The impact of metabolic supply lines - and the patterns between them - on the development of distant metastases in 64 women with breast cancer

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Abstract. Cancer cells upregulate their metabolism to underlie the increased malignant activity. This requires an increased amount of ‘metabolic building materials’, for example glucose, amino acids etc., which have the blood circulation as their principal supply lines. Targeting these metabolic supply lines, and thus the availability of metabolic building materials in the blood, may therefore carry treatment potential. A central observation is that the malignant alterations comprise great complexity and that compensatory mechanisms exist. Therefore, targeted supply lines should presumably constitute specific patterns to achieve therapeutic effect. The aim of the present study was to investigate if such patterns could be seen to correlate with the development of distant metastases. The study was conducted using a case-cohort design. In total, 64 women diagnosed with breast cancer between January 2011 and December 2015 were included. Among these, 32 had developed distant metastases and 32 had not. From a blood sample drawn at the time of diagnosis, the levels of glucose (HbA1c), glutamine, arginine and cystathionine were measured. Cox regression was applied to investigate the impact of the supply lines of these ‘building materials’ and specifically the patterns between them on the development of distant metastases. The results demonstrate a significant impact of the investigated metabolic supply lines, centrally in relation to interaction between them and in relation to the impact of the increased cumulated utilization of multiple supply lines simultaneously. In conclusion, the results indicated that the metabolic supply lines may impact clinical outcome, and, in this regard, the results placed a substantial emphasis on the effect of the patterns between these supply lines.

Introduction

Cancer cells, in contrast to normal cells, are rapidly proliferating, invasive and metastasizing. To facilitate this increased malignant activity, cancer cells reprogram and upregulate their metabolism (1,2). This consequently generates an increased degree of utilization and hence need for ‘metabolic building materials’, for example glucose, amino acids etc. - any component participating in the concerned metabolic processes. The blood circulation constitutes the principal supply lines for these building materials, and targeting these metabolic supply lines, practically defined as the availability of the specific building materials in the blood, could therefore carry treatment potential (3).

Glucose and amino acids are among the metabolic building materials which are central to the metabolic alterations in cancer cells (4), and studies have indicated that the blood levels of these might have a clinical impact. A meta-analysis including nearly 10,000 patients diagnosed with cancer reported that hyperglycemia was associated with shorter overall survival as well as shorter disease-free survival (5), with similar results also being reported by other large studies (n=1770-301,948) (6-9). Furthermore, other studies have found an association between glucose level and the occurrence of distant metastases in different cancers (10,11). Likewise, the levels of various amino acids in the blood have been shown to associate with both metastasis occurrence and survival (12-16).

A central aspect in this context is that the processes involved in malignancy are incredibly complex. This materializes with multiple supply lines delivering various building materials to multiple different processes (4,17). Furthermore, cancer cells are metabolically flexible, which may enable them, in the event that one supply line is limited, to compensate through upregulation of another (18). Therefore, to eventually achieve therapeutic effect, presumably more supply lines should be targeted, and these should constitute patterns that are most

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crucial to the malignant processes and prevents compensation from occurring (3).

Thus, the aim should be to target the metabolic supply line patterns underlying the processes essential to malignancy, for instance uncontrolled proliferation, metastasis development etc., as this would in theory compromise the delivery of the most basal components required to exert these processes. A key aspect in this strategy is that it targets the thermodynamic foundation which enables the activities that ‘make a cancer a cancer’ (3).

As an initial step, this study exploratively investigates whether such metabolic supply line patterns can be seen to correlate with the development of distant metastases. The examined supply lines were those of glucose, glutamine, arginine and cystathionine. They were selected because they are involved in central malignant processes and because they can be interpreted to supplement each other in these processes. Therefore, they serve the purpose of investigating the combinatorial effects of metabolic patterns. Specifically, this study investigates whether a pattern comprising the levels of glucose (HbA1c), glutamine, arginine and cystathionine in the blood can be seen to correlate with the development of distant metastases in 64 women diagnosed with breast cancer.

Materials and methods

Patient population and blood samples. The study was approved by the Danish Committees on Health Research Ethics (H-19042347). 64 women diagnosed with breast cancer between 2011 and 2015 were included in the study. Among these, 32 had developed distant metastases and 32 had not. The patients were age 50-80 years at the time of diagnosis. Tumors were either estrogen-receptor-positive (ER+) ductal carcinomas or ER+ lobular carcinomas. Exclusion criteria were 1) previous or any other current cancer, 2) neoadjuvant treatment and 3) known diabetes mellitus or any other metabolic disease. Among the patients who had developed distant metastases, the mean age was 63.9 years (SD: 8.34) while the histological distribution included 26 (81.3%) ER+ ductal carcinomas and 6 (18.8%) ER+ lobular carcinomas. Among the patients who had not developed distant metastases, the mean age was 63.5 years (SD: 7.78) while the histological distribution was 25 (78.1%) ER+ ductal carcinomas and 7 (21.9%) ER+ lobular carcinomas.

Within 2 weeks prior to surgery, a blood sample was drawn from the patients and subsequently administered and stored in the Danish Cancer Biobank (Bio- and Genome Bank, Denmark, http://rbgb.dk/cancer) as EDTA whole blood, EDTA buffy coat, EDTA serum and plasma fractions. The samples were stored at -80°C. To ensure optimal conditions for the metabolic analyses, all samples were processed and placed in the freezer within 3 h. The patients included in the study were from two locations, Herlev Hospital, Copenhagen University Hospital, Copenhagen and Rigshospitalet, Copenhagen University Hospital, Copenhagen.

Metabolic analyses. The level of glucose in the blood was measured as Hemoglobin A1c (HbA1c). EDTA whole blood samples were thawed and 20 µl of whole blood were diluted with 1,500 ml wash (HSi Hemolysis and Wash Solution-L) (Tosoh Bioscience, USA) and then analyzed using the Tosoh G8 (HLC-723G8) HPLC Analyzer (Tosoh Bioscience, USA). HbA1c levels were expressed in mmol/mol. The analyses were carried out at the Department of Clinical Biochemistry, Rigshospitalet.

The levels of free glutamine, arginine and cystathionine in EDTA plasma were determined using the MassTrak Amino Acid Analysis (AAA) Solution Kit (Waters Corporation, USA), an Acquity UHPLC system with a C18 BEH column (1.7 µm; 2.1x150 mm) and an integrated photodiode array (PDA) detector (operating at λ=260 nm) (all from Waters Corporation, USA). 100 µl of thawed EDTA plasma was deproteinized with an equivalent amount of 10% sulfosalicylic acid with norvaline as internal standard. The samples were then thoroughly mixed followed by centrifugation at 14,000 g. 20 µl of the supernatant were alkalized with a borate buffer/NaOH solution and derivatized with 6-aminooquinolyl-N-hydroxysuccinimidyl carbamate (AQC) and analyzed by UHPLC-UV using a gradient of provided eluents, a column temperature of 43°C and a flowrate of 0.45 ml/min. UHPLC conditions were set according to the instructions provided by the manufacturer with specific exceptions: 1) to enhance the separation of amino acid eluting midway in the chromatogram, AccQ-Taq Ultra Eluent B (Waters Corporation, USA) was chosen instead of the MassTrak AAA Eluent B (19); 2) to enhance the separation of arginine and glycine, a steeper gradient curve between 2 and 5.5 min was applied. Concentrations were expressed in µmol/l. The analyses were carried out at the Department of Clinical Genetics, The Metabolic Laboratory, Rigshospitalet.

For the interpretation, it is important to note that during the analyses, the supply lines are represented by the blood concentrations of the metabolic building materials. The blood glucose levels are measured as HbA1c and higher HbA1c values will directly correspond to a higher circulatory availability of glucose. The interpretation of the blood levels of glutamine, arginine and cystathionine is, however, slightly more complex. The general interpretation provided is that the higher use of these materials in cancer cells can lead to a lower concentration in the blood. The observation of lower levels will therefore be presumed to be indicative of a greater consumption and thus higher utilization of the supply lines (20). Accordingly, these observations concerning the supply lines of the metabolic building materials constitute the general framework for the interpretation of the following results.

Study design and statistical analysis. The study was conducted using a case-cohort study design. The 32 patients who had developed distant metastases were selected as cases, whereas the 32 patients who had not developed distant metastases were randomly sampled as the subcohort. All 64 patients were selected/sampled from a total cohort consisting of 816 patients diagnosed with breast cancer who were potentially eligible for inclusion. The patients were followed from the day the blood sample was drawn between 2011 and 2015 until November 30, 2019. During that period, any pathologically verified distant metastasis occurring was recorded.

Cox regression was used to determine the impact of the levels of the metabolic building materials on the development of distant metastases. To account for the non-random sampling
of the cases inherent to the case-cohort design, inverse probability weighting was applied in the regressions using Lin-Ying weights.

First, regressions were performed to initially assess the impact of the supply lines for the metabolic building materials individually while adjusting for tumor histology and age. Next, a regression model was created containing the supply lines of all selected metabolic building materials, i.e., HbA1c, glutamine, arginine and cystathionine at the same time, along with tumor histology and age as covariates. In an attempt to elucidate potential pattern effects, this model was subsequently modified to include an interaction term based on a selected set of supply lines. Finally, an ‘index model’ was created to examine the potential impact of metabolic supply line patterns comprising the cumulated increased utilization of multiple supply lines simultaneously. In this model, an ‘index value’ of 0 to 4 was calculated for each of the 64 patients where 1 point is given for displaying a higher utilization of glucose, glutamine, arginine and cystathionine, respectively. Specifically, 1 point is given for displaying an HbA1c value above the third quartile, 1 point is given for displaying a glutamine value below the median, 1 point is given for displaying an arginine value below the median and 1 point is given for displaying a cystathionine value below the median. The third quartile is used for the HbA1c values since the HbA1c analysis presents an averaged value of the blood glucose concentration. For glutamine, arginine and cystathionine, the median is used since these values are less stable and more prone to be presenting fluctuations. Thus, the ‘index value’ is the summed value of these points and can therefore range from 0 to 4. The ‘index model’ then performs a Cox regression investigating the association between this ‘index value’ and distant metastasis development. Afterwards, a small set of variations of the model are run to further detail this association.

P-values <0.05 were considered statistically significant.
All statistical analyses were performed using R statistical software version 3.6.1.

Results

In the regression analyses examining the effects of the metabolic supply lines individually, only HbA1c was significantly associated with the development of distant metastases, when adjusted for tumor histology and age. For glutamine, arginine and cystathionine, no significant association was found. Likewise, for tumor histology and age, no significant association was found (Table I).

In the regression model including the effects of the supply lines of glucose (HbA1c), glutamine, arginine and cystathionine plus tumor histology and age, at the same time, HbA1c and cystathionine appeared significantly associated with the development of distant metastases (Table II). Hence, HbA1c and cystathionine appeared significantly associated with the development of distant metastases (Table II). Hence, HbA1c and cystathionine appeared significantly associated with the development of distant metastases. However, at the same time, the results also open the possibility of potential nuances to this association.

Discussion

HbA1c appeared significantly associated with the development of distant metastases both individually and in the model including all the investigated metabolites. Furthermore, it figures as a component of the significant ‘index value’ in the
An augmented uptake and use of glucose is a central and presumably the most well-known alteration in the metabolic reprogramming occurring in cancer cells. The Warburg effect describes this change in glucose metabolism and comprises that cancer cells direct glucose through glycolysis despite oxygen being adequately available. The resulting amplified glycolytic flux provides an increased amount of intermediates available to branching pathways, which are

Table I. Development of distant metastases: Individual impact of the metabolic supply lines (adjusted for tumor histology and age).

| Parameter                          | Hazard ratio | 95% CI       | P-value |
|------------------------------------|--------------|--------------|---------|
| HbA1c (glucose)                    |              |              |         |
| HbA1c, mmol/mol                    | 1.148        | (1.001, 1.317)| 0.048   |
| Age, years                         | 0.996        | (0.925, 1.073)| 0.916   |
| Tumor histology (ER+ ILC)          | 0.536        | (0.137, 2.097)| 0.370   |
| Glutamine                          |              |              |         |
| Glutamine, µmol/l                  | 0.996        | (0.989, 1.003)| 0.267   |
| Age, years                         | 1.018        | (0.949, 1.093)| 0.612   |
| Tumor histology (ER+ ILC)          | 0.913        | (0.241, 3.456)| 0.894   |
| Arginine                           |              |              |         |
| Arginine, µmol/l                   | 0.997        | (0.973, 1.021)| 0.802   |
| Age, years                         | 1.017        | (0.947, 1.092)| 0.641   |
| Tumor histology (ER+ ILC)          | 0.815        | (0.230, 2.892)| 0.752   |
| Cystathionine                      |              |              |         |
| Cystathionine, µmol/l              | 0.644        | (0.285, 1.454)| 0.289   |
| Age, years                         | 1.019        | (0.950, 1.093)| 0.602   |
| Tumor histology (ER+ ILC)          | 0.717        | (0.197, 2.614)| 0.614   |

ER+ ILC, Estrogen-receptor-positive invasive lobular carcinoma.

Table II. Development of distant metastases: Multivariate model including all metabolic supply lines (plus tumor histology and age).

| Parameter                          | Hazard ratio | 95% CI       | P-value |
|------------------------------------|--------------|--------------|---------|
| HbA1c, mmol/mol                    | 1.309        | (1.149, 1.490)| <0.001  |
| Glutamine, µmol/l                  | 1.000        | (0.992, 1.009)| 0.925   |
| Arginine, µmol/l                   | 0.968        | (0.927, 1.011)| 0.144   |
| Cystathionine, µmol/l              | 0.145        | (0.032, 0.665)| 0.013   |
| Age, years                         | 0.951        | (0.872, 1.036)| 0.249   |
| Tumor histology (ER+ ILC)          | 0.397        | (0.101, 1.567)| 0.187   |

ER+ ILC, Estrogen-receptor-positive invasive lobular carcinoma.

Table III. Development of distant metastases: Interaction between the supply lines of glucose and cystathionine.

| Parameter                          | Hazard ratio | 95% CI       | P-value |
|------------------------------------|--------------|--------------|---------|
| HbA1c: Cystathionine (high)        | 0.906        | (0.738, 1.111)| 0.343   |
| HbA1c: Cystathionine (low)         | 1.371        | (1.236, 1.521)| <0.001  |

Table III shows the estimated effect of HbA1c when cystathionine is ‘high’ or ‘low’. Cystathionine was categorized based on the blood concentration into two groups, ‘(high)’ with higher blood concentrations (representing lower utilization) and ‘(low)’ with lower concentrations (representing higher utilization). The effect is significantly different as the P-value for the interaction term was <0.001.

'index model'. An augmented uptake and use of glucose is a central and presumably the most well-known alteration in the metabolic reprogramming occurring in cancer cells. The Warburg effect describes this change in glucose metabolism and comprises that cancer cells direct glucose through glycolysis despite oxygen being adequately available. The resulting amplified glycolytic flux provides an increased amount of intermediates available to branching pathways, which are
Table IV. Development of distant metastases: Index model and variations of the index model.

| Parameter                          | Hazard ratio | 95% CI            | P-value |
|------------------------------------|--------------|-------------------|---------|
| **Index model**                    |              |                   |         |
| Index value >3 points              | 1.935        | (1.028, 3.640)    | 0.041   |
| Index value >2 points              | 3.785        | (0.964, 14.864)   | 0.056   |
| **Variations of the index model**  |              |                   |         |
| Index value >2 points              | 44.150       | (10.440, 186.708) | <0.001  |

The above examples are hypothesized possible interpretations of the basis for the observed interaction effect and more interpretations could be made. What remains central in this study, is that the observed interaction effect points towards the effect of patterns as a central aspect. Furthermore, this is in line with the results of the ‘index model’.

The ‘index model’ proposes a general relationship where the greatest risk of developing distant metastases occurs during a supply line pattern where high supplies from multiple supply lines are present at the same time. This reflects the complexity of cancer metabolism with multiple metabolic processes being involved in malignant progression. Moreover, it is in accordance with an emphasis on the importance of pattern effects.
High supplies from multiple supply lines may provide a set of favorable conditions for cancer to develop. In general, such conditions may ensure the fueling of the various processes driving different aspects of malignancy. For example, while glucose and cystathionine may facilitate ROS-mitigation, other metabolites may facilitate different functions likewise contributing to the malignant progression. Arginine may potentially fuel processes involved in immune evasion (29). Likewise, glutamine is a building material central to the metabolic alterations in cancer cells, and it has been demonstrated that highly invasive cancer cells can be characterized by upregulated glutamine metabolism (30). This observation can be extrapolated to include more potential effects derived from any additionally utilized supply of building materials. In this way, a supply line pattern comprising high supplies from multiple supply lines may potentially facilitate the employment of different malignant processes at the same time, for instance ROS-mitigation, immune evasion, invasiveness etc., which together and combined may propel disease progression. Moreover, utilization of multiple supply lines is a prerequisite for the interacting and synergistically working supply lines patterns, as described with regard to glucose and cystathionine. More of such interacting patterns obviously exist, and the simultaneous involvement of multiple supply lines serves as the foundation for the manifestation of these patterns.

Thus, a metabolic supply line pattern comprising multiple supply lines may hypothetically be able to simultaneously underlie multiple malignant processes, thereby enabling the manifestation of a cancer with more comprehensive malignant capacity.

It is important to note that the results appeared to allow for nuances in the relationship concerning the simultaneous utilization of multiple supply lines. While the general association is that increased utilization of high supplies of multiple building materials may support metastatic development, it is possible that in some cases, a low circulatory supply of a given building material might be beneficial to the cancer. For example, arginine is, while potentially being involved in immune evasion processes, coincidentally also required by immune cells to maintain their optimal function (29,31). Based on this, it is possible that the supply line pattern driving malignancy most effectively might potentially also include a restricted supply of given metabolites. Nevertheless, an emphasis on the effect of patterns is maintained in both cases.

Together, the results from this study collectively seem to demonstrate that the condition of metabolic supply lines may impact outcome in patients with cancer, and furthermore, the results place a significant emphasis on the effects of patterns with regard to these supply lines.

When evaluating the results of this study, there are certain aspects and limitations that must be taken into consideration. When interpreting the results for glutamine, arginine and cystathionine, it is important to acknowledge that the observed blood concentrations are presumed to be indicative of the utilization of these materials rather than their actual availability in the blood; it does therefore not directly follow from this that intervening this availability would carry an effect. A potential effect of such an intervention could, however, for example be considered with reference to the current clinical use of asparaginase, which is used to lower circulatory asparagine in the treatment of acute lymphoblastic leukemia (ALL). Furthermore, it is important to consider that plasma generally contains cystathionine at very low concentrations, which are around the limit of quantification for the method, and the measurement of cystathionine is therefore subjected to a degree of uncertainty. However, it seems improbable that this measurement uncertainty would apply differently based on following metastasis status, and that this would manifest as significant associations. Such non-differential measurement error would be presumed to attenuate the associations (32). The inclusion of cystathionine as a binary variable in the interaction analysis and index model would also reduce this uncertainty. Moreover, common difficulties when examining amino acid concentrations in relation to cancer exist. While the general interpretation provided is that, for the amino acids, a higher use will lead to a lower concentration in the blood, it is important to note that higher concentrations can sometimes also be found to correlate with malignancy, and that generally multiple conditions may influence the association (20). Studies have demonstrated the observation that lower concentrations can reflect an increased use. For instance, this has been performed during colon cancer surgery by determining the arterio-venous difference of the amino acid levels in the tumor region and in the adjacent non-tumor region. The study generally observed a significantly greater arterio-venous difference for multiple amino acids in the tumor region, which, accordingly, was considered to result from an increased uptake by the tumor (33). However, the aforementioned difficulties should be maintained. Furthermore, it is important to note that the scale of this study is relatively small in terms of the number of included patients,
the focus on one type of cancer and the fact that few metabolic building materials are examined. Furthermore, corresponding tissue enzyme activity for the metabolites measured in the blood was not investigated. In general, the explorative nature of this work must be considered. This study should be seen as an initial step aiming to investigate any potential effect of patterns occurring between the metabolic supply lines underlying malignant processes in relation to the clinical outcome in patients with cancer. The results from this study seem to indicate that such pattern effects may in fact correlate with clinical outcome, and ensuing studies are therefore warranted. Concerning the reflections upon a certain level of the supply lines compromising malignant capacity, a purely descriptive observation of the HbA1c values seems relevant. When the HbA1c values are divided according to whether the patients had developed distant metastases or not, it is noteworthy that, among the patients who had developed distant metastases, no HbA1c value below ~32 mmol/mol was displayed, while among the patients who had not developed distant metastases, multiple patients did present values below this point (Fig. 2).

It must be stressed that it is possible that the observation, to some extent, occurs randomly due to a relatively small number of included patients. On the contrary, the daring supposition would be to interpret this as to some degree consistent with the contemplation that an adequate supply from the metabolic supply lines may potentially be required to facilitate the processes of malignancy, and likewise, more importantly, that an intervention of the supply lines could potentially compromise these processes.

The potential of the approach presented in this study is based on the observation that the metabolic supply lines and the supply patterns between them serve as the most basic foundation for the different malignant processes of a cancer. They deliver the building blocks that are needed to perform rapid proliferation, metastatic development etc.; in other words, the different processes that intrinsically constitute and define the disease. Therefore, intervening the circulatory availability of the patterns most crucial to these processes would, in theory, target the thermodynamic foundation that facilitates the activities that ‘make a cancer a cancer’ (3).

In conclusion, the results from this study indicate that the levels of metabolic supply lines and the patterns between them may impact clinical outcome in patients with cancer. The results particularly place a significant emphasis on the effect of supply line patterns. Ensuing attempts to conduct investigations identifying the patterns most crucial to malignancy should therefore be made. This aim is based on the contemplation that intervening the circulatory availability of these patterns may compromise the most basic foundation for exerting these processes intrinsic to the disease.

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Availability of data and materials

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

Authors’ contributions

OA conceived the idea for the study and drafted the manuscript. EH took part in all planning. OA, EB, MC, FW, EBj and EH designed the study and performed critical evaluation of the work. All authors provided scientific expertise within their respective fields. MC carried out the amino acid analysis. OA and EBj performed the statistical analysis. OA and EH confirm the authenticity of all the raw data. All authors edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Danish Committees on Health Research Ethics (approval no. H-19042347). Informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
2. DeBerardinis RJ and Chandel NS: Fundamentals of cancer metabolism. Sci Adv 2: e1600200, 2016.
3. Abrahamsen O, Balslev E and Hegdall E: Targeting the supply lines of cancer—A possible strategy for combating the disease? Anticancer Res 41: 2737-2744, 2021.
4. Pavlova NN and Thompson CB: The emerging hallmarks of cancer metabolism. Cell Metab 23: 27-47, 2016.
5. Barua R, Templeton AJ, Seruga B, Ocaña A, Amir E and Ethier JL: Hyperglycaemia and survival in solid Tumours: A systematic review and Meta-analysis. Clin Oncol (R Coll Radiol) 30: 215-224, 2018.
6. Simon JM, Thomas F, Czernichow S, Hanon O, Lemogne C, Simon T, Pannier B and Danchin N: Hyperglycaemia is associated with cancer-related but not non-cancer-related deaths: Evidence from the IPC cohort. Diabetologia 61: 1089-1097, 2018.
7. Murtoja T, Sälli SM, Talala K, Taari K, Tammela TLJ and Auvinen A: Blood glucose, glucose balance, and disease-specific survival after prostate cancer diagnosis in the Finnish randomized study of screening for prostate cancer. Prostate Cancer Prostatic Dis 22: 453-460, 2019.
8. Chen S, Tao M, Zhao L and Zhang X: The association between diabetes/hyperglycemia and the prognosis of cervical cancer patients: A systematic review and meta-analysis. Medicine (Baltimore) 96: e7981, 2017.
9. Hu D, Peng F, Lin X, Chen G, Liang B, Li C, Zhang H, Liao X, Lin J, Zheng X and Niu W: The elevated preoperative fasting blood glucose predicts a poor prognosis in patients with esophageal squamous cell carcinoma: The Fujian prospective investigation of cancer (FIESTA) study. Oncotarget 7: 65247-65256, 2016.
10. Contiero P, Berrino F, Tagliaabue G, Mastromarini A, Di Mauro MG, Fabiano S, Annulli M and Muti P: Fasting blood glucose and long-term prognosis of non-metastatic breast cancer: A cohort study. Breast Cancer Res Treat 138: 951-959, 2013.
11. Nik-Ahd F, Howard LE, Eisenberg AT, Aronson WJ, Terris MK, Cooperberg MR, Amling CL, Kane CJ and Freedland SJ: Poorly controlled diabetes increases the risk of metastases and castration-resistant prostate cancer in men undergoing radical prostatectomy: Results from the SEARCH database. Cancer 125: 2861-2867, 2019.

12. Berker Y, Vandergrift LA, Wagner I, Su L, Kurth J, Schuler A, Dinges SS, Habbel P, Nowak J, Mark E, et al: Magnetic resonance spectroscopy-based metabolomic biomarkers for typing, staging, and survival estimation of early-stage human lung cancer. Sci Rep 9: 10319, 2019.

13. Ling HH, Pan YP, Fan CW, Tseng WK, Huang JS, Wu TH, Chou WC, Wang CH, Yeh KY, Chang PH, et al: Clinical significance of serum glutamine level in patients with colorectal cancer. Nutrients 11: 898, 2019.

14. Ma H, Hasim A, Mamtimin B, Kong B, Zhang HP and Sheyhidin I: Plasma free amino acid profiling of esophageal cancer using high-performance liquid chromatography spectroscopy. World J Gastroenterol 20: 8653-8659, 2014.

15. Zheng H, Dong B, Ning J, Shao X, Zhao L, Jiang Q, Ji H, Cai A, Xue W and Gao H: NMR-based metabolomics analysis identifies discriminatory metabolic disturbances in tissue and biofluid samples for progressive prostate cancer. Clin Chim Acta 501: 241-251, 2020.

16. Jobard E, Pontoiseau C, Blaise BJ, Bachelot T, Elena-Herrmann B and Tredan O: A serum nuclear magnetic resonance-based metabolomic signature of advanced metastatic human breast cancer. Cancer Lett 343: 33-41, 2014.

17. Cantor JR and Sabatini DM: Cancer cell metabolism: One hallmark, many faces. Cancer Discov 2: 881-898, 2012.

18. Boroughs LK and Deberardinis RJ: Metabolic pathways promoting cancer cell survival and growth. Nat Cell Biol 17: 351-359, 2015.

19. Peake RWA, Law T, Hoover PN, Gaewsky L, Shkreta A and Kellogg MD: Improved separation and analysis of plasma amino acids by modification of the MassTrak™ AAA Solution UltraPerformance™ liquid chromatography method. Clin Chim Acta 423: 75-82, 2013.

20. Bi X and Henry CJ: Plasma-free amino acid profiles are predictors of cancer and diabetes development. Nutr Diabetes 7: e249, 2017.

21. Vander-Heiden MG, Cantley LC and Thompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 324: 1029-1033, 2009.

22. Teoh ST and Lunt SY: Metabolism in cancer metastasis: Bioenergetics, biosynthesis, and beyond. Wiley Interdiscip Rev Syst Biol Med 10, 2018 doi: 10.1002/wsbm.1406.