.
[28] Malka D, Vasseur S, Bodeker H, et al. Tumor necrosis factor alpha triggers antiapoptotic mechanisms in rat pancreatic cells through pancreatitis-associated protein I activation. Gastroenterology 2000;119:816–28.
[29] Eggimann P, Que YA, Rebeaud F. Measurement of pancreatic stone protein in the identification and management of sepsis. Biomark Med 2019;13:135–45.