Observational Study

Medicine

OPEN

The correlation between APOE expression and the clinical characteristics and prognosis of patients with endometrial cancer

Chaoying Wu, MM[a,b], Ting Li, MM[c], Wenjun Cheng, PhD[a,*]

Abstract

To analyze the expression of apolipoprotein E (APOE) in endometrial cancer and its influence on the long-term prognostic survival of endometrial cancer patients. The specimens of tumor tissues and adjacent normal tissues from 96 endometrial cancer patients from January 2013 to December 2015 were included in this study. Immunohistochemistry was used to measure the expression of APOE in tumor tissues and adjacent normal tissues. Statistical analysis was used to examine the correlation between APOE expression and the clinicopathological characteristics and survival of patients. Kaplan–Meier survival curve was drawn to study the effects of APOE on the prognosis of patients. The positive rate of APOE in endometrial cancer tissue was higher than that in adjacent normal tissues. The expression level of APOE in endometrial cancer was correlated with histological grade, lymph node metastasis, and FIGO stage ($P < .05$). Lymph node metastasis and APOE were independent risk factors affecting the prognosis and survival of patients ($P < .05$). The results of Kaplan–Meier survival analysis showed that the survival time of APOE high expression group was shorter than that of low APOE expression. APOE is overexpressed in endometrial cancer tissues, and its expression level can provide important information for clinical diagnosis and treatment.

Abbreviations: EC = endometrial carcinoma, FIGO = Federation International of gynecology and Obstetrics.

Keywords: APOE, endometrial carcinoma, immunohistochemistry, prognosis

1. Introduction

Endometrial carcinoma (EC) is 1 of the 3 major malignant tumors in the female reproductive tract. Every year, there are 380,000 newly diagnosed endometrial cancer cases and 89,000 deaths in the world, which seriously affect women's health.[1]

The risk factors for endometrial cancer development include early menarche, late menopause, obesity, tamoxifen exposure, and infertility.[2,3] Obesity is closely related to the occurrence of high blood pressure, dyslipidemia, diabetes, fatty liver, as well as the development of endometrial cancer.[4,5] Studies have confirmed that apolipoprotein E (APOE) gene is related to dyslipidemia and obesity.[6,7] In recent years, APOE has attracted widespread attention as an important protein related to tumorigenesis and metastasis.[8–10] Studies have shown that APOE is an effective biomarker for evaluating lymph node metastasis in patients with non-small cell lung cancer.[11] Moreover, APOE overexpression is associated with the progression of colon cancer, especially with the poor prognosis of stage II patients and the patients with liver metastases.[12] This study analyzed the expression of APOE in endometrial cancer and its influence on the long-term prognosis and survival of endometrial cancer patients.

2. Materials and Methods

2.1. Clinical data

The specimens from 96 endometrial cancer patients who were admitted to Changzhou Maternal and Child Health Care Hospital from January 2013 to December 2015 were collected. All patients had complete clinical and pathological data. Inclusion criteria for patients with endometrial cancer were as follows: Received standard surgical treatment, including at least total hysterectomy and bilateral Salpingo-oophorectomy, with or without pelvic and para-aortic lymph node resection, and tumor cell reduction if necessary. Complete patient data: including age, complete surgical records, pathological results (pathological type and degree of tissue differentiation; depth of myometrial invasion, the proportion of the entire myometrium; cervical stroma or gland involvement; lymphovascular

This study was funded by grants from the Application Fundamental Project Fund of Changzhou Science and Technology Bureau (CJ20190032).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article.

[a] Department of Gynecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China, [b] Department of Gynecology, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, Jiangsu, China, [c] Department of Pathology, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, Jiangsu, China.

** Correspondence: Wenjun Cheng, Department of Gynecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China (e-mail: wjchengdoc@163.com).*

How to cite this article: Wu C, Li T, Cheng W. The correlation between APOE expression and the clinical characteristics and prognosis of patients with endometrial cancer. Medicine 2022;101:37(e30536).

Received: 28 February 2022 / Received in final form: 8 August 2022 / Accepted: 9 August 2022

http://dx.doi.org/10.1097/MD.0000000000030536

invasion). The exclusion criteria are as follows: Patients who have not received standard surgical treatment due to surgical contraindications; Patients with other malignant tumors; Patients who have received hormone therapy, radiotherapy or chemotherapy before surgery; Metastatic uterus Endometrial cancer; Patients with incomplete clinical data. All patients with endometrial cancer were evaluated and operated by senior professional physicians of gynecological oncology department with rich experience in our hospital. Preoperative evaluation included upper, middle and lower abdomen, chest imaging and hematological examination. All postoperative specimens were read by the pathologist in the pathology department of our hospital to make clear the diagnosis, histological classification and surgical pathological stage. Surgical pathological staging was performed according to the guidelines of the Federation International of gynecology and Obstetrics (FIGO) for endometrial cancer. According to whether high-risk factors are combined after operation, whether to supplement radiotherapy, chemotherapy and endocrine therapy after operation is determined by multidisciplinary discussion and in combination with the guidelines of the national comprehensive cancer network. The 96 endometrial cancer patients were 43 to 76 years old, with an average age of 60.7 years. The other clinical parameters of the patients were as follows: tumor diameter: <3 cm, 54 cases, ≥3 cm, 42 cases; FIGO stage (international federation of gynecology and obstetrics): stage I and II 74 cases, stage III and IV 22 cases; lymph node metastasis, 19 cases, no lymph node metastasis, 77 cases; histopathological grade: G1 51 cases, G2 28 cases, G3 17 cases. The pathological types of these patients were: endometrioid adenocarcinoma, 71 cases; non-endometrioid carcinomas, 25 cases, which included 12 cases of serous carcinoma, 7 cases of carcinosarcoma, 4 cases of clear cell carcinoma, and 2 cases of mucinous carcinoma (Table 1). This study was approved by the hospital medical ethics committee (No. 2018018).

2.2. Study design

The specimens of tumor tissues and adjacent normal tissues (more than 2 cm away from tumor tissue) from 96 endometrial cancer patients who were admitted to our hospital from January 2013 to December 2015 were included in this study. Immunohistochemistry was used to measure the expression of APOE in endometrial cancer tissues and adjacent normal tissues. Complete clinical and pathological data of patients with endometrial cancer were collected. Statistical analysis was used to examine the correlation between APOE expression and the clinicopathological characteristics and survival of patients. Kaplan–Meier survival curve was drawn to study the effects of APOE on the prognosis of patients.

Table 1

The characteristics of EC patients.

Clinicopathological parameters		n
Age	<55 yr	39
	≥55 yr	57
Tumor diameter	<3 cm	54
	≥3 cm	42
Pathological type	Endometrial adenocarcinoma	71
	Non-endometrioid carcinomas	25
Histopathological grade	G1	51
	G2	28
	G3	17
Lymph node metastasis	Yes	19
	No	77
FIGO stage	I + II	74
	III + IV	22

EC = endometrial carcinoma, FIGO = Federation International of gynecology and Obstetrics.

The surgically excised tissues were labeled separately according to endometrial cancer tissue and adjacent normal tissue samples, and placed in 10% formaldehyde for 24 hours. Then they were embedded in paraffin, and the sections were subjected to immunohistochemical staining. Endometrial cancer tissue and adjacent normal tissue samples were used for immunohistochemistry staining in our study. The paraffin sections were de-paraffinized and hydrated. Then, peroxidase blocking was performed with 3% H_2O_2 in methanol for 15 minutes at 37°C. The sections were incubated with primary antibody overnight and then with secondary antibody for 1 hour, followed by incubation with diaminobenzidine and counterstain with hematoxylin. Finally, the staining was analyzed by evaluating the percentage of APOE-positive cells and the signal intensity, which were used to calculate the immunoreactivity score.

All cases were followed up completely from the beginning of operation to death. The main follow-up methods were telephone follow-up, outpatient and inpatient reexamination. The time of operation was taken as the start time of survival, and death was taken as the end event. The time interval between the end event time and the start time was defined as the total survival time of patients.

SPSS26.0 statistical software was used for statistical analysis. The expression difference of APOE protein between different groups and its relationship with clinicopathological characteristics were tested by χ^2 test, Cox proportional hazards regression model was used to analyze the risk factors affecting the postoperative prognosis of patients with endometrial cancer, and $P < .05$ was considered statistically significant. The Kaplan–Meier survival curve was used to analyze the impact of APOE on the prognosis of patients.

3. Results

3.1. Comparison of APOE expression in endometrial cancer tissues and adjacent normal tissues

APOE was under or not expressed in normal endometrial tissues, but was highly expressed in EC tissues (Fig. 1). Among the EC tissues, 58 out of 96 cases (60.42%) were APOE-positive, while in adjacent normal tissues, 35 out of 96 cases (36.46%) were APOE-positive. The difference was statistically significant ($\chi^2 = 11.032$, $P < .05$) (Table 2).

3.2. The relationship between APOE expression in EC tissues and patient clinicopathological characteristics

The expression of APOE in EC tissues was correlated with histological grade, lymph node metastasis, and FIGO stage ($P < .05$), but not with age, pathological classification, or tumor size ($P > .05$) (Table 3).

3.3. Univariate analysis of prognosis in patients with endometrial cancer

The univariate analysis showed that, histopathological grade, lymph node metastasis, FIGO stage and APOE were the factors affecting the prognosis of patients with endometrial cancer ($P < .05$) (Table 4).

3.4. Multivariate analysis of prognostic factors in patients with endometrial cancer

Cox proportional hazards regression model was used to analyze the risk factors affecting the postoperative prognosis of patients with endometrial cancer. The results showed that lymph node metastasis and APOE were the independent risk factors affecting the prognosis and survival of patients with endometrial cancer ($P < .05$) (Table 5).

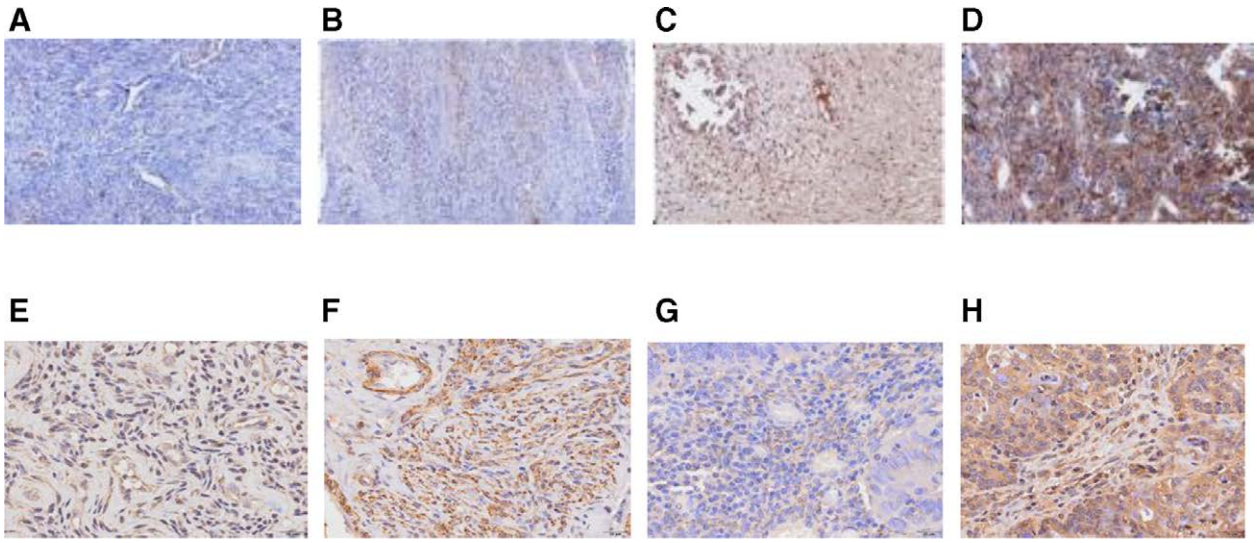

Figure 1. APOE protein expression in EC tissues and adjacent normal tissues. (A) APOE is negative in EC tissues; (B) APOE is weakly positive in pathological grade I EC tissues; (C) APOE is positive in pathological grade II EC tissue; (D) APOE is strongly positive in pathological grade III EC tissue; (E) APOE is positive in endometrial serous carcinoma tissue; (F) APOE is positive in endometrial clear cell carcinoma tissue; (G) APOE is weakly positive in endometrial cancer tissue without lymph node metastasis; (H) APOE is strongly positive in endometrial cancer tissue with lymph node metastasis. APOE = apolipoprotein E, EC = endometrial carcinoma.

Table 2

Comparison of the APOE-positive rate in EC tissues and adjacent normal tissues.

	APOE protein expression				
	n	+	Positive rate (%)	χ^2	*P* value
EC tissues	96	58	60.42	11.032	.001
Adjacent normal tissues	96	35	36.46		

APOE = apolipoprotein E, EC = endometrial carcinoma.

3.5. The relationship between lymph node metastasis, APOE expression and survival rate in patients with EC

Kaplan–Meier survival analysis showed that the survival time of patients with high APOE expression was shorter than that with low APOE expression, and the survival time of endometrial cancer patients with lymph node metastasis was shorter than that of endometrial cancer patients without lymph node metastasis (Figs. 2 and 3).

4. Discussion

Endometrial cancer is a common malignant tumor of the female reproductive tract. Its prognosis largely depends on the histological grade and clinical stage,[13] and 8% to 10% of early endometrial cancer will recur and have distant metastasis.[14] Obesity is 1 of the risk factors for endometrial cancer. Several biologically active molecules produced by adipose tissue, such as insulin-like growth factor, insulin, sex hormones, and their activation signals, can promote the development of endometrial cancer.[15] Adipocytes secrete a series of cytokines and other proteins for signal transduction and reaction with other organs, and 1 of the molecules is APOE.[16] Some previous studies have shown that human APOE plays an important role in adipocyte function and body fat.[17–19]

APOE is a new amyloid-associated protein that is abundant in amyloid plaques.[20] APOE is a 34 kDa protein, which binds to lipoprotein particles and mediates its binding to receptors and endocytosis.[21] APOE is 1 of the important components of plasma lipoproteins and is also related to the growth and differentiation of many cell types. In recent years, there are many reports on the relationship between APOE and cancer

Table 3

The relationship between APOE expression and the clinicopathological characteristics of EC patients.

			APOE protein expression			
Clinicopathological parameters		n	+	Positive rate (%)	χ^2 value	P value
Age	<55 yr	39	24	61.54	0.035	.853
	≥55 yr	57	34	59.65		
Tumor diameter	<3 cm	54	35	64.81	0.998	.318
	≥3 cm	42	23	54.76		
Pathological type	Endometrial adenocarcinoma	71	41	57.75	0.813	.367
	Non-endometrioid carcinomas	25	17	68.99		
Histopathological grade	G1	51	26	50.98	7.401	.025
	G2	28	17	60.71		
	G3	17	15	88.24		
Lymph node metastasis	Yes	19	16	84.21	5.608	.018
	No	77	42	54.55		
FIGO stage	I + II	74	39	52.70	8.035	.005
	III + IV	22	19	86.36		

APOE = apolipoprotein E, EC = endometrial carcinoma, FIGO = Federation International of gynecology and Obstetrics.

Table 4

Univariate analysis of prognosis in patients with endometrial cancer.

Clinicopathological parameters		n	5-year survival rate (%)		χ^2 value	*P* value
			n	Survival rate (%)		
Age	<55 yr	39	33	84.62	0.191	.662
	≥55 yr	57	50	87.72		
Tumor diameter	<3 cm	54	47	87.04	0.035	.851
	≥3 cm	42	36	85.71		
Pathological type	Endometrial adenocarcinoma	71	62	87.32	0.006	.938
	Non-endometrioid carcinomas	25	21	84.00		
Histopathological grade	G1	51	49	96.08	13.043	.001
	G2	28	24	85.71		
	G3	17	10	58.82		
Lymph node metastasis	No	77	72	93.51	8.643	.003
	Yes	19	11	57.89		
FIGO stage	I + II	74	69	93.24	10.294	.001
	III + IV	22	14	63.64		
APOE	–	38	37	97.37	6.394	.011
	+	58	46	79.31		

APOE = apolipoprotein E, FIGO = Federation International of gynecology and Obstetrics.

Table 5

Multivariate cox analysis of prognosis in patients with endometrial cancer.

Influencing factors	*B*	SE	Wald	*P* value	HR value	95% CI
Lymph node metastasis	–4.137	1.032	16.059	<.01	0.016	0.002~0.121
APOE	–2.285	1.151	3.942	.047	0.102	0.011~0.971

APOE = apolipoprotein E, CI = confidence interval, HR = hazard ratio, SE = standard error.

development. APOE is considered to be a biomarker of ovarian cancer.[22] Studies have shown that inhibiting APOE can lead to tumor cell apoptosis, and the survival rate of patients with low APOE expression is significantly higher.[22] Other studies have shown that the APOE expression in lymph node metastatic cells of lung adenocarcinoma can reach 3 times higher than that of non-metastatic cells[9]; the APOE expression in tumor tissue and serum of patients with pancreatic duct adenocarcinoma also increased significantly, and the expression was related to disease progression to a certain extent[23]; moreover, the level of APOE in malignant pleural effusion was also significantly higher than that of benign pleural effusion.[24] These studies showed that APOE might play important roles in the occurrence and development of many cancer types. In human lung cancer, the expression of APOE in cancer tissue was significantly higher than that in adjacent non-cancerous tissues.[25] Also, serum APOE was related to lymph node metastasis in patients with lung adenocarcinoma.[10] High level of APOE can promote the spread and migration of cancer cells, and aggravate the clinical course of patients with lung adenocarcinoma.[26]

Existing evidence have shown that APOE was overexpressed in gastric cancer, lung cancer, and bowel cancer.[11,12,27] Previous studies have confirmed that knocking down APOE can slow down the growth of lung cancer cells, make them more sensitive to cisplatin, and significantly reduce cell migration[26]; moreover, APOE is a highly specific and effective protein in the exosomes derived from M2 macrophages, and it is the main driving force that determines the migration potential of gastric cancer cells.[28]

Studies have confirmed that APOE is closely related with mitogen-activated protein kinase (MAPK) signaling pathways. APOE and APOE mimetic peptides exert their anti-inflammatory function through MAPK signaling pathways.[29] Researches on brain neurons have shown that APOE affects the growth and regeneration of axons in vitro through MAPK signaling pathways,[30] and injured neurons can absorb and secrete APOE to promote neuron repair by activating MAPK signaling pathways.[31] In addition, studies have shown that the metabolic regulation of APOE in human liver cells is affected by interfering MAPK/extracellular regulated protein kinases (ERK) signaling pathway,[32] and APOE stimulates the survival of neural stem cells through regulating MAPK/ERK signaling pathway.[33] Since APOE is related to the ERK signaling pathway, can APOE affect EC metastasis through the ERK signaling pathway? In this study, we detected the expression level of APOE in endometrial cancer tissues and adjacent tissues, and analyzed its relationship with clinical characteristics and prognosis, so as to find an effective reference for the prognosis evaluation of endometrial cancer patients. Our results showed that the survival time of APOE high expression group was shorter than that of APOE low expression endometrial cancer patients. The findings of this study suggest that APOE can become a molecular marker for the prognosis evaluation of EC, and add some additional evidence. However, the specific role and molecular regulatory mechanism of how APOE affects the development of EC are not yet clear, and further in vitro experiments are needed to confirm it. Therefore, we will take APOE and ERK as the entry point to study in depth the regulation mechanism of APOE in the process of EC cell migration through MAPK/ERK signaling pathway.

Many clinical studies also show that APOE can be used as a tumor marker for a variety of tumors, which may directly affect the occurrence, development and prognosis of tumors. However, the influence of APOE on different tumors is very different, and its functional roles need further investigation.

5. Conclusions

In this study, we examined the expression level of APOE in endometrial cancer tissues and adjacent normal tissues, and analyzed its relationship with clinical features and prognosis. The results provided a scientific reference for the prognosis evaluation of endometrial cancer patients. However, whether APOE can be a new therapeutic target need further in-depth studies.

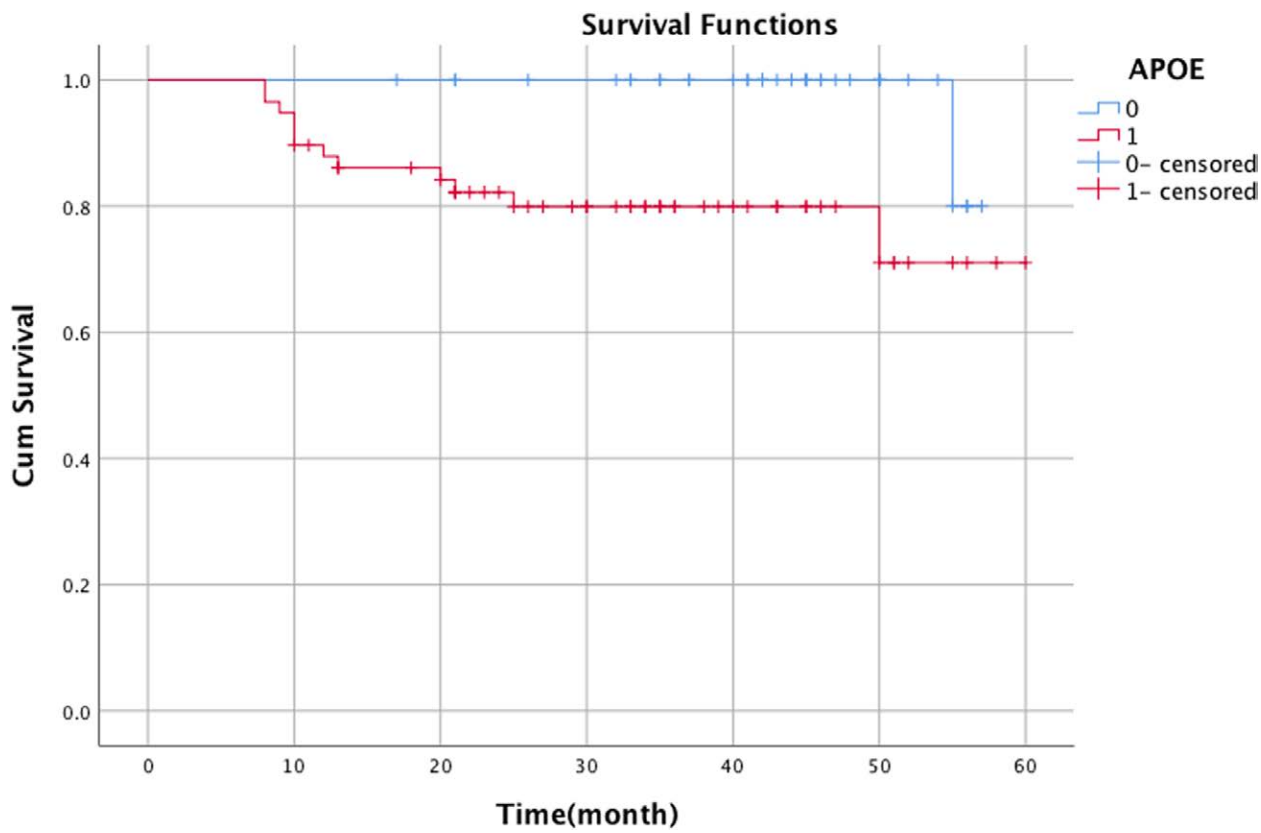

Figure 2. The relationship between APOE and survival time of patients with endometrial cancer. APOE = apolipoprotein E.

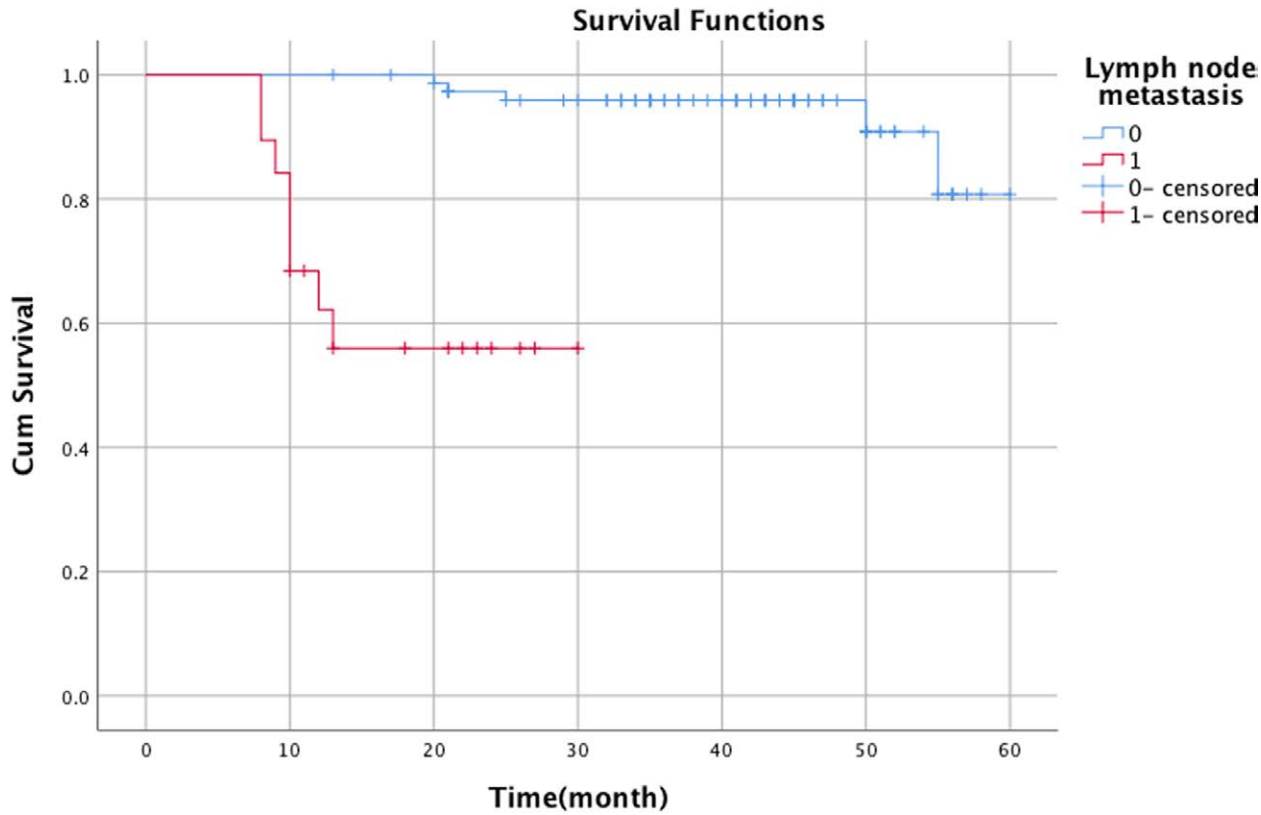

Figure 3. The relationship between lymph node metastasis and survival time of patients with endometrial cancer.

Author contributions

Conceptualization: Chaoying Wu, Wenjun Cheng.
Data curation: Chaoying Wu, Ting Li,
Formal analysis: Chaoying Wu, Ting Li, Wenjun Cheng.
Funding acquisition: Wenjun Cheng.
Investigation: Chaoying Wu,
Project administration: Wenjun Cheng
Resources: Chaoying Wu, Ting Li,
Software: Chaoying Wu, Ting Li,
Validation: Chaoying Wu, Ting Li, Wenjun Cheng.
Writing – original draft: Chaoying Wu,
Writing – review & editing: Chaoying Wu, Wenjun Cheng.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
[2] Morice P, Leary A, Creutzberg C, et al. Endometrial cancer. Lancet. 2016;387:1094–108.
[3] Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Int J Gynecol Cancer. 2016;26:2–30.
[4] Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer--viewpoint of the IARC working group. N Engl J Med. 2016;375:794–8.
[5] Bhaskaran K, Douglas I, Forbes H, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet. 2014;384:755–65.
[6] Gasparin CC, Leite N, Tureck LV, et al. Effects of polymorphisms in APOB, APOE, HSD11beta1, PLIN4, and ADIPOQ genes on lipid profile and anthropometric variables related to obesity in children and adolescents. Genet Mol Biol. 2018;41:735–41.
[7] Franco LP, Gonçalves Zardini Silveira A, Sobral de Assis Vasconcelos Lima R, et al. APOE genotype associates with food consumption and body composition to predict dyslipidaemia in Brazilian adults with normal-weight obesity syndrome. Clin Nutr. 2018, 37:1722–1727.
[8] Yim SY, Ryu E, Lim JY, et al. Serum fibronectin 1 and ApoE levels increase with risk of lymphedema in Korean breast cancer survivors. Support Care Cancer. 2015;23:2319–26.
[9] Liu Z, Gao Y, Hao F, et al. Secretomes are a potential source of molecular targets for cancer therapies and indicate that APOE is a candidate biomarker for lung adenocarcinoma metastasis. Mol Biol Rep. 2014;41:7507–23.
[10] Luo J, Song J, Feng P, et al. Elevated serum apolipoprotein E is associated with metastasis and poor prognosis of non-small cell lung cancer. Tumour Biol. 2016;37:10715–21.
[11] An HJ, Koh HM, Song DH. Apolipoprotein E is a predictive marker for assessing non-small cell lung cancer patients with lymph node metastasis. Pathol Res Pract. 2019;215:152607.
[12] Zhao Z, Zou S, Guan X, et al. Apolipoprotein E overexpression is associated with tumor progression and poor survival in colorectal cancer. Front Genet. 2018;9:650.
[13] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87–108.
[14] Abdulfatah E, Ahmed Q, Alosh B, et al. Gynecologic cancers: molecular updates 2018. Clin Lab Med. 2018;38:421–38.
[15] Gelsomino L, Naimo GD, Catalano S, et al. The emerging role of adiponectin in female malignancies. Int J Mol Sci . 2019;20:2127.
[16] Zechner R, Moser R, Newman TC, et al. Apolipoprotein E gene expression in mouse 3T3-L1 adipocytes and human adipose tissue and its regulation by differentiation and lipid content. J Biol Chem. 1991;266:10583–8.
[17] Elosua R, Demissie S, Cupples LA, et al. Obesity modulates the association among APOE genotype, insulin, and glucose in men. Obes Res. 2003;11:1502–8.
[18] Volcik KA, Barkley RA, Hutchinson RG, et al. Apolipoprotein E polymorphisms predict low density lipoprotein cholesterol levels and carotid artery wall thickness but not incident coronary heart disease in 12,491 ARIC study participants. Am J Epidemiol. 2006;164:342–8.
[19] Feitosa MF, Rice T, North KE, et al. Pleiotropic QTL on chromosome 19q13 for triglycerides and adiposity: the HERITAGE Family study. Atherosclerosis. 2006;185:426–32.
[20] Wisniewski T, Drummond E. APOE-amyloid interaction: therapeutic targets. Neurobiol Dis. 2020;138:104784.
[21] Knouff C, Hinsdale ME, Mezdour H, et al. Apo E structure determines VLDL clearance and atherosclerosis risk in mice. J Clin Invest. 1999;103:1579–86.
[22] Kulminski AM, Arbeev KG, Culminskaya I, et al. Age, gender, and cancer but not neurodegenerative and cardiovascular diseases strongly modulate systemic effect of the Apolipoprotein E4 allele on lifespan. PLoS Genet. 2014;10:e1004141.
[23] Chen J, Chen LJ, Yang RB, et al. Expression and clinical significance of apolipoprotein E in pancreatic ductal adenocarcinoma. Med Oncol. 2013;30:583.
[24] Wang Y, Chen Z, Chen J, et al. The diagnostic value of apolipoprotein E in malignant pleural effusion associated with non-small cell lung cancer. Clin Chim Acta. 2013;421:230–5.
[25] Trost Z, Marc J, Sok M, et al. Increased apolipoprotein E gene expression and protein concentration in lung cancer tissue do not contribute to the clinical assessment of non-small cell lung cancer patients. Arch Med Res. 2008;39:663–7.
[26] Su WP, Chen YT, Lai WW, et al. Apolipoprotein E expression promotes lung adenocarcinoma proliferation and migration and as a potential survival marker in lung cancer. Lung Cancer. 2011;71:28–33.
[27] Sakashita K, Tanaka F, Zhang X, et al. Clinical significance of ApoE expression in human gastric cancer. Oncol Rep. 2008;20:1313–9.
[28] Zheng P, Luo Q, Wang W, et al. Tumor-associated macrophages-derived exosomes promote the migration of gastric cancer cells by transfer of functional Apolipoprotein E. Cell Death Dis. 2018;9:434.
[29] Wang L, Hou H, Zi D, et al. Novel apoE receptor mimetics reduce LPS-induced microglial inflammation. Am J Transl Res. 2019;11:5076–85.
[30] Yin C, Guo ZD, He ZZ, et al. Apolipoprotein E affects in vitro axonal growth and regeneration via the MAPK signaling pathway. Cell Transplant. 2019;28:691–703.
[31] Chen M, Xie M, Peng C, et al. The absorption of apolipoprotein E by damaged neurons facilitates neuronal repair. Cell Biol Int. 2019;43:623–33.
[32] Knebel B, Lehr S, Hartwig S, et al. Phosphorylation of sterol regulatory element-binding protein (SREBP)-1c by p38 kinases, ERK and JNK influences lipid metabolism and the secretome of human liver cell line HepG2. Arch Physiol Biochem. 2014;120:216–27.
[33] Gan HT, Tham M, Hariharan S, et al. Identification of ApoE as an autocrine/paracrine factor that stimulates neural stem cell survival via MAPK/ERK signaling pathway. J Neurochem. 2011;117:565–78.