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Single nucleotide polymorphism of leptin and leptin receptor genes in oral cancer - A systematic review

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Abstract

Oral cancer is one of the serious health problems diagnosed worldwide including Malaysia. While much research has been done on the gene polymorphism of leptin and leptin receptor genes in other cancers, few researchers have considered oral cancer. Hence, this study aims to provide an insight into the association of a single nucleotide polymorphism of leptin and leptin receptor genes with oral cancer, as well as its contribution in increasing the risk for oral cancer development. Literature searches were conducted in six databases including Scopus, ScienceDirect, Web of Science, PubMed, Google Scholar, and Dimensions; focusing on articles published between 2000 to 2020. All relevant articles were screened accordingly using search terms "leptin", "leptin receptor", "single nucleotide polymorphism" and "oral cancer". A total of 2699 articles were retrieved. After following the inclusion and exclusion criteria, only four articles were included in this systematic review highlighting the three commonly studied polymorphic variant of leptin and leptin receptor which are *LEP* -2548 G/A, *LEPR* Gln223Arg, and *LEPR* K109R. Single nucleotide polymorphism of leptin and leptin receptor genes specifically *LEPR* Gln223Arg and *LEP* -2548 G/A may increase the risk of development of oral cancer. There were limited sources available to support the findings. Further research and investigations are needed to explore the mechanism of leptin and leptin receptor genes in the development of oral cancer.

Keywords: *leptin, leptin receptor, oral cancer, oral squamous cell carcinoma, single nucleotide polymorphism*

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Introduction

Oral cancer is one of the serious health problems diagnosed worldwide including Malaysia. Globally, the prevalence of oral cancer is high and has a poor prognosis, making this disease a public health problem. Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer. Oral cancer may be caused by several factors, such as chewing tobacco, smoking, alcohol

consumption, human papillomavirus (HPV) infection, and multiple genetic alterations. The current clinical screening rule which encompasses general examination including intraoral examination with comprehensive medical history, appears to be insufficient for prevention, since approximately 30% of OSCC patients had done screening in the last three years. Oral cancer prevention could be more effective if the population at risk could be identified prior to developing oral cancer and more attention was paid to them (Yapijakis *et al.,* 2009).

Leptin (LEP) is a protein from the cytokine family, consisting of 167 amino acids and is a common hormone of regulating energy expenditure by inhibiting hunger. It is an adipocyte-specific hormone which is predominantly secreted from adipose tissue, and barely in the placenta, salivary glands, and skeletal muscle. Leptin is a pleiotropic cytokine involved in diverse physiological and pathological processes such as angiogenesis, tumor growth, thrombosis, metastasis as well as proinflammatory immune response in multiple organs (Sobrinho Santos *et al.,* 2017; Hung *et al.,* 2019). The function of leptin gene *(LEP)* is achieved when it binds to its receptor, the leptin receptor protein (Ahima & Osei, 2004). Leptin receptor (LEPR) is a type I cytokine receptor, encoded by the *LEPR* gene and acts as a receptor for the hormone LEP (Rong *et al.,* 2019). LEPR is a single transmembrane-domain receptor; composed of extracellular, transmembrane, and intracellular sections, commonly found in the cell membranes of various tissues throughout the body, in which neurons of hypothalamus are the most abundant region. The role of LEP in oral region is confined to induce wound healing and taste sensitivity, by nurturing keratinocyte proliferation and taste bud cells respectively (Yapijakis *et al.,* 2009). Thus, LEP/LEPR signaling may be implicated in stimulating angiogenesis, facilitating cell proliferation, and preventing epithelial cell apoptosis (Tilg & Moschen, 2006).

LEP has been commonly associated with diseases such as obesity and it was widely studied in numerous papers. Due to the nature of *LEP* associating with various pathological processes, unregulated expression of *LEP* will cause detrimental effects towards the body and its functions. In addition, countless studies have demonstrated that *LEP* is one of the causes of development of some types of cancer such as breast cancer (Atoum *et al.,* 2020). Previous studies on human and rodent cell lines exhibited clear association of *LEP* and *LEPR* with increased cancer cells, metastasis development and growth of blood vessels in benign and malignant tumors of various regions including breast, kidney, pancreas, adipose tissue, liver, colon and glia (Yapijakis *et al.,* 2009). While much research has been done on the gene polymorphism of *LEP* and *LEPR* in other cancers, few researchers have considered its' polymorphism in oral cancer.

Single nucleotide polymorphisms (SNPs) are changes in DNA involving single nucleotide either A, G, C or T. SNPs are by far the most common source of genetic variation. The use of SNPs in specific genes such as *LEP* gene and *LEPR* gene has resulted in the genetic association of these genes with increased risk of carcinogenesis in the oral region. Both *LEP* and *LEPR* play critical roles in mediating physiological responses and oncogenesis which may be of use as candidate biomarkers for oral cancer (Hung *et al.,* 2019).

There are some common polymorphic alleles which have been studied in oral cancer, but the role of the variants in the development and progression of oral cancer are still not well understood. Nonetheless, these polymorphisms have also been associated with the incidence of other types of cancer (Rodrigues *et al.,* 2015; Yang & Niu 2018; Rong *et al.,* 2019). Further studies about polymorphisms of *LEP* and *LEPR* genes in relation to oral cancer provide the opportunities to detect and intervene the progression of the disease in the earlier stage via screening and prevention. Hence, this study aims to provide an insight into the association of single nucleotide polymorphisms of *LEP* and *LEPR* genes with oral cancer, as well as its contribution in increasing the risk for oral cancer

development. This would benefit the medical practitioner in preventing the development of oral cancer at an early stage and provide greater attention.

Materials and Methods

Selection procedure

Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA-P) 2020 was used as the guideline for the selection procedure of related articles. Its objective is to enhance the quality of guidelines of systematic review, which is interchangeable to the effect gained by several reporting guidelines. Articles that were found during screening from all the databases were removed if duplications were found and the keywords were not included in the title of the articles. Only the articles that fulfilled the intended criteria were assessed and reviewed for eligibility and were chosen for this study.

Formulation of review question

This review question was constructed according to PICO formulation which exemplifies population of studies (P), intervention or exposure (I), comparison of intervention or exposure (C), and outcome of interest (O) (Methley *et al.,* 2014). It is usually accustomed to recognize key components that are used in systematic reviews for evidence-based medicine and is advocated by the Cochrane Collaboration in the *Cochrane handbook for Systematic Reviews of Intervention.* Therefore, the formulated question for this systematic review was "What is the association of polymorphism of leptin and leptin receptor genes with oral cancer?"

Search strategy

A comprehensive electronic search was performed using the following databases: Scopus, ScienceDirect, Web of Science, PubMed, Google Scholar and Dimensions. The databases were chosen due to their reliability in healthcare and medical-related issues. Throughout the search, the following key terms were used: ("leptin" OR "leptin receptor") AND ("oral cancer" OR "oral squamous cell carcinoma") AND ("single nucleotide polymorphism" OR "polymorphism"). The Boolean words such as "AND" and "OR" were applied to improve the specificity of search articles. Identical search strategies were applied in all databases. The data collection was done from January to September 2022 looking into articles published from 2000 to 2020.

Inclusion and exclusion criteria

The inclusion criteria of the articles selected included articles published in English, the type of articles were research and some related review articles published from the year of 2000 to 2020. This was implemented to gain access to the maximum number of papers available on this topic. Any other criteria that were not included in the listed standards were excluded from the study. Book series, chapters in books, magazines, case studies and conference articles; both abstract and proceeding were also excluded.

Data extraction

The screening process (title, abstract and full text) was done independently by the authors. Any differences in opinion that arose were undertaken by the authors through discussion. The articles were selected for qualitative synthesis and were thoroughly read by the researcher to identify the key data. There was no risk assessment of bias done between the authors.

Results

A total of 2699 articles were retrieved from six different databases. Of those, 2499 articles were removed due to being published in a form other than research or related review articles. 183 duplicates were removed and a total of 17 full-text articles were assessed. 13 of the selected articles did not fulfil the inclusion criteria and thus, only four articles that fulfilled all the inclusion criteria were included in the systematic review. Figure one depicts the PRISMA diagram flow for this review.

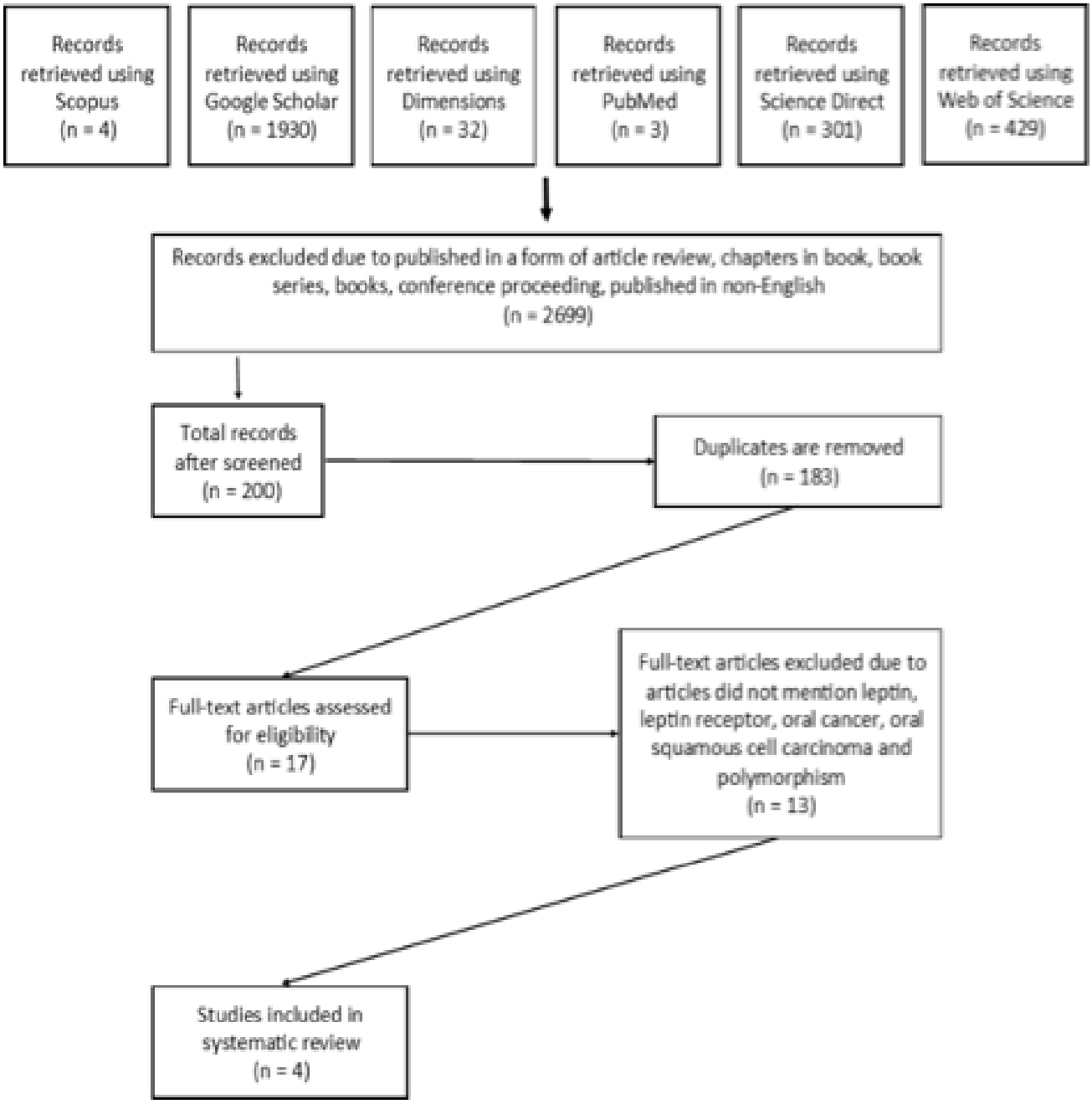

Figure 1. The PRISMA diagram.

All the included articles were based on case-control studies done in different populations and geographical areas (Table I). There were three polymorphisms mentioned by the articles, including *LEP* -2548 G/A, *LEPR* Gln223Arg (*LEPR* A688G) and *LEPR* K109R. Out of four articles, three of them studied *LEP* -2548 G/A polymorphism while two of them studied *LEPR* Gln223Arg polymorphism while one of the studies analysed *LEPR* K109R respectively. These findings correlate with the common polymorphisms found in other cancer types.

Table 1. Criteria of included studies.

Author	Study Design	Population	Total Sample Size	Polymorphisms Studied	Ref seq
Hung *et al.,* (2019)	Case-control study	Taiwanese	1127	*LEP -2548 G/A* *LEPR Q223R* *LEPR K109R*	rs7799039 rs1137101 rs1137100
Yapijakis *et al.,* (2009)	Case-control study	Greeks and Germans	302	*LEP -2548 G/A* *LEPR Q223R*	*NS*
Domingos *et al.,* (2014)	Case-control study	Brazilians	139	*LEPR Gln223Arg*	rs1137101
Hussain *et al.,* (2015)	Case-control study	Indians	534	*LEP -2548 G/A* *LEPR A688G (Q223R)*	*NS*

NS= Not stated

LEP -2548 G/A

Out of four articles, two articles showed association of polymorphism of *LEP* -2548 G/A with risk of oral cancer (Table II). An AA allele was proved to have low risk for OSCC, however it can develop to a poorer clinical stage of OSCC, if present. In comparison to AA allele, AG and GG allele possess higher risk for development of OSCC (Hung *et al.,* 2019). This finding was supported with evidence of association of AA allele with a risk for advanced stages of OSCC when looking into other criteria such as cancer stage and family history of either cancer or thrombophilia (Yapijakis *et al.,* 2009). A study showed an increase of AA and GA allele in oral cancer patients which correlates with escalating risk for oral cancer (Hussain *et al.,* 2015). Hussain *et al.,* (2015) also observed the frequency of mutant allele A to be significantly increased (p = 0.0002) in OSCC patients compared to control. However, study done by Hung *et al.,* (2019) observed no significant differences between AA, AG and GG alleles in oral cancer patients in comparison to the control group (Hung *et al.,* 2019).

LEPR Gln223Arg

Three out of four articles agree that there was an association of LEPR Gln223Arg with increased risk of oral cancer (Table III). GG genotype seems to be the common polymorphism found in OSCC which predisposes to higher risk of cancer while AA genotype was found in potentially malignant oral lesion (PMOL) (Domingos *et al.,* 2014). This was supported by a study that claimed there was an association of G allele with increased risk of development of oral cancer. In addition, this study also found that G allele was frequently observed in patients with early cancer stages (Yapijakis *et al.,* 2009). Another article stated that *LEPR* Gln223Arg polymorphism was associated with the risk of oral cancer relapse whereby this article found different evidence in which polymorphic variant GG is responsible for increasing the risk for oral cancer development (Hussain *et al.,* 2015). They observed higher frequency of G allele in OSCC patients in comparison to the controls ($p \leq 0.0001$) when analysing the leptin receptor A668G (Gln223Arg) gene polymorphism. In terms of genotypic frequency, a high increase of GG homozygous alleles ($p \leq 0.0001$) and a slight rise of AG heterozygous alleles ($p=0.007$) was observed in OSCC patients compared to the controls. However, Hung *et al.,* (2019) observed no association between all *LEPR* genotypes with risk for oral cancer in their study.

Table 2. Summary on studies of *LEP*-2548 G/A polymorphism.

Studies	Group	*LEP* genotype (*LEP -2548 G/A*)		
		GG (%)	GA (%)	AA (%)
Yapijakis *et al.,* (2009)	Control	21.7	65.1	13.2
	OSCC	22.3	52.0	26.7
	p value	-	*NS*	*NS*
Hussain *et al.,* (2015)	Control	49.5	40.3	10.0
	OSCC	33.3	50.3	16.3
	p value	-	*0.001**	*0.002**
Hung *et al.,* (2019)	Control	5.7	37.9	56.4
	OSCC	7.4	40.4	52.2
	p value	*0.574*	*0.274*	-

NS= not significant

LEPR K109R

Out of four articles, only one article mentioned *LEPR* K109R polymorphism which revealed no significant difference in the genotypic distribution between the control group and oral cancer patients (Hung *et al.,* 2019) (Table IV).

Discussion

This paper summarizes the findings whether the polymorphic variant of *LEP* and *LEPR* genes have an influence for oral cancer development by measuring the genetic constitution of healthy subjects as control in comparison to oral cancer patients.

LEP -2548 G/A (rs7799039) polymorphism takes place as a result of a G to A substitution at nucleotide -2548 in the promoter region of *LEP* gene. This polymorphism is related to increased LEP production and secretion, resulting in increased circulating LEP and over gene expression. The overall obtained data exhibits an association of *LEP* -2548 AA variant with a poorer clinical stage of oral cancer. This is approved by the fact that LEP functions in promoting growth and invasiveness of cancer (Yapijakis *et al.,* 2009). Besides, A allele shows abundant number in patients with advanced clinical stages of cancer in comparison to G allele or AG allele (Hung *et al.,* 2019). However, this does not indicate that *LEP* -2548 G/A increases the risk for oral cancer as the study showed no correlation between this polymorphism with the risk of oral cancer development (Yapijakis *et al.,* 2009).

Table 3. Summary on studies of *LEPR* Gln223Arg polymorphism.

Studies	**Group**	***LEPR* genotype (*LEPR* Gln223Arg)**		
		GG (%)	**GA (%)**	**AA (%)**
Domingos *et al.,* (2014)	Control	12.4	42.7	44.9
	OSCC	24.0	28.0	48.0
	p value		*0.011**	
Hung *et al.,* (2019)	Control	78.9	19.3	1.8
	OSCC	78.5	20.6	0.9
	p value	-	*0.607*	*0.945*
Yapijakis *et al.,* (2009)	Control	4.0	52.6	43.4
	OSCC	12.0	58.7	29.3
	p value	*0.0028**	*0.0497**	-
Hussain *et al.,* (2015)	Control	63.1	31.5	5.26
	OSCC	48.3	35.9	15.6
	p value	*<0.0001**	*0.007**	-

Table 4. Summary on studies of *LEPR* K109R polymorphism.

Studies	**Group**	***LEPR* genotype**		
		GG (%)	**GA (%)**	**AA (%)**
Hung *et al.,* (2019)	Control	70.7	26.6	2.7
	OSCC	72.0	25.9	2.1
	p value	-	*0.922*	*0.889*

The *LEPR* Gln223Arg (rs1137101) polymorphism or known as *LEPR* Q223R occurs due to non-conservative A to G substitution at codon 223 in exon six of *LEPR* gene (Domingos *et al.,* 2014). This variation of polymorphism decreases binding of LEP, consequently, impedes the LEP signaling. The results reveal an association of the G allele of this polymorphic variant with increased risk for oral cancer. In addition, the GG genotype was seen only in those early cancer stage patients, excluding the advanced cases (Yapijakis *et al.,* 2009). However, in comparison to G allele, A allele was significantly associated with PMOL (Domingos *et al.,* 2014). PMOL is a lesion with a potential to differentiate into malignant tumor. Another article found different evidence in which polymorphic variant GG is the one that is responsible in increasing the risk for oral cancer development (Hussain *et al.,* 2015).

The *LEPR* K109R (rs1137100) polymorphism is an A to G substitution in exon four. This polymorphic variant is not well studied yet, therefore limited sources are available to discuss in depth. According to Hung *et al.,* (2019), there was no correlation between all genotypes of *LEPR* K109R polymorphism with oral cancer risk. However, there was no available data to support the claim.

From the articles selected, two articles show association of polymorphism of *LEP* -2548 G/A with risk of oral cancer. Three out of four articles agree that there was an association of *LEPR* Gln223Arg with increased risk of oral cancer. Out of four articles, only one article mentioned *LEPR* K109R polymorphism which revealed no association with oral cancer.

Conclusion

Single nucleotide polymorphism of *LEP* and *LEPR* genes specifically *LEP* -2548 G/A and *LEPR* Gln223Arg may increase the risk of development of oral cancer. However, there is very limited data to support the findings from this review. The association of polymorphism in *LEP* gene and its receptor is more significant when other criteria were analyzed such as stages of cancer, family history of cancer or having tobacco. Additionally, the source of population as well as demographic factors might also affect the outcome of the analysis. Hence, additional research and investigations are needed to explore and understand the mechanism of *LEP* and *LEPR* genes in the development and progression of oral cancer, although these polymorphisms may be used as a genetic marker for susceptibility and to monitor the progress of cancer progression in the oral cavity,

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Conflict of Interest

None.

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