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Serum Fucose Level is a Reliable Biomarker to Astrocytoma: Case-control study-A systematic study and meta-analysis

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Abstract:

Cancer is one of the main leading diseases causing death. The current study aims to evaluate the concentration of fucose in the blood serum of astrocytoma patients. Also, a systematic study with sequential meta-analysis was performed. Web of Science, PubMed, EBSCO and Scopus, and published reference lists were searched up to end of May 2023. This meta-analysis indicates a statistically significant mean difference in fucose in serum between cancer patients and controls . The current search included 12 of 3611 titles: 562 cancer cases and 401 normal. Meta-analysis concluded that serum fucose can differentiate cancer patients from controls. Significant heterogeneity was found between studies: P < 0.0001 and I2 94.48%. A significant publication bias was observed (Begg, p = 0007; E gger, p = 0. 00092). there was a differences in Forest Plot of TF level between patients and control groups. Also, study estimated pooled effect size.

CONCLUSIONS: Circulating total fucose were associated with cancer.

Keywords: Fucose, Astrocytomas, Cancer , Malignant, Mannose, glycan.

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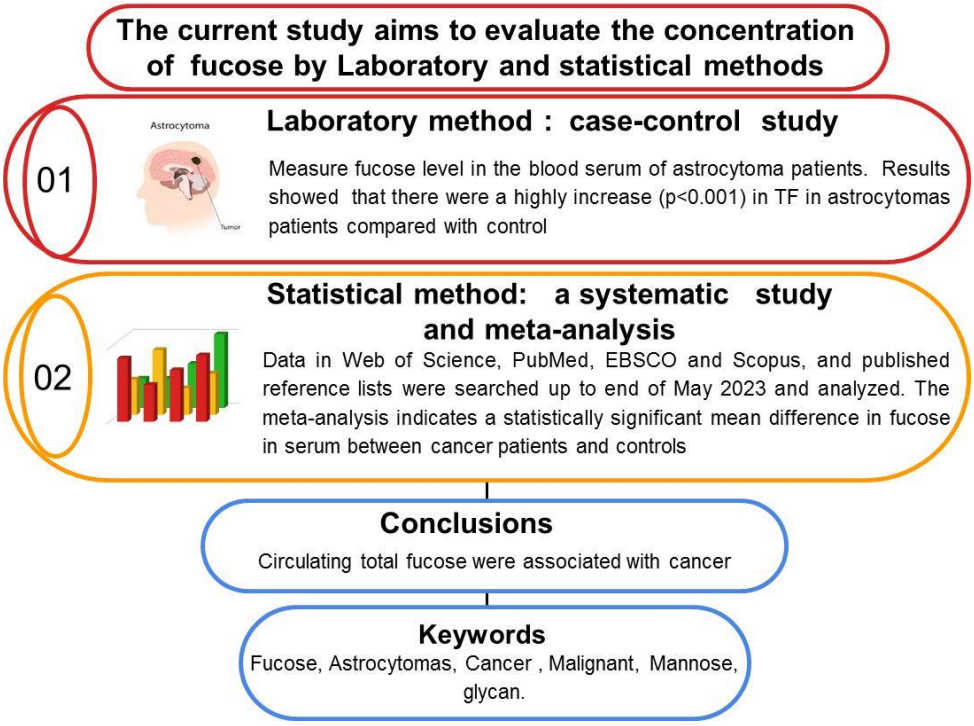
Graphical abstract



Introduction

Cancer incidence and death rate still so far unacceptably high; thus obvious fact is a strong excuse for more investigation into the field of cancer studies. A tumor is abnormal growing of aberrant somatic cells (Abnormal Meiosis). Over the steps of tumorigenesis, the features and properties of the tumor mutates and change dramatically[1]. Cell binding glycoconjugates are very important in the pathway of cancer formation, the altered properties and characteristics of cancerous are specifically expressed on the surface of the cells. Glycans either exist as free forms or conjecated forms that are attached to various molecules like peptides , proteins or lipids on the surface of cells. The cell surface changes and transforms during carcinogenesis and is critical to the abnormal growth and malignant behavior of cancer cells. Glycoconjugate (glycans) molecules such as fucose are imported of **cell membrane and associated with progression of tumor [2-4]. Increased glycoprotein levels have been reported in the majority of studies in lung cancer [5], bladder cancer [6], melanoma [7], breast cancer [8], thyroid cancer [9], and liver metastasis [10]. Cancer cells modify surface by increasing fucosylation to evade recognition, underpinning several abnormal properties of cancer cells [11] and found to be a powerful immune modulator as it is distributed in macrophages [12].**

Astrocytoma is one of the fairly common brain tumors. It forms and originates in astrocytes, which are supportive tissue, and they are classified according to nature and severity to several grades of tumors from I to IV [13].

A systematic review in a current search summarize published studies that reporting correlation fucose for the cancer and the association between response-based outcomes in primarily degree , advanced cancer or metastatic , across any tumour site, in order to assess whether response-based outcomes may be considered as valid parameters for cancer. To the best of knowledge there is no studies type meta-analysis that describes the significance of TF in cancer.

Methodology and Strategy

The fifty patients suffering from Astrocytoma were participated. Ages ranged from 35 to 60 years, collected during the period from August 2019 to February 2021 . All patients were diagnosed by a specialist doctor. **Chemicals:** H_2SO_4, Bio Maghreb organization; L-cysteine: Sigma organization

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. L-Fucose: were estimated by chromogen method (figure 1) by adding L-cysteine and H_2SO_4. All hexosesaccharides, including fucose, appear at 396 nm, and the shading produce by fucose about no assimilation at 430 nm [14] , [15].

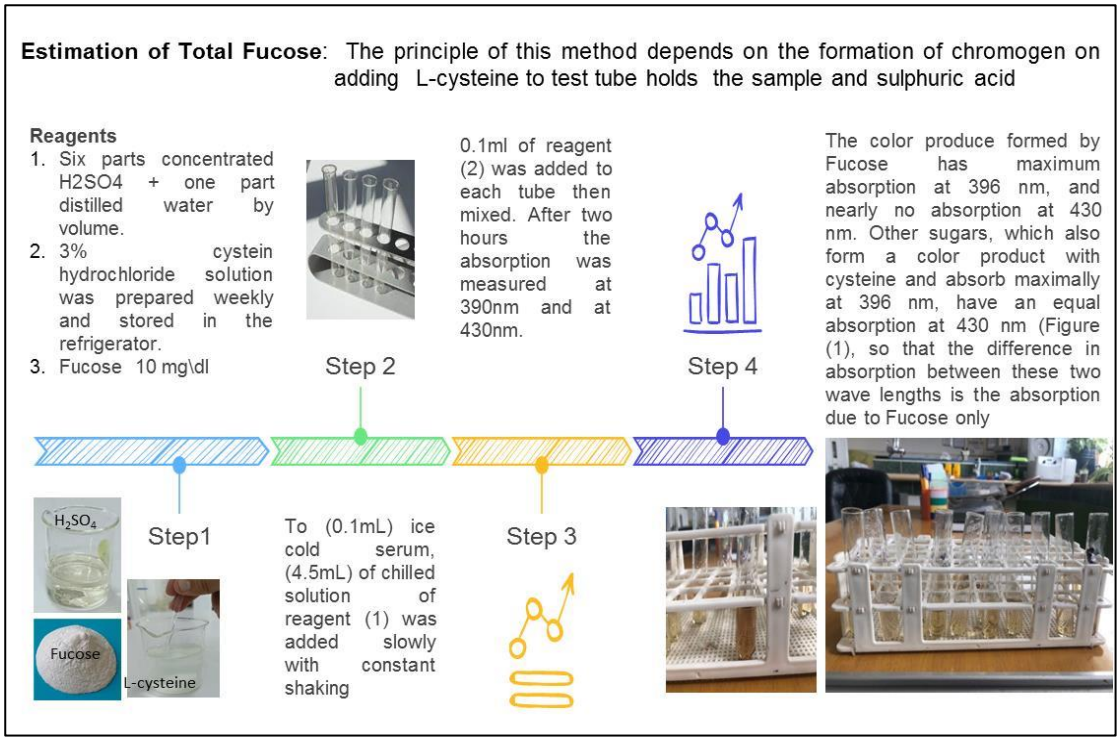

Figure (1): Serum test for TF

Calculations: Total fucose (mg/dL) = $\frac{A_X \text{at} 390\text{nm} - A_X \text{at} 430\text{nm}}{\text{Ast at} 390\text{nm} - \text{Ast at} 430\text{nm}} \times 12$

Systematic and meta-analysis were done according to the PRISMA guidelines [16]. An extensive research was conducted till January 2023 in databases (PubMed/Medline, Scopus, EBSCO) .

Search strategies consisting of free text words, in articles titles and abstracts, and that in medical subject headings , design, and outcomes studies, and use "AND" & "OR" , without restrictions in language or publication (Table 1) .

Table (1): Search strategy

Criteria	Search terms
Study population	Cancer OR tumor OR malignant
Terms of exposure	"Fucose" OR fucose [MeSH] OR "glycoprotein" OR "Glycoconjugate"
Terms of outcome	"fucose levels in cancer" OR "effect cancer on serum glycoprotein" OR -glycoprotein in disease[MeSH] OR serum tumor biomarker OR serum tumor fucose OR serum cancer glycoprotein

Study Selection Criteria

- The inclusion criteria were developed using Population, Exposure, Comparator, Outcomes, and Study characteristics (PECOS) framework as follows studies: (i) mean serum fucose in cancer patients; (ii) clinical trials .

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- Exclusion criteria included studies**:** (i) without control group or mean/median (ii) without the type of samples, clinical series, ideas, and reviews; (iii) studies with mean/median fucose levels [17],[18].

Literature Quality Assessment

We used the Newcastle-Ottawa Scale (NOS) to assess the quality of literature[8].The NOS evaluated nine questions, with one point for each satisfactory answer. Studies achieving six or more points were considered to be of high quality .

Publication Bias

Publication bias was assessed by visual inspection of funnel plots and by evaluating the symmetry of the distribution[19-21].

Data Synthesis and Analysis

In all the included studies, we estimated mean fucose levels in two groups of cancer patients and healthy subject. All analyses below were done in MedCalc software.

1. T. Test
2. All data on mean units (dl/ml).
3. Standard deviation (SD) and standard error (SE) were calculated in studies that Standard error by: multiply it by the square root of the sample size
4. Heterogeneity of SMDs across studies was assessed using the Q statistic quantified using I^2 statistic ,and ($p < 0.10$) was considered statistically significant. While heterogeneity between studies measured by I2 statistic (I2 < 25%, no heterogeneity; I2 between 25% and 50%, moderate heterogeneity; I2 between 50% and 75%, large heterogeneity; I2 > 75%, extreme heterogeneity). A random-effects model was applied to calculate the corresponding 95% confidence intervals and pooled SMDs. Funnel plots, means of Begg's adjusted rank correlation tests, and Egger's regression asymmetry tests were used to assess potential publication bias ($p < 0.05$ was considered statistically significant). (22-26).

Results and Discussion

A- Case control study

Table (2) and figure (2) contain TF mean (±SD) concentration in serum groups are illustrated in table (2). Results showed that there were a highly increase ($p<0.001$) in TF in astrocytomas patients compared with control.

Table (2): Serum Level of TF in studied groups

Groups	Mean ± SD		P value
	Control	Patients	
TF (mg\dl)	13.81+1.41	19.97+2.13	<0.001

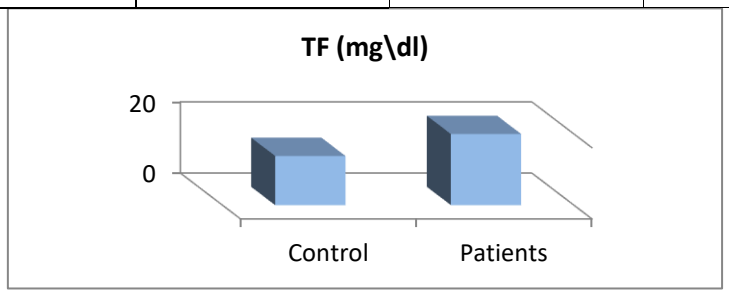

Figure (2): Serum Level of TF

Winzler [27] suggested that: due to heterogeneity of glycan or glycoprotein and presence of many different in components or molecules may have a many pathological processes. L-Fucose is found in glycan (glycolipids and glycoproteins) like in antigens blood group [26]. There was a number of changes in the fucosylation of glycan molecules in the cells and tissues of cancer patients. This is attributed to increased activity of the fucosyltransferase enzyme, especially in malignant

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tumors or highly metastatic tumors: colon, liver, and breast cancer. The levels of fucose in the serum of cancer patients were higher than those of healthy people [29],[30].

Elevated fucose are due to tissue proliferation and destruction or may be hepatic in origin, reflecting the process of protein biosynthesis. Many studies have also been referred to by many researchers to support the explanation of increased blood glycoproteins in malignant tumors and other diseases. The increased was due to biosynthesis and release of glycoproteins by cancer cells to blood or be a feature of the some tumor effects on metabolism. [31-33].

B- systematic review and meta-analysis

- **Characteristics of Eligible Studies and Data Extraction**

3611 studies were obtained in current study by strategy (search strategy : EBSCO = 3401, PubMed/Medline=140, Scopus =55, other sources =5). After removing search that duplicates, 686 studies were remained and assessed for inclusion.while, 557 studies were excluded (as in Study Selection Criteria paragraph). The 12 full texts studies were reviewed(48-59) , included and quality assessment.

Figure (3) shows PRISMA flow chart for study selection process. The characteristics and quality assessment of the studies that searched about the TF in cancer selected searches are presented in Table (3) and (4).

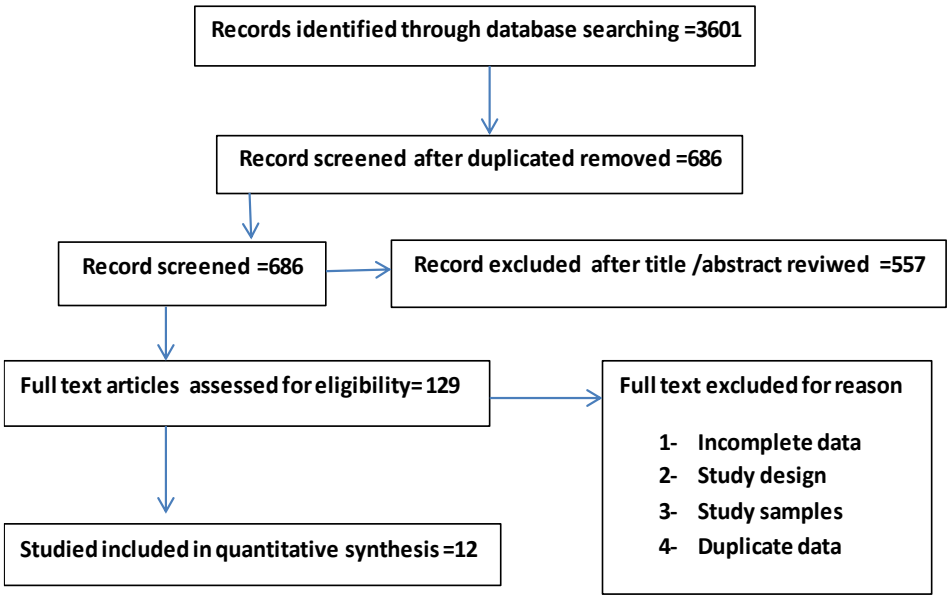

Figure (3):- the PRISMA flow chart for study

- **Meta-Analysis**

Studied and estimated of random-effects by meta-analysis analysis showed that patients with cancer have high levels of fucose compared with control (SMD=2.174, 95% CI 1.498 to 2.851). Significant heterogeneity was found between studies: $P < 0.0001$ and I^2 94.48%. A significant publication bias was observed (Begg, p = 0007; E gger, p = 0. 00092). Figure (4) showed there was a differences in Forest Plot of TF level between patients and control groups. Also, study estimated pooled effect size. Figure (5) showed Funnel plot of studies investigating cancer patients.

Table (3). Quality assessment of the prospective and retrospective studies included.

Author	NOS)Stars(	year	Type of cancer	Random selection in population	Defined inslusion /	Report loss to follow-up	Validated measurements	Statistical analysis	Estimated potential risk of bias

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					exclusion criteria				
Manjula S, et al. (34)	8	2010	brain tumor	Cases / Controls	yes	No	yes	yes	high
Sabah Hussin Khorshed et al.(35)	8	2011	brain tumor	Cases / Controls	yes	No	yes	yes	high
Nadia ahmed al-joboury (36)	7	2014	prostate cancer	Cases / Controls	yes	No	yes	yes	moderate
Narendra Prakash *Rai et al* (37)	8	2015	Oral squamous cell carcinoma	Cases / Controls	yes	No	yes	yes	low
Kumar S, et al. (38)	7	2015	oral cancer	Cases / Controls	yes	No	yes	Yes	moderate
Manchil PR, (39)	9	2016	oral cancer	Cases / Controls	yes	No	yes	yes	low
Kumar S, et al(40)	7	2019	oral cancer	Cases / Controls	yes	No	yes	yes	moderate
Kamble AS et al.(41)	9	2019	breast malignancy	Cases / Controls	yes	No	yes	yes	moderate
Abbasi Natajomrani R . et al. (42)	9	2020	Colorectal Cancer	Cases / Controls	yes	No	yes	yes	high
Fawzi H. Zayr & Nagham Q. Khadim(43)	7	2021	breast Cancer	Cases / Controls	yes	No	yes	yes	low
Rathore et al (44)	8	2021	Oral Cancer	Cases / Controls	yes	No	yes	yes	high
Mohammed AK,	7	2021	Nasal and	Cases /	yes	No	yes	yes	moderat

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et al. (45)			Paranasal Sinus Malignancies	Controls					

Table (4) : Summarize evidence on selected papers

	AUTHOR	SAMPLE SIZE	AGE	DETECTION METHOD	MEAN ± SD OR MEAN ± SE mg/dl)(	RELEVANCE ABOUT FUCOSE
1.	Manjula S, et al.	Control= 35 Case=99	10–75	Spectrophotometric method	Control =16.87 ± 6.5 Case = 21.47 ± 10.85	It may be considered an additional sign of brain tumors and cancers
2.	Sabah Hussin Khorshed et al.	Control= 54 Case=85	3-70	Spectrophotometric method	Control =13.625 ± 1.21 Case = 22.35 ± 11.0	Fucose can be an additional tool for diagnosis
3.	Nadia ahmed al-joboury	Control= 25 Case=30	40–60	Spectrophotometric method	Control =15.26 ±1.08 Case = 39.54 ± 7.29	Serum fucose levels altered in prostate cancer
4.	Narendra Prakash Rai et al	Control= 20 Case=20	30-66	Spectrophotometric method	Control =5.29±2.18 Case = 13.85±4.34	There was progressive elevation in serum L-fucose level in oral cancer
5.	Kumar S., et al.	Control= 50 Case=75	30-36	Spectrophotometric method	Control =7.22±1.83 Case = 15.11±8.7	Serum fucose levels play as a biomarker role
6.	Manchil PR,	Control= 30 Case=60	25-75	Spectrophotometric method	Control = 3.47±0.021 Case =10.85±1.00557	There was a positive correlation between the serum L-fucose levels and oral cancer
7.	Kumar S, et al	Control= 25 Case=25	20-60	Spectrophotometric method	Control =7.22± 1.83 Case = 15.11±8.7	It's a tool for prognostic studies
8.	Kamble AS et al.	Control= 15 Case= 31	31-70	Spectrophotometric method	Control =8.9±0.6 Case = 25.6±11.7	It is possible to use it as a screening test for malignancy

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9.	Abbasi Natajomrani R . et al.	Control= 40 Case=40	30-70	Spectrophotometric method	Control =18.64±3.1 Case = 27.46±4.8	Sensitivity and specificity of L-fucose as a potential biomarker in the diagnosis
10.	Fawzi H. Zayr & Nagham Q. Khadhim	Control= 29 Case= 31	-	Spectrophotometric method	Control = 12.46±3.64 Case = 22.28±8.1	Total serum fucose has higher diagnostic validity values
11.	Rathore et al	Control= 50 Case= 50	15–60	Spectrophotometric method	Control = 7.22±1.28 Case = 35.28±21.01	help in observation early changes in malignant
12.	Mohammed AK,et al.	Control= 28 Case=16	38–67	Spectrophotometric method	Control =5.49±0.93 Case = 8.02±3.47	Can be an additional tool for diagnosis

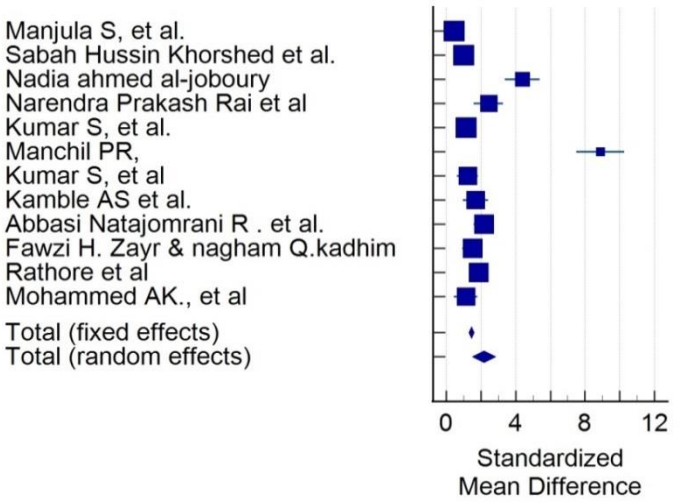

Figure (4): Forest Plot of serum of serum TF level

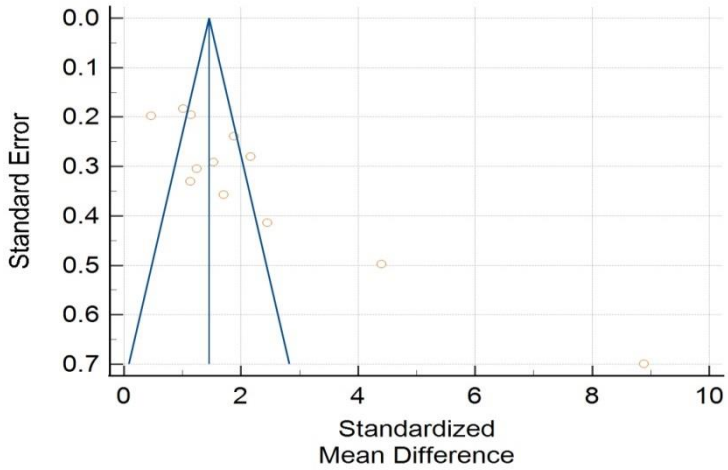

Figure (5): Funnel plot of studies investigating

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In meta-analysis, results found: patients cancer have a high TF levels compared with control subjects, suggest it as a biomarker help in prognostic studies in patients with cancer.

There was some limitations due to small sample sizes (n). Results from Egger's tests with funnel plots found a strong and big publication bias, which may due to researchers and editors tendency to report about positive results

Treatment and increasing survival rates for oncology and cancer patients depend primarily on early intervention through early examination and diagnosis of lesions within the early stages. Laboratory testing, especially using urine, blood, or liquid biopsy samples as compared to imaging or histopathology, is an affordable, non-invasive, and repeatable method for cancer prediction by testing -specific biomarkers for cancer such as DNA, proteins, metabolites, and others [46],[47].

High fucosylation is one of the hallmarks of malignant tumors, mostly because malignant tissues show enhanced activity of enzymes of its pathway, especially fucosyl transferase [48],[49].

Fucosylation is a modification of an oligosaccharide , have a critical role in benign and malignant tumors and immune response. Changes in the state and type of glycosylation affect cellular functions by glycoproteins (glycosylated proteins or glycan), like enzyme-linked receptors and cell surface proteins (adhesion molecules).

Advances in glycomics stats have showed many types of different biomarkers like: fucosylation-related factors [50]. Recently, there is great interest in the glycosylation profiles of many types of tumors and cancers, especially in immunotherapeutic targets and there types [51].

Conclusions: Circulating total fucose were associated with cancer , and high levels may be a sign of cancer

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