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

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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 Arabsians 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 EGENS 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...
The Frequency of Cancer Susceptibility pri-miR-26a-1 rs7372209 Single Nucleotide Polymorphism

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

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

Statistical Analysis:

The Pearson’s $\chi^2$ 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotype observed (n)</th>
<th>Genotype Expected (n)</th>
<th>MAF</th>
<th>p-value (HWE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC</td>
<td>CT</td>
<td>TT</td>
<td>CC</td>
</tr>
<tr>
<td>Al Qahtani et al, 2017</td>
<td>309</td>
<td>84</td>
<td>7</td>
<td>308</td>
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</tbody>
</table>
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,

### 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Source of subjects</th>
<th>Disease/ Cancer type</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>Allele C</th>
<th>Allele T</th>
<th>Total Alleles</th>
<th>T allele frequency</th>
<th>C Allele frequency</th>
<th>p value</th>
<th>MAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Al Qhtami 2017</td>
<td>HB</td>
<td>HCC</td>
<td>309</td>
<td>84</td>
<td>7</td>
<td>702</td>
<td>98</td>
<td>800</td>
<td>0.123</td>
<td>0.8775</td>
<td>Ref</td>
<td>12.25</td>
</tr>
<tr>
<td>2</td>
<td>Yang 2017</td>
<td>HB</td>
<td>OSCC</td>
<td>90</td>
<td>80</td>
<td>26</td>
<td>260</td>
<td>132</td>
<td>392</td>
<td>0.337</td>
<td>0.66326306</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>3</td>
<td>Ying 2016</td>
<td>PB</td>
<td>CRC</td>
<td>582</td>
<td>432</td>
<td>65</td>
<td>1356</td>
<td>562</td>
<td>2358</td>
<td>0.260</td>
<td>0.73957367</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>4</td>
<td>Yin 2016</td>
<td>HB</td>
<td>LC</td>
<td>125</td>
<td>129</td>
<td>12</td>
<td>379</td>
<td>153</td>
<td>532</td>
<td>0.288</td>
<td>0.71240015</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>5</td>
<td>Xiao 2014</td>
<td>PB</td>
<td>ESCC</td>
<td>630</td>
<td>540</td>
<td>109</td>
<td>1800</td>
<td>758</td>
<td>2558</td>
<td>0.296</td>
<td>0.70567416</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>Li 2014</td>
<td>HB</td>
<td>UC</td>
<td>291</td>
<td>315</td>
<td>64</td>
<td>901</td>
<td>443</td>
<td>1344</td>
<td>0.330</td>
<td>0.67038605</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>7</td>
<td>Zhong 2014</td>
<td>PB</td>
<td>ESCC</td>
<td>628</td>
<td>538</td>
<td>109</td>
<td>1394</td>
<td>756</td>
<td>2550</td>
<td>0.296</td>
<td>0.70350012</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>8</td>
<td>Xiong 2014</td>
<td>HB</td>
<td>Gynecological cancer</td>
<td>221</td>
<td>167</td>
<td>29</td>
<td>609</td>
<td>225</td>
<td>834</td>
<td>0.270</td>
<td>0.73021582</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>9</td>
<td>Wei 2013</td>
<td>HB</td>
<td>ESCC</td>
<td>178</td>
<td>178</td>
<td>24</td>
<td>524</td>
<td>326</td>
<td>760</td>
<td>0.297</td>
<td>0.70563579</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>10</td>
<td>Wang-a 2013</td>
<td>PB</td>
<td>ESCC</td>
<td>546</td>
<td>32</td>
<td>0</td>
<td>1124</td>
<td>32</td>
<td>1336</td>
<td>0.028</td>
<td>0.97230319</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>11</td>
<td>Wang-b 2013</td>
<td>PB</td>
<td>ESCC</td>
<td>307</td>
<td>110</td>
<td>3</td>
<td>724</td>
<td>116</td>
<td>840</td>
<td>0.138</td>
<td>0.86190476</td>
<td>0.345202</td>
<td>13.81</td>
</tr>
<tr>
<td>12</td>
<td>Ye 2008</td>
<td>HB</td>
<td>Esophageal cancer</td>
<td>179</td>
<td>140</td>
<td>27</td>
<td>498</td>
<td>194</td>
<td>692</td>
<td>0.280</td>
<td>0.71906317</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
<tr>
<td>13</td>
<td>Yang 2008</td>
<td>PB</td>
<td>Bladder cancer</td>
<td>378</td>
<td>288</td>
<td>62</td>
<td>1044</td>
<td>412</td>
<td>1456</td>
<td>0.283</td>
<td>0.71703256</td>
<td>&lt;0.001</td>
<td>*</td>
</tr>
</tbody>
</table>

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

178 Abdulmajeed A.A. Sindi
pri-miRNA, 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.

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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.
The Frequency of Cancer Susceptibility pri-miR-26a-1 rs7372209 Single Nucleotide Polymorphism


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


