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# Can Insulin Like Growth Factors Be Used As A Biomarkers Of Oral Cancer?-A Systematic Review

Review Article

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## Abstract

**Background:** Insulin like growth factor (IGF) has been linked with cancers of the gastro-intestinal and breast origin. They are involved in the proliferation of cells and have an anti-apoptotic role in cancer cells The role of serum and salivary IGF in oral cancer is not well established though, IGF-1 has been found to be elevated in the tissue levels of oral cancer sites.
**Methods:** Electronic searches were carried out in the Embase,Medline,Scopus databases for clinical studies which measured the levels of Insulin-like growth factors in patients with oral cancer.Only studies which measured serum or salivary IGF-1 and IGFBP's in oral cancer patients were included in the search.The studies' quality was determined using the National Heart,Lung and Blood Institute (NHLBI) checklist.
**Results:**Four studies were included in the review out of a total of 116 articles.3 of these articles reported on serum levels of the IGF and only one measured the salivary levels.The studies which measured serum IGF and IGFBP's in oral cancer patients reported decreased levels when compared to the controls,whereas the study which assessed the salivary levels concluded that there was a117% increase in the IGF-1 levels among oral cancer patients.
**Conclusion:**With the availability of limited data, the role and utility of salivary and serum IGF-1 and IGFBP-3 as prognostic biomarkers in oral cancer patients cannot be assessed. More clinical studies designed and standardized to measure the values of IGFwith a long term follow up of the patients will give a more clearer picture of the actual role of IGF-1 and its role in oral cancer.

**Keywords:** Oral Cancer; IGF; IGFBP; Serum; Saliva.

## Introduction

Globally, cancer is one of the leading causes of death accounting for approximately an estimated 10 million deaths in 2020.[1] Oral cancer, which is the growth of malignant cells in the oral cavity (lips, mouth and tongue) is associated with significant morbidity and mortality.[2] Oral cancer is the sixteenth most prevalent cancer worldwide, according to the GLOBOCAN 2020 survey, with 377,713 new cases (2.0 %) and 177,757 deaths (1.6%) in 2020.1 Oral cancers are highly frequent in South Central Asia which includes India, Sri Lanka, and Pakistan, reflecting the popularity of aka chewing (smokeless tobacco) and betel quid without tobacco in these countries.[3, 4] According to GLOBOCAN 2020, cancers of the lip and oral cavity are the leading cause of cancer death among men in India.[1]

Due to the increased burden of cancers, including oral cancer, investigation of molecular pathways associated with it and the identification of novel therapeutic targets have become the need of the hour. Circulating insulin-like growth factor (IGF) has a significant role in tissue growth and development and has been shown to be associated with cancers.[5, 6] IGF plays a key role in controlling cell proliferation, inhibiting apoptosis, differentiation, metabolism, angiogenesis and metastatic activities in various cancers.[7] The IGF family encompasses insulin and two IGF-1 and IGF-2, their related receptors (IGFR-1 and -2), six IGF-binding proteins (IGFBPs), and IGFBP proteases.[8] Numerous studies have suggested that the IGF family plays a significant role in dif-

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ferent malignancies such as colorectal [9], breast [10], ovarian [11], prostate cancer [12] pancreas [13], esophagus [14], stomach [15] and several others, but evidence related to oral cancers are limited.

Serum IGF levels have been shown to be a potential diagnostic biomarker to detect early-stage of certain cancers.[16, 17] To our knowledge there are few studies that have examined the utility of serum IGF levels as a promising biomarker in the diagnosis/prognosis of oral cancer. In addition, the use of salivary IGF levels as noninvasive biomarkers for diagnosis/prognosis of oral cancer is also not clear. Therefore, the purpose of this is to systematically review the available literature reporting on circulating serum/salivary IGF levels and its association with oral cancer.

## Materials And Methods

### Focussed question

Can serum or salivary IGF-1/IGFBP-3 be used a biomarker to evaluate the risk of oral cancer?

### Study Selection Criteria

The following criteria were used to select the studies to be included in the study:

- Studies designed to measure the levels of any of the IGF family members in only oral cancer patients
- Studies which utilized only salivary and serum samples for the measurement
- Studies should be in the English language

### Search Strategy

A systematic search was carried out using the electronic databases (PUBMED, Science direct, Embase) for clinical studies which measured IGF in patients with oral cancer. The key words used in the search builder were Insulin-like growth factor, Insulin-like growth factor-1, Insulin-like growth factor-2, IGF-1, IGF-2, Insulin like growth factor binding proteins, IGFBP-3, IGFBP-1, IGFBP-2, Oral cancer,Oral squamous cell carcinoma,Salivary biomarkers and Serum Biomarkers. Manual search of the main journals of oral oncology and maxillofacial surgery was also done. All titles and abstracts of all the articles were analysed by the author.

### Outcome Measures

IGF-1 Measurements: IGF-1 values measured from saliva and serum samples by ELISA,IRMA,Chemiluminisence methods reported in ng/ml and pg/ml

IGFBP-1,2,3- IGF-1 values measured from saliva and serum samples by ELISA methods reported in ng/ml orpg/ml

### Data Extraction

Following the search, all the returned articles were assessed based on their title and abstracts and were included if they met the inclusion criteria.The included articles were assessed completely and the data was represented in tables. Data pertaining to the author name, year of publication, study type, biomarkers analysed, source of markers, level of markers, conclusions, limitations were extracted from the articles.

### Quality Assessment

All articles were subjected to a quality assessment checklist put forth by the National Heart,Lung and Blood Institute (NIHLB). [18] The checklist is a 12 point list for assessing case control studies.Level of evidence of all the articles were determined using the Oxford centre of evidence based medicine criteria.[19]

## Results

The electronic search initially returned 115 articles.Following title and abstract review, 95articles were excluded from the list.After full review of the remaining 20 articles, a total of 4 articles were identified for inclusion in the review and a data extraction was performed for them.(Figure 1)

Out of the 4 includedarticles, only one article measured the salivary values of IGF-1 in oral cancer patients.[20] The rest of the articles measured the circulating levels of IGF-1 and its binding proteins.[21-23] Table 1summarizes the characteristics, methods, results and conclusions of the 4 selected articles.

### Studies measuring Salivary IGF-1

Only one study has measured the salivary levels of IGF-1.20 25 subjects with OSCC and 25 healthy subjects were included as controls. The values were measured using enzyme-linked immunosorbent assay (ELISA).

### Studies measuring Serum IGF-1 and IGFBP

The serum levels of IGF-1 and IGFBP were assessed in three studies. [21-23] These studies included a total of 158 subjects with oral squamous cell carcinoma and 109 healthy subjects as controls. The values of IGF-1 and its binding proteins were analysed by using immuno-radiometric assay (IRMA), enzyme-linked immunosorbant assay (ELISA) and a Chemiluminescence Immunoassay.

### IGF-1 Levels

All the 3 studies that measured the circulating levels of IGF-1 have reported that the levels are lesser with respect to the control group. This data was statistically significant in two of the three studies (Table 2). Shpitzer et al., reported that the salivary concentrations of IGF-1 was found to be 117% higher than the controls and was also statistically significant.[20]

### IGF binding proteins

Only two studies have measured IGF binding proteins.[22, 23] The mean IGFBP-1 and IGFBP-2 in plasma were significantly higher in OSCC patients than in the healthy controls. IGFBP-3 was found to be significantly higher in the controls when compared to the OSCC group(Table 2).

### IGF-1 and IGFBP-3 Correlation

One study which measured both IGF-1 and IGFBP-3, found a strong positive co-relation between them, which was statistically

**Table 1. Characteristics, results and conclusions of the selected articles.**

| Author, Year | Methods | Level of Evidence* | Markers analyzed | | Source of Markers | Results | Conclusion |
|---|---|---|---|---|---|---|---|
| | | | IGF Family | Other markers | | | |
| Shpitzer et al.,2007 [20] | Case-Control Study; 25 patientswith OSCC and 25 controls | 3b | IGF-1 | Na,K, Ca, P, Mg, TP, Alb, LDH, Amy, IgG, Sec. IgA, EGF, MMP | Saliva | 117% increase in salivary IGF-1 value compared to the control (p=0.03) | IGF-1 plays an important role in OSCC pathogenesis |
| Bhatavdekar et al.,1993 [21] | Case-Control Study; 52 patients with OSCC and 25 controls | 3b | IGF-1 | TPS, EGF and Prolactin | Serum | Low levels of IGF-1 in cancer patients compared to the control | IGF-1 is not a predictor of short-term prognosis |
| Brady et al.,2007 [22] | Case-Control Study; 27 patients with OSCC and 31 controls | 3b | IGF-1, IGFBP-1, IGFBP-2, IGFBP-3 | - | Serum | The mean plasma levels of IGF-1 and IGFBP-3 were significantly reduced in cancer patients when compared to controls. Mean plasma levels of IGFBP-1 and IGFBP-2 were significantly higher when compared to the controls | Circulating levels of IGF-1 and IGFBP-3 may be lowered in patients with head and neck cancers |
| Schiegnitz et al., 2017 [23] | Case-Control Study; 81 untreated OSCC patients, 49 controls and 75 individuals with OPL | 3b | IGF-1, IGFBP-3 | MMP-2,MMP-3,MMP-13 | Serum | Mean IGF-1 and IGFBP-3 levels in OSCC patients were significantly lower when compared to healthy controls. IGF-1 levels <130 ng/ml and IGFBP-3 levels <3.1 micrograms resulted in a lower 12 month survival rate | IGF-1 and IGFBP-3 have a role on the pathogenesis of OSCC and indicates that they can be used as useful prognostic tools. |

IGF - insulin growth factor ; IGFBP- insulin growth factor binding protein ; TPS- tissue polypeptide-specific antigen;EGF-epidermal growth factor;Na-sodium; K- potassium; CA-calcium; P- inorganic phosphate; Mg- magnesium ; TP- total protein; Alb- albumin ; LDH- lactate dehydrogenase; Amy-amylase ; IgG- total immunoglobulin G; Sec. IgA -secretory immunoglobulin A; and MMP-metalloproteinases ; OSCC- oral squamous cell carcinoma; OPL- oral premalignant lesion

*Oxford Centre for Evidence-Based Medicine: Levels of Evidence

**Table 2. Insulin growth factor and Insulin growth factor binding protein levels in the selected studies.**

| | IGF-1 | | IGFBP-3 | | IGFBP-2 | | IGFBP-1 | |
|---|---|---|---|---|---|---|---|---|
| | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| **SERUM LEVELS*** | | | | | | | | |
| Brady et al.,2007[22] | 86.2 ± 8.4 ng/ml | 190.6 ± 10.2 ng/ml | 1995.5 ± 142 ng/ml | 2935 ± 180.5 ng/ml | 758.8 ± 86.7 ng/ml | 302 ± 30.8 ng/ml | 149.6 ± 17.7 ng/ml | 51.4 ± 4.9 ng/ml |
| Schiegnitz et al., 2017[23] | 129 ± 51 pg/ml | 161 ± 59 pg/ml | 3.2 ± 1.1 µg/l | 4.0 ± 1 µg/ml | - | - | - | - |
| **SALIVARY LEVELS** | | | | | | | | |
| Shpitzer et al.,2007[20] | 0.20 ng/ml** | 0.17 ng/ml | - | - | - | - | - | - |

*Data not available for Bhatavdekar et al.,199321; ** Calculated

significant.[23]

### Survival levels

In tongue cancer patients, when the IGF-1 levels were <50.0 ng/ml,the mean survival in months was 14.16 ± 1.08 and when the levels were>50.0 ng/ml, it was 13.83 ± 2.37, which was non-significant.[21] Similarly, OCSS patients with IGF-1 values <130 ng/ml showed a lower survival rate for 1 year (80.8%) compared to those with values ≥130 ng/ml(94.9%), which was statistically significant and IGFBP-3 values <3.1 µ/ml also indicated a lower survival rate (82.9%) compared to those with values ≥3.1 µ/ml (92.7%), however, the difference was not statistically significant.23The combined IGF-1 levels (<130 ng/ml) and IGFBP-3 levels (<3.1 µ/ml) had a substantially lower survival rates (78.5%) compared to those with combined values of ≥130 ng/ml and ≥3.1 µ/ml respectively.[23]

### Quality assessment of the studies

Table 3 shows the quality assessment of all the included studies.

**Table 3. Quality Assessment of the studies.**

| | Bhatavdekar et al.,1993 [21] | Shpitzer et al.,2007 [20] | Brady et al.,2007 [22] | Schiegnitz et al., 2017 [23] |
|---|---|---|---|---|
| Was the research question or objective in this paper clearly stated and appropriate? | Yes | Yes | Yes | Yes |
| Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes |
| Sample size justification | No | No | No | No |
| Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same time-frame)? | CD | CD | CD | CD |
| Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes |
| Were the cases clearly defined and differentiated from controls? | Yes | Yes | Yes | Yes |
| If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? | CD | CD | CD | CD |
| Was there use of concurrent controls? | CD | CD | CD | CD |
| Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? | NA | NA | NA | NA |
| Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? | Yes | Yes | Yes | Yes |
| Were the assessors of exposure/risk blinded to the case or control status of participants? | NR | NR | NR | NR |
| Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis? | NR | NR | NR | No |

NA-Not applicable; NR-Not Reported; CD-Cannot be Determined

## Discussion

A systematic review of published studies on the relationship between serum/salivary IGF-I and IGFBP-3 levels and the risk of oral cancer was conducted. The data from the three studies which assessed the serum concentration have demonstrated that reduced levels of IGF-I and IGFBP-3 were linked with oral cancer. While the study which assessed the salivary levels reported that in individuals with oral cancer, salivary levels of IGF1 increased significantly compared to healthy controls.

IGF's are multifunctional peptides that have systemic and hormonal effects on cell activity, which are present in highlevels in the circulation.[24] Growth factors such as IGF-1 and IGF-2 are closely linked with development and growth of cancer. The IGF-1 receptor, which is involved in tumor-induced cell transformation, regulates the action of IGFs. These effects are dependent on IGF bioavailability, which is regulated by IGFBPs. IGF-I binds to the key IGF binding protein, IGFBP-3, in the circulation, and both of these proteins play distinct roles in normal somatic growth by fostering cellular proliferation and inhibiting apoptosis both in vivo and in vitro.[25] As tumors grow due to excessive growth and a lack of apoptosis, it could be postulated that both IGF-1 and IGFBP-3 significantly contribute in its development. Concentrations of IGF-I and IGFBP-3 differ significantly between individuals, which could influence the risk of cancer.

High circulating IGF-I concentrations have previously been linked to an increased risk of various cancers, while high IGFBP-3 concentrations have been linked to a lower risk. [26-28] In most circumstances, IGFBP-3 inhibits IGF-mitogenic activity, and is thus inversely related to the risk of cancer.Serum levels of IGF-1 were found to be elevated in patients who had secondary primary tumors.[29] IGF-I and IGFBP-3 concentrations can be easily determined in both blood and saliva and can be useful in determining cancer risk.

Saliva is a very easily obtained, bio-specimen with a non-invasive sample collection method. As saliva is in close proximity to the site of the cancer, its role as a source of biomarkers is highly invaluable.[30] A recent study has diagnosed oral cancer from salivary metabolic profiling with a rate of 86.7% accuracy.[31] The utility of saliva as a diagnostic fluid cannot be understated.

Many therapeutic strategies that target IGF signaling have been investigated in several cancers over the last few decades. Of late, monoclonal antibodies such as ganitumab, figitumumab and others have targeted the IGF-1 receptor to obstruct the binding of IGF-1 and thereby inhibiting the IGF-1 signaling pathway which in turn reduces cancer progression. This stresses the need for a

reliable, non-invasive and cost effecting method to screen and identify patients with altered IGF levels so as to provide a better treatment option and a good quality of life. [32, 33]

Majority of the articles which we excluded were based on tissue analysis post-operatively, which was an exclusion criteria being in line with the aim of the study. All of the excluded articles which have reported on the tissue levels of IGF-1 and its binding proteins have observed an over expression of the factors and have stated their role as a prognostic biomarker.Studies which included other head and neck squamous cell carcinomas were also excluded.

This review has its own limitations.In the four articles, a total of three techniques were utilized to measure the values of IGF-1 and its binding proteins. This caused us to doubt as to whether these values can be taken together to be compared. Also a meta-analysis could not be done as only two articles mentioned the values, while for one study it was calculated from the available data and the other article represented the values in percentage. The inclusion criteria adopted by us could also have resulted in the reduced number of articles.

As evident from our systematic review, research involving the salivary and serum IGF-1 concentration and its binding proteins are very few with respect to oral cancers. We were able to find only four articles which studied them, but all four of them used a different methodology to measure the values. A well-designed prospective studies based on salivary samples which can clearly identify the biological action of IGF-1 in oral cancers are needed. Case-control studies of larger number of patients are also required to identify the possibility of whether IGF-1 and IGFBP-3 may be utilized as a valid diagnostic and prognostic marker for oral cancer.

## Conclusion

With the availability of limited data, the role and utility of salivary and serum IGF-1 and IGFBP-3 as prognostic biomarkers in oral cancer patients cannot be assessed. More clinical studies designed and standardized to measure the values of IGF with a long term follow up of the patients will give a more clearer picture of the actual role of IGF-1 and its binding proteins role in oral cancer.

## References


[1]. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209-49.

[2]. van der Waal I. Are we able to reduce the mortality and morbidity of oral cancer; some considerations. Med Oral Patol Oral Cir Bucal. 2013 Jan 1;18(1):e33-7.Pubmed PMID: 23229266.

[3]. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon, France: IARC.2020. Available from: https://gco.iarc.fr/today, accessed 05 March 2021.

[4]. Gupta B, Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in South Asia and the Pacific. PLoS One. 2014 Nov 20;9(11):e113385.Pubmed PMID: 25411778.

[5]. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004 Apr 24;363(9418):1346-53.Pubmed PMID: 15110491.

[6]. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol. 2010 Jun;11(6):530-42.Pubmed PMID: 20472501.

[7]. Brahmkhatri VP, Prasanna C, Atreya HS. Insulin-like growth factor system in cancer: novel targeted therapies. Biomed Res Int. 2015 Oct;2015:538019.

[8]. van Beijnum JR, Pieters W, Nowak-Sliwinska P, Griffioen AW. Insulin-like growth factor axis targeting in cancer and tumour angiogenesis - the missing link. Biol Rev Camb Philos Soc. 2017 Aug;92(3):1755-1768.Pubmed PMID: 27779364.

[9]. Rinaldi S, Cleveland R, Norat T, Biessy C, Rohrmann S, Linseisen J, et al. Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. Int J Cancer. 2010 Apr 1;126(7):1702-15.Pubmed PMID: 19810099.

[10]. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol. 2010 Jun;11(6):530-42.Pubmed PMID: 20472501.

[11]. Lukanova A, Lundin E, Toniolo P, Micheli A, Akhmedkhanov A, Rinaldi S, et al. Circulating levels of insulin-like growth factor-I and risk of ovarian cancer. Int J Cancer. 2002 Oct 20;101(6):549-54.

[12]. Travis RC, Appleby PN, Martin RM, Holly JMP, Albanes D, Black A, et al. A Meta-analysis of Individual Participant Data Reveals an Association between Circulating Levels of IGF-I and Prostate Cancer Risk. Cancer Res. 2016 Apr 15;76(8):2288-2300.Pubmed PMID: 26921328.

[13]. Gong Y, Zhang B, Liao Y, Tang Y, Mai C, Chen T, et al. Serum Insulin-Like Growth Factor Axis and the Risk of Pancreatic Cancer: Systematic Review and Meta-Analysis. Nutrients. 2017 Apr 18;9(4):394.Pubmed PMID: 28420208.

[14]. Adachi Y, Nojima M, Mori M, Yamashita K, Yamano HO, Nakase H, et al. Insulin-like growth factor-1, IGF binding protein-3, and the risk of esophageal cancer in a nested case-control study. World J Gastroenterol. 2017 May 21;23(19):3488-3495.Pubmed PMID: 28596684.

[15]. Pham TM, Fujino Y, Kikuchi S, Tamakoshi A, Yatsuya H, Matsuda S, et al. A nested case-control study of stomach cancer and serum insulin-like growth factor (IGF)-1, IGF-2 and IGF-binding protein (IGFBP)-3. Eur J Cancer. 2007 Jul 1;43(10):1611-6.

[16]. Xu YW, Chen H, Hong CQ, Chu LY, Yang SH, Huang LS, et al. Serum IGFBP-1 as a potential biomarker for diagnosis of early-stage upper gastrointestinal tumour. EBioMedicine. 2020 Jan;51:102566.Pubmed PMID: 31901863.

[17]. Tas F, Bilgin E, Tastekin D, Erturk K, Duranyildiz D. Serum IGF-1 and IGFBP-3 levels as clinical markers for patients with lung cancer. Biomed Rep. 2016 May 1;4(5):609-14.

[18]. NHLBI Study Quality Assessment tool available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed on 25/3/2021

[19]. Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009).

[20]. Shpitzer T, Bahar G, Feinmesser R, Nagler RM. A comprehensive salivary analysis for oral cancer diagnosis. J Cancer Res Clin Oncol. 2007 Sep;133(9):613-7.

[21]. Bhatavdekar JM, Patel DD, Vora HH, Balar DB. Circulating markers and growth factors as prognosticators in men with advanced tongue cancer. Tumour Biol. 1993;14(1):55-8.Pubmed PMID: 8493451.

[22]. Brady G, O'Regan E, Miller I, Ogungbowale A, Kapas S, Crean SJ. Serum levels of insulin-like growth factors (IGFs) and their binding proteins (IGFBPs), -1, -2, -3, in oral cancer. Int J Oral Maxillofac Surg. 2007 Mar;36(3):259-62.Pubmed PMID: 17113753.

[23]. Schiegnitz E, Kämmerer PW, Schön H, Gülle C, Berres M, Sagheb K, et al. The matrix metalloproteinase and insulin-like growth factor system in oral cancer - a prospective clinical study. Onco Targets Ther. 2017 Oct 24;10:5099-5105.Pubmed PMID: 29123408.

[24]. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. Endocrine reviews. 1995 Feb 1;16(1):3-4.

[25]. Ferry RJ, Katz LE, Grimberg A, Cohen P, Weinzimer SA. Cellular actions of insulin-like growth factor binding proteins. HormMetab Res. 1999 Jan;31(02/03):192-202.

[26]. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating concentrations of insulin-like growth factor I and risk of breast cancer. Lancet. 1998 May 9;351(9113):1393-6.

[27]. Yu H, Spitz MR, Mistry J, Gu J, Hong WK, Wu X. Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. J Natl Cancer Inst. 1999 Jan 20;91(2):151-6.Pubmed PMID: 9923856.

[28]. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr. 2001 Nov 1;131(11):3109S-20S.

[29]. Shanmugalingam T, Bosco C, Ridley AJ, Van Hemelrijck M. Is there a role

for IGF-1 in the development of second primary cancers? Cancer Med. 2016 Nov;5(11):3353-3367.Pubmed PMID: 27734632.

[30]. Zhang A, Sun H, Wang X. Saliva metabolomics opens door to biomarker discovery, disease diagnosis, and treatment. Appl Biochem Biotechnol. 2012 Nov;168(6):1718-27.Pubmed PMID: 22971835.

[31]. Song X, Yang X, Narayanan R, Shankar V, Ethiraj S, Wang X, et al. Oral squamous cell carcinoma diagnosed from saliva metabolic profiling. Proc Natl Acad Sci. 2020 Jul 14;117(28):16167-73.

[32]. Beltran PJ, Mitchell P, Chung YA, Cajulis E, Lu J, Belmontes B, et al. AMG 479, a fully human anti-insulin-like growth factor receptor type I monoclonal antibody, inhibits the growth and survival of pancreatic carcinoma cells. Mol Cancer Ther. 2009 May;8(5):1095-105.Pubmed PMID: 19366899.

[33]. Zhang T, Shen H, Dong W, Qu X, Liu Q, Du J. Antitumor effects and molecular mechanisms of figitumumab, a humanized monoclonal antibody to IGF-1 receptor, in esophageal carcinoma. Sci Rep. 2014 Oct 31;4:6855. Pubmed PMID: 25358597.