Journal of BUON **14:** 501-506, 2009

ORIGINAL ARTICLE

Lipid profile as a prognostic factor in cancer patients

Z. Cvetkovic[1], B. Cvetkovic[2], M. Petrovic[3], M. Ranic[4], J. Debeljak-Martarcic[4], V. Vucic[4], M. Glibetic[4]

[1]Department of Hematology and [2]Department of Urology, Clinical Hospital Center Zemun, Belgrade; [3]Institute for Hematology, Clinical Center of Serbia, Belgrade; [4]Institute for Medical Research, Department for Nutrition and Metabolism, University of Belgrade, Belgrade, Serbia

Summary

Purpose: *The relationship between plasma lipid levels and neoplastic diseases is still unclear. The aim of this study was to analyse the lipid profile of individuals with non-Hodgkin's lymphoma (NHL) or prostate carcinoma (CaP) and to follow serum lipid levels changes in NHL patients according to their response to chemotherapy.*

Patients and methods: *Forty-seven patients with NHL, 57 patients with CaP, two control groups composed of 29 and 43 age- and sex-matched healthy adults, related to NHL and CaP patients, respectively, were included in the study. Follow-up studies of NHL patients were carried out after the 3rd and 6th cycle of chemotherapy.*

Results: *Initial plasma cholesterol (Chol), HDL-cholesterol (HDL-Chol) and phospholipids (PL) values were significantly lower in patients with NHL or CaP than in controls. Following chemotherapy, we noticed a progressive increase in lipid levels in NHL patients with complete remission (CR) and stable disease (SD), and further decrease in patients with the disease progression.*

Conclusion: *Decreased plasma Chol, HDL-Chol and PL levels of patients with NHL or CaP can be considered as nonspecific prognostic parameters in patients with these malignancies.*

Key words: cholesterol, HDL-cholesterol, non-Hodgkin's lymphoma, phospholipids, prognostic factors, prostate cancer

Introduction

The past decades have seen an impressive increase in the incidence of many types of cancer worldwide. The reasons for this increase remain poorly understood. A number of epidemiological studies has been published, investigating the relation between cancer incidence and a broad range of endogenous and exogenous factors, including decreased Chol and/or other lipids levels. However, data on the cancer-lipids relation are inconsistent. Although several early investigations have proposed that hypocholesterolemia is a predisposing factor for cancer development, no causative relation has been established so far [1]. Some cohort studies have found no relation between Chol and all cancer types [2,3]. Other studies have even reported a positive association between serum Chol levels and certain cancers [3], while inverse association between Chol and different cancer types can also be found in many reports [4-6]. In particular, some findings showed that low serum HDL-Chol was associated with an increasing risk of malignancy [7] and a decreased concentration of plasma PL has been detected in certain solid cancers as well [8]. More recently, studies using the statin class of Chol synthesis inhibitors have suggested an inverse association with different cancers [9,10], but other epidemiological studies [11,12] and clinical trials [13] have not provided any evidence for such an association. Thus, the lipid profile analysis in patients with malignant diseases presents itself as an interesting challenge, especially because of its potential contribution to a better treatment on the basis of an

Correspondence to: Vesna Vucic, PhD. Institute for Medical Research, Department for Nutrition and Metabolism, University of Belgrade, Tadeusa Koscuskog 1, 11129 Belgrade, Serbia. Tel: +381 11 303 1997, Fax: +381 11 2030 169, E-mail: vesna.vucic.imr@gmail.com

Received 21-11-2008; Accepted 25-02-2009

increased prognostic significance and an investigation of new substances it may lead to.

In the human male population, CaP is first in incidence and the second leading cause of cancer-related mortality [14]. NHL are lymphoid tissue malignancies representing the 6th most common type of cancer diagnosed in male and female population in the USA and showing one of the most impressive increases observed among all cancers [15]. Both types of cancer are also very common among the Serbian population.

In the present study we examined the lipid parameters (Chol, HDL-Chol, triglycerides [TG] and total PL) in patients suffering from two malignant diseases of different origin: NHL (blood cancer) and CaP (solid cancer), and compared the obtained values with the corresponding parameters in healthy persons.

The aim of our study was to determine lipid profile changes in patients with different types of cancer according to the stage and aggressiveness of these diseases. Furthermore, in all patients with newly diagnosed NHL who received chemotherapy, we studied lipid parameter changes in relation to their response to therapy, in order to clarify whether analysis of lipid profile may represent a sensitive, non-specific prognostic factor.

Patients and methods

Eligibility of patients with NHL

A total of 47 adult patients with newly diagnosed NHL (26 male and 21 female, median age 57 years, range 19-74), entered this study. None of the patients had other malignant or serious non-malignant chronic disease. After lymph node biopsy or biopsy of primary extranodal site, histological diagnosis was made according to the revised European-American Lymphoma classification / World Health Organization classification [16] and patients were divided into 3 groups: group I – patients with indolent i.e. low risk NHL (n=15); group A – patients with aggressive i.e. intermediate risk NHL (n=23); and group VA – patients with very aggressive disease i.e. high risk NHL (n=9). The clinical stage (CS) of disease was defined according to the Ann Arbor staging classification [17]: CS I - 6 patients, CS II -10 patients, CS III - 12 patients and CS IV -19 patients.

Data from the control group 1 (Control 1) of 29 healthy persons (15 men and 14 women, median age 53 years, range 23-71) were used for the comparison of lipid parameters with the NHL patients.

Eligibility of patients with CaP

A total of 57 adult patients with newly diagnosed CaP, median age 74 years (range 53-94) entered the study. All of the patients had no other malignant disease or a serious chronic disease. Serum prostate specific antigen (PSA) level [18] and Gleason score (GS) [19] were used as important prognostic parameters. According to the level of these factors all of the patients were divided into 3 groups: group I (n=14) with PSA levels < 20 ng/ml and GS 2-4; group II (n=21) with PSA level 20 – 100 ng/ml and GS 5-7; and group III (n=22) with PSA >100 ng/ml and GS 8-10.

Sex- and age-matched control group 2 (Control 2) included 43 healthy male individuals aged 53-86 years (median 72). Data from Control 2 were used for the comparison of lipid parameters changes in CaP patients.

All patients and control subjects had body mass index between 20 and 30 kg/m^2. All study participants provided written informed consent, which was approved by the Ethics Review Boards of the participating institutions in accordance with the principles of the Declaration of Helsinki.

Study design

Lipid parameters (Chol, HDL-Chol, TG and PL) in the plasma of patients with newly diagnosed NHL or CaP were determined and compared to those of the corresponding control groups (1 and 2, respectively).

In NHL patients, after the diagnosis and determination of the histological type and clinical stage of disease, first-line chemotherapy of 6 cycles was administered. Three of 47 patients that entered this study abandoned further treatment, 7 patients died during treatment, and in 37 alive patients response to therapy was evaluated after 6 cycles of chemotherapy. Complete remission (CR) was achieved in 11 patients, 13 patients had stable disease (SD), and disease progression (PD) was confirmed in 13 patients. Lipid parameters were determined prior to treatment (measurement I), after the 3rd cycle of chemotherapy (measurement II) and after the 6th cycle of chemotherapy (measurement III).

The fact that patients with CaP underwent different treatment modalities after diagnosis might have caused a different influence on lipid parameters levels, thus making an adequate study design and lipid parameters follow up not possible.

Analytical methods

Total Chol and TG concentrations were measured in serum after 12 h-fast, using the automated enzymatic methods with Chol oxidase and glycerol oxidase, respectively (EliTech Diagnostic, Sees, France). Serum HDL-Chol was determined by measuring Chol concentration in

the supernatant liquid precipitation of the other classes of lipoproteins with phosphotungstic acid and magnesium chloride [20]. LDL-Chol was estimated using the Friedwald et al. formula [21]. The total PL concentration in serum was determined by the Zilversmit method [22].

Statistical analysis

All the results were expressed as the mean±SD. Normality was tested using the Shapiro-Wilks test. One-way ANOVA, followed by the Tuckey post *hoc* test, was used to compare the normally distributed variables. The nonparametric Fisher test and x^2 test were used for non-normally distributed variables analysis. The comparisons between two groups were performed using the Student's t-test. The differences were considered significant at $p \leq 0.05$.

Results

The average concentrations of total and HDL-Chol, TG and PL in the control subjects (Control 1 and Control 2), as well as in the NHL and CaP groups of patients are shown in Table 1. The plasma total Chol, HDL-Chol and total PL concentrations were significantly lower ($p < 0.05$) in both groups of the cancer patients than in the corresponding healthy subjects. All these parameters were slightly lower in the NHL patients than in the CaP group. There were no differences in plasma TG concentrations between the study groups.

It is important to point out that in the NHL patients and Control group 1 all measurements were made according to gender. The only significant difference between male and female subjects was found in HDL-Chol levels of healthy subjects: 1.36±0.27 mmol/l in women and 1.09±0.19 mmol/l in men ($p < 0.05$), but within the group of NHL patients there was no difference according to sex (1.05±0.19 mmol/l in women, 1.03±0.15 in men, $p > 0.05$). All other lipid parameters, including Chol, TG and PL, showed no significant differences according to gender, neither in the patients nor in the control group.

The initial values of lipid profile in the NHL patients in relation with the aggressiveness of lymphoma and its CS are presented in Tables 2A and B, respectively. The concentrations of Chol ($p < 0.01$), HDL-Chol ($p = 0.05$) and PL ($p < 0.05$) were significantly lower in patients with more aggressive lymphomas than in those with indolent NHL. Results of TG concentrations showed no difference in relation with the aggressiveness of NHL (Table 2A). Plasma lipid profile of the NHL patients, divided into 4 groups according to the CS, showed no significant differences between groups ($p > 0.05$, Table 2B).

The baseline concentrations of plasma lipids in the CaP patients are shown in Table 3. Those patients were divided into groups I-III according to PSA levels and Gleason score. The concentrations of plasma Chol ($p < 0.05$), HDL-Chol ($p < 0.05$) and PL ($p < 0.01$) lowered with advancing disease, while TG level was similar in all groups.

Table 1. Total cholesterol, HDL-cholesterol, triglycerides and total phospholipid levels in patients with non Hodgkin's lymphoma and prostate cancer and in control groups. All parameters are shown as mean±SD (mmol/l)

	Chol	*HDL-Chol*	*TG*	*PL*
NHL	3.57±0.63**	1.03±0.16**	1.51±0.35	2.19±0.33**
Control 1	5.29±0.63	1.24±0.27	1.38±0.26	2.9±0.39
CaP	3.77±0.49**	1.12±0.18*	1.16±0.19	2.31±0.27*
Control 2	5.09±0.73	1.2±0.25	1.23±0.31	2.79±0.25

CHOL: total cholesterol, HDL-Chol: HDL cholesterol, TG: triglycerides, PL: total phospholipids, NHL: patients with non-Hodgkin's lymphoma, CaP: patients with prostate adenocarcinoma, Control 1 and 2 – healthy subjects compared with NHL and CaP, respectively. *p <0.05, **p <0.01

Table 2. The initial values (mmol/l) of lipid parameters in non Hodgkin's lymphoma patients in relation with disease aggressiveness (A) and its clinical stage (B). All parameters are shown as mean±SD

A *Disease aggresiveness*	*Chol*	*HDL-Chol*	*TG*	*PL*
I	4.27±0.60	1.13±0.13	1.47±0.25	2.43±0.36
A	3.34±0.44**	0.98±0.16*	1.53±0.33	2.09±0.23*
VA	2.99±0.60**	1.00±0.14*	1.55±0.28	2.06±0.30*
B *Clinical stage*	*Chol*	*HDL-Chol*	*TG*	*PL*
I	3.27±0.99	1.03±0.11	1.43±0.18	2.39±0.47
II	3.75±0.59	1.10±0.17	1.71±0.22	2.31±0.22
III	3.80±0.57	1.06±0.10	1.46±0.11	2.22±0.22
IV	3.43±0.75	0.97±0.17	1.45±0.26	2.06±0.36

I: indolent lymphomas, A: aggressive lymphomas, VA: very aggressive lymphomas. Other abbreviations as in Table 1. *p <0.05, **p <0.01.

Table 3. The initial values (mmol/l) of lipid parameters in patients with prostate adenocarcinoma group according to PSA levels and Gleason score. All parameters are shown as mean±SD

Group	*Chol*	*HDL-Chol*	*TG*	*PL*
I	4.38±0.57	1.19±0.24	1.12±0.14	2.79±0.37
II	3.95±0.44*	1.18±0.24	1.16±0.19	2.22±0.33*
III	3.21±0.36**	1.02±0.14*	1.17±0.19	1.70±0.29**

Group I: PSA <20 ng/ml and Gleason score 2-4, Group II: PSA 20-100 ng/ml and Gleason score 5-7, Group III: PSA >100 ng/ml and Gleason score 8-10. For other abbreviations see footnote of Table 1. *p <0.05, **p <0.01.

Given the fact that both groups of patients with cancers of different origin had lower concentrations of plasma Chol in comparison to the healthy subjects, we next studied the changes in lipid profiles during (and after) chemotherapy. Of the 47 NHL patients, 7 died before the completion of the 6 chemotherapy courses of chemotherapy. Relating to the outcome, the baseline concentrations of Chol ($p < 0.01$), HDL-Chol ($p < 0.01$), and PL ($p < 0.05$) were significantly lower in patients who died during therapy than in the patients who survived (Table 4). The values of TG were similar in both groups ($p = 0.23$).

Based on the response to chemotherapy, the baseline level of Chol was significantly higher ($p < 0.01$) and reached normal values in patients who achieved CR compared with patients with PD. A different response to therapy also induced different changes in Chol concentrations: in patients with CR, the values of Chol were constantly increasing during therapy, whereas a slight, insignificant increase in Chol was also observed in the patients with SD; concentrations of Chol further decreased in the patients with PD (Figure 1). The HDL-Chol and PL values in relation to response to therapy showed a similar trend (Figures 2 and 3, respectively).

Table 4. The initial values (mmol/l) of lipid parameters in non Hodgkin's lymphoma patients in relation with clinical outcome. All parameters are shown as mean±SD

Outcome	*Chol*	*HDL-Chol*	*TG*	*PL*
Alive	3.72±0.68	1.06±0.15	1.53±0.38	2.26±0.33
Dead	2.80 ± 0.48**	0.85±0.12**	1.37±0.14	1.91±0.21*

Abbreviations as in Table 1. *p <0.05, **p <0.01.

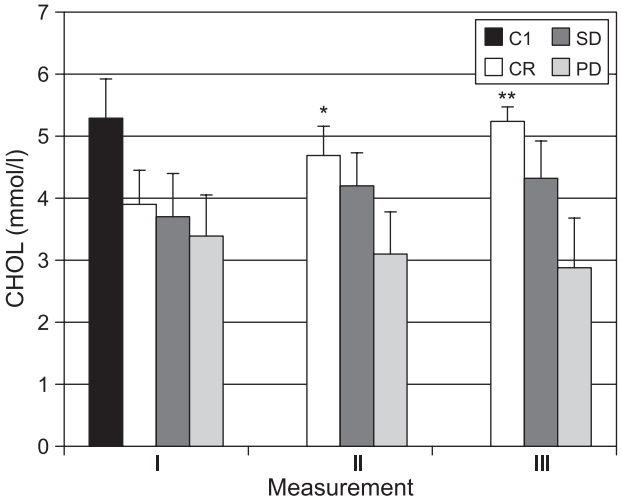

Figure 1. Total cholesterol values in relation with response to therapy. C1: Control group 1, CR: complete remission, SD: stable disease, PD: progressive disease, I: initial values, II: values after the 3rd course of chemotherapy, III: values after 6th course of chemotherapy. *p<0.05, **p<0.01 when compared to initial values.

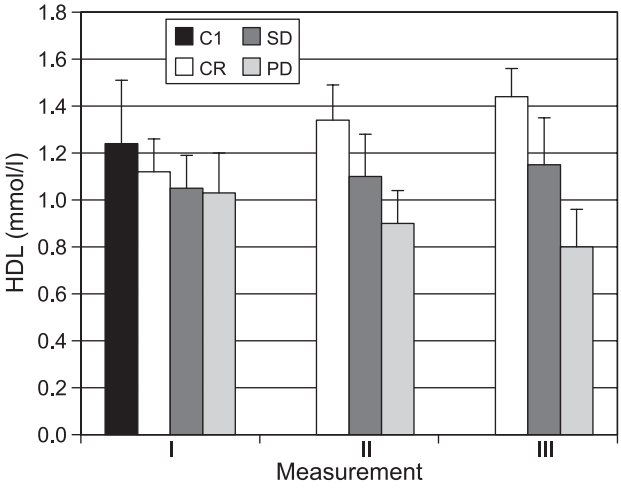

Figure 2. HDL-cholesterol values in relation with response to therapy. p-values non significant. Abbreviations as in Figure 1.

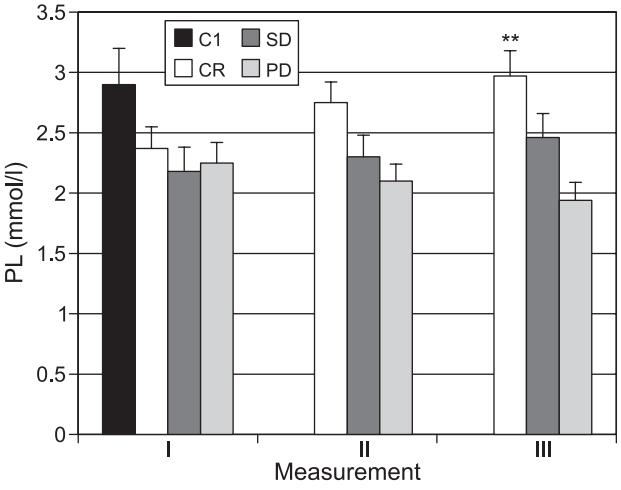

Figure 3. Total phospholipid values in relation with response to therapy. Abbreviations as in Figure 1. **p <0.01 when compared to initial values.

The determination of TG levels showed no significant alterations in these groups of patients ($p = 0.45$).

Discussion

The results obtained in this study showed significantly lower concentrations of total Chol, HDL-Chol and PL in patients with NHL and CaP, compared to age- and sex-matched healthy subjects. The lower levels of these lipid parameters were found in both kinds of cancers: one solid (CaP), and one hematological (NHL). In all of the patients, the levels of Chol, HDL-Chol and PL were significantly lower in patients with more ag-

gressive disease according to histological type of NHL or Gleason score and PSA concentration in CaP.

The reasons behind the decreased lipids in plasma of cancer patients are a matter that requires further investigations. One of the possible reasons could be an increased import of Chol in cancer tissue, which has been documented in acute myeloid leukemia cells and in various solid tumors, because rapidly proliferating tumor cells presumably require Chol for new membrane synthesis [23]. Hypocholesterolemia could also occur due to an increased LDL receptor activity in cancer cells [24,25], which normally controls the degradation of low-density lipoproteins, the major Chol transport protein in human plasma [25].

The link between HDL-Chol and cancers has also been a subject in a number of investigations. The epidemiological study of Kritchevsky and al. [26] suggested that low HDL-Chol may be the first sign of a malignant disease in the preclinical stage. Recently, Lim et al. reported that high serum HDL-Chol was associated with a lower risk of all NHL subtypes [27]. These findings implicate HDL-Chol as a preclinical indicator of NHL and provide a solid foundation for some further prospective investigations based on its etiologic contribution. Low serum HDL-Chol has also been described as an independent predictor of increased postmenopausal breast cancer risk among overweight and obese women [28]. As expected, in our study we found higher HDL-Chol levels in healthy females than in healthy men, due to the protecting effects of estrogen [29]. However, no significant difference in HDL-Chol concentrations according to gender was observed in NHL patients, which implies that the effect of malignancy on serum HDL-Chol level is stronger than the effect of sex hormones.

In contrast to Chol, there are not many reports describing the link between cancer and PL. In the present study we found significantly lower plasma PL in both groups of cancer patients compared to the healthy subjects. Similarly to our findings, Taylor et al. have recently described decreased concentrations of the PC-degradation product lyso-phosphatidylcholine (LPC) in patients with cancer [8]. The reason for these observations might be the observed rapid PL-turnover of tumor cells resulting in an increased plasma LPC utilization by tumor calls. Since an increased turnover of membrane PL appears to be associated with tumor progression and metastasis, the authors proposed that LPC blood concentrations might well be a strong marker for tumor progression [8].

We also found that more aggressive types of NHL were associated with lower plasma Chol, HDL-Chol and PL, which is in accordance with the relevant literature [30,31]. The follow up study of the NHL patients demonstrated that patients with lower initial Chol, HDL-Chol and PL had significantly more detrimental clinical outcome, either death before the end of chemotherapy, or PD. In contrast, although no difference in plasma lipid levels in relation to CS of NHL patients was detected, we found a constant increase and even normalization in these lipid parameters in patients with CS II; this group of patients achieved the best clinical outcome.

The concentrations of TG showed no significant differences of NHL or CaP patients in comparison to the control groups and between the groups of patients themselves, which is in accordance with other published data [26]. However, in their study of 32 patients with hematological malignancies, Dessi et al. presented clues for a significant increase in TG levels which was explained by a possible decrease in lipoprotein lipase activity [30].

These findings suggest that abnormally low lipid parameters in cancer patients could be nonspecific indicators of a worse prognosis, as our results showed that increased lipid parameters were linked with CR or, at least, SD. Based on these findings, we think that lipid status of cancer patients at first presentation/diagnosis, as well as during therapy, may contribute to clinical outcome prognosis, and can be a sensitive, but not specific prognostic parameter in the process of follow-up of patients with malignant diseases.

Acknowledgments

This work was supported by the Project 145071 financed by the Ministry of Science of the Republic of Serbia.

References

1. Rose G, Shipley MJ. Plasma lipids and mortality: a source of error. Lancet 1980; 315: 523-526.
2. Keys A, Aravanis C, Blackburn H, et al. Serum cholesterol and cancer mortality in the Seven Countries Study. Am J Epidemiol 1985; 121: 870-883.
3. Tornberg SA, Holm LE, Carstensen JM, Eklund GA. Risks of cancer of the colon and rectum in relation to serum cholesterol and beta-lipoprotein. N Engl J Med 1986; 315: 1629-1633.
4. Asano K, Kubo M, Yonemoto K et al. Impact of serum total cholesterol on the incidence of gastric cancer in a population-based prospective study: the Hisayama study. Int J Cancer 2008; 122: 909-914.
5. Schatzkin A, Hoover RN, Taylor PR et al. Site-specific analysis of total serum cholesterol and incident cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Cancer Res 1988; 48: 452-458.
6. Vatten LJ, Foss OP. Total serum cholesterol and triglycerides

and risk of breast cancer: a prospective study of 24,329 Norwegian women. Cancer Res 1990; 50: 2341-2346.
7. Shor R, Wainstein J, Oz D et al. Low HDL levels and the risk of death, sepsis and malignancy. Clin Res Cardiol 2008; 97: 227-233.
8. Taylor LA, Arends J, Hodina AK, Unger C, Massing U. Plasma lyso-phosphatidylcholine concentration is decreased in cancer patients with weight loss and activated inflammatory status. Lipids Health Dis 2007; 6: 17-23.
9. Friis S, Poulsen AH, Johnsen SP et al. Cancer risk among statin users: a population-based cohort study. Int J Cancer 2005; 114: 643-647.
10. Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. J Clin Oncol 2004; 22: 2388-2394.
11. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Serum lipids, lipid-lowering drugs, and the risk of breast cancer. Arch Intern Med 2005; 165 :2264-2271.
12. Jacobs EJ, Rodriguez C, Brady KA, Connell CJ, Thun MJ, Calle EE. Cholesterol-lowering drugs and colorectal cancer incidence in a large United States cohort. J Natl Cancer Inst 2006; 98: 69-72.
13. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006; 295: 74-80.
14. Grubb RL, Kibel AS. Prostate cancer: screening, diagnosis and management in 2007. Mo Med 2007; 104: 408-413.
15. Clarke CA, Glaser SL, Dorfman RF, Bracci PM, Eberle E, Holly EA. Expert review of non-Hodgkin's lymphomas in a population-based cancer registry: reliability of diagnosis and subtype classifications. Cancer Epidemiol Biomarkers Prev 2004; 13: 138-143.
16. Harris NL, Stein H, Coupland SE et al. New approaches to lymphoma diagnosis. Hematology 2001; 1: 194-220.
17. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971; 31: 1860-1861.
18. Stamey TA, Kabalin JN, Ferrari M, Yang N. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. IV. Anti-androgen treated patients. J Urol 1989; 141: 1088-1090.
19. Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep 1966; 50: 125-128.
20. Lopes-Virella MF, Stone P, Ellis S, Colwell JA. Cholesterol determination in high-density lipoproteins separated by three different methods. Clin Chem 1977; 23: 882-884.
21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.
22. Zilversmit DB, Davis AK. Microdetermination of plasma phospholipids by trichloroacetic acid precipitation. J Lab Clin Med 1950; 35: 155-160.
23. Banker DE, Mayer SJ, Li HY, Willman CL, Appelbaum FR, Zager RA. Cholesterol synthesis and import contribute to protective cholesterol increments in acute myeloid leukemia cells. Blood 2004; 104: 1816-1824.
24. Vitols S, Gahrton G, Bjorkholm M, Peterson C. Hypocholesterolaemia in malignancy due to elevated low-density-lipoprotein-receptor activity in tumour cells: evidence from studies in patients with leukaemia. Lancet 1985; 326: 1150-1154.
25. Hughes-Fulford M, Chen Y, Tjandrawinata RR. Fatty acid regulates gene expression and growth of human prostate cancer PC-3 cells. Carcinogenesis 2001; 22: 701-707.
26. Kritchevsky SB, Wilcosky TC, Morris DL, Truong KN, Tyroler HA. Changes in plasma lipid and lipoprotein cholesterol and weight prior to the diagnosis of cancer. Cancer Res 1991; 51: 3198-3203.
27. Lim U, Gayles T, Katki HA et al. Serum high-density lipoprotein cholesterol and risk of non-Hodgkin's lymphoma. Cancer Res 2007; 67: 5569-5574.
28. Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst 2004; 96: 1152-1160.
29. Page ST, Mohr BA, Link CL, O'Donnell AB, Bremner WJ, McKinlay JB. Higher testosterone levels are associated with increased high-density lipoprotein cholesterol in men with cardiovascular disease: results from the Massachusetts Male Aging Study. Asian J Androl 2008; 10: 193-200.
30. Dessi S, Batetta B, Spano O et al. Clinical remission is associated with restoration of normal high-density lipoprotein cholesterol levels in children with malignancies. Clin Sci (Lond) 1995; 89: 505-510.
31. Kuliszkiewicz-Janus M, Baczynski S. Application of 31P NMR spectroscopy to monitor chemotherapy-associated changes of serum phospholipids in patients with malignant lymphomas. Magn Reson Med 1996; 35: 449-456.