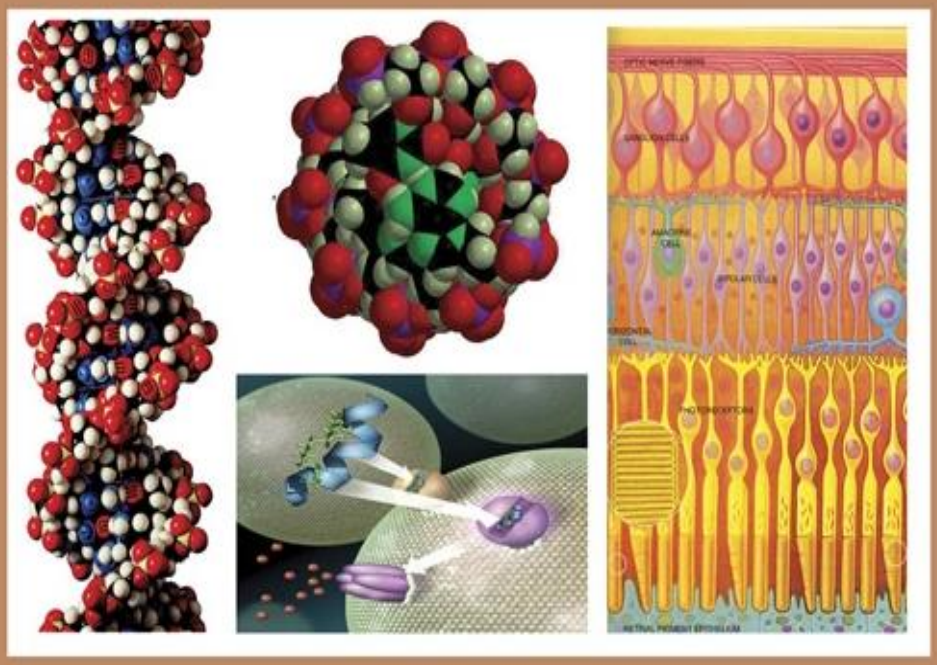
EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

PHYSIOLOGY & MOLECULARBIOLOGY

C



ISSN
2090-0767

WWW.EAJBS.EG.NET

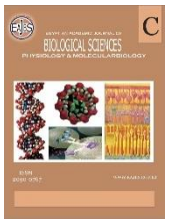
Vol. 14 No. 2 (2022)

.

Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 14(2) pp175-183 (2022)*
DOI: 10.21608/EAJBSC.2022.263033

Egypt. Acad. J. Biolog. Sci., 14(2):175-183(2022)

Egyptian Academic Journal of Biological Sciences
C. Physiology & Molecular Biology
ISSN 2090-0767
www.eajbsc.journals.ekb.eg



The Frequency of Cancer Susceptibility pri-miR-26a-1 rs7372209 Single Nucleotide Polymorphism in Saudi and other Ethnic Groups

Abdulmajeed A.A. Sindi
Department of Basic Medical Science, Faculty of Applied Medical Sciences, Albaha University, Albaha 65779, Saudi Arabia
*E. Mail: asindi@bu.edu.sa

ARTICLE INFO
Article History
Received:2/8/2022
Accepted:1/10/2022
Available:3/10/2022

Keywords:
Cancer; Micro RNAs; pri-miR-26a-1 rs7372209; Saudi population; Single nucleotide polymorphism (SNP).

ABSTRACT

MicroRNAs (miRNAs) are single-stranded non-coding RNA sequences with about 22 nucleotides that regulate gene expression post-transcriptionally. miRNAs play a crucial role as gene regulators; nevertheless, they also have an influence on the etiology of many disorders, including cancer. Both population-based and functional studies have investigated the function of miRNAs in the onset and progression of cancer. However, research on the impact of miRNA polymorphisms on human cancer susceptibility to initiation, development, and prognosis is still growing. The pri-miR-26a-1 may have an impact on miR-26, which has been hypothesized to have a tumor-suppressive function in the genesis of cancer. Early study has shown cancer risk associated with the pri-miR-26a-1 rs7372209 C >T polymorphism in molecular epidemiology research. The data regarding the impact of pri-miR-26a-1 rs7372209 C >T polymorphism on cancer risk among the Saudi population lacks. The present study sought to determine the allelic frequency and distribution of the pri-miR-26a-1 rs7372209 C >T polymorphism in the Saudi Arabian population and to compare it to populations from other parts of the world. Data from epidemiological studies conducted in various ethnic groups were extracted using PUBMED (Medline) and other similar web databases. An estimated 12.25 percent of the Saudi population harbors the pri-miR-26a-1 rs7372209 variant allele (T). When the Saudi prevalence is compared to that of other populations, it is observed that China, the USA, and South Africa (black ancestry) have significantly different frequencies ($p<.0001$). Only one South African report with participants of mixed ancestry from the Western Cape and a population with significant ancestral components from the indigenous Khoisan, Bantu-speaking Africans, Europeans, and Asians revealed comparable pri-miR-26a-1 rs7372209 frequency ($p=0.34$). Clearly, the pri-miR-26a-1 rs7372209 polymorphism variant allele has a very unique pattern in the Saudi Arabian population, which may be a result of racial differences. The findings could assist in the risk assessment of people carrying pri-miR-26a-1 rs7372209 TT mutant predisposed to develop different types of cancers in the Saudi population.

INTRODUCTION

Cancer is the top cause of mortality globally (Siegel *et al.,* 2019). Around 14.1 million individuals worldwide were diagnosed with cancer in 2012, and 8.2 million people died from it (Torre *et al.,* 2015). New instances of cancer and fatalities from cancer rose sharply in 2018 to 18.1 and 9.6 million, respectively (Khazaei *et al.,* 2019).

As mortality and incidence rise globally, cancer is currently regarded as the leading cause of death (Chen *et al.,* 2016). Many different forms of therapies, including surgery, radiation, chemotherapy, and others, have been used to treat this illness. But there are negative side effects to every medication. Dysfunctions brought on by tissue and organ damage drastically lower quality of life. Additionally, cancer care and treatment place a significant financial and emotional strain. In recent decades, a number of studies have been carried out to investigate the pathophysiology and etiology of cancer formation. However, little is known about the disease's underlying mechanism or susceptibility. Cancer is linked to environmental factors, bad lifestyle choices, viral infections, and chronic inflammation.

Genetic heterogeneity across human populations affects susceptibility to human malignancies, according to genetic epidemiology research. To identify the key genes and translate these findings into biological mechanistic explanations, a number of challenges must be addressed (Burgner *et al.,* 2006; Haralambous *et al.,* 2003). Cancer formation and irregularities in cell proliferation are brought on by the improper expression of associated genes in a cell. The microRNA family includes tiny non-coding RNA molecules that are double-stranded and have a length of 21–25 nucleotides (Ambros 2004; Lee *et al.,* 1993). These molecules develop from primordial transcripts (pri-miRNAs) through a continual maturation process. When microRNA (miRNA) binds to target gene mRNAs with imperfect complementary sequences in the 3′-UTR (3-UTR), it can control the posttranscriptional suppression of those genes (Bartel 2004). According to a number of research (Knirsh *et al.,* 2016; Wang *et al.,* 2018), the abnormally produced microRNA can function as a proto-oncogene as well as an anti-oncogene via different cellular signaling pathways. A novel microRNA called MiRNA-26a prevents the proliferation, invasion, and metastasis of cancer cells during the cell cycle, which suppresses the growth of tumors (Chen *et al.,* 2017; Zhang *et al.,* 2016).

When compared to normal tissues, cancer cells exhibit considerably lower levels of miRNA-26a expression, and these levels are highly correlated with tumor size, pathologic differentiation, clinical stage, and prognosis as a whole (Cho *et al.,* 2017; Qiu *et al.,* 2017). Numerous biosynthetic pathways can change the function of miRNA or pri-miRNA due to gene mutation. One of the most frequent types of gene mutations is single nucleotide polymorphism (SNP), and SNPs in pri-miRNA genes have the ability to alter the spatial structure, alter the miRNA-mRNA interaction network, trigger the aberrant expression of target genes, and raise the risk of cancer. rs7372209 C >T is the most frequent locus for pri-miR-26a-1 that has garnered significant attention.

Numerous epidemiological studies have been conducted to investigate the connection between the pri-miR-26a-1 rs7372209 C >T polymorphism and the chance of developing cancer. Despite being situated in a crucial genomic area for cancer risk, the presence and effects of the pri-miR-26a-1 rs7372209 C >T polymorphism in the Saudi population have not yet been fully understood. The purpose of this study was to determine the frequency of genetic variations in pri-miR-26a-1 rs7372209 C>T linked to cancer susceptibility. In the current study, the frequency distribution of the pri-miR-26a-1 rs7372209 C>T polymorphism among Saudi Arabians in normal health was compared to that of several epidemiologic investigations carried out all over the world.

MATERIALS AND METHODS

Search Criteria:

The databases of PUBMED (Medline), Web of Science, and EGEMS were searched for papers containing the keywords "pri-miR-26a-1," "rs7372209 C >T," and "polymorphism." The searches covered all studies with human subjects, regardless of language. Studies reporting genotype frequencies for the control

population were accepted, whereas studies reporting just allele frequencies and no genotype frequencies were omitted. The initial author's name, the year the study was published, the nation of the subjects, the number of controls, the research design, the inclusion/exclusion standards, and the subjects' frequencies of alleles and genotypes were all abstracted for each study that satisfied the requirements. Data for the Saudi population were taken from the most recent report. In the current research, the prevalence of the pri-miR-26a-1 rs7372209 C >T polymorphism was extracted from 48 studies and compared to the Saudi Arabian population (Al-Qahtani *et al.*, 2017) (Table 1).

Table 1. Studies included in the pri-miR-26a-1 rs7372209 gene variant analysis in different populations

S. No.	Author	Year	Country	Ethnicity	Total number of subjects	Reference
1.	Yang	2017	China	Asian	196	(Yang *et al.*, 2008)
2.	Ying	2016	China	Asian	1079	(Ying *et al.*, 2016)
3.	Yin	2016	China	Asian	266	(Yin *et al.*, 2016)
4.	Xiao	2014	China	Asian	1279	(Xiong *et al.*, 2014)
5.	Li	2014	China	Asian	672	(Li 2014)
6.	Zhang	2014	China	Asian	1275	(Zhang *et al.*, 2014)
7.	Xiong	2014	China	Asian	417	(Xiong *et al.*, 2014)
8.	Wei	2013	China	Asian	380	(Wei *et al.*, 2013)
9.	Wang-a	2013	South Africa	Black Ancestory	578	(Wang *et al.*, 2013)
10.	Wang-b	2013	South Africa	Mixed Ancestry	420	(Wang *et al.*, 2013)
11.	Ye	2008	USA	Caucasian	346	(Ye *et al.*, 2008)
12.	Yang	2008	USA	Caucasian	728	(Yang *et al.*, 2008)

Statistical Analysis:

The Pearson's χ^2 test was performed to compare the genotype and allelic frequencies of diverse populations using the statistical program SPSS (version 21). Court-Lab was used to explore the Hardy-Weinberg equilibrium, and 0.05 was determined to be the statistically significant p value.

RESULTS

According to the genotype distribution, which was consistent with Hardy-Weinberg equilibrium (HWE), the minor allele frequency (MAF) of the pri-miR-26a-1 rs7372209 C>T polymorphism in the Saudi Arabian population was 12.25 percent (Table 2). The genotypic (CC, CT, and TT) and allelic frequency distributions of the examined polymorphism among distinct populations revealed different minor allele frequencies (Table 3). A significantly different MAF was identified for the ethnicities of China, the USA, and South Africa (Black ancestry) when the pri-miR-26a-1 rs7372209 frequency found in Saudi Arabia was compared to that of other populations ($p < 0.0001$).

Table 2. Observed and expected genotypic frequencies of pri-miR-26a-1 rs7372209 polymorphism in the control group

Study	Genotype observed (n)			Genotype Expected (n)			MAF	p-value (HWE)
	CC	CT	TT	CC	CT	TT		
Al Qahtani *et al,* 2017	309	84	7	308	86	6	0.1225	0.64

Table 3. pri-miR-26a-1 rs7372209 gene variant genotype and allele frequency distribution in different populations and p-values in contrast to Saudi Arabian population

	Genotype distribution of pri-miR-26a-1 rs7372209													
	Study	**Year**	**Source of subjects**	**Disease/ Cancer type**	CC	CT	TT	**Allele C**	**Allele T**	**Total Alleles**	**T allele frequency**	**C Allele frequency**	**p value**	**MAF**
1	Al Qahtani	2017	HB	HCC	309	84	7	702	98	800	0.123	0.8775	Ref	12.25
2	Yang	2017	HB	OSCC	90	80	26	260	132	392	0.337	0.663265306	<.0001 *	33.67
3	Ying	2016	PB	CRC	582	432	65	1596	562	2158	0.260	0.739573679	<.0001 *	26.04
4	Yin	2016	HB	LC	125	129	12	379	153	532	0.288	0.712406015	<.0001 *	28.76
5	Xiao	2014	PB	ESCC	630	540	109	1800	758	2558	0.296	0.703674746	<.0001 *	29.63
6	Li	2014	HB	LC	293	315	64	901	443	1344	0.330	0.670386905	<.0001 *	32.96
7	Zhang	2014	PB	ESCC	628	538	109	1794	756	2550	0.296	0.703529412	<.0001 *	29.65
8	Xiong	2014	HB	Cervical cancer	221	167	29	609	225	834	0.270	0.730215827	<.0001 *	26.98
9	Wei	2013	HB	ESCC	178	178	24	534	226	760	0.297	0.702631579	<.0001 *	29.74
10	Wang-a	2013	PB	ESCC	546	32	0	1124	32	1156	0.028	0.972318339	<.0001 *	2.77
11	Wang-b	2013	PB	ESCC	307	110	3	724	116	840	0.138	0.861904762	0.348202	13.81
12	Ye	2008	HB	Esophageal cancer	179	140	27	498	194	692	0.280	0.719653179	<.0001 *	28.03
13	Yang	2008	PB	Bladder cancer	378	288	62	1044	412	1456	0.283	0.717032967	<.0001 *	28.30

HCC, Hepatcellular Carcinoma; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; HB, hospital based; LC, lung cancer; OSCC, oral squamous cell carcinoma; PB, population based.

DISCUSSION

The origin of cancer and its pathophysiology is yet unknown. However, growing evidence suggests that some miRNAs and miRNA genetic variations are linked to cancer risk. Generally speaking, the development of tumors is a complicated process that frequently includes a number of different proteins, components, and signal transduction networks. It's possible that changes in a single gene or locus have a significant impact on the complete signaling system in carcinogenesis.

MiRNAs are a subclass of non-coding short RNAs (ncsRNAs) that include 22–25 nucleotides and may bind to the 3'-UTRs of target genes to control the expression of those genes via the post-transcriptional pathway (Lagos-Quintana *et al.*, 2001). The miRNA sequences have shown significant conservation throughout evolution and are involved in a variety of physiological and pathological processes, such as cell division, proliferation, and apoptosis (Ambros 2003). The aberrant mutation of pri-miRNAs may alter their nucleotide sequence and spatial organization, interfering with the physiological functions of the cells and, as a result, promoting the growth and division of abnormal tumor cells (Chang *et al.*, 2018; He *et al.*, 2018; Zang *et al.*, 2017; Zhu *et al.*, 2017). The new short RNA Pri-miR-26a-1 inhibits the growth and spread of cancer by binding to Lin28B and Zcchc11 and acting as a tumor suppressor in tumorigenesis and cancer development (Fu *et al.*, 2014; Qian *et al.*, 2017). The rs7372209 C>T polymorphism is the most significant SNP site in the pri-miR-26a-1 gene and is highly connected with susceptibility to many types of malignancies. The pri-miR-26a-1 gene is found on human chromosome 3q21.3.

The characterization of exon miRNAs is intriguing because it reveals a potential method for posttranscriptional control of gene expression. The production of exon miRNAs may impair the stability of the associated protein-encoding transcripts and decrease protein synthesis (Colaiacovo *et al.*, 2012). Researchers have been interested in miRNAs because they are one of the most prevalent classes of gene regulatory molecules in multicellular animals and because they have the potential to influence the production of numerous protein-coding genes (Park and Shin 2014). Furthermore, several studies have shown that miRNAs were essential elements in the development of tumors (Farazi *et al.*, 2013). miRNA are linked to the onset and progression of cervical cancer, lung cancer, breast cancer, esophageal squamous cell carcinoma, ovarian cancer, and five other types of cancer. The modulation of the transcription of the main transcript,

primiRNA, and pre-miRNA processing and maturation, or miRNA messenger RNA interactions, might be used to show that single-nucleotide polymorphisms (SNPs) in miRNA genes have an effect on function (Ryan *et al.,* 2010). Numerous studies have already demonstrated how the common polymorphism rs7372209 in miR-26a-1 may influence cancer susceptibility.

The prevalence of the rs7372209 C >T polymorphism in bladder cancer patients indicated a lower susceptibility in the US (Yang *et al.,* 2008). The rs7372209 C>T polymorphism was then studied by Wei et al. (Wei *et al.,* 2013) and Zhang *et al.* (Zhang *et al.,* 2014) to determine its impact on Chinese individuals' susceptibility to developing esophageal cancer.

Li X.2014 looked into the relationship between the rs7372209 C>T polymorphism and the risk of developing lung cancer and discovered that those with the T allele of the rs7372209 C >T polymorphism had a higher risk of developing cancer (Li 2014). On the other hand, different case-control research carried out by Yin et al. examined the relationship between lung cancer and the rs7372209 C >T polymorphism. This investigation demonstrated that there was no discernible link between this variation and the risk of lung cancer (Yin et al., 2016). Case-control research on the relationship between the rs7372209 C>T polymorphism and the incidence of cervical cancer in southern Chinese women was carried out by Xiong et al (Xiong *et al.,* 2014).

The discrepancy among different reports may be attributed to the following factors: (1) the populations assessed were of different ethnicities; (2) different genotype methods may have an impact on results; (3) some studies may have shown deviation from HWE; and (4) the design and method of each study were different, reducing consistency. Moreover, cancers and other human illnesses have complex inheritance patterns. The start and course of the disease are the consequence of a complex interplay of genetic elements, including copy number variation, epistatic interactions, and modifier effects, as well as various environmental influences.

Due to the multitude of variables that may or may not exceed the liability threshold, it is challenging to determine whether a disease will manifest itself when there is discontinuous trait variation. Genome-wide association studies can identify common alleles that contribute to the hereditary component of prevalent multifactorial illnesses (GWAS). Since the effect sizes of the alleles found using this technique are often tiny, they cannot fully explain illness susceptibility. The difficulties of using GWAS to detect uncommon variants with low to medium penetrance may be the cause of this disparity. Penetration is measured by the proportion of a population that shares a certain allele and exhibits the corresponding phenotype. Contrary to multifactorial disorders, mendelian diseases have a high penetrance and a very low allele frequency. To better understand complex diseases, several methodologies have been developed. Genome-wide association studies (GWAS) identify the typical genetic factors causing the most serious complicated diseases.

However, there is still a lot to learn about the causes and characteristics of many complex diseases. The vast majority of illnesses are multifactorial, the result of a complex network of inherited and environmental variables that influence how the illness manifests itself throughout the course of a person's lifetime. A rising amount of evidence indicates that genetic diversity increases a person's risk of developing diseases including diabetes, cardiovascular disease, and cancer (Eccles and Tapper 2010; Hanahan and Weinberg 2000; Schmith *et al.,* 2003). The identification of genetic variation associated with common difficult diseases is thus a top goal in our knowledge of the pathophysiological processes underlying common human illnesses. Growing interest has been shown in the potential influence of common, functional germline

polymorphisms on illness risk, progression, and prognosis. Genomic differences within a population or species are referred to as genetic diversity (Nevo 1978). Given the complexity of the human genome, genetic diversity is understood to have a role in phenotypic variation (Kaneko and Furusawa 2006). Genetic diversity, or the variance in individual genes, is a strategy for population survival that enables adaptability to a changing environment. Genetic variability within and between populations has long been considered the key to understanding the biology of human illness (McKeigue 1997; Shriver 1997; Shriver *et al.*, 2005).

Genetic variations found in genes for miRNAs or genes for miRNA-binding sites are still being studied. New SNPs will be explained as research advances, and new findings about the effects of miRNA SNPs on viral illnesses will be provided. There is much more research looking into miRNA SNPs in Asian populations than in non-Asian ones. In order to better understand the vulnerability and course of illnesses in various ethnic/genetic backgrounds, it is crucial to research the frequencies of miRNA SNPs in global populations. Understanding the biological importance of such genetic variables would need the discovery of SNPs that affect the clinical outcome or susceptibility traits in various populations. However, other bottlenecks, including statistical and computational trials as well as the repeatability factor, must be resolved before new genetic biomarkers for use in gene-disease-association research may be found (Hirschhorn and Daly 2005).

Conclusion

The Saudi population's pri-miR-26a-1 rs7372209 C>T polymorphism variant allele differs significantly from that of many other groups throughout the world. The findings may help with population screening and evaluations of cancer susceptibility. Future large-scale studies examining gene-gene and gene-environment interactions are required to use this polymorphism as a biomarker.

Conflict of Interest:

The author declares no conflict of interest.

REFERENCES

Al-Qahtani A, Al-Anazi M, Nazir N, Wani K, Abdo A, Sanai F, Khan M, Al-Ashgar H, Albenmousa A, Al-hamoudi W. (2017). Association of single nucleotide polymorphisms in micro RNA s with susceptibility to hepatitis B virus infection and HBV-related liver complications: A study in a Saudi Arabian population. *Journal of viral hepatitis*, 24:1132-1142.

Ambros V. (2003). MicroRNA pathways in flies and worms: growth, death, fat, stress, and timing. *Cell*,113:673-676.

Ambros V. (2004). The functions of animal microRNAs. *Nature*, 431:350-355.

Bartel DP. (2004). MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*, 116:281-297.

Burgner D, Jamieson SE, Blackwell JM. (2006). Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? *The Lancet infectious diseases*, 6:653-663.

Chang RK, Li X, Mu N, Hrydziuszko O, Garcia-Majano B, Larsson C, Lui W-O. (2018). MicroRNA expression profiles in non-epithelial ovarian tumors. *International Journal of Oncology*, 52:55-66.

Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. (2016). Cancer statistics in China, 2015. *CA: a cancer journal for clinicians*, 66:115-132.

Chen X, Xiao W, Chen W, Liu X, Wu M, Bo Q, Luo Y, Ye S, Cao Y, Liu Y. (2017). MicroRNA-26a and-26b inhibit lens fibrosis and cataract by negatively regulating Jagged-1/Notch signaling pathway. *Cell Death & Differentiation*, 24:1431-1442.

Cho HJ, Kim SS, Nam JS, Kim JK, Lee JH, Kim B, Wang HJ, Kim BW, Lee J-

D, Kang DY. (2017). Low levels of circulating microRNA-26a/29a as poor prognostic markers in patients with hepatocellular carcinoma who underwent curative treatment. *Clinics and Research in Hepatology and Gastroenterology*, 41:181-189.

Colaiacovo M, Lamontanara A, Bernardo L, Alberici R, Crosatti C, Giusti L, Cattivelli L, Faccioli P. (2012). On the complexity of miRNA-mediated regulation in plants: novel insights into the genomic organization of plant miRNAs. *Biology direct*, 7:1-7.

Eccles D, Tapper W. (2010). The influence of common polymorphisms on breast cancer. *Cancer treatment and research*, 155:15-32.

Farazi TA, Hoell JI, Morozov P, Tuschl T. (2013). MicroRNAs in human cancer. *MicroRNA cancer regulation*,1-20.

Fu X, Meng Z, Liang W, Tian Y, Wang X, Han W, Lou G, Lou F, Yen Y, Yu H. (2014). miR-26a enhances miRNA biogenesis by targeting Lin28B and Zcchc11 to suppress tumor growth and metastasis. *Oncogene*, 33:4296-4306.

Hanahan D, Weinberg RA. (2000). The hallmarks of cancer. Cell 100:57-70.

Haralambous E, Weiss H, Radalowicz A, Hibberd M, Booy R, Levin M. (2003). Sibling familial risk ratio of meningococcal disease in UK Caucasians. *Epidemiology & Infection*, 130:413-418.

He Y, Deng F, Yang S, Wang D, Chen X, Zhong S, Zhao J, Tang J. (2018). Exosomal microRNA: a novel biomarker for breast cancer. *Biomarkers in medicine*, 12:177-188.

Hirschhorn JN, Daly MJ. (2005). Genome-wide association studies for common diseases and complex traits. *Nature Reviews Genetics*, 6:95-108.

Kaneko K, Furusawa C. (2006). An evolutionary relationship between genetic variation and phenotypic fluctuation. *Journal of theoretical biology*, 240:78-86.

Khazaei Z, Jarrahi AM, Momenabadi V, Ghorat F, Adineh H, Sohrabivafa M, Goodarzi E. (2019). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide stomach cancers and their relationship with the human development index (HDI). *Advances in Human Biology*, 9:245-250.

Knirsh R, Ben-Dror I, Modai S, Shomron N, Vardimon L. (2016). MicroRNA 10b promotes abnormal expression of the proto-oncogene c-Jun in metastatic breast cancer cells. *Oncotarget*, 7:59932.

Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. (2001). Identification of novel genes coding for small expressed RNAs. *Science*, 294:853-858.

Lee RC, Feinbaum RL, Ambros V. (1993). The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell*, 75:843-854.

Li X. (2014). Genetic variations in miRNAs with susceptibility and prognosis of lung adenocarcinoma. Dissertation]. 2014.. China Medical University.

McKeigue PM. (1997). Mapping genes underlying ethnic differences in disease risk by linkage disequilibrium in recently admixed populations. *American journal of human genetics*, 60:188-96.

Nevo E. (1978). Genetic variation in natural populations: patterns and theory. *Theoretical population biology*, 13:121-77.

Park JH, Shin C. (2014). MicroRNA-directed cleavage of targets: mechanism and experimental approaches. *BMB reports*, 47:417.

Qian H, Yang C, Yang Y. (2017).

MicroRNA-26a inhibits the growth and invasiveness of malignant melanoma and directly targets on MITF gene. *Cell death discovery*, 3:1-9.

Qiu X, Zhu H, Liu S, Tao G, Jin J, Chu H, Wang M, Tong N, Gong W, Zhao Q. (2017). Expression and prognostic value of microRNA-26a and microRNA-148a in gastric cancer. *Journal of gastroenterology and hepatology*, 32:819-827.

Ryan BM, Robles AI, Harris CC. (2010). Genetic variation in microRNA networks: the implications for cancer research. *Nature reviews cancer*, 10:389-402.

Schmith VD, Campbell DA, Sehgal S, Anderson WH, Burns DK, Middleton LT, Roses AD. (2003). Pharmacogenetics and disease genetics of complex diseases. *Cellular and molecular life sciences*, CMLS 60:1636-46.

Shriver MD. (1997). Ethnic variation as a key to the biology of human disease. *Annals of internal medicine*, 127:401-3.

Shriver MD, Mei R, Parra EJ, Sonpar V, Halder I, Tishkoff SA, Schurr TG, Zhadanov SI, Osipova LP, Brutsaert TD and others. (2005). Large-scale SNP analysis reveals clustered and continuous patterns of human genetic variation. *Human genomics*, 2:81-9.

Siegel RL, Miller KD, Jemal A. (2019). Cancer statistics, 2019. *CA: a cancer journal for clinicians*, 69:7-34.

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. (2015). Global cancer statistics, 2012. *CA: a cancer journal for clinicians*, 65:87-108.

Wang S, Han H, Hu Y, Yang W, Lv Y, Wang L, Zhang L, Ji J. (2018). MicroRNA-130a-3p suppresses cell migration and invasion by inhibition of TBL1XR1-mediated EMT in human gastric carcinoma. *Molecular carcinogenesis*, 57:383-392.

Wang Y, Vogelsang M, Schaefer G, Matejcic M, Parker MI. (2013). MicroRNA polymorphisms and environmental smoke exposure as risk factors for oesophageal squamous cell carcinoma. *PLoS One*, 8:e78520.

Wei J, Zheng L, Liu S, Yin J, Wang L, Wang X, Shi Y, Shao A, Tang W, Ding G. (2013). MiR-196a2 rs11614913 T> C polymorphism and risk of esophageal cancer in a Chinese population. *Human immunology, 74*:1199-1205.

Xiong X-D, Luo X-P, Cheng J, Liu X, Li E-M, Zeng L-Q. (2014). A genetic variant in pre-miR-27a is associated with a reduced cervical cancer risk in southern Chinese women. *Gynecologic oncology*, 132:450-454.

Yang H, Dinney CP, Ye Y, Zhu Y, Grossman HB, Wu X. (2008). Evaluation of genetic variants in microRNA-related genes and risk of bladder cancer. *Cancer research*, 68:2530-2537.

Ye Y, Wang KK, Gu J, Yang H, Lin J, Ajani JA, Wu X. (2008). Genetic variations in microRNA-related genes are novel susceptibility loci for esophageal cancer risk. *Cancer prevention research*, 1:460-469.

Yin Z, Li H, Cui Z, Ren Y, Li X, Wu W, Guan P, Qian B, Rothman N, Lan Q. (2016). Polymorphisms in pre-miRNA genes and cooking oil fume exposure as well as their interaction on the risk of lung cancer in a Chinese nonsmoking female population. *OncoTargets and therapy*, 9:395.

Ying H-Q, Peng H-X, He B-S, Pan Y-Q, Wang F, Sun H-L, Liu X, Chen J, Lin K, Wang S-K. (2016). MiR-608, pre-miR-124-1 and pre-miR26a-1 polymorphisms modify

susceptibility and recurrence-free survival in surgically resected CRC individuals. *Oncotarget*, 7:75865.

Zang H, Peng J, Wang W, Fan S. (2017). Roles of microRNAs in the resistance to platinum based chemotherapy in the non-small cell lung cancer. *Journal of Cancer*, 8:3856.

Zhang J, Huang X, Xiao J, Yang Y, Zhou Y, Wang X, Liu Q, Yang J, Wang M, Qiu L. (2014). Pri-miR-124 rs531564 and pri-miR-34b/c rs4938723 polymorphisms are associated with decreased risk of esophageal squamous cell carcinoma in Chinese populations. *PLoS One,* 9:e100055.

Zhang J, Liang J, Huang J. (2016). Downregulated microRNA-26a modulates prostate cancer cell proliferation and apoptosis by targeting COX-2. *Oncology letters*,12:3397-3402.

Zhu Y, Li T, Chen G, Yan G, Zhang X, Wan Y, Li Q, Zhu B, Zhuo W. (2017). Identification of a serum microRNA expression signature for detection of lung cancer, involving miR-23b, miR-221, miR-148b and miR-423-3p. *Lung cancer*, 114:6-11.