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REVIEW ARTICLE

Molecular epidemiology of lung cancer in Iran: implications for drug development and cancer prevention

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Abstract

Epidemiological studies undertaken over the past decades reveal a gradual but progressive increase in the incidence and mortality attributable to lung cancer in the Islamic Republic of Iran, a sovereign state geographically situated at the crossroads of Central Eurasia and Western Asia. We identified references published in English and Persian through searches of PubMed, EMBASE, Web of Science, Scopus, and the Scientific Information Database (SID)—a specialized Iranian database, which indexes Iranian scientific journals—between inception and 15 September 2017. Of 1475 references identified through electronic searches, we reviewed the full text of 88 studies, and included 38 studies in the review. Potentially druggable NSCLC targets, which have been studied in Iran include EGFR, ALK, ERBB2, and KIT; but no studies were found, which examined the impact of MET, ROS1, BRAF, PIK3CA, and FGFR1 aberrations. We were able to identify some literature on DNA repair genes and xenobiotic metabolism, including TP53, TP63, ERCC2, XRCC2, SIRT1, PTEN, CYP1A1, CYP1B1, GSTT1, and GSTM1. We also found an increasing amount of research performed in relation to the tumor microenvironment and immune contexture, including CTLA4, MAGE, FOXP3, IFN-γ, and various interleukins, chemokines, and transcription factors; but did not identify any publication concerning the expression of PD-1/PD-L1 in lung cancer. Our survey of research performed in Iran has revealed a dearth of studies in topics, which are otherwise highly pursued in developed countries, but nevertheless, has begun to hint at a distinct biology of lung cancer in this part of the world.

Introduction

In Iran, primary lung cancer is the second leading cause of cancer-related mortality after stomach malignancies [1, 2], imposing a financial burden of US$ 96 779 957 on the Iranian economy in 2010 [3, 4]. The age-adjusted annual incidence rate for males and females was 8.04 and 3.55 per 100 000 persons, respectively, in 2008 [5], however it should be noted that these estimates are likely confounded by systemic under-reporting. The actual number of incident cases and deaths attributable to lung cancer are estimated to be 20–40% higher after adjusting for unreported or mis-diagnosed cases [6–9].

Like many Western nations, cigarette smoking is the most common cause of lung carcinogenesis in Iran, conferring an overall odds ratio (OR) of 5.4 (95% confidence interval (CI), 3.2–9.9) [10], and accounting for 55% of lung cancer deaths in men and 20% in women [11]. However, this is contrasted with Western data wherein a higher proportion (80% and 50% in males and females, respectively) of lung cancer deaths are attributable to smoking [12]. Indeed, with nearly two-thirds of the labor force employed in the agriculture and industrial sector (hydrocarbon, mining, manufacturing, and construction), approximately 12% and 1.5% of incident cases are attributed to workplace carcinogens [13]. Independent risk factors for lung cancer among Iranians include occupational exposures to heavy metals (OR = 3.0; 95% CI, 1.3–7.0), chemical compounds

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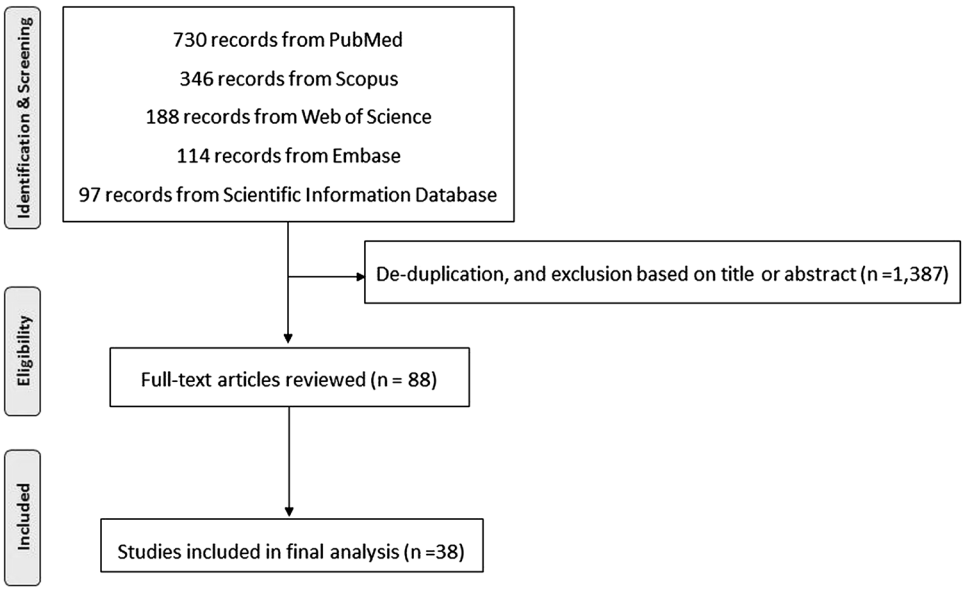

Fig. 1 Flow chart for screening of eligible publications

(OR = 3.4; 95% CI, 2.1–5.6), and inorganic dusts (OR = 4.2; 95% CI, 2.8–6.7) [10].

Given the diverse etiologies in which lung cancer arises in this part of the world and population variation in the frequencies of genetic susceptibility alleles [14], it is imperative to synthesize and appraise the results of molecular studies, which have been done in Iran, and consider their implications for drug development and cancer prevention efforts in the region. Analysis of cancer genomes and their normal counterparts often reflect the unique biological mechanisms operative in carcinogenesis. For instance, Bakhtiarizadeh et al. demonstrated that the number of trinucleotides, particularly GGC and CGC, in expressed sequence tags (ESTs) of lung cancer was approximately three times higher than that of normal tissue, resulting in differences in protein expression patterns (with EST-SSR-derived amino acids, Arg, Pro, Ser, Gly, and Lys being more common in cancerous tissue) [15]. Thus, these molecular patterns hint at potentially unique mechanisms of lung carcinogenesis specific to the Iranian population.

In this review, we will focus on non-small-cell lung cancer (NSCLC), as that is the most common subtype of all primary lung malignancies, although some of the references cited herein also include lung cancer of the small-cell subtype. Furthermore, epidemiological trends in Iran indicate that squamous cell carcinoma is the predominant subtype of NSCLC among men while adenocarcinomas represent the major histological subtype in women [10]. This review is intended to provide a comprehensive overview of pioneering lung cancer research, which has been done in Iran, with an emphasis on studies elucidating the germline and somatic variation in genes that (1) constitute potentially actionable drivers, (2) influence tumor immunosurveillance, or are (3) involved in resistance mechanisms to cancer treatment.

Systematic review

Search strategy

We identified references for this review through searches of PubMed, EMBASE, Web of Science, Scopus, and the Scientific Information Database (SID) between inception and 15 September 2017, with the search terms {"lung cancer" OR "NSCLC" OR "non-small cell lung cancer"} AND {"Iran" OR "Iranian"}. Notably, the SID is a specialized Iranian database which indexes Iranian scientific journals. References were also identified from the authors' own files and through the reference lists of included articles. Papers published in English and Persian were reviewed.

Inclusion and exclusion criteria

We included studies that examined the (1) molecular and genetic basis of lung cancer as well as their clinicopathological correlations and impact on treatment outcomes; (2) studies focused on the Iranian population or originating from Iran; and (3) full articles published in English or Persian. We excluded letters to the editor and book references.

This search strategy yielded 730 articles in PubMed, 346 articles in Scopus, 114 articles in Embase, 188 articles in ISI Web of Science, and 97 articles in SID databases. In all, 38 original studies, comprising 2566 Iranian patients with lung cancer (most of whom were male participants with

Table 1 The genetic changes reported in Iranian population with lung cancer

Category of genes	First author/year	Genes	Location	Type of samples	Total No.	Type of tumors	Technique
Druggable oncogenic drivers	Haghgoo/2017 [16]	*EGFR*	7p11.2	FFPE	98	ADC: 67/SSC:23/other: 8	PCR
	Ghayumi/2006 [20]	*ERBB2*	17q12	Blood	43	ADC: 2/ SCC: 32/ SCLC: 9	ELISA
	Ziaian/2014 [21]	*ERBB2*	17q12	Blood	42	ADC: 29/SCC: 13	IHC
	Roudi/2016 [18]	*ALK*	2p23	FFPE	140	ADC: 62/SCC: 64/LCC: 14	TMA
	Roudi/2016 [22]	*c-KIT*	4q12	FFPE	122	ADC: 37/SCC: 51/LCC: 8/SCLC: 26	TMA
DNA repair pathway	Mohammadi/2008 [25]	*TP53*	17p13.1	FFPE	25	SCC	PCR
	Jafari/2013 [26]	*TP53*	17p13.1	FFPE	50	SCC	Nested PCR
	Nadji/2007 [27]	*TP53*	17p13.1	FFPE	141	ADC: 16/SCC: 104/LCC: 3/ SCLC: 18	PCR
	Eydian/2016 [28]	*TP53*	17p13.1	Blood	200	ADC: 79/SCC: 37/LCC: 5/ other: 11/SCLC: 68	PCR-RFLP
	Naghshvar/2009 [29]	*TP63*	3q28	FFPE	100	SCC	TMA
	Motovali-Bashi/2014 [30]	*ERCC2*	19q13.32	Blood	288	ADC: 120/SCC: 48/LCC: 32 /other: 48/SCLC: 40	PCR
	Hamedi/2016 [31]	*XRCC1*	19q13.31	Blood	100	NSCLC	ARMS-PCR
	Gharabaghi/2016 [32]	*BIRC6*	2p22.3	FFPE	40	NSCLC	qRT-PCR and IHC
		SIRT1	10q21.3				
Immune- and tumor microenvironment-related genes	Golmoghaddam/2011 [47]	*CD1a&d*	1q23.1	Blood	64	ADC: 6/SCC: 36/other: 1 /SCLC: 15 /ND: 6	PCR-SSP
	Roudi/2014 [52]	*CD44*	11p13	FFPE	195	ADC: 61/SCC: 74/LCC: 23/SCLC: 37	TMA
	Roudi/2015 [55]	*CD133*	4p15.32	FFPE	133	ADC: 44/SCC: 48/LCC: 13/SCLC: 28	TMA
	Erfani/2012 [34]	*CTLA4*	2q33	Blood	23	ADC: 61/SCC: 74/LCC: 23/SCLC: 37	Flow cytometry
	Khaghanzadeh/2010 [35]	*CTLA4*	2q33	Blood	127	ADC: 13/SCC: 69/SCLC: 25/other: 20	PCR-RFLP
	Razmkhah/2005 [46]	*SDF1*	10q11	Blood	72	ADC: 7/SCC: 43/other: 1/SCLC: 15/other:6	PCR-RFLP
	Haghighi/2015 [39]	*FOXP3*	Xp11	Blood	156	NSCLC: 123/SCLC: 29/other: 4	PCR-RFLP
	Sameni/2009 [41]	*IL13*	5q31	Blood	141	ADC: 17/SCC: 70/other: 3/SCLC: 33	PCR-RFLP
	Erfani/2014 [40]	*CCL22*	16q16	Blood	148	NSCLC: 116/SCLC: 29/other: 3	PCR-RFLP
		CCR4	3p22				
	Farjadfar/2009 [43]	*IL18*	11q23	Blood	73	SCC: 53/SCLC: 20	AS-PCR
	Ghayumi/2011 [44]	*IL2*	4q27	Blood	44	NSCLC	ELISA
		IL4	5q31.1				
		IL10	1q32.1				
		IFNγ	12q15				
	Karimi/2012 [37]	*MAGE*	X	FFPE	29	ADC: 13/SCC: 16/LCC: 1/other: 1	Nested RT-PCR
Xenobiotic metabolism and other genes	Motovali-Bashi/2013 [58]	*CYP1B1*	2p22	Blood	65	ADC: 22/SCC: 9/SCLC: 9/ other: 25	PCR-RFLP
	Motovali-Bashi/2012 [57]	*CYP1A1*	15q24.1	Blood	65	ADC: 22/SCC: 9/SCLC: 9/other: 25	PCR-RFLP
					112	NSCLC	

Table 1 (continued)

Category of genes	First author/year	Genes	Location	Type of samples	Total No.	Type of tumors	Technique
	Mehrabi/2017 [64]	*CHRNA3*	15q25	NA	147	NSCLC	PCR-SSCP
	Roudi/2015 [55]	*ALDH1*	9q21.13	FFPE	133	ADC: 44/SCC: 48/LCC: 13/SCLC: 28	TMA
	Haghirasadat/2013 [69]	*GSTT1*	22q11.23	Blood	30	Lung cancer	Multiplex PCR
		GSTM1	1p13.3				
	Zarghami/2009 [70]	*TERC*	3q26.2	NA	50	NSCLC:32/SCLC:18	TRAP-PCR
	Alani/2008 [71]	*TERC*	3q26.2	Blood	50	NSCLC and SCLC	PCR-ELISA
	Motovali-Bashi/2012 [72]	*MMP9*	20q13.12	Blood	172	NSCLC	PCR-RFLP
	Sigari/2014 [73]	*KRT19*	17q21.2	Serum	30	ADC:1/SCC: 22/LCC: 1/SCLC: 6	ELISA
	Mohamadnia/2016 [74]	*KRT19*	17q21.2	Blood	50	NSCLC	RT-PCR/ ELISA
	Karimi/2015 [75]	*BPIFA1*	20q11.21	Blood	30	NSCLC	qRT-PCR
	Jamshidzadeh/2001 [76]	*TST*	22q12.3	Fresh tissue	5	ADC: 1/SCC: 4	Enzymatic assays of rhodanese and arginase
		ARG1	6q23.2				
	Ahmadi/2017 [68]	*GRP78*	9q33.3	FFPE	36	NSCLC	RT-qPCR

FFPE formalin fixed paraffin embedded, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *LCC* large-cell carcinoma, *NSCLC* non-small-cell lung cancer, *SCLC* small-cell lung cancer, *TMA* tissue microarray, *IHC* immunohistochemistry, *NA* not available

squamous cell carcinoma (SCC)) were selected for full-text review (Fig. 1).

Data collection and synthesis

Two authors (ZF and RR) independently identified eligible studies, and disagreements were resolved by appeal to a third author (NLS). The following data were extracted: first author; year of publication; genes inspected and experimental techniques used; sample type; and tumor type (Table 1). We categorized the findings of these studies according to the following themes: (1) druggable oncogenic drivers; (2) DNA repair pathway; (3) immune- and tumor microenvironment-related genes; and (4) xenobiotic metabolism and other genes (Fig. 2). We did not perform meta-analysis as we were not able to identify studies that were deemed to be sufficiently similar in terms of study design and experimental techniques used genetic variants that were examined, or manner in which the results were presented.

Druggable oncogenic drivers

Epidermal growth factor receptor

In a study done in 2016 on 98 formalin-fixed paraffin-embedded (FFPE) lung cancer samples in the Iranian population (68% adenocarcinoma and the others SCC), 37% (36/98) of the samples had *EGFR* mutations, of which 72.2% were exon 19 deletions and 27.8% were exon 21 substitution mutations [16]. Although L858R substitution is among the most frequent mutation in NSCLC in East Asian and Western populations [17], no such mutations were observed in Iranian lung cancer patients [16]. Meanwhile, the most prevalent alterations were E872K in exon 21 mutation-positive patients (9/10; 90%) [16], which is peculiar because this mutation otherwise represents a rare mutation in other populations and there is little published data regarding the sensitivity of E872K-mutant NSCLC to peidermal growth factor receptor (EGFR)-directed tyrosine kinase inhibitors.

Anaplastic lymphoma kinase

Anaplastic lymphoma kinase (ALK) rearrangements are rare (1%) driver events in NSCLC, which can be targeted with approved small-molecule inhibitors such as crizotinib, ceritinib, brigatinib, and alectinib. In a study by Roudi et al. [18, 19] comparing the level of ALK expression in lung cancer samples by immunohistochemistry, a high level of ALK expression was found to be associated with poorly differentiated adenocarcinoma, high nuclear grade, and poor prognostic features.

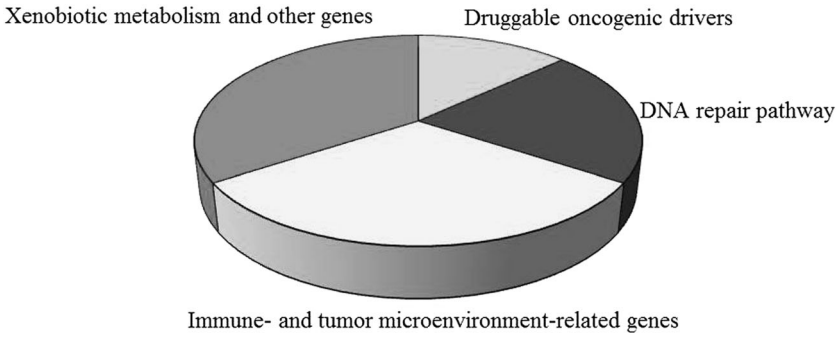

Fig. 2 Distribution of Iranian publications based on the germline and somatic variation in genes that includes (1) druggable oncogenic drivers, (2) DNA repair pathway, (3) immune- and tumor microenvironment-related genes, and (4) xenobiotic metabolism and other genes

Receptor tyrosine-protein kinase erbB-2 (ERBB2; HER2)

Ghayumi et al. evaluated the serum levels of soluble HER2/neu in 43 patients with lung cancer (32 SCC, 9 small-cell lung cancer (SCLC), and 2 adenocarcinomas) and 42 controls by an enzyme immunoassay method in Iranian population. Their study showed that the level of HER2 was increased in lung cancer patients. They also found that HER2 serum levels had a high specificity (95%) but low sensitivity (14%) for diagnosis of lung cancers [20]. Ziaian et al. assessed the status of HER using the immunohistochemical HercepTest in 42 Iranian patients, and reported that one-third were HER2-positive, including 9 (21.4%) weakly stained (1+) and 5 (11.9%) moderately stained (2+) samples [21], suggesting that HER2-positivity rates are far higher in the Iranian lung cancer population as compared to East Asian and Caucasian ethnic populations [14]. They further assessed lactate dehydrogenase and glucose levels in malignant pleural effusions by photometric assay kits, and reported a significant relationship between low pleural glucose levels and HER2-positivity in lung cancer, which may be attributed to the high metabolic activities of HER2-overexpressed lung tumors [21]. Consequently, the potential utility of HER2-directed agents such as trastuzumab, pertuzumab, and lapatinib warrants investigation in Iranian lung cancer patients.

c-KIT proto-oncogene receptor tyrosine kinase (KIT)

In a study by Roudi et al. [22] based on tissue microarrays, the expression levels of c-KIT in lung adenocarcinomas were found to be higher as compared with SCLCs and large-cell lung carcinomas.

BRAF, PIK3CA, MET, ROS1, FGFR1

We did not identify any published articles examining the above-mentioned genes in Iranian lung cancer patients, although reports were found on other cancer types, including *BRAF* mutations in papillary thyroid carcinoma [23] and *PIK3CA* mutations in breast cancer [24].

DNA repair pathway

Mutations in the DNA repair pathway have predictive and prognostic significance. For instance, ongoing research has suggested that *TP53* mutations may confer sensitivity to WEE1 inhibitors, while deleterious mutations in the homologous recombination repair pathway are currently being investigation as predictive biomarkers for checkpoint blockade immunotherapy and PARP inhibitor response. Furthermore, acquired mutations in the DNA repair pathway may be associated with either sensitivity or resistance to chemotherapeutic agents depending on context. In this section, we systematically synthesize published literature of DNA repair pathway aberrations in Iranian NSCLC patients.

Tumor suppressor p53

In a study by Mohammadi et al. [25] on 25 FFPE SCC patient samples, 18/22 (81.8%) of evaluable cases harbored mutations in exon 5 (which were mostly deletions) and 15/18 (83.3%) contained mutations in exon 8 (mostly A to T and G to T transversions and deletions). In another study be Jafari et al. [26], *TP53* mutations in exons 5–7 were found in 27.7% of lung SCC samples. The most frequent mutations were c.409C > G in exon 5 and c.770T > A in exon 7 [26]. Controversy exists as to the importance of a codon 72 polymorphism (R72P) and lung cancer predisposition in an Iranian population: Nadji et al. [27] reported an increased risk of lung cancer in a study of 92 healthy controls and 141 North Iranian lung cancer patients, whereas Eydian et al. [28] found no such association based on a case–control study comprising 200 lung cancer patients and 200 healthy controls.

Tumor suppressor p63

Naghshvar et al. [29] evaluated p63 immunohistochemical staining intensity in re-cut and de-stained sections of 100 Iranian lung cancer specimens, and found that 93.93% of SCC but none of the SCLC were stained by p63.

ERCC2

In a case–control study involving 288 lung cancer patients and 352 healthy Iranian controls, individuals heterozygous for the Lys751Gln polymorphism had approximately twice the risk of lung cancer compared those with the Lys/Lys genotype. There was also no association between the risk of lung cancer and homozygous individuals for the glutamine allele [30].

X-ray repair cross complementing 1

Hamedi et al. examined the effect of the X-ray repair cross complementing 1 Arg399Gln polymorphism by amplification-refractory mutation system-polymerase chain reaction (ARMS-PCR) in a case–control study involving 100 NSCLC patients and 100 healthy controls. In the overall population, no association between the Arg399Gln polymorphism and risk of lung cancer was delineated. Intriguingly, in subgroup analysis, the Gln/Gln genotype appeared to increase the susceptibility of lung cancer among men [31].

Sirtuin 1

Gharabaghi [32] evaluated the prognostic and diagnostic value of sirtuin 1 (*SIRT1*) expression in NSCLC in 40 patients, and demonstrated that *SIRT1* was upregulated in 67.5% of NSCLC samples, and was associated with advanced pathological T stage and poor differentiation status.

Phosphatase and tensin homolog

We did not identify any published articles examining *PTEN* mutations in Iranian lung cancer patients, although reports were found on other cancer types such as prostate cancer [33].

Immune- and tumor microenvironment-related genes

Cytotoxic T-lymphocyte-associated protein 4

It is currently not clear whether molecular aberrations involving the cytotoxic T-lymphocyte-associated protein 4 (*CTLA4*) gene may influence antitumor immunity or response to anti-CTLA-4/B-7 checkpoint inhibitors. Nevertheless, Erfani et al. [34] assessed lymphocytic cell surface and intracellular expression of CTLA-4 in peripheral blood of 23 NSCLC patients and 16 healthy controls, and reported that <1% of all lymphocytes subsets (CD4+, CD8+, and CD19+) expressed CTLA-4 on the surface and most of the CTLA-4 molecules were present in the intracellular compartment of SurCTLA-4+CD8+ lymphocytes in both patients and controls. In another study by Khaghanzadeh et al. [35] involving 127 patients with lung cancer and 124 controls, CTLA4 polymorphisms (−1722 T/C, −1661 A/G, −318 C/T, +49 A/G, +1822 C/T, and +6230 A/G (CT60)) did not appear to modulate the risk of lung cancer in persons of Iranian descent.

Melanoma-associated antigen

The melanoma-associated antigen (MAGE) protein family is located in clusters on the X chromosome, and their gene products are members of the cancer-testis antigen group. Type 1 MAGE is expressed in testes and various tumor types, including lung cancers. Accumulating evidence suggests that the overexpression of *MAGE* gene products in lung cancers can serve as a tumor marker for diagnosis, as well as a target for cancer immunotherapy as it can be presented by major histocompatibility complexes (MHCs) on cancer cell surfaces to cytotoxic T lymphocytes [36]. Karimi et al. examined the expression of *MAGE* in both tumoral and normal tissue, using FFPE samples of 29 Iranian patients (SCC: 16 and adenocarcinomas: 13) and a nested reverse transcriptase–PCR to detect the expression frequency of the *MAGE-A* family. This analysis revealed that at least one *MAGE-A* gene is expressed in 59.4% of lung SCC and 69.2% of adenocarcinomas from Iranian patients, and *MAGE-A4* gene was most frequently expressed among *MAGE-A* genes [37]. For contrast, other studies have found that *MAGE-A3* is the most prevalent form of *MAGE-A* (30–60% of NSCLC) [38].

Forkhead box P3

Forkhead box P3 (*FOXP3*) is located on the Xp11 chromosome and its product is a transcription factor that has critical roles in CD4+CD25+FOXP3+ regulatory T (Treg) cells. This transcription factor binds to specific sites on DNA and under normal contexts, is responsible for autoimmune suppression. In a case–control study, Haghighi et al. analyzed the association of two *FOXP3* polymorphisms, rs3761549 (in the promoter region; −2383 C/T) and rs2280883 (in the internal region; IVS9 +459 T/C) in 156 patients with lung cancer and 156 controls in a Southern Iranian population [39]. The frequency of the T allele of the rs3761549 variant was 11.8% among cases and 5.9% among controls; while the T allele frequency at rs2280883 was also higher among cases compared to controls, or among patients aged 55 years or older (69.9% vs. 59.9%), and in SCC patients [39].

C-C motif chemokine 22 and C-C chemokine receptor type 4

The C-C motif chemokine 22 (*CCL22*) gene is located on the 16q16 chromosome and is a chemokine that attracts monocytes, dendritic cells, natural killer cells and T lymphocytes. The C-C chemokine receptor type 4 (*CCR4*) gene is located on the chromosome 3p22 and is a G-protein coupled receptor for CCL22. *CCR4* is expressed on the surface of T helper type 2 (Th2) and Treg cells, and is involved in their homing to tumors. In a study by Erfani et al. [40] of 148 patients with lung cancer and 148 controls in 2014, no significant differences in the genotypic frequencies of *CCL22* rs4359426 (16C > A) and *CCR4* rs2228428 (C1014T) were identified in cases and controls in Iranians.

Interleukin-13

Interleukin (IL)-13 is an immunoregulatory cytokine synthesized and secreted by Th2 cells. Several polymorphisms have been reported for this gene. Sameni et al. [41] reviewed the status of two variants +2044 G/A and −1055 C/T in 141 patients with lung cancer and 113 controls in 2009, and found no significant difference in the frequency of genotypes, alleles, or haplotypes at positions, suggesting that these variants do not constitute predisposition variants in individuals of Iranian ancestry.

Interleukin-18

IL-18 is a chemokine produced and released by macrophages, epithelial cells, osteoblasts, and cancer cells, especially under states of inflammation. IL-18, through stimulating interferon-gamma (IFN-γ) release by T lymphocytes, induces apoptosis or arrest in cancer cells. IL-18 expression is reduced in the presence of the promoter −607 C/A and −137 G/C polymorphisms, which are localized in the transcription factor-binding sites [42]. Farjadfar et al. [43] examined the IL-18 gene polymorphisms in 73 patients with lung cancer and 97 controls in Iranian population and reported a significantly higher A allele frequency at position −607, which is associated with diminished IL-18 production, in lung cancer patients. Furthermore, individuals with the −607 CA and the AA genotypes had an increased susceptibility to lung cancer [43].

IL-2, IL-4, IL-10, and IFN-γ

Ghayumi et al. examined the levels of IL-4, IL-10, IL-2, and IFN-γ levels by enzyme-linked immunosorbent assay (ELISA) in 44 NSCLC patients, 16 extra-thoracic tumors, 8 tuberculosis patients, and 8 congestive heart failure patients. The findings suggested a lower IFN-γ level but possibly increased levels of IL-10 and IL-4 in malignant tumors. IL-2 was below the detectable concentration of the assay [44].

Stromal cell-derived factor-1

The gene encoding stromal cell-derived factor-1 (SDF-1), also known as C-X-C motif chemokine ligand 12, is located at 10q11. This chemokine attaches to the CXCR4 receptor and has been implicated in a host of processes related to cancer immunity and metastatic outgrowth. The G801A (rs1801157) substitution is a noteworthy polymorphism in the 3′-untranslated region of the *SDF-1* gene, which is associated with enhanced gene expression in homozygous and heterozygous conditions, as well as an increased risk of cancer [45]. In a study by Razmkhah et al. [46] comprising 72 patients with lung cancer and 262 controls in Iran, 12.5% of cases were found to be homozygous for the A allele and 52.8% were heterozygotes, whereas among controls, 7.7% were A/A and 37% were heterozygous, suggesting that this variant may be a weakly penetrant susceptibility allele in the Iranian population.

Cluster of differentiation 1

The human genome contains five cluster of differentiation 1 (*CD1*) family genes organized as a cluster on chromosome 1 (1q23.1). These genes encode membrane glycoproteins that are located on the surface of the antigen-presenting cells, and are related to the class I MHC molecules. CD1a assists in presenting lipid antigens to T lymphocytes while CD1d is considered to present glycolic lipid antigens to natural killer T cells. Golmoghaddam et al. [47] examined exon 2 polymorphisms in CD1a and CD1d in 64 lung cancer patients and 95 healthy individuals in an Iranian population, but did not elucidate any significant association between the CD1 polymorphisms and lung cancer prognosis.

Cluster of differentiation 44

Cluster of differentiation 44 (*CD44*) is located on the short arm of the chromosome 11 (11p13) and encodes a transmembrane glycoprotein, which may be involved in cancer proliferation, lymphocytic activation, and tumor metastasis [48]. CD44 has been identified as a crucial molecule on the surface of cancer stem cells (CSCs) [49]. Genetic variation and expression of CD44 may be associated with progressive disease in various human malignancies, including lung cancer [50, 51]. Roudi et al. [52] performed immunohistochemical evaluation of the expression of CD44 in 195 lung cancer samples and found higher level of CD44 expression in NSCLC compared to SCLC, and this difference was

accentuated in the SCC histotype. Furthermore, CD44 expression was significantly correlated with higher-grade tumors and poor prognosis.

Prominin 1

PROM1 is located on the short arm of the chromosome 4 (4p15.32) and encodes a pentaspan membrane glycoprotein known as CD133, which is considered to regulate the MAPK and Akt signaling pathways. CD133 also serves as a stem cell marker for CSCs and is expressed in the lung CSC population [53, 54]. Roudi et al. evaluated the expression of CD133 in 133 FFPE lung cancer samples by immunohistochemistry in an Iranian population. CD133 expression was markedly higher in NSCLC SCC as compared to SCLC. The authors concluded that $CD133^{high}$ phenotype can therefore be considered as a reliable CSC marker in some lung cancer subtypes [55].

Programmed cell death protein 1 and programmed death-ligand 1

We did not identify any published investigations examining the expression and mutational patterns of programmed cell death protein 1 (PD-1) and it's ligand programmed death-ligand 1 (PD-L1) that were performed in an Iranian lung cancer population. The authors note that this paucity of studies on PD-1/PD-L1 in Iran may hamper drug development and translational efforts in effectively utilizing immunotherapy, and is contrasted with the numerous publications originating from Western and East Asian countries.

Xenobiotic metabolism and other genes

Cytochrome P450 family 1 subfamily A member 1

Motovali-Bashi et al. [56] investigated the frequency of cytochrome P450 family 1 subfamily A member 1 (CYP1A1) MspI (6235T > C) polymorphism in 65 lung cancer patients (AC: 22, SCC: 9, SCLC: 9, others: 25) and 80 healthy, and determined that the frequency of the variant CYP1A1*2A allele was higher in lung cancer patients, with a significantly increased risk of lung cancer among heterozygotes (*1/*2A). These findings were corroborated by another case–control study involving 112 lung cancer patients and 120 controls, again reflecting the same trend [57].

Cytochrome P450 family 1 subfamily B member 1

Cytochrome P450 family 1 subfamily B member (C1YP1B1) is involved in the oxidation and activation of polycyclic aromatic hydrocarbons (PAHs) and nitrosamines in cigarette smoke into carcinogenic compounds that can form adducts with nuclear DNA. The most frequent polymorphisms in *CYP1B1* include 4326C/G (L432V; rs1056836) in exon 3. This polymorphism augments the catalytic activity of the heme-binding domain of the enzyme, resulting in increased activation of PAHs and nitrosamines, and is associated with an enhanced risk of cancer. Accordingly, Motovali-Bashi et al. [58] have reported that the CC genotype is associated with elevated lung cancer risk in persons with a smoking history, but not in non-smokers.

Aldehyde dehydrogenase 1

Aldehyde dehydrogenase (ALDH1) belongs to a superfamily with 19 ALDH genes, which have spread throughout the genome. There are 6 ALDH1 in human genome; ALDH1A1 (9q21.13), ALDH1A2 (15q21.3), ALDH1A3 (15q26.3), ALDH1B1 (9p13.1), ALDH1L1 (3q21.3), and ALDH1L2 (12q23.3) [59]. All these enzymes catalyze the oxidation of aldehydes in liver and also are expressed at high levels in stem cells and play critical roles in stem cell functions [60]. ALDH1 can act as a potential CSC marker in several cancers such as ovarian and lung cancer, and is associated with poor prognosis in NSCLC [61, 62]. Roudi et al. evaluate the expression of ALDH1 in 133 FFPE lung cancer tumors by immunohistochemistry method in Iranian population. They found that ALDH1 had higher expression levels in the NSCLC (especially SCC) compared to the SCLC, so $ALDH1^{high}$ phenotype can be considered as a CSC marker in some lung cancer subtypes [55].

Cholinergic receptor nicotinic alpha 3

Cholinergic receptor nicotinic alpha 3 (*CHRNA3*) encodes a ligand-gated nicotinic acetylcholine receptor. CHRNA3 binds to nicotine and nitrosamines contained in cigarettes and food in epithelial cells of the lung. The exact mechanisms by which *CHRNA3* modulates lung cancer risk is debated, but have been postulated to increase smoking addiction via nicotine dependence, as well as the direct induction of cancer cell proliferation via nicotine–receptor interaction [63]. In a study by Mehrabi et al. [64] of 147 NSCLC patients and 145 controls, three polymorphisms in exon 3 of CHRNA3 (rs8040868, rs763384023, and rs2869547) were analyzed. The latter two variants appear to be unique to the Iranian lung cancer population, whereas the rs8040868 polymorphisms have previously been reported to indirectly increase the risk of lung cancer by engendering nicotine (and alcohol) dependence [65, 66].

Heat shock protein family A member 5

The *HSPA5* gene is located on the long arm of the chromosome 9 (9q33.3) and is a member of the heat shock protein 70 family. It is alternatively known as glucose-regulated protein 78 (GRP78), and is involved in the folding and assembly of multimeric proteins complexes in the endoplasmic reticulum and is an important member of unfolded protein response pathway. Its expression is increased in cancer cells and is associated with proliferation, carcinogenesis, metastasis, and drug resistance [67]. Ahmadi et al evaluated the expression of GRP78 in 36 FFPE lung cancer samples by reverse transcription quantitative real-time PCR (RT-qPCR) and confirmed that GRP78 was upregulated in tumor samples [68].

Glutathione *S*-transferase T1 and glutathione *S*-transferase M1

Haghirasadat et al. scrutinized the frequencies of glutathione *S*-transferase T1 (*GSTT1*) and glutathione *S*-transferase M1 (*GSTM1*) deletion variants in 30 lung cancer patients and 70 healthy controls using multiplex PCR, and found that 16.7% of cases and 7.1% of controls respectively exhibited deletions within the *GSTT1* gene, whereas 30% of cases and 10% of controls exhibited deletions of the *GSTM1* gene. Deletion of at least one of the *GSTM1* or *GSTT1* genes was significantly higher in patients group in compared to the controls ($P = 0.033$) [69].

Telomerase RNA component

Zarghami et al. measured the expression of telomerase gene using the TRAP assay and the concentrations of Zn and Cu, by atomic absorption spectrophotometry in 50 lung cancer patients and a control group comprising 20 patients with other lung diseases. Their results suggested a higher expression of telomerase in lung cancer patients, which was correlated with higher concentrations of Cu as well as Cu/Zn ratio. Cu concentration in SCLC was found to be significantly higher than NSCLC ($P < 0.05$) [70]. Another study by Alani et al. [71], in which telomerase activity of 50 biopsy specimens of lung cancer patients and serum CEA and Cyfra21-1 were assessed using PCR-ELISA and ELISA, respectively, telomerase activity was found to be increased, especially in SCLC as compared with NSCLC, whereas serum levels of CEA and Cyfra21-1 were increased in NSCLC in comparison with SCLC.

Matrix metallopeptidase 9

Motovali-Bashi et al. analyzed the associations between the C(−1562)T polymorphism of the type IV collagenase gene and the risk of lung cancer according to the different age categories in the Iranian population. This study reported that individuals under the age of 60 harboring the TT genotype were approximately considerably more likely to develop lung cancer (OR = 19.89; 95% CI = 3.21–120.60) [72].

Tumor markers (CYFRA21-1, CEA, NSE)

Sigari et al. [73] evaluated the serum levels of CYFRA21-1 (CK19), CEA, and NSE in 30 subjects with malignant and 81 with benign lung cancer in Kurdistan (a province in Western Iran), and validated the concentration of serum tumor markers, especially CYFRA21-1 and NSE, as being significantly higher in the malignant group than in the benign subjects. In another study by Mohamadnia et al. [74] involving 30 NSCLC patients and 30 controls, CEA serum levels were confirmed to be increased in NSCLC patients. Although the sensitivity of CK19 mRNA appeared to be low, it proved to be a specific marker for the early detection of lung cancer [74].

PI fold containing family A member 1 (BPIFA1, LUNX)

Karimi et al. [75] inspected the serum levels of LUNX and CEA in 30 NSCLC patients and 30 controls and determined the sensitivity of LUNX and CEA to be 70% and 80%, respectively, suggesting that the combination of LUNX and CEA mRNA markers in peripheral blood could represent useful non-invasive tools for the detection of NSCLC.

Arginase 1

Jamshidzadeh et al. [76] investigated the activities of arginase and rhodanese in normal and cancerous human tissues in the Iranian population. Arginase activity was found to be enhanced in the cancerous tissue while rhodanese activity was significantly suppressed ($P < 0.05$).

Baculoviral inhibitors of apoptosis protein repeat containing 6

The baculoviral inhibitors of apoptosis proteins (IAP) repeat containing 6 (*BIRC6*) gene is located on the short arm of chromosome 2 (2p22.3) and is a member of the family of the IAPs. BIRC6 has a single N-terminal baculovirus IAP repeat (BIR) domain and a C-terminal ubiquitin-conjugating domain. BIRC6 can inhibit the caspase cascade and cause anti-apoptotic activity, and plays important roles in cell proliferation. Gharabaghi et al. [32] evaluated the prognostic and diagnostic value of *BIRC6* expression in NSCLC in 40 Iranian patients and found that *BIRC6* was upregulated in 75% of NSCLC samples, and was associated with advanced tumor stage, poor differentiation, and lymph node metastasis.

Conclusions and future directions

Contemporary lung cancer research in Iran has begun to shed light on the molecular underpinnings of the disease in this population. Amidst an increasing trend in incident lung cancer cases and socioeconomic burden, these formative studies—however limited by quality and scope—represent crucial stepping stones for the next generation of translation cancer research and prevention in Iran and other less-developed nations in Central Eurasia and Western Asia.

In contrast to data from developed countries, the epidemiology of molecular alterations in genes involved in cancer immunosurveillance, xenobiotic metabolism, DNA repair, and those that encode potentially actionable oncogenic drivers are—in several aforementioned instances—distinct in the Iranian population. These disparities likely allude to the unique environmental exposures and population genetics of the Iranian populace [77]. Regardless, these data affirm the need for Iran to drive its own cancer research agendas, as findings derived from ethnographically distinct populations (eg., highly developed Western and East Asian nations) may not extrapolate to an Iranian lung cancer patient population.

Furthermore, our survey of lung cancer studies performed in Iran has revealed a dearth of studies in topics that are otherwise highly pursued in developed countries. Notably, we were not able to identify any publication from Iran concerning the expression of PD-1/PD-L1 in lung cancer. On the other hand, it can be argued that checkpoint blockade immunotherapies [78] are prohibitively costly in Iran's healthcare system, thus de-prioritizing research on tumor immunology in NSCLC. Nevertheless, such studies should be encouraged as they may form the backbone of future drug development efforts in the region. With the concerted efforts of laboratory scientists and translational physicians and the commitment of the government to nurturing a national research infrastructure, the full potential of lung cancer research in Iran may eventually be realized to give all Iranians the best chance at preventing and overcoming lung cancer.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Karami-Matin B, Najafi F, Rezaei S, Khosravi A, Soofi M. Estimating the economic burden of premature mortality caused by cancer in Iran: 2006-2010. Asian Pac J Cancer Prev. 2016;17:2131–6.
2. Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H. Five common cancers in Iran. Arch Iran Med. 2010;13:143–6.
3. Rezaei S, Akbari Sari A, Woldemichael A, Soofi M, Kazemi A, Karami Matin B. Estimating the economic burden of lung cancer in Iran. Asian Pac J Cancer Prev. 2016;17:4729–33.
4. Khorasani S, Rezaei S, Rashidian H, Daroudi R. Years of potential life lost and productivity costs due to premature cancer-related mortality in Iran. Asian Pac J Cancer Prev. 2015;16:1845–50.
5. Almasi Z, Salehiniya H, Amoori N, Enayatrad M. Epidemiology characteristics and trends of lung cancer incidence in Iran. Asian Pac J Cancer Prev. 2016;17:557–62.
6. Vahedi M, Pourhoseingholi MA, Baghestani A, Abadi A, Sobhi S, Fazeli Z. Bayesian analysis of lung cancer mortality in the presence of misclassification. Iran J Cancer Prev. 2013;6:1–5.
7. Marzban M, Haghdoost AA, Dortaj E, Bahrampour A, Zendehdel K. Completeness and underestimation of cancer mortality rate in Iran: a report from Fars Province in southern Iran. Arch Iran Med. 2015;18:160–6.
8. Pourhoseingholi MA, Baghestani A, Abadi A, Hajizadeh N. Iranian regional cancer incidence is misclassified in neighborhood's provinces. Gastroenterol Hepatol Bed Bench. 2016;9:75–77.
9. Mohammadi G, Akbari ME, Mehrab IY, Ghanbari Motlagh A. Quality assessment of the national cancer registry in Iran: completeness and validity. Iran J Cancer Prev. 2016;9:e8479.
10. Hosseini M, Naghan PA, Karimi S, SeyedAlinaghi S, Bahadori M, Khodadad K, et al. Environmental risk factors for lung cancer in Iran: a case–control study. Int J Epidemiol. 2009;38:989–96.
11. Rezaei S, Akbari Sari A, Arab M, Majdzadeh R, Mohammadpoorasl A. Estimating economic burden of cancer deaths attributable to smoking in Iran. J Res Health Sci. 2015;15:228–33.
12. Tarver T. Cancer facts & figures 2012. American Cancer Society (ACS). J Consumer Health Internet. 2012;16:366–367.
13. Mosavi-Jarrahi A, Mohagheghi M, Kalaghchi B, Mousavi-Jarrahi Y, Noori MK. Estimating the incidence of lung cancer attributable to occupational exposure in Iran. Popul Health Metr. 2009;7:7–13.
14. Heong, V, Syn, NL, Lee, XW, Sapari, NS, Koh, XQ, Adam Isa, ZF et al. Value of a molecular screening program to support clinical trial enrollment in Asian cancer patients: The Integrated Molecular Analysis of Cancer (IMAC) study. Int J Cancer. 2018;**142**:1890–1900.
15. Bakhtiarizadeh MR, Ebrahimi M, Ebrahimie E. Discovery of EST-SSRs in lung cancer: tagged ESTs with SSRs lead to differential amino acid and protein expression patterns in cancerous tissues. PLoS ONE. 2011;6:e27118.
16. Haghgoo SM, Khosravi A, Mortaz E, Pourabdollah-Toutkaboni M, Seifi S, Sabour S, et al. Prognostic value of rare and complex mutations in EGFR and serum levels of soluble EGFR and its ligands in non-small cell lung carcinoma patients. Clin Biochem. 2017;6:293–300.
17. Syn NL, Yong WP, Goh BC, Lee SC. Evolving landscape of tumor molecular profiling for personalized cancer therapy: a comprehensive review. Expert Opin Drug Metab Toxicol. 2016;12:911–22.
18. Roudi R, Haji G, Madjd Z, Shariftabrizi A, Mehrazma M. Evaluation of anaplastic lymphoma kinase expression in nonsmall cell lung cancer; a tissue microarray analysis. J Cancer Res Ther. 2016;12:1065–9.
19. Mehrazma M, Roudi R, Madjd Z, Haji G. Evaluation of ALK expression in non-small cell lung cancer: a tissue microarray analysis. Virchows Arch. 2015;467:S257.
20. Ghayumi SMA, Aghasadeghi K, Dorouchi M, Ghaderi A. Determination of soluble HER-2/neu (sher-2/neu) in Iranian patients with lung cancer. Iran J Immunol. 2006;3:61–5.
21. Ziaian B, Saberi A, Ghayyoumi MA, Safaei A, Ghaderi A, Mojtahedi Z. Association of high LDH and low glucose levels in

pleural space with HER2 expression in non-small cell lung cancer. Asian Pac J Cancer Prev. 2014;15:1617–20.
22. Roudi R, Madjd Z, Ebrahimi M, Najafi A, Korourian A, Shariftabrizi A, et al. Evidence for embryonic stem-like signature and epithelial-mesenchymal transition features in the spheroid cells derived from lung adenocarcinoma. Tumour Biol. 2016;37:11843–59.
23. Ranjbari N, Almasi S, Mohammadi-Asl J, Rahim F. BRAF mutations in Iranian patients with papillary thyroid carcinoma. Asian Pac J Cancer Prev. 2013;14:2521–3.
24. Azizi Tabesh G, Izadi P, Fereidooni F, Emami Razavi AN, Tavakkoly Bazzaz J. The High frequency of PIK3CA mutations in iranian breast cancer patients. Cancer Invest. 2017;35:36–42.
25. Mohammadi A, Vaziri Gohar A, Shakibaie MR. Mutations in tumor suppressor TP53 gene in formalin-fixed, paraffin embedded tissues of squamous cell carcinoma (SCC) of lung cancer. Am J Biochem Biotechnol. 2008;4:1–6.
26. Jafari H, Gharemohammadlou R, Fakhrjou A, Ebrahimi A, Nejati-Koshki K, Nadri M, et al. Genotyping of human papillomavirus and TP53 mutaions at exons 5 to 7 in lung cancer patients from Iran. Bioimpacts. 2013;3:135–40.
27. Nadji SA, Mahmoodi M, Ziaee AA, Naghshvar F, Torabizadeh J, Yahyapour Y, et al. An increased lung cancer risk associated with codon 72 polymorphism in the TP53 gene and human papillomavirus infection in Mazandaran province, Iran. Lung Cancer. 2007;56:145–51.
28. Eydian Z, Asna'ashari AM, Behravan J, Sharifi-Rad J, Entezari Heravi R. Association of P53 codon 72 polymorphism and lung cancer in an ethnic Iranian population. Cell Mol Biol. 2016;62:34–8.
29. Naghshvar F, Torabizadeh Z, Mohammadian Roshan M, Ghahremani M. Comparison of p63 staining intensity between re-cut sections and de-stained sections of patient specimens with lung cancer. J Mazandaran Univ Med Sci. 2009;19:1–6.
30. Motovali-Bashi M, Rezaei H, Dehghanian F, Rezaei H. Association between XPD (Lys751G1n) polymorphism and lung cancer risk: a population-based study in Iran. Cell J. 2014;16:309–14.
31. Hamedi RF, Tahmaseb M, Ghadri A. Prognostic importance of polymorphisms in DNA-repair gene (XRCC1 Arg399Gln) in patients with lung cancer in Fars province, Iran. J Isfahan Med Sch. 2016;34:1244–50.
32. Gharabaghi MA. Diagnostic investigation of BIRC6 and SIRT1 protein expression level as potential prognostic biomarkers in patients with non-small cell lung cancer. Clin Respir J. 2018;**12**:633–8.
33. Pourmand G, Ziaee AA, Abedi AR, Mehrsai A, Alavi HA, Ahmadi A, et al. Role of PTEN gene in progression of prostate cancer. Urol J. 2009;4:95–100.
34. Erfani N, Mehrabadi SM, Ghayumi MA, Haghshenas MR, Mojtahedi Z, Ghaderi A, et al. Increase of regulatory T cells in metastatic stage and CTLA-4 over expression in lymphocytes of patients with non-small cell lung cancer (NSCLC). Lung Cancer. 2012;77:306–11.
35. Khaghanzadeh N, Erfani N, Ghayumi MA, Ghaderi A. CTLA4 gene variations and haplotypes in patients with lung cancer. Cancer Genet Cytogenet. 2010;196:171–4.
36. Syn NL, Wang L, Chow EK, Lim CT, Goh BC. Exosomes in cancer nanomedicine and immunotherapy: prospects and challenges. Trends Biotechnol. 2017;35:665–76.
37. Karimi S, Mohammadi F, Porabdollah M, Mohajerani SA, Khodadad K, Nadji SA. Characterization of melanoma-associated antigen-a genes family differential expression in non-small-cell lung cancers. Clin Lung Cancer. 2012;13:214–9.
38. Chinnasamy N, Wargo JA, Yu Z, Rao M, Frankel TL, Riley JP, et al. A TCR targeting the HLA-A* 0201–restricted epitope of MAGE-A3 recognizes multiple epitopes of the MAGE-A antigen superfamily in several types of cancer. J Immunol. 2011;186:685–96.
39. Fazelzadeh Haghighi M, Ali Ghayumi M, Behzadnia F, Erfani N. Investigation of FOXP3 genetic variations at positions-2383 C/T and IVS9+459 T/C in southern Iranian patients with lung carcinoma. Iran J Basic Med Sci. 2015;18:465–71.
40. Erfani N, Nedaei, Ahmadi AS, Ghayumi MA, Mojtahedi Z. Genetic polymorphisms of CCL22 and CCR4 in patients with lung cancer. Iran J Med Sci. 2014;39:367.
41. Sameni S, Ghayumi MA, Mortazavi G, Faghih Z, Kashef MA, Ghaderi A. Lack of association between interleukin-13 gene polymorphisms (−1055 C/T and +2044 G/A) in Iranian patients with lung cancer. Mol Biol Rep. 2009;36:1001–5.
42. Giedraitis V, He B, Huang WX, Hillert J. Cloning and mutation analysis of the human IL-18 promoter: a possible role of polymorphisms in expression regulation. J Neuroimmunol. 2001;112:146–52.
43. Farjadfar A, Mojtahedi Z, Ghayumi MA, Erfani N, Haghshenas MR, Ghaderi A. Interleukin-18 promoter polymorphism is associated with lung cancer: a case-control study. Acta Oncol. 2009;48:971–6.
44. Ghayumi MA, Mojtahedi Z, Fattahi MJ. Th1 and Th2 cytokine profiles in malignant pleural effusion. Iran J Immunol. 2011;8:195–200.
45. Tong X, Ma Y, Deng H, Wang X, Liu S, Yan Z. et al. The SDF-1rs1801157 polymorphism is associated with cancer risk: an update pooled analysis and FPRP test of 17,876 participants. Sci Rep. 2016;6:27466.
46. Razmkhah M, Doroudchi M, Ghayumi SM, Erfani N, Ghaderi A. Stromal cell-derived factor-1 (SDF-1) gene and susceptibility of Iranian patients with lung cancer. Lung Cancer. 2005;49:311–5.
47. Golmoghaddam H, Pezeshki AM, Ghaderi A, Doroudchi M. CD1a and CD1d genes polymorphisms in breast, colorectal and lung cancers. Pathol Oncol Res. 2011;17:669–75.
48. Morath I, Hartmann TN, Orian-Rousseau V. CD44: more than a mere stem cell marker. Int J Biochem Cell Biol. 2016;81:166–73.
49. Ponta H, Sherman L, Herrlich PA. CD44: from adhesion molecules to signalling regulators. Nat Rev Mol Cell Biol. 2003;4:33–45.
50. Situ D, Long H, Lin P, Zhu Z, Wang J, Zhang X, et al. Expression and prognostic relevance of CD44v6 in stage I non-small cell lung carcinoma. J Cancer Res Clin Oncol. 2010;136:1213–9.
51. Fasano M, Sabatini MT, Wieczorek R, Sidhu G, Goswami S, Jagirdar J. CD44 and its v6 spliced variant in lung tumors: a role in histogenesis? Cancer. 1997;80:34–41.
52. Roudi R, Madjd Z, Korourian A, Mehrazma M, Molanae S, Sabet MN, et al. Clinical significance of putative cancer stem cell marker CD44 in different histological subtypes of lung cancer. Cancer Biomark. 2014;14:457–67.
53. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, et al. Identification of human brain tumour initiating cells. Nature. 2004;432:396–401.
54. Eramo A, Lotti F, Sette G, Pilozzi E, Biffoni M, Di Virgilio A, et al. Identification and expansion of the tumorigenic lung cancer stem cell population. Cell Death Differ. 2008;15:504–14.
55. Roudi R, Korourian A, Shariftabrizi A, Madjd Z. Differential expression of cancer stem cell markers ALDH1 and CD133 in various lung cancer subtypes. Cancer Invest. 2015;33:294–302.
56. Motovali-Bashi M, Biglari M, Hojati Z, Hemati S, Khodadad K. Role of CYP1A1 MspI polymorphism in CYP1A1 gene with susceptibility to lung cancer in Iranian patients. J Res Med Sci. 2012;17(Spec 2):S242–6.
57. Motovali-Bashi M, Bordbar M, Rezaei H. Study of the relationship between T/C single-nucleotide polymorphism in CYP1A1 gene with onset of illness and smoking in patients with lung cancer. Res Med. 2012;36:151–6.

58. Motovali-Bashi M, Biglari M, Rezaei H, Dehghanian F. CYP1B1 L432V polymorphism and lung cancer risk in the Iranian population. Iran J Biotechnol. 2013;11:199–204.
59. Aldehyde dehydrogenases (ALDH). http://www.genenames.org/cgi-bin/genefamilies/set/398 (2018).
60. Marchitti SA, Brocker C, Stagos D, Vasiliou V. Non-P450 aldehyde oxidizing enzymes: the aldehyde dehydrogenase superfamily. Expert Opin Drug Metab Toxicol. 2008;4:697–720.
61. Chang B, Liu G, Xue F, Rosen DG, Xiao L, Wang X, et al. ALDH1 expression correlates with favorable prognosis in ovarian cancers. Mod Pathol. 2009;22:817–23.
62. Jiang F, Qiu Q, Khanna A, Todd NW, Deepak J, Xing L, et al. Aldehyde dehydrogenase 1 is a tumor stem cell-associated marker in lung cancer. Mol Cancer Res. 2009;7:330–8.
63. Schuller HM. Nitrosamines as nicotinic receptor ligands. Life Sci. 2007;80:2274–80.
64. Mehrabi N, Moshtaghioun SM, Neamatzadeh H. Novel mutations of the CHRNA3 gene in non-small cell lung cancer in an Iranian population. Asian Pac J Cancer Prev. 2017;18:253–5.
65. Schlaepfer IR, Hoft NR, Collins AC, Corley RP, Hewitt JK, Hopfer CJ, et al. The CHRNA5/A3/B4 gene cluster variability as an important determinant of early alcohol and tobacco initiation in young adults. Biol Psychiatry. 2008;63:1039–46.
66. Truong T, Hung RJ, Amos CI, Wu X, Bickeböller H, Rosenberger A, et al. Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium. J Natl Cancer Inst. 2010;102:959–71.
67. Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature. 2010;466:835–40.
68. Ahmadi A, Khansarinejad B, Hosseinkhani S, Ghanei M, Mowla SJ. miR-199a-5p and miR-495 target GRP78 within UPR pathway of lung cancer. Gene. 2017;620:15–22.
69. Haghirasadat F, Nazari T, Omodi M, Azimzadeh M, Sheikhha M. Investigating the rate of glutathione S-transferase T1 and M1 genes deletion in patients with lung cancer. Bimon J Hormozgan Univ Med Sci. 2013;17:385–93.
70. Zarghami N, Mikaeili H, Ansarin K, Mohajeri A, Haji HR. Correlation between serum levels of zinc and copper and telomerase gene expression in lung cancer patients. Pharm Sci. 2009;14:183–90.
71. Alani B, Ansarin K, Selmizadeh MJ, Cheraghi E. Comparison study of Cyfra 21-1, carcinoembryonic antigen and telomerase activity between non small cell and small cell lung cancer patients. Sci J Hamadan Univ Med Sci. 2008;15:18–24.
72. Motovali-Bashi M, Taghvaei S, Hemmati S. The association between the C (-1562) T polymorphism of type IV collagenase gene and reduced age of onset of lung cancer. J Isfahan Med Sch. 2012;30:1–9.
73. Sigari N, Mohsenpour B, Nikkhoo B, Ghaderi B, Afkhamzadeh A, Azadi NA, et al. Determination of the best prognostic value of serum tumor markers in patients with suspected lung cancer in an Iranian population. Clin Lab. 2014;60:23–7.
74. Mohamadnia A, Karimi S, Yadegar Azari R, Naji SA, Khosravi A, Bahrami N, et al. Expression of CK19 gene in patients with lung cancer and its comparison with carcinoembryonic antigen in peripheral blood. Payavard. 2016;9:459–68.
75. Karimi S, Mohamadnia A, Nadji SA, Yadegarazari R, Khosravi A, Bahrami N, et al. Expression of two basic mRNA biomarkers in peripheral blood of patients with non-small cell lung cancer detected by real-time rt-PCR, individually and simultaneously. Iran Biomed J. 2015;19:17–22.
76. Jamshidzadeh A, Aminlari M, Rasekh HR. Rhodanese and arginase activity in normal and cancerous tissues of human breast, esophagus, stomach and lung. Arch Iran Med. 2001;4:88–92.
77. Syn NL, Yong WP, Lee SC, Goh BC. Genetic factors affecting drug disposition in Asian cancer patients. Expert Opin Drug Metab Toxicol. 2015;11:1879–92.
78. Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol. 2017;18:e731–41.