# VAST OPPORTUNITY TO STUDY MICRORNA (miRNA) IN HEAD AND NECK CANCER AMONG MALAYSIAN POPULATION

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**ABSTRACT**

Head and neck cancer (HNC) is among the common cancer in Malaysia. Depending on the location of the cancer in head and neck region, each type of HNC has its own characteristics and prevalence to specific gender and ethnicity. The remote and inaccessible location of the cancer also cause the difficulty to detect the cancer. This make the cancer usually diagnosed at late stage and make the treatment very challenges and ended with low survival rate of post-treatment among HNC patients. In fact, the detection of HNC at early stage could promise high successful recovery rate. This situation demand lots of studies to explore the carcinogenesis of HNC and searching for robust diagnostic, prognostic and therapeutic biomarkers. MicroRNA (miRNA) is a class of non-coding RNA that regulate cellular physiology at post-transcriptional level. miRNAs expression has been found to deregulate in various disease state, including cancer. A few studies revealed that miRNAs can behave as oncogenic and tumour suppressor in HNC. Even HNC is common in Malaysia, the studies of miRNA in HNC are still scarce. In this review article, we highlight the studies of miRNA in HNC that have been published by Malaysian researchers with aim to call more Malaysian researchers to focus on miRNA researches in HNC.

**KEYWORDS:** head and neck cancer, microRNA, Malaysia

## INTRODUCTION

### Head And Neck Cancer In Malaysia

Head and neck region, especially oral cavity, lips, nose and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, salivary and thyroid glands, is an area with high susceptibility to be affected with cancers such as squamous cell carcinoma (Yeow et al. 2010; Stenson 2016). Head and neck cancer (HNC) is a group of cancers with multitude histological appearance (Lee et al. 2011) and its geographical distribution is depending on the risk habits practiced in a population (Menvielle et al. 2004). It is the sixth most common malignancy in the world with the expectation of 500,000 new cases per year (Fanucchi et al. 2006; Bonomi et al. 2014). In Malaysia, 2,884 cases of HNC have been reported in which 34% were of nasopharyngeal carcinoma. This has made HNC among the most common cancers in Malaysia in 2006 together with breast (3,525 cases), colorectal (2,866 cases) and lung (2,048 cases) cancer (Yeow et al. 2010). The recent Malaysian National Cancer Registry Report 2007 – 2011 revealed that, HNC, represented by nasopharyngeal carcinoma, was among the top 5 cancers that commonly reported in Malaysia (Azizah Ab. et al. 2015). The distribution of HNC in Malaysia depends on ethnicity. Laryngeal, oral and pharyngeal cancers were common in Indians while nasopharyngeal cancer was common in Chinese (Nurul-Syakima et al. 2011). Malaysian men have 1.2 times higher chance of getting HNC as compared to Malaysian women. Nasopharyngeal, laryngeal and pharyngeal cancers were the most common HNC affecting Malaysian men (Yeow et al. 2010) (Table 1).

**Table 1** Number of cases and male:female ratio of HNC in Malaysia in 2006 (Yeow et al. 2010).

| Cancers | Number of cases | Male:female ratio |
|---|---|---|
| Nasopharyngeal | 981 | 3.2:1 |
| Thyroid | 891 | 0.3:1 |
| Oral | 428 | 0.8:1 |
| Laryngeal | 216 | 5.5:1 |
| Salivary gland | 142 | 0.8:1 |
| Laryngeal | 113 | 2.2:1 |
| Sinonasal | 113 | 1.6:1 |

Delayed diagnosis was among the challenges in having effective treatment and improving 5-years survival rate of HNC patients (Kowalski and Carvalho 2001). Generally, HNC has a survival rate of less than 50% with even lower than that for those who are diagnosed with regional or distant tumour (Altekruse et al. 2010; Jemal et al. 2011). Nasopharyngeal carcinoma HNC that is not easily visible and palpable on clinical examination as compared to other HNC. However, lower education level of the patients was among the factors in Malaysia that contributed to the delayed diagnosis of HNC even though for some easily examined HNC. Overall, more than 90% of HNC in Malaysia were detected at a late stage (Prasad and Pua 2000; Lee et al. 2011).

Several common risk factors have been identified in previous studies that have association with HNC in Malaysia. Cigarette smoking was presented in Malaysian patients of HNC and was contributed to the increased risk of HNC (Armstrong et al. 2000; Cheong et al. 2009; Razak et al. 2009; Karen-Ng et al. 2011). Some viral infections such as Epstein-Barr virus for nasopharyngeal carcinoma (Wong et al. 2005) and human papillomavirus for oropharyngeal squamous cell carcinoma (Saini et al. 2011; Wong et al. 2014; Bruni et al. 2017) were found to have association with HNC. Other environmental factors such as betel nut chewing (Gupta and Warnakulasuriya 2002; Cheong et al. 2009), occupational exposure (Armstrong et al. 2000) and diet, such as salted food including fishes, vegetables, eggs and roots, and alcoholic drinks (Armstrong et al. 1998) also have been found to correlate with HNC.

**MicroRNA**

MicroRNA (miRNA) is an evolutionary conserved short non-coding RNA with the length between 18 – 25 nucleotides (Bartel 2004; Friedman et al. 2009; Kim et al. 2009). It was first discovered in *Caenorhabditis elegans* by Victor Ambros' laboratory in 1993 as small temporal RNA that involved in the regulation of *C. elegans* developmental transitions (Lee et al. 1993; Pasquinelli and Ruvkun 2002). The miRNA acts at post-transcriptional level by perfect or nearly perfect binding to complementary sequences at 3' untranslated region (UTR) of target mRNA and eventually degrade or attenuate the translational process (He and Hannon 2004; Fabian et al. 2010). One miRNA acts on several different mRNA. It is estimated that at least one miRNA can act on more than 60% mammalian mRNAs (Friedman et al. 2009). MiRNAs regulate many cellular functions such as cell growth, proliferation, differentiation and apoptosis (Schickel et al. 2008). Since their expression are dependent on cellular behavior and correct body development and functions, changes in cellular environment and function, such as in disease state, will change the miRNA profile and makes miRNA a candidate to be be analyzed for the prediction of disease occurrence (Hernando 2007; Perera and Ray 2007; Ortega et al. 2010).

**MiRNA biogenesis**

MiRNAs are transcribed in the nucleus by RNA polymerase II either from their own genes or introns of protein-coding genes as long precursors of RNA that contains a local hairpin structure (Krol et al. 2010). However, miRNAs which lie within repetitive elements in the genome will be transcribed by RNA polymerase III (Borchert et al. 2006). This long precursor miRNA is known as primary miRNA (pri-miRNA), which is about 500-3000 bases long.

Excision of miRNA is done by RNase III enzyme Drosha, an endonuclease that resides within the nucleus and consists of two domains which are dsRNA binding domain and amino-terminal segment. Drosha will turn the pri-miRNA into shorter precursor miRNA (pre-miRNA), which is about 70 bases long with hairpin structure (Lee at al. 2003). The efficiency of Drosha activity depends on the terminal loop size, the stem structure and the flanking sequence of the Drosha cleavage site. The shortening of terminal loop, disruption of complementarity within the stem and removal or mutation of sequences that flank the Drosha cleavage site will significantly decrease the Drosha processing of pri-miRNA (Lee at al. 2003; Zeng and Cullen 2003).

Pre-miRNA will then be transported out of the nucleus by Ran-G7p and a receptor, Exportin-5, into the cytoplasm. In the cytoplasm, pre-miRNA will be cleaved by RNase III enzyme Dicer into small, imperfect double-stranded RNA duplex (miRNA:miRNA*) that contains 21 to 25 nucleotides mature strand and its complementary strand (miRNA*) (Hutvagner et al. 2001; Grishok et al. 2001; Ketting et al. 2001). Dicer contains a putative helicase domain, a DUF283 domain, a PAZ (Piwi-Argonaute-Zwilli) domain, two tandem RNase-III domains and a dsRNA binding domain (Bernstein et al. 2001). The efficient Dicer cleavage requires the presence of the overhang and a minimal stem length (Carmell and Hannon 2004).

Mature miRNA from miRNA:miRNA* duplex will be then selectively incorporated into RNA-induced silencing complex (RISC) for target recognition while the miRNA* will be degraded upon its exclusion from RISC due to its lower recovery rate by ~100-fold compared to miRNA (Schwarz et al. 2003; Khvorova et al. 2003). However, in some cases, both strands are thought to be functional in the regulation of mRNA translation (Hu et al. 2009). RISC contains a member of Argonaute protein family, a core component of the complex which tightly binds the RNA in the complex (Hammond et al. 2001; Hutvágner and Zamore 2002; Martinez et al. 2002; Mourelatos et al. 2002). Argonaute and its homologs are approximately 100 kDa proteins which also called as PPD proteins because they share PAZ and PIWI domains (Cerutti et al. 2000). Previous genetic data demonstrated that they are crucial in RNA interference and analogous processes (Tabara et al. 1999; Catalanotto et al. 2000; Fagard et al. 2000). As part of RISC, miRNA will bind to its target mRNA and induce the repression, deadenylation or degradation of the mRNA which eventually inhibit the protein translation (Krol et al. 2010).

**Extracellular miRNAs**

Instead of within the cell, miRNAs can be found extracellularly including in various body fluids (Weber et al. 2010; Wang et al. 2010; Zubakaov et al. 2010). While most RNAs are not stable to exist in

extracellular environment, miRNAs have been found to be surprisingly stable in this environment (Mitchell et al. 2008). Besides that, their expression profiles are distinguishable among different fluids and health status (Reid et al. 2010). The presence of miRNAs in serum and other body fluids which are known to contain ribonucleases tells that miRNAs are being packaged by lipid vesicles, binding protein or both to protect them from being digested by RNases (Valadi et al. 2007; Gibbings et al. 2009). Furthermore, a few recent studies have found nucleophosmin, argonaute 2 and HDL as alternative transport mechanisms of miRNAs in the circulatory system which give more precious information in the discovery of circulating miRNAs function (Wang et al. 2010; Arroyo et al. 2011; Vickers et al. 2011). While the origin and function of extracellular miRNAs are still poorly understood, some researchers suggest that they are used in cell-cell communication, where some miRNAs are intentionally produced to be exported out of cell, being recognized, taken up and used by other cells (Wang et al. 2010; Iguchi et al. 2010).

## miRNAS IN HEAD AND NECK CANCER

Internationally, several studies have been done to discover the signature of miRNAs in HNC using *in vivo* (Hou et al. 2015; Koshizuka et al. 2017), *in vitro* (Fukumoto et al. 2016; Yata et al. 2015) and *in silico* (Wong et al. 2016; Yan et al. 2016) approaches. The roles and functions of miRNAs as carcinogenic and tumour-suppressive in HNC have been demonstrated and compiled in many review articles (John et al. 2013; Courthod et al. 2014; Sethi et al. 2014: Khawar et al. 2017). The role of miRNAs in desensitizing HNC cells towards treatment also have been illustrated in some studies (Summerer et al. 2013; de Jong et al. 2015).

Several researchers were very committed to understand the behaviour of miRNAs in HNC and to find out the potential miRNAs to be the biomarkers for HNC through a few consecutive studies. Studies by Severino et al. (2013a and 2013b) have been extensively conducted using *in vivo* and *in vitro* approaches with different advanced technologies to gain mechanistic understanding that underlies the carcinogenesis of HNC. Meanwhile, an initial study by Summerer et al. (2013) has found miR-106b-5p, miR-21-5p, miR-425-5p and miR-93-5p were therapeutic-responsive and tumour-specific for head and neck cancer. The study was furthered to investigate the circulating miRNAs as prognostic biomarkers HNC in an independent validation cohort and found that circulating miR-142-3p, miR-186-5p, miR-195-5p, miR-374b-5p and miR-574-3p were promising prognostic and therapy monitoring biomarkers for HNC (Summerer et al. 2015a). In order to gain better understanding on biological network and processes involve in HNC, Summerer et al. (2015b) performed an integrative miRNA and mRNA analysis and they found the heterogeneity characteristic in HNC. Furthermore, Summerer et al. (2015b) have found miRNAs that targeted HNC-associated mRNA that have been suggested in the study by Summerer et al. (2013), indirectly supported the potential of these miRNAs to be the promising therapeutic-responsive biomarker for HNC.

Another dedicated group of researchers has extensively studied the miRNA-associated carcinogenesis in HNC and the roles of certain miRNAs in various pathways (Kikkawa et al. 2010; Nohata et al. 2011; Kinoshita et al. 2012; Kinoshita et al. 2013; Fukumoto et al. 2015). They found the role of miR-489, miR-874, miR-218, miR-29a/b/c and miR-26a/b as tumour-suppressor that regulated *PTPN11*, *PPP1CA*, laminin-332, *LAMC2* and *ITGA6*, and *TMEM184B*, respectively. Then, Fukumoto et al. (2016) further studied the possible targets of tumour-suppressive miRNAs that they found in their previous studies which were miR-26a/b, miR-29a/b/c and miR-218, and found these miRNAs were concertedly suppressed *LOXL2* which involved in HNC metastasis.

## PUBLISHED miRNA STUDIES IN HEAD AND NECK CANCER IN MALAYSIA

### Human studies

The first published human miRNA study in HNC that used Malaysian population was done by Nurul-Syakima et al. (2011). This study has found 10 miRNAs that were differentially expressed in HNC tissues (buccal, supraglottic, nasopharynx, retromolar, external ear and nasal cavity) as compared to normal tissues. Among these miRNAs, the dysregulation of miR-181 family (Kozaki et al. 2008; Wong et al. 2008; Cervigne at al. 2009) and hsa-miR-95 (Kozaki et al. 2008) were consistent with previous studies while the dysregulation of hsa-miR-

101 (Li et al. 2015; Liu et al. 2015), hsa-miR-141 (Wang et al. 2015) and hsa-miR-744 (Fang et al. 2015; Li et al. 2016) were consistent with later studies, that used non-Malaysian population. This indicate the bio-similarity of these miRNAs' regulation across the population. However, the dysregulation of hsa-miR-141 in study by Liu et al. (2016) and hsa-miR-744 in study by Vojtechova et al. (2016) were contradict with the study by Nurul-Syakima et al. (2011). Conserved and various expression of miRNAs across the population has been described in previous studies (Huang et al. 2011; Dluzen et al. 2016) and review (Li and Zhang 2013). Thus, the consistency of miRNA expression in all studies pertaining to HNC need to be considered, especially in selecting the candidate of miRNAs for biomarker that will be applied in worldwide population. In fact, even though the study by Nurul-Syakima et al. (2011) found similar expression of hsa-miR-744 in the study by Fang et al. (2015) and Li et al. (2016) who used nasopharyngeal carcinoma and laryngeal carcinoma patients, respectively, but a study by Vojtechova et al. (2016) found the contradict result in tonsillar tumour patients. This could underestimate the risk of certain type of HNC. Therefore, the miRNAs that could behave consistently in all types of HNC would be better biomarkers in HNC, especially for diagnostic purpose.

The next human study on miRNA in HNC was furthered by Nurul-Syakima et al. (2014) where they investigated the localization of hsa-miR-205 in head and neck tissue with various conditions using *in situ* hybridization technique. However, the study used commercialized human head and neck tissue array which originated from non-Malaysian populations. The tissue array consisted of inflammatory, benign and malignant of neck, oronasopharynx, larynx and salivary glands tissues. The study showed a significantly high staining intensity of hsa-miR-205 in cytoplasmic region of most head and neck tissues and in certain nuclear region of certain tissues, indirectly confirmed the result of previous studies which found the high expression of hsa-miR-205 in HNC tissues (Tran et al. 2007; Kimura et al. 2010). They also found that hsa-miR-205 was not exclusively expressed in squamous cell carcinoma tissues as what has been claimed by Fletcher et al. (2008) but it also expressed in other type of malignancy such as rhabdomyosarcoma, chondrosarcoma and metastatic adenocarcinoma.

**Cell culture studies**

Mutalib et al. (2012) have furthered the study by Nurul-Syakima et al. (2011) to observe the potential of miR-181a as a therapeutic agent for hypopharyngeal carcinoma using commercial HTB-43 cell line. The study has successfully demonstrated the role of miR-181a in restoring the normal function of some cellular pathways upon miR-181a inhibition such as p53/DNA damage, TGFβ, MAPK/ERK, MAPK/JNK, Wnt and NFkB pathways. This initiative was further continued by Cheah et al. (2014) to investigate miR-181a role specifically in one of the cancer-associated pathway that has been revealed by Mutalib et al. (2012), which is p53 pathway. They found that the inhibition of miR-181a expression in HTB-43 cell line up-regulated the expression of *TP53* gene and level of p53 protein, indicating the role of miR-181a as an oncogenic miRNA in hypopharyngeal carcinoma. Indirectly, this study validated the results obtained in the studies by Nurul-Syakima et al. (2011) and Mutalib et al. (2012).

The correlation of growth factors and cytokines with nasopharyngeal carcinoma (NPC) has been described by Xu et al. (1999) and Lin et al. (2000). A study conducted by Lee et al. (2013) has found the effects of transforming growth factor-beta one (TGF-β1) and interleukin-6 (IL-6) cytokine on miRNA expression in NPC cell line, TW01 that has been infected and uninfected with *LMP1* gene of Epstein-Barr virus. Intriguingly, they found that 97% of the 88 studied miRNAs were up-regulated in LMP1-positive NPC cell line including miR-181 family, where the same finding was observed by Nurul-Syakima et al. (2011) and Mutalib et al. (2012). This study was further continued by Tan et al. (2014) where they focused on deregulation of miR-372, which has been found to be down-regulated in a study by Lee et al. (2013). The functions of miR-372 in NPC was not reported in any other studies yet. They found that the up-regulation of miR-372 in NPC cells caused cell cycle arrest, probably due to down-regulation of *CDK2* and *CCNA1* genes, and up-regulation of *CDKN1A* and *INCA1* genes. This finding indicated the function of miR-372 as tumour suppressor.

## CONCLUSION

The study on miRNA in HNC in Malaysia is still lacking. While some epidemiological data found an alarming result in NPC in Malaysia during 1996 until 1998 (Devi et al. 2004) and 2003 until 2005 (Lim et al. 2008), study on NPC from miRNA perspective is very scarce. The published studies mostly focus on mechanism of miRNA that contribute to HNC development. No initiative to evaluate the potential of miRNA as biomarker for diagnostic, prognostic and therapeutic purposes. Additionally, increasing evidences have shown the potential of extracellular miRNAs such as circulating (Summerer et al. 2015; Hou et al. 2015) and salivary miRNAs (Park et al. 2009; Salazar et al. 2014) as biomarkers for HNC. However, no study on extracellular miRNAs was conducted using Malaysian population yet. Even though much studies have been done to evaluate the potential of miRNA as biomarker for HNC, validation study across populations is worth to perform in considering the biological differences in various populations. Therefore, much efforts need to be worked out in order to understand and cope with the occurrence of HNC in Malaysia, particularly from miRNA perspective.

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