Role of plasma Progastrin phenotypes as a potential biomarker for screening and diagnosis of cancer - A Scoping Review

ABSTRACT

INTRODUCTION: Globally, over 18 million new cancer cases are identified and approximately 10 million people have died from this disease in 2018. Over the years, biomarkers have developed with several applications in the field of cancer research; one such biomarker is progastrin - a neuropeptide hormone, a precursor of gastrin hormone and secreted by the G cells of the antrum. Among the various phenotypes produced, Hpg80 and ProGastrin peptide realizing hormone (Pro GRP) are the two most common types seen among patients with cancer.

AIM: The aim of this scoping review is to gather literature on the role of Hpg80 and Pro GRP in common type of carcinomas occurring globally which include Lung, gastric, breasts, head neck and oral cancer.

MATERIALS AND METHODS: Relevant studies were searched via MEDLINE (PUBMED), COCHRANE and GOOGLE SCHOLAR and 9 relevant studies were reviewed based on the inclusion and exclusion criteria from the period of January 2012 to December 2021.

RESULTS: The main findings point to provide concrete evidence associating elevated levels of Hpg80 and Pro GRP in Lung carcinoma.

CONCLUSION: In light of the increasing interest in cancer diagnosis, Hpg80 and Pro GRP can be considered as a differentiating marker in screening and diagnosis of carcinomas.

Keywords: Biomarker, Human Progastrin 80, carcinoma, screening

1. INTRODUCTION

In 2015, cancer was the second leading cause of non -communicable disease deaths in the world. Globally, over 18 million new cancer cases were identified and approximately 10 million people died from the disease in 2018.[1] The projected incidence of patients with cancer in India among males was 679,421 (94.1 per 100,000) and among females 712,758 (103.6 per 100,000) for the year 2020. One in 68 males (lung cancer), 1 in 29 females (breast cancer), and 1 in 9 Indians will develop cancer during their lifetime.[2]Contributing factors such as tobacco smoking, urbanization, pollution, diet and a rapidly aging population have been theorized to be responsible for this explosive cancer incidence.[3]
Representations of cancer have always been a mystery since most cancer remains asymptomatic. Even if there are any symptoms present, they are nonspecific like lymphadenopathy, weight loss, or persistent cough. Thus, these are ignored by the patients due their poor literacy skills, financial or cultural barriers.[4]

By the time the patients seek a medical care, the care becomes economically costlier or availability of care is difficult. Moreover, late detection of cancer makes treatment difficult because of progressive advancement in disease stage and metastasis. Although early detection programs have increased, particularly in the developed world, such programs typically rely on symptomatic presentation. However, early cancer symptoms can be nonspecific and can be easily confused for other conditions, contributing to the delay in diagnosis and the progression of the disease.[5]

Over the years biopsy has been the gold standard in detecting and confirming cancer conditions, but one up roaring field of cancer diagnostics is search of novel biomarkers. Biomarker is a molecule that can be detected in blood, saliva or any body fluid indicating a pathological condition.[6] Over the years, biomarkers have developed several applications in the field of cancer research that they are not only restricted to diagnosis but also used to evaluate risk assessment, differential diagnosis, determination of prognosis, prediction of treatment and monitor progression of cancer.[7] Literature is abundant on the importance of various cytogenic and circulating biomarkers and their role in various cancers, including lung, colon etc.

One such biomarker of interest is progastrin - a neuropeptide hormone, a precursor of gastrin hormone and is found to maturate to various phenotypes upon enzyme reactions. Among the various phenotypes produced Human Progastrin 80 (Hpg80) and ProGastrin peptide realizing hormone (Pro GRP) are the two most common types seen among patients with cancer.[8] Various theories have been proposed to understand how a pro hormone behaves as a biomarker for cancer. One acceptable hypothesis is proGRP act as growth modifying factor which induces cell proliferation and maturation along with pro angiogenesis.[9] Even though progastrin is physiological hormone having important functions, its pathological role in cancers can further be attributed with the fact that the gene GAST coding for progastrin is a direct target gene of the WNT/ß-catenin oncogenic pathway. The activation of this oncogenic pathway is an early event in cancer development. Chronic activation of the WNT/ß-catenin oncogenic pathway occurs in almost all human solid tumors and is a central mechanism in cancer biology that induces cellular proliferation, blocking of differentiation leading to primary tumor growth and metastasis formation.[10]
With this background, this scoping review was indented to gather literature on the role of Hpg80 and Pro GRP as a potential biomarker for various cancers. The outcome of this research would throw light on the role of these biomarkers on various cancers and thus could be suggested as an universal biomarker for general screening for cancer on a population level program.

2. MATERIAL AND METHODS

2.1 **DESIGN**

This review was undertaken using Ashley and O' Malley guidelines which has the following steps:

1. Identifying the research question
2. Identifying relevant studies
3. Selecting studies
4. Collecting data
5. Mapping findings

2.2 **RESEARCH QUESTION**

Role of Hpg80 and Pro GRP as potential biomarkers for various cancers.

2.3. **RELEVANT DATA IDENTIFICATION**

INCLUSION CRITERIA

- ✓ Studies which assessed Hpg80 and Pro GRP levels for cancer diagnosis, prognosis or treatment monitoring
- ✓ The search included only studies published in English.
- ✓ Studies published in the last 10 years (2012 to 2021) were included.
- ✓ Analytical study designs were included

EXCLUSION CRITERIA

- ✓ Qualitative studies, reviews, expert opinion, systematic reviews and meta-analysis
- ✓ Publications with no abstract and those which were widely out of scope of the study were eliminated.
- ✓ Studies that required translation to English language.

The remaining studies were sorted on basis of their title and abstract. Finally, those studies in which the abstract fulfill all inclusion criteria were selected for full-text reading. In those cases, in which a study met the eligibility criteria but the information in the abstract was insufficient, full texts of the articles were also obtained. Further literature search was performed based on the bibliography of the selected articles.

2.4 **SEARCH STRATERGY**

Relevant studies were included from the period of January 2012 to December 2021 via MEDLINE (PUBMED), COCHRANE and GOOGLE SCHOLAR. A detailed search strategy was developed for MEDLINE through the use of MeSH terms and was modified for other search engines. 'Progastrin'; 'biomarker';' Cancer diagnosis (HEAD AND NECK; BREAST; GASTRIC; COLORECTAL; OESOPHAGUS; LUNG; ORAL CANCER)';' tumor';' early detection' were terms used along with Boolean operators "AND; 'OR' Data searches were done at September 2021 and again at January 2022. Manual searches were carried out with the reference list and also with journals that have a core scope on novel

technologies used of cancer diagnosis. Although systematic reviews, qualitative studies, case series were excluded, reference lists were checked to ensure all primary research was located for inclusion. Only full papers written in English were included. Where multiple publications reporting on the same study existed in different databases, data from the study were extracted and reviewed only once. Duplication of article was identified using software. (Mendeley version 2.67)

2.5 **STUDY SELECTION**

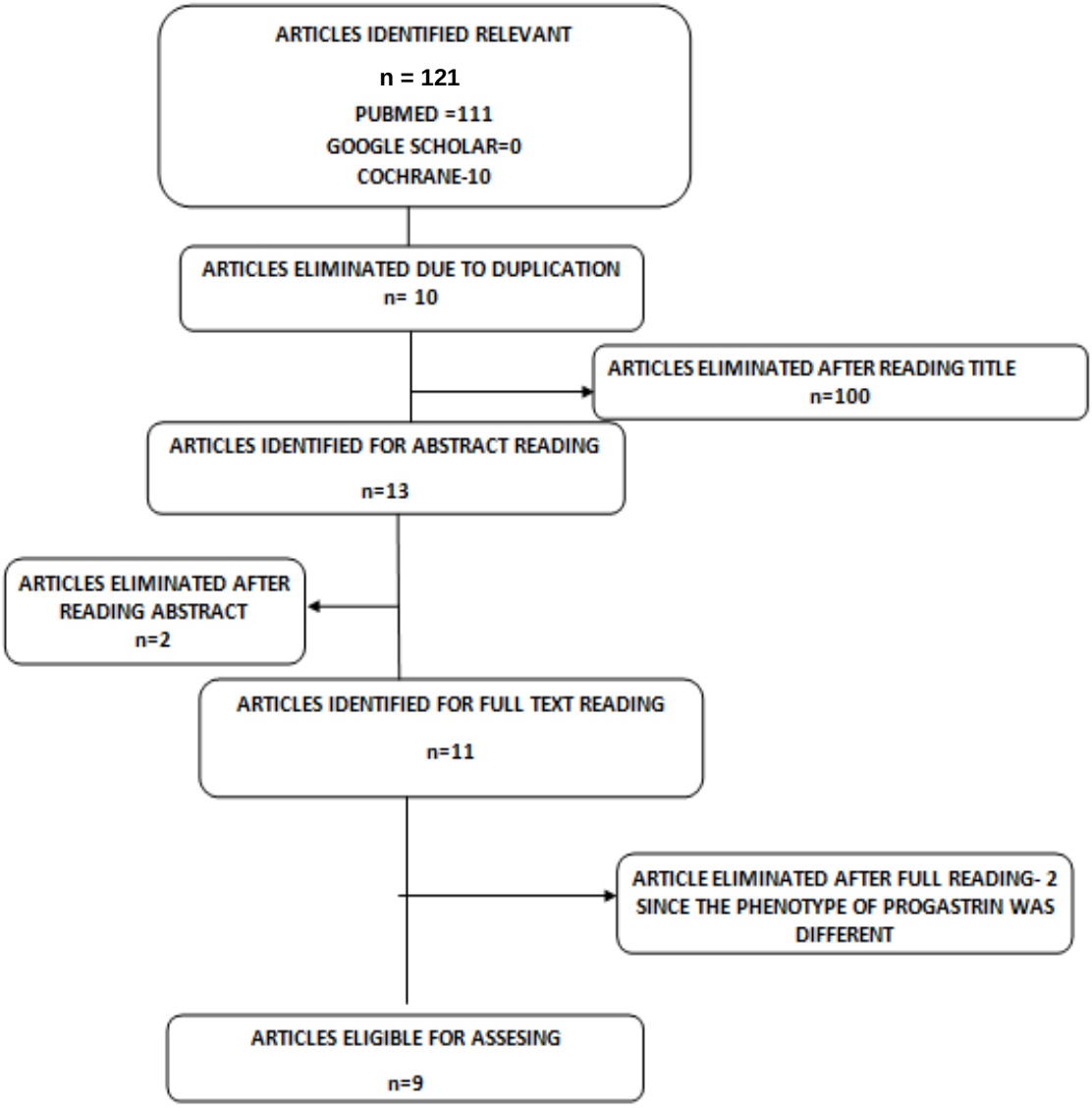
Study selection was conducted by two authors (kappa value -0.8, computed using SPSS version 20) who independently screened titles and abstracts against the inclusion/exclusion criteria and identified relevant papers. Then the same two authors independently reviewed the full text studies unable to be excluded by title and abstract alone. Comparison of papers was completed between the two authors with no disagreements regarding inclusion.

STUDY DESCRIPTION

Initial search yielded 40 studies for lung cancer, 60 studies for colorectal/gastric/esophageal cancer and 13 studies for head and neck cancer. There were null results for the “oral cancer” or “breast cancer”.

Among the final 9 studies, 8 studies represented lung cancer and one study on medullary thyroid carcinoma. All the studies evaluated progastrin phenotype ProGRP in serum using enzyme sorbent assay. (Figure 1)

Figure 1 shows the flow chart of articles narrowed down for final analysis.



A total of 121 studies were obtained initially which were evaluated for duplication and 9 relevant studies were selected based on the inclusion and exclusion criteria.

3. RESULTS

The outcome of the assessed studies have been described in Table 1.

LUNG CARCINOMA FINDINGS

Lung carcinoma being the most common type of cancer had 8 final studies, SCLC (small cell lung carcinoma) and NSCLC (non-small cell carcinoma) were conditions seen. Progastrin was considered to be one among the other biomarkers like CEA, SCC –An, CYFRA whose sensitivity and specificity ranged from 18%-76% and 57% to 97% respectively. ProGRP marker is an accurate biomarker to differentiate SCLC and NSCLC and it is also a reliable marker to diagnose SCLC. Levels of ProGRP is above <120ng/ml in case of malignant conditions and >>80ng/ml in benign cases.

HEAD AND NECK FINDINGS

Among the 9 studies only one study satisfied the eligibility criteria for analysis. In that study medullary thyroid carcinoma was the condition seen, the serum ProGRp measured had a sensitivity of 53% and specificity of 96.8% and it was concluded that progastrin was better at differentiating medullary thyroid carcinoma.

OTHER FINDINGS

No studies was done so far in the field of oral cancer and breast cancer diagnosis.

Table 1 shows the data extraction of the 9 studies included for final analysis.

Sl no.	Author, year	Disease studies	Method of progastrin analyzed	Result	Conclusion
1.	Barchiesi[11] V, 2021	Small cell lung cancer and Non small cell lung cancer differentiation	Serum proGRP	Increased levels of serum proGRP was seen among SCLC	proGRP is an accurate indicator for discrimating SCLC and non SCLC
2	Molina R[12] 2009	SCLC AND NSCLC	Serum proGRP	Increased levels seen among SCLC with sensitivity of 76.7% and specificity of 97.2%	ProGRP Can Be Used A Good Tumor Differentiation
3	Ni J[13] 2016	Clinical stages of lung carcinoma	ProGRP, SCC-Ag, Cyfra21-1 and CEA- serum levels	Increased levels seen with different stages with sensitivity and specificity of proGRP was 75.3% and 57.4%.	Serum proGRP predicts extensive stages
4	Korkamz[14], 2018	Patients diagnosed with LC	Progastrin releasing peptide (ProGRP), squamous cell carcinoma antigen (SCCAg), cytokeratin 19-fragments (CYFRA 21.1), human epididymis protein 4 (HE4), Chromogranin A (CgA) and neuron specific	sensitivity and specificity of tumormarkers were 72%, 83% for CYFRA 21.1; 70%, 57% for HE4; 18%, 93% for ProGRP; 43%, 77% for SCCAg; 54%, 53% for CgA; 73%, 50% for NSE	panel of three tumor markers CYFRA 21.1, HE4 and ProGRP may play a role for discriminating LC from benign lung disease and subtyping as SCLC

			enolase (NSE) levels were measured		
5	Molina R[15] 2004	Lung cancer	Serum pro GRP levels were measured	Abnormal lvels>80ng/ml was seen in benign conditions and >120ng/ml seen in malignancy.	proGRp is a more sensitive marker for SCLC
6	Uchida K[16] 2002	Patients with SCLC	Serum proGRP	proGRP protein expression was higher among SCLC	GRP may function as an autocrine growth factor for cancer cells in a subgroup of SCLC patients
7	Muley T[17] 2020	Patients with small-cell lung cancer (any stage) receiving chemotherapy	ProGRP was measured at baseline and after each chemotherapy	Decline(>.25%) in proGRP after cycle 1 and 2 showed zero intermittent progression of tumor in CT scan even after 2 weeks.	ProGRP may be a simple, reliable, and repeatable tool for monitoring response to chemotherapy and provide valuable prognostic information
8	Molina R[18] 2005	Marhker comparison among SCLC	ProGRP, CEA, SCC, CYFRA 21-1 and NSE	most sensitive combinations of tumor markers were ProGRP and NSE in SCLC (88%), and CEA plus CYFRA in NSCLC (82%)	ProGRP is the tumor marker of choice in SCLC and NSE is a complementary tumor marker in this histological type.
9	Liang 2020[19]	Medullary thyroid carcinoma	Serum ProGRP and FNA-ProGRP were measured	serum ProGRP was increased with a 53.85% sensitivity, 96.98% specificity	ProGRP measurement could be served as an ancillary method for the differential diagnosis between MTC and non-MTC thyroid nodules

ProGRP – Progastrin Releasing Peptide, SCLC - Small Cell Lung Carcinoma, NSCLC -Non-Small Cell Lung Carcinoma, LC – Lung Carcinoma, CYFRA - cytokeratin fragments, HE4 – Human Epididymis protein 4, NSE - Neuron Specific Enolase, CgA - Chromogranin A, MTC – Medullary Thyroid Carcinoma, SCCAg - Squamous Cell Carcinoma Antigen,CEA – Carcinoembryonic Antigen, CT – Computerized Tomography

4. DISCUSSION

Findings from the above scoping review provide concrete evidence on Lung carcinoma but not much exploration is done in field of other carcinomas. The relationship between progastrin and cancer diagnosis is explained with the WNT –m oncogenic pathways.

The WNT signalling pathway is an ancient and evolutionarily conserved pathway that regulates crucial aspects of cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development. The WNTs are secreted glycoproteins and comprise a large family of nineteen proteins in humans hinting to a daunting complexity of signalling regulation, function and biological output. [21]

A connection of the Wnt pathway to cancer was implicated by the discovery that activation of int1 (Wnt1), which, either by proviral insertion into the Wnt1 locus or transgenic overexpression in mice, resulted in mammary hyperplasia and tumors. Many experimental data further suggested that direct link between Wnt signalling and human cancer. [22]

In the past years, many genetic and biochemical studies have sought to identify novel Wnt pathway components and their functions. Identified components and processes include the Wnt secretory machinery, Wnt co-receptors, components of the β-catenin destruction complex and nuclear co-factors. With the advance in sequencing technology and the comprehensive structural characterization of cancer genomes it became evident that mutations in the Wnt pathway occur frequently in human cancers.[23] Progastrin (progrp) a physiological hormone is found in the blood of patients with different cancers mostly lung and gastric. This could be explained by the theory that a gene GAST which codes directly for progastrin is a target gene of WNT /ß-catenin oncogenic pathway.[24]

The activation of this oncogenic pathway is an early event in cancer development.

Chronic activation of the WNT/ß-catenin oncogenic pathway occurs in almost all human solid tumours and is a central mechanism in cancer biology that induces cellular proliferation, blocking of differentiation leading to primary tumour growth and metastasis formation. [25]

Thus, Progastrin measured in the peripheral blood of patients on treatments, could be a new powerful marker for diagnosis and prognosis at different stages. Thus, this scoping review is an attempt to understand the relation between ProGRP levels and different carcinomas.

5. CONCLUSION

It can be concluded with the above findings that progastrin is definitely a reliable differentiating marker in lung carcinomas and a good prognostic marker in head and neck cancers. To further understand the role of progastrin in oral cancer and other different carcinomas more exploratory trials need to be conducted to cope up with the dearth of evidence present.

CONSENT (WHERE EVER APPLICABLE)

Since this was a literature review, consent was not applicable for this manuscript.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

Since this was a literature review, ethical approval was not applicable for this manuscript.

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