Predictive role of serum cholesterol and triglycerides in cervical cancer survival

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HIGHLIGHTS

- Elevated total cholesterol and triglycerides correlated with worse overall survival for cervical cancer.
- The overall survival of patients in the low- and intermediate-level groups did not differ.
- In the high-level group, patients were more likely to be older and have hypertension and diabetes.

ABSTRACT

Objective Lipids have been evaluated for their possible role in cancer survival prediction. The aim of the current study was to investigate the prognostic value of lipids on overall survival for stage IB1-IIA2 cervical cancer patients.

Methods A retrospective study including cervical cancer patients with early-stage (FIGO 2009 stage IB1-IIA2) disease was conducted from January 2012 to February 2017. Patients with any history of liver disease or other cancers, and patients who took any medications known to influence lipid metabolism, were excluded. We measured various factors in patients' lipid profiles including total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein, and assessed these four parameters together with clinicopathological features to identify the significant prognostic factors for overall survival.

Results A total of 583 patients with median age 53 (range 25–82) years were included. Among them, 283 (48.5%) patients were in FIGO stage IB1, 44 patients (7.6%) in stage IB2, 189 (32.4%) patients in stage IIA1, and the remaining 67 (11.5%) patients were in stage IIA2. Using univariable Cox proportional hazard analysis and subsequent multivariable analysis, total cholesterol, triglycerides, and pelvic lymph node status were shown to be independent prognostic factors for overall survival ($p<0.05$ for all). Furthermore, the results of the Kaplan–Meier survival curves showed that both the high total cholesterol group and the high triglycerides group were associated with worse overall survival ($p=0.002$ and $p=0.001$, respectively)

Conclusions Our study showed that total triglycerides and total cholesterol may serve as potential predictors for overall survival in patients with cervical cancer. Cervical cancer patients may benefit from treatments after adjusting their triglycerides and total cholesterol levels.

INTRODUCTION

Regardless of global efforts to eliminate cervical cancer by early detection or prevention, cervical cancer remains the leading cause of cancer-related death in women in eastern, western, middle, and southern Africa. An estimated 570 000 women were diagnosed with cervical cancer and approximately 311 000 died from this tumor worldwide in 2018. More than a third of the global cervical burden was contributed by China and India, with 106 000 cases in China and 97 000 cases in India, and 48 000 deaths in China and 60 000 deaths in India.[1]

Serum lipid profile, including total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein, are mainly synthesized by the liver in humans, which are essential for cell membrane biogenesis, cell proliferation, cell migration, angiogenesis, and energy storage.[2] As a well-established etiological risk factor for cardiovascular diseases,[3] lipid profile had become the focus of attention as regards a possible role in the development of different cancers.[4–6] Furthermore, clinical and experimental evidence had suggested that alterations in cholesterol metabolism may impact carcinogenesis and/or metastasis.[7]

The relationship between the lipid profile and clinical outcomes of various cancers[8–10] has been studied. Li et al showed that pre-operative lower triglycerides and high-density lipoprotein-C levels were risk factors for breast cancer patients. Decreased high-density lipoprotein-C level was significantly associated with worse overall survival, whereas decreased triglycerides level showed significant association with worse disease-free survival;[11] however, the prognostic role of lipids remains unclear in cervical cancer. Therefore, the aim of the current study was to investigate the prognostic role of serum lipid profiles on overall survival in early-stage cervical cancer patients.

METHODS

Patients

A retrospective and consecutive cohort study from January 2012 to February 2017 in the First Affiliated Hospital of Wenzhou Medical University was performed. Patients with any history of liver disease or other cancers, and patients who took any medications known to influence lipid metabolism, were excluded. A total of 583 patients who underwent radical hysterectomy and bilateral pelvic lymph node dissection for early-stage cervical cancer (International Federation

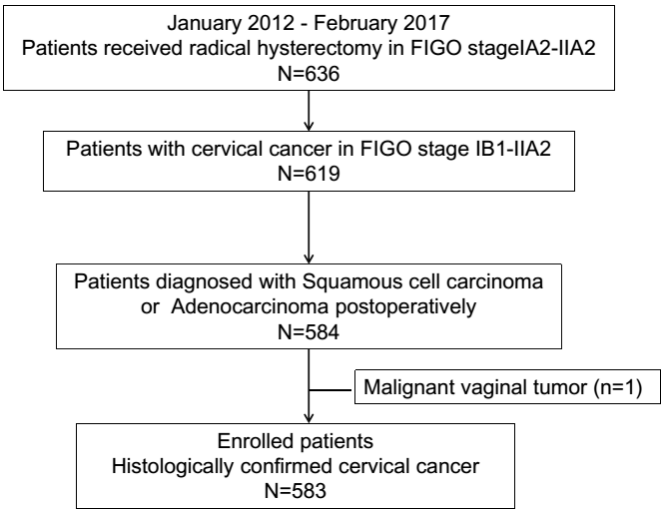

Figure 1 Flowchart of patient enrollment in the study. FIGO, International Federation of Gynecology and Obstetrics.

of Gynecology and Obstetrics (FIGO) 2009 stage IB1-IIA2) were enrolled finally. Among them, 375 patients received additional adjuvant therapy post-operatively (Figure 1). Approval of the Hospital Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University was obtained. The data are available on reasonable request from Dr Feng Lin (234898067@qq.com); however, only with the hospital's approval can the data be reused.

Data Collection

Detailed clinical data were collected within 1 week prior to the patients' operations. Data including total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein were obtained. Patients' pathological and clinical parameters such as FIGO stage, histological types, lymphovascular space invasion status, pelvic lymph node metastasis status, depth of stromal invasion, tumor size, age at diagnosis, and evidence of hypertension and diabetes mellitus were also reviewed and collected.

Follow-up and Study Endpoint

At each visit, a series of laboratory tests, cervical cytology, transvaginal ultrasound scanning, and computed tomography (CT) and/or magnetic resonance imaging (MRI) when there was a clinical suspicion of recurrent disease judged by patients' complaints and gynecological examination were performed. The endpoint in our study was overall survival, defined as the time from surgery to the time of death regardless of cause. Living patients were censored on the date of the last follow-up.

Statistical Analysis

The aim of the study was to investigate the associations between lipid profile and oncological outcomes. The best threshold cut-off of the continuous variables (such as serum lipid profile and age at diagnosis) was selected by using receiver operating characteristic (ROC) curve analysis. Univariate and multivariate regression analyses were performed. Multivariate Cox regression analysis was performed by backward stepwise selection for statistically significant variables in univariate analysis. Survival curves were performed using the Kaplan–Meier method and log-rank test. Continuous variables were expressed as mean±SD and compared by using t-tests. Categorical variables were analyzed by adopting Chi-square test or Fisher's exact test. A p value <0.05 was considered to be statistically significant.

RESULTS

Patient Characteristics

Our study included 583 cervical cancer patients. Among them, 283 (48.5%) patients were in FIGO stage IB1, 44 patients (7.6%) in stage IB2, 189 (32.4%) patients in stage IIA1, and the remaining 67 (11.5%) patients were in stage IIA2. Median age was 53 (range 25–82) years and the median follow-up period was 56 (range 1–87) months. The continuous data, such as serum lipids and age, were expressed as the mean±SD. Most patients had squamous cell cancer (90.2%). A total of 39 patients had died by the time of the last follow-up. One patient died of post-operative pulmonary embolism and another died of infection.

Cut-off Determination and Prognostic Significance

In ROC curve analysis we found that the best cut-off values for the serum total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein were 7.19, 2.18, 1.44, and 4.12 mmol/L, respectively, with the maximum joint sensitivity and specificity.

To investigate the prognostic significance of lipids in cervical cancer, lipid profile and clinicopathological parameters were evaluated using the univariate and multivariable Cox regression model. Table 1 shows that the serum total cholesterol, triglycerides, and low-density lipoprotein were significantly associated with overall survival as categorical variables (p<0.05 for all). However, the high-density lipoprotein was not significant for overall survival (p=0.058). The four parameters were then evaluated by multivariate analysis together with age, lymphovascular space invasion status, pelvic lymph node status, depth of stromal invasion, and tumor size (Table 1). Multivariate analysis suggested that the total cholesterol and triglycerides were independent prognostic factors for overall survival (hazard ratio (HR) 3.5, 95% confidence interval (95% CI) 1.50 to 8.23, p=0.004; HR 1.95, 95% CI 1.01 to 3.78, p=0.048, respectively).

Further Analysis of Independent Prognostic Factors

The study cohort was divided into low- and high-total cholesterol (<7.19 and ≥7.19 mmol/L)and low- and high-triglycerides (<2.18 and ≥2.18 mmol/L) groups, which were determined by their optimized threshold values, respectively. The Kaplan–Meier survival curves for overall survival stratified by total cholesterol and triglycerides, respectively, are shown in Figure 2A,B. The analysis demonstrated that the high-total cholesterol group had worse overall survival (p=0.002). Similarly, the survival curve also showed that the group with high triglycerides was associated with significantly worse overall survival (p=0.001).

Moreover, the cumulative 3-year (97.7%) and 5-year (94.7%) overall survival rate in the low-total cholesterol group was higher (89.7% and 82.1%, respectively) than that in the high-total cholesterol group (p=0.028 and p=0.002, respectively). In addition, patients with low triglycerides had better 3- and 5-year overall survival rates (97.3% and 95.8%) than the high triglycerides group (93.9% and 89.4%, p=0.045 and p=0.003, respectively).

Table 1 Univariate and multivariate Cox proportional hazards regression models of prognostic factors associated with overall survival in cervical cancer patients

	Overall survival			
	Univariate		Multivariate	
Variable	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.039 (1.009 to 1.070)	0.011		
<60	1		1	
≥60	2.548 (1.353 to 4.798)	0.004	1.884 (0.989 to 3.591)	0.054
High BP				
No	1			
Yes	1.549 (0.785 to 3.059)	0.207		
DM				
No	1			
Yes	1.185 (0.365 to 3.849)	0.777		
TC (mmol/L)	1.184 (0.932 to 1.502)	0.116		
<7.19	1		1	
≥7.19	3.295 (1.454 to 7.468)	0.004	3.519 (1.504 to 8.233)	0.004
TG (mmol/L)	1.223 (1.047 to 1.428)	0.011		
<2.18	1		1	
≥2.18	2.678 (1.427 to 5.028)	0.002	1.950 (1.007 to 3.778)	0.048
HDL (mmol/L)	0.382 (0.117 to 1.245)	0.110		
<1.44	1		1	
≥1.44	0.431 (0.181 to 1.030)	0.058	0.492 (0.199 to 1.213)	0.123
LDL (mmol/L)	1.156 (0.848 to 1.576)	0.360		
<4.12	1		1	
≥4.12	2.128 (1.010 to 4.485)	0.047	1.499 (0.488 to 4.602)	0.479
LVSI status				
No	1		1	
Yes	2.082 (1.082 to 4.008)	0.028	1.464 (0.718 to 9.142)	0.294
PLN status				
No	1		1	
Yes	4.215 (2.226 to 7.183)	<0.001	4.766 (2.485 to 9.142)	<0.001
Histological type				
SCC	1			
ACC	0.780 (0.240 to 2.533)	0.679		
Stromal invasion				
Superficial	1		1	
Middle	1.696 (0.424 to 6.781)	0.455	1.557 (0.386 to 6.285)	0.534
Deep	4.575 (1.616 to 12.962)	0.004	2.472 (0.830 to 7.362)	0.104
Tumor size (cm)				
<2	1		1	
≥2	2.219 (0.978 to 5.023)	0.057	1.142 (0.467 to 2.797)	0.771

ACC, adenocarcinoma for cervical cancer; BP, blood pressure; CI, confidence interval; Deep, outer third cervical stromal invasion; DM, diabetes mellitus; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; LVSI, lymphovascular space invasion; Middle, middle third cervical stromal invasion; PLN, pelvic lymph node; SCC, squamous cell carcinoma for cervical cancer; Superficial, inner third cervical stromal invasion; TC, total cholesterol; TG, triglycerides.

Furthermore, we combined the optimized value of total cholesterol and triglycerides with their reference value range, and separated patients into three subgroups (total cholesterol: low-level <5.17 mmol/L, intermediate-level 5.17–7.19 mmol/L, high-level >7.19 mmol/L; triglycerides: low-level <1.7 mmol/L, intermediate-level: 1.7–2.18 mmol/L, high-level: >2.18 mmol/L). As shown in

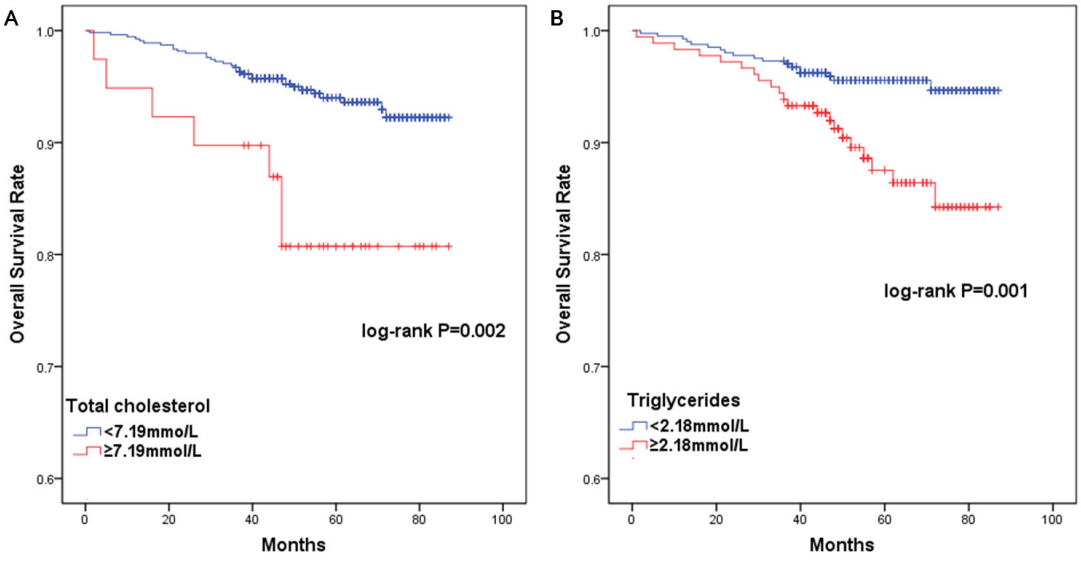

Figure 2 Kaplan–Meier survival curves for cervical cancer patients stratified into two subgroups by the best cut-off value for serum total cholesterol (A) and triglycerides (B), respectively. The high-total cholesterol group had worse overall survival (p=0.002). Similarly, the survival curve also showed that the group with high triglycerides was associated with significantly worse overall survival (p=0.001).

Figure 3A,B the overall survival curves of the intermediate-level group and the low-level group were shown to be insignificant both in the total cholesterol and triglycerides groups (total cholesterol: p=0.835; triglycerides: p=0.35).

Correlations between Serum Total Cholesterol, Triglycerides, and Clinicopathological Features of Cervical Cancer

Clinicopathologic features were compared between patients divided by serum total cholesterol and triglycerides, respectively. As shown in Table 2, higher levels of serum total cholesterol and triglycerides were both associated with older age and hypertension (p<0.005 for all). Furthermore, a higher triglycerides level was significantly related to diabetes mellitus (p<0.001). However, there was no difference in the lymphovascular space invasion status, pelvic lymph node status, histological type, depth of stromal invasion, and tumor size in the high- and low-total cholesterol and triglycerides groups (p>0.05 for all).

DISCUSSION

In our study, both pre-operative total cholesterol and triglycerides were identified to be independent prognostic factors for early-stage cervical cancer patients. The overall survival of the

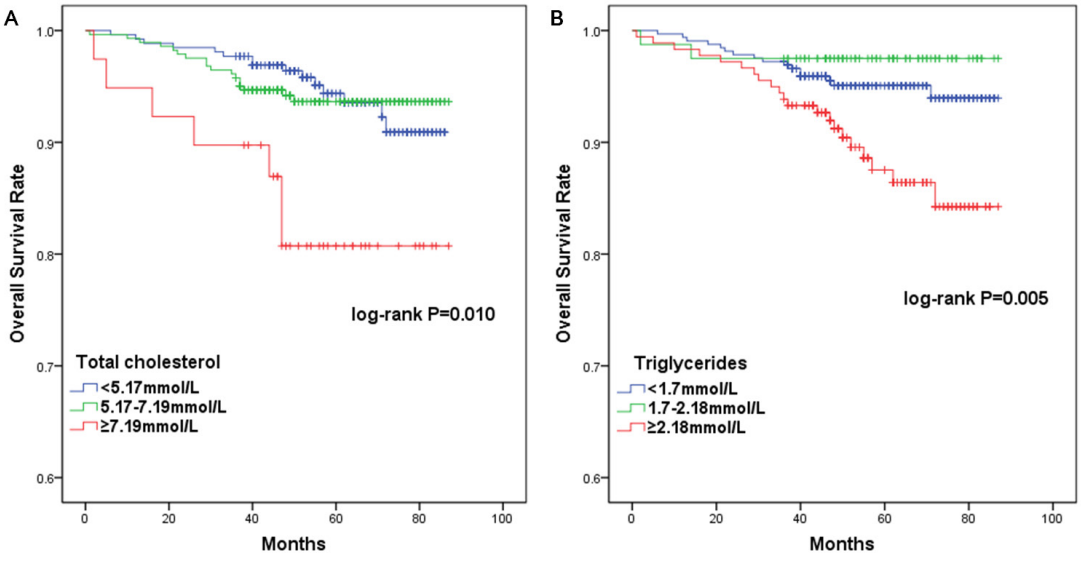

Figure 3 Kaplan–Meier survival curves for cervical cancer patients stratified into three subgroups by combining the optimized value and reference value range of total cholesterol (A) and triglycerides (B), respectively. The overall survival curves of the intermediate-level group and the low-level group closely approached those of both the total cholesterol and triglycerides groups (total cholesterol: p=0.84; triglycerides: p=0.35).

Table 2 Baseline characteristics of cervical cancer patients stratified by total cholesterol and triglycerides

Variables	Total cholesterol (mmol/L)			Triglycerides (mmol/L)		
	<7.19 n (n=544)	≥7.19 n (n=39)	P value	<2.18 n (n=404)	≥2.18 n (n=179)	P value
Age (years) (range)	53±10.7	60±8.4	<0.001	52±10.4	56±10.8	<0.001
High BP						
No	424	25		326	123	
Yes	120	14	0.047	78	56	0.002
DM						
No	509	35		388	156	
Yes	35	4	0.356	16	23	<0.001
LVSI status						
No	419	33		313	139	
Yes	125	6	0.272	91	40	0.962
PLN status						
No	459	34		342	151	
Yes	85	5	0.640	62	28	0.927
Histological type						
SCC	488	38		365	161	
ACC	56	1	0.197	39	18	0.880
Stromal invasion						
Superficial	164	9		123	50	
Middle	99	6		78	27	
Deep	281	24	0.484	203	102	0.277
Tumor size (cm)						
<2	173	9		129	53	
≥2	371	30	0.256	275	126	0.577

ACC, adenocarcinoma for cervical cancer; BP, blood pressure; Deep, outer third cervical stromal invasion; DM, diabetes mellitus; LVSI, lymphovascular space invasion; Middle, middle third cervical stromal invasion; PLN, pelvic lymph node; SCC, squamous cell carcinoma for cervical cancer; Superficial, inner third cervical stromal invasion.;

intermediate-level group and the low-level group were not different. Furthermore, in the hypertriglyceridemia and hypercholesterolemia groups, patients were more likely to be older and have been diagnosed with hypertension and diabetes; however, pathological parameters were similar in the two groups.

Our study suggested that pre-operative high triglycerides and cholesterol levels were associated with higher overall mortality. Yang et al also indicated that higher blood lipid levels of total triglycerides and cholesterol were associated with an increased risk of cancer-specific mortality and all-cause mortality in colorectal cancer patients.[12] Lofterød et al suggested that hypertriglyceridemia was inversely related to overall mortality in HER-2-enriched breast cancer patients.[13] Allott et al indicated that elevated serum triglycerides were related to increased risk of prostate cancer recurrence, while elevated cholesterol was associated with increased risk of recurrence among men with dyslipidemia.[14]

The relationship between metabolic disorders and the immune system has been investigated previously. Hypertriglyceridemia and hypercholesterolemia, as metabolic syndromes, are characterized by continuous efflux of inflammatory cytokines and chemokines.[15] Prolonged chronic inflammation status, hypertriglyceridemia, and hypercholesterolemia may stimulate myeloid-derived suppressor cells, which are known to be immunosuppressive and may result in both reduced immune surveillance and anti-tumor cytotoxicity.[15 16] Therefore, we could hypothesize that hypertriglyceridemia and hypercholesterolemia may lead to hypoimmunity status and tumor proliferation, then worsening the clinical outcomes. However, the detailed mechanisms of hypertriglyceridemia and hypercholesterolemia in cancer survival require further research.

Nevertheless, many metabolic pathways are involved in cancer development. One of the most noteworthy pathways is the transition from catabolism to anabolism.[17] Cancer cells require large amounts of cholesterol for the biosynthesis of new cell membrane for their growth and proliferation.[18] Therefore, for high cholesterol consumption, patients with intermediate-level lipids may have similar survival outcomes as for low-level lipids.

Furthermore, we observed that patients in the high-level group were older and had more co-morbidities such as hypertension and diabetes. Gillani et al showed that patients with type 2 diabetes have a significantly higher rate of mortality in both overall mortality (28.3%) and cancer-specific mortality (11.7%) as compared with non-diabetes patients (12.7% and 9.1%, respectively; p<0.001).[19]

Harding et al suggested that both treated and untreated hypertension is associated with an increased risk for cancer mortality.[20] Age, hypertension, and diabetes may be associated with inflammation, having secretions of numerous proteases and cytokines, including IL-6 and mechanical changes in the extracellular matrix that promote tumor growth,[21 22] leading to worse survival outcomes. Therefore, when we evaluate patient outcomes we should not only consider the treatment methods and pathological parameters, but also consider the patient's systemic resistance. In our study, one patient died of post-operative pulmonary thrombosis and another died of infection. Both diseases are immune-related diseases.[23 24] Consequently, patients may benefit from targeted treatments after adjusting their triglycerides and total cholesterol levels, in addition to routine cancer therapies.

Our study has a number of limitations including the small sample size, the retrospective design, the selection bias due to the availability of lipid tests for inclusion, the lack of control of post-operative lipid levels, and other health factors impacting surveillance or treatment. Moreover, patients' overall nutrient status and medications used for controlling hypertension and diabetes which could affect the prognosis were also not evaluated. Further future prospective studies should be carried out to confirm the role of plasmatic lipid levels in identifying patients' survival.

In conclusion, our study indicates that triglycerides and total cholesterol may serve as potential predictors of overall survival in patients with cervical cancer. Consequently, patients may benefit from treatments after adjusting their triglycerides and total cholesterol levels, in addition to routine cancer therapies. Patients at risk may be advised to be followed more closely, and clinical trials evaluating the effect of lipid-altering medications on cervical cancer prognosis may also be performed in the future.

Contributors FL, XY, FQ: conceptualization, data curation, writing original draft preparation, manuscript preparation, supervision. RZ: data collection. CY: data analysis and interpretation. YS: statistical analysis. All authors read and approved the final manuscript.

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Competing interests None declared.

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Data availability statement Study data are available upon reasonable request from Dr Feng Lin (234898067@qq.com).

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REFERENCES

1 Arbyn M, Weiderpass E, Bruni L, *et al*. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health* 2020;8:e191–203.
2 Buchwald H. Cholesterol inhibition, cancer, and chemotherapy. *Lancet* 1992;339:1154–6.
3 McBride PE. Triglycerides and risk for coronary heart disease. *JAMA* 2007;298:336–8.
4 Fiorenza AM, Branchi A, Sommariva D. Serum lipoprotein profile in patients with cancer. A comparison with non-cancer subjects. *Int J Clin Lab Res* 2000;30:141–5.
5 Tulinius H, Sigfússon N, Sigvaldason H, *et al*. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. *Cancer Epidemiol Biomarkers Prev* 1997;6:863–73.
6 Ulmer H, Borena W, Rapp K, *et al*. Serum triglyceride concentrations and cancer risk in a large cohort study in Austria. *Br J Cancer* 2009;101:1202–6.
7 Silvente-Poirot S, Poirot M. Cholesterol metabolism and cancer: the good, the bad and the ugly. *Curr Opin Pharmacol* 2012;12:673–6.
8 de Figueiredo Junior AG, Serafim PVP, de Melo AA, *et al*. Analysis of the lipid profile in patients with colorectal cancer in advanced stages. *Asian Pac J Cancer Prev* 2018;19:1287–93.
9 Sant'Anna-Silva ACB, Santos GC, Campos SPC, *et al*. Metabolic profile of oral squamous carcinoma cell lines relies on a higher demand of lipid metabolism in metastatic cells. *Front Oncol* 2018;8:13.
10 Arthur R, Møller H, Garmo H, *et al*. Serum glucose, triglycerides, and cholesterol in relation to prostate cancer death in the Swedish AMORIS study. *Cancer Causes Control* 2019;30:195–206.
11 Li X, Tang H, Wang J, *et al*. The effect of preoperative serum triglycerides and high-density lipoprotein-cholesterol levels on the prognosis of breast cancer. *Breast* 2017;32:1–6.
12 Yang Y, Gao G, Shi J, *et al*. Increased blood lipid level is associated with cancer-specific mortality and all-cause mortality in patients with colorectal cancer (≥65 years): a population-based prospective cohort study. *Risk Manag Healthc Policy* 2020;13:855–63.
13 Lofterød T, Mortensen ES, Nalwoga H, *et al*. Impact of pre-diagnostic triglycerides and HDL-cholesterol on breast cancer recurrence and survival by breast cancer subtypes. *BMC Cancer* 2018;18:654.
14 Allott EH, Howard LE, Cooperberg MR, *et al*. Serum lipid profile and risk of prostate cancer recurrence: results from the search database. *Cancer Epidemiol Biomarkers Prev* 2014;23:2349–56.
15 Porta C, Marino A, Consonni FM, *et al*. Metabolic influence on the differentiation of suppressive myeloid cells in cancer. *Carcinogenesis* 2018;39:1095–104.
16 Bekkering S, Quintin J, Joosten LAB, *et al*. Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. *Arterioscler Thromb Vasc Biol* 2014;34:1731–8.
17 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–74.
18 Solomon KR, Freeman MR. The complex interplay between cholesterol and prostate malignancy. *Urol Clin North Am* 2011;38:243–59.
19 Gillani SW, Zaghloul HA, Ansari IA, *et al*. Multivariate analysis on the effects of diabetes and related clinical parameters on cervical cancer survival probability. *Sci Rep* 2019;9:1084.
20 Harding JL, Sooriyakumaran M, Anstey KJ, *et al*. Hypertension, antihypertensive treatment and cancer incidence and mortality: a pooled collaborative analysis of 12 Australian and New Zealand cohorts. *J Hypertens* 2016;34:149–55.
21 Dirat B, Bochet L, Dabek M, *et al*. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. *Cancer Res* 2011;71:2455–65.
22 Bochet L, Lehuédé C, Dauvillier S, *et al*. Adipocyte-derived fibroblasts promote tumor progression and contribute to the desmoplastic reaction in breast cancer. *Cancer Res* 2013;73:5657–68.
23 Ridker PM, MacFadyen JG, Thuren T, *et al*. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:1833–42.
24 Mukhopadhyay S, Johnson TA, Duru N, *et al*. Fibrinolysis and inflammation in venous thrombus resolution. *Front Immunol* 2019;10:1348.