RESEARCH ARTICLE

Editorial Process: Submission:10/22/2023 Acceptance:02/19/2024

Lack of Association between *TP73 G4C14-A4T14* Polymorphism and Cervical Cancer Risk in Overall and Asian Women: A Meta-Analysis

Maryam Motamedinasab[1,2], Mojgan Karimi-Zarchi[3]*, Zahra Marzbanrad[1]*, Seyedeh Roghayeh Mirmajidi[4], Mohammad Vakili-Ojarood[5], Sepideh Azizi[6], Maedeh Barahman[7], Maryam Yeganegy[8], Maryam Aghasipour[9], Sahel Khajehnoori[10], Kazem Aghili[11], Hossein Neamatzadeh[12]

Abstract

Background: Growing studies revealed the association between polymorphisms in Tumor Protein *TP73 (TP73)* and susceptibility to cancer, especially with gynecological cancers. but, the results remained inconsistent. This meta-analysis was carried out to examine the relationship of the *TP73 G4C14*-to-*A4T14* polymorphism (hereafter, *G4C14*-to-*A4T14*) with susceptibility to cervical cancer globally and by ethnicity. **Methods:** Eligible studies were collected by retrieving PubMed, Scopus, Web of Science, Embase, Wan Fang, and CNKI published before 25 October, 2023. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of such association. **Results:** A total of 10 case-control studies with 1804 cervical cancer cases and 2433 healthy controls were included to this study. The pooled results showed that *TP73 G4C14*-to-*A4T14* polymorphism was not associated with cervical cancer risk in overall. in terms of stratified analyses by ethnicity, this polymorphism was not associated with risk of cervical cancer among East-Asian women. however, there was a significant association based source of control among hospital-based studies.**Conclusions:** Inconsistent with previous meta-analyses, our pooled results revealed that *TP73 G4C14-to-A4T14* polymorphism might not be a risk factor for development of cervical cancer globally and among East-Asian women. Moreover, further studies examining the effect of gene-gene and gene-environment interactions may eventually provide a better knowledge.

Keywords: Uterine Cervical Neoplasms- Tumor Protein TP73- Polymorphism

Asian Pac J Cancer Prev, **25 (2)**, 661-670

Introduction

Cervical cancer is a major public health issue and the third most frequent cancer and the fourth leading cause of cancer death among women globally [1-3]. It is estimated 57000 new cases and 311000 deaths in 2018 and will cause 474,000 women per year by 2030 [4, 5]. About 90% of the new cases and deaths worldwide in 2020 occurred in low- and middle-income countries. It was estimated that the rate of cervical cancer was between 0.36 and 3.73 per 100,000 women among Iranian women [6], which most of them are unaware of screening tests and Pap smears test [7, 8]. However, it seems that prevalence of this cancer in Iran is less than that of western countries [9, 10]. A retrospective cohort study by using data of Iranian National Cancer Registry System from 2008 to

*[1]Department of Obstetrics and Gynecology, Firoozgar Clinical Research Development Center, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran. [2]Department of Obstetrics and Gynecology, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [3]Department of Gynecologic Oncology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran. [4]Department of Obstetrics and Gynecology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran. [5]Department of Surgery, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran. [6]Shahid Akbarabadi Clinical Research Development Unit, Iran University of Medical Sciences, Tehran, Iran. [7]Department of Radiation Oncology, Firoozgar Clinical Research Development Center, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran. [8]Department of Obstetrics and Gynecology, Iranshahr University of Medical Sciences, Iranshahr, Iran. [9]Department of Cancer Biology, College of Medicine, University of Cincinnati, Ohio, USA. [10]Hematology and Oncology Research Center, Shahid Sadoughi Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [11]Department of Radiology, Shahid Rahnemoun Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [12]Mother and Newborn Health Research Center, Shahid Sadoughi Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. *For Correspondence: mk.zarchi55@gmail.com, dr.zahramarzbanrad@gmail.com*

2014 showed that the mean age of the cervical cases was 51.91 years and their 5- and 10-year survival rates were 58% and 50%, respectively [11, 12].

The primary and main causative factor of cervical cancer is the high-risk oncogenic human papillomavirus (HR-HPV) [13-15]. More than 90% of patients with cervical cancer show a positive long-lasting infection with certain types of HPV especially in western countries [16-18]. Family history is beyond control when assessing the risks for cancer, but if the mother or sister of a patient has had cervical cancer, the likelihood of developing cancer increases by two to three times [10, 19, 20]. Genetic factors contributing to the development of cervical cancer are largely unknown. There were reported a few familial clustering of cervical cancer cases indicating that high-penetrance germline variants are rare in this cancer and heritable risk of cervical cancer may be accounted for by low- and intermediate-penetrant genetic factors [21, 22]. However, some evidence from epidemiological studies have been shown that a genetic background could predispose to cervical cancer, and that some of the genes likely to be involved are *IRF3, TLR2, EXO1, CYBA, XRCC1 and FANCA, OAS3, SULF1, IFNG, DUT, DMC1, GTF2H4, EVER1/2, ERAP1, LMP7, TAP2, TP53, TERT* and *IL-17* [23, 24]. Several studies showed that *TP73* expression is up-regulated in cervical cancer tissues in comparison in normal cervical squamous epithelium, and negatively associated with clinical progression in cervical cancer patients [25, 19].

Tumor Protein *TP73* (*TP73*) is an essential member of a gene family that comprises *TP63 (p63)* and the well-characterized tumor suppressor *TP53 (p53)* [26-28]. *TP73* is plays important roles in embryonic development and differentiation, and located on chromosome 1p36-33, mapping on a region often deleted in different cancers [25, 27]. two single polymorphisms G4A (rs2273953) and C14T (rs1801173) in the 5′-UTR of exon 2 of the TP73 gene is reported. These polymorphisms are in complete disequilibrium with each other and are jointly referred to as G4C14-A4T14 [29, 30]. This set of polymorphisms are located above the translation initiation site and has been shown to affect TP73 gene expression levels by forming a stem-loop-like structure and therefore have functional outcomes [31, 3].

In recent years, *TP73 G4C14-A4T14* polymorphism have been reported implicated in the development of cervical cancer [32, 25]. Nevertheless, data arising from these published case-control studies were not consistent. With the rapid growth of literatures, there is increasing need to make meaningful inferences from a comprehensive and complex body of evidence, a thorough meta-analysis of the literature helps to explore more evidence of association between *TP73 G4C14-A4T14* polymorphism and cervical cancer risk. thus, we performed this meta-analysis to examine the relationship of the *TP73 G4C14-to-A4T14* polymorphism with susceptibility to cervical cancer globally. To the best of our knowledge, this is the most comprehensive meta-analysis regarding the *TP73 G4C14-A4T14* polymorphism and its association with cervical cancer risk.

Materials and Methods

Search Strategy

The need for obtaining informed consent from participants was not applicable because no participants were involved in this meta-analysis. We systematically searched PubMed, EMBASE, Wed of Science, Elsevier, Google Scholar, Cochrane Library, SciELO, SID, WanFang, VIP, Chinese Biomedical Database (CBD) and Chinese National Knowledge Infrastructure (CNKI) comprehensively for all publications regarding the association *TP73 G4C14-A4T14* polymorphism and cervical cancer risk up to November 10, 2019. The combination of following keywords and terms were used: (''Uterine Cervical Neoplasm'' OR ''Cervix Cancer'' OR ''Cervical Cancer'' OR ''Cervical Neoplasm'' OR ''Cervical Carcinoma'') AND (''TP73'' OR ''TP73' OR ''G4C14-A4T14'' Or ''rs2273953'' OR ''rs1801173'') AND (''Polymorphism'' OR ''Mutation'' OR ''Genotype'' OR ''Allele'' OR ''Variation'' OR ''Variant''). Meanwhile, hand searching of the references in retrieved reviews and eligible articles were performed as sources to find other relevant publications. Languages were limited to English and Chinese.

Including and Excluding Criteria

We set these inclusive criteria for recruited publications: a) studies with case-control or cohort design; 2) published studies in English, Chinese and Farsi; 3) studies evaluated the association of *TP73 G4C14-A4T14* polymorphism with risk of cervical cancer; and 4) enough and available data to figure out odds ratios (ORs) and 95% confidence intervals (CIs). In addition, we also restricted these exclusive criteria: 1) studies without control group (case only studies); 2) insufficient data offered to analyze or unavailable data; 3) studies were carried out based on animals and in vitro studies; 4) studies evaluated the association of other polymorphisms at *TP73* genes with cervical cancer; 5) case reports, case series, letters, comments, reviews, and previous meta-analyses 6) overlapped data or duplication.

Data extraction

Eligible studies containing the required data were selected and the data were organized for further analysis by comprehensive screening. All recruited studies had to be seriously scanned by two individual researchers separately. If there was a dispute between the two researchers, they would reach a consensus by discussing or a third researcher. We extracted the following information from eligible studies: name of the first author, year of publication, country of origin, ethnicity of participants, genotyping methods, source of controls, total numbers of cases and controls, genotyping method, genotypes frequencies of cases and controls, minor allele frequencies (MAFs) and Hardy-Weinberg equilibrium test in control subjects.

Statistical Analysis

An ethical approval was not necessary as this study was a meta-analysis based on previous studies. The strength

of association of *TP73 G4C14-A4T14* polymorphism with risk of cervical cancer was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The statistical significance of the pooled OR was determined using the Z-test. Pooled estimates of the OR were obtained by calculating a weighted average of OR from each study. The pooled ORs was calculated under all five genetic models, i.e., allele (AT vs. GC), homozygote (AT/AT vs. GC/GC), heterozygote (GC/AT vs. GC/GC), dominant (AT/AT+ GC/AT vs. GC/GC), and recessive (AT/AT vs. GC/AT+GC/GC). A χ2-based Q test was calculated for assessing the heterogeneity among recruited investigations and if the P-value of Q test exceeded 0.05 that meant there was no obvious heterogeneity [33, 34]. In addition, I^2-value was used to quantify the proportion of the between study heterogeneity (range of 0 to 100%: I^2=0-25%, no heterogeneity; I^2=25-50%, moderate heterogeneity; I^2= 50–75%, large heterogeneity; I^2=75–100%, extreme heterogeneity). Random-effect models (DerSimonian-Laird method) would be adopted for analyses if I^2 was >50%. Otherwise, analyses would be conducted with fixed-effect models (Mantel- Haenszel method) [35-37].Genotype frequencies of controls for each study using goodness-of-fit test (chi-square) and a p-value less than 0.05 was considered as significant disequilibrium (HWE-violating) [38, 39]. Sensitivity analysis was conducted by excluding one study at a time to examine the stability of the pooled results [38, 40, 41]. Begg's funnel plot and Egger's linear regression test were applied to assess potential publication bias, in which P<0.05 was considered statistically significant. All of the statistical calculations were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided P-values < 0.05 were considered statistically significant.

Results

The selection process of eligible studies is presented in Figure 1. Initially, 316 papers were obtained through publication search in electronic databases and other sources. Then, de-duplicate all the documents we have retrieved, and then remove the documents irrelevant to *TP73 G4C14-A4T14* polymorphism or cervical cancer by reading the title and abstract of the article. Therefore, 76 publications were deleted for obvious irrelevance. Finally, a total of 10 case-control studies [42-49, 25]. with 1804 cervical cancer cases and 2433 healthy controls were included in this meta-analysis. The studies were published between 2004 and 2022, and nine studies were published in English and one in Chinese. These studies were published among Japanese, Hong Kong, Indian, Chinese and Portuguese women. Among these studies, nine studies were conducted among Asians and one study among Caucasian women. Six studies were population-based (PB) studies and remaining were hospital-based (HB) studies, and used a case-control study design. Five different genotyping techniques were used: PCR (polymerase chain reaction), PCR-CTPP (polymerase chain reaction with confronting two-pair primers), restriction fragment length polymorphism (PCR-RFLP),

Table 1. Characteristics of the Studies Included in Meta-Analysis

First Author/Year	Ethnicity (Country)	SOC	Genotyping Methods	Case/Control	Patients					Healthy Control					MAFs	HWE
					Genotypes			Alleles		Genotypes			Alleles			
					AA	AB	BB	A	B	AA	AB	BB	A	B		
Niwa 2004	Japan(Asian)	HB	PCR-CTPP	112/442	57	52	3	166	58	270	150	22	690	194	0.219	0.843
Liu 2007	Hong Kong(Asian)	PB	TaqMan	504/716	327	152	25	806	202	420	253	43	1093	339	0.237	0.552
Zheng 2008	China(Asian)	PB	PCR-RFLP	101/100	71	28	2	170	32	77	19	4	173	27	0.135	0.062
Zheng 2008	China(Asian)	PB	PCR-RFLP	82/100	58	22	2	138	26	77	19	4	173	27	0.135	0.062
Craveiro 2012	Portugal(Caucasian)	PB	PCR	141/176	95	38	8	228	54	119	48	9	286	66	0.188	0.164
Jha 2012	India(Asian)	PB	PCR	101/100	71	28	2	170	32	77	19	4	173	27	0.135	0.062
Sun 2012	China(Asian)	PB	PCR-CTPP	218/220	107	100	11	314	122	128	80	12	336	104	0.236	0.913
Guo 2016	China(Asian)	HB	HRM-PCR	175/189	107	46	22	260	90	109	70	10	288	90	0.238	0.774
Feng 2017	China(Asian)	HB	PCR	180/180	103	67	10	273	87	114	55	11	283	77	0.214	0.22
Guo 2022	China(Asian)	HB	PCR-CTPP	190/210	105	60	25	270	110	140	56	14	336	84	0.2	0.015

SOC, Source of Controls; HB, Hospital Based; PB, Population Based; PCR, polymerase chain reaction; PCR-CTPP, polymerase chain reaction with confronting two-pair primers; HRM;, High resolution melt analysis; PCR-RFLP, Restriction Fragment Length Polymorphism; HWE, Hardy-Weinberg equilibrium; MAF, Minor Allele Frequency.

Table 2. Summary Risk Estimates for Association between *TP73* Polymorphism and Risk of Cervical Cancer

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio (OR)				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{OR}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	B vs. A	Fixed	46.4	0.052	1.09	0.980-1.213	1.0586	0.113	0.531	0.085
	BB vs. AA	Fixed	26.73	0.198	1.112	0.840-1.473	0.742	0.458	0.325	0.503
	BA vs. AA	Random	62.11	0.005	1.208	0.954-1.530	1.57	0.116	0.788	0.059
	BB+BA vs. AA	Random	55.56	0.016	1.199	0.976-1.474	1.725	0.085	0.928	0.038
	BB vs. BA+AA	Fixed	32.85	0.145	1.095	0.828-1.439	0.622	0.534	0.42	0.312
Ethnicity										
Asian	B vs. A	Random	52.09	0.033	1.161	0.978-1.380	1.701	0.089	0.531	0.087
	BB vs. AA	Fixed	34.87	0.139	1.112	0.830-1.490	0.711	0.477	0.404	0.528
	BA vs. AA	Fixed	66.35	0.003	1.238	0.954-1.607	1.609	0.108	0.676	0.06
	BB+BA vs. AA	Random	60.18	0.01	1.226	0.976-1.540	1.75	0.08	0.834	0.039
	BB vs. BA+AA	Fixed	40.3	0.099	1.09	0.817-1.453	0.584	0.559	0.531	0.337
Chinese	B vs. A	Random	56.52	0.024	1.154	0.951-1.401	1.45	0.147	0.804	0.117
	BB vs. AA	Fixed	39.14	0.118	1.148	0.850-1.552	0.9	0.368	0.322	0.67
	BA vs. AA	Random	65.04	0.006	1.19	0.903-1.568	1.237	0.216	0.804	0.065
	BB+BA vs. AA	Random	60.74	0.013	1.192	0.933-1.524	1.405	0.16	0.804	0.051
	BB vs. BA+AA	Fixed	41.47	0.102	1.137	0.845-1.529	0.85	0.395	0.457	0.484
SOC										
HB	B vs. A	Fixed	3	0.378	1.28	1.082-1.516	2.872	0.004	0.734	0.215
	BB vs. AA	Fixed	39.86	0.173	1.652	1.079-2.529	2.31	0.021	0.089	0.084
	BA vs. AA	Random	67.23	0.027	1.212	0.824-1.785	0.976	0.329	0.089	0.14
	BB+BA vs. AA	Fixed	32.89	0.154	1.292	1.050-1.591	2.418	0.016	0.308	0.444
	BB vs. BA+AA	Fixed	56.29	0.076	1.574	1.037-2.391	2.129	0.033	0.308	0.127
PB	B vs. A	Fixed	36.53	0.163	0.979	0.853-1.124	-0.301	0.764	0.85	0.084
	BB vs. AA	Fixed	0	0.921	0.821	0.565-1.192	-1.038	0.299	1	0.694
	BA vs. AA	Random	62.47	0.021	1.209	0.876-1.669	1.156	0.248	0.85	0.049
	BB+BA vs. AA	Random	57.17	0.04	1.142	0.857-1.521	0.907	0.365	0.85	0.055
	BB vs. BA+AA	Fixed	0	0.935	0.821	0.568-1.187	-1.048	0.295	0.573	0.256

SOC, Source of Controls; HB, Hospital Based; PB, Population Based.

High resolution melt analysis (HRM) and TaqMan. The genotype, allele and minor allele frequency (MAF) in each study are shown in Table 1. Moreover, the distribution of genotypes in the controls was in agreement with Hardy-Weinberg equilibrium (HWE) for all selected studies, except for one study.

Evidence synthesis

Table 2 listed the main results of the meta-analysis of *TP73 G4C14-A4T14* polymorphism and cervical cancer risk. We pooled all the 10 case-control studies together to assess the overall association between this polymorphism and risk of cervical cancer. Pooled analysis did not show a significant association between *TP73 G4C14-A4T14* polymorphism and cervical cancer risk under all the five genetic models (Figure 2A-2E). The studies were further stratified based on the ethnicity or country. When subgroup analysis by ethnicity was performed, a significant association between *TP73 G4C14-A4T14* polymorphism and cervical cancer risk not found among Asian and Chinese women. The meta-analysis results for the Asian and Chinese women are listed in Table 2. Moreover, in the stratified analysis by source of controls, results revealed that the *IL TP73 G4C14-A4T14* polymorphism was associated with cervical cancer risk in HB group under four genetic models, i.e., allele (AT vs. GC: OR= 1.280, 95% CI 1.082-1.516, p=0.004), homozygote (AT/AT vs. GC/GC: OR= 1.652, 95% CI 1.079-2.529, p=0.021), dominant (AT/AT+ GC/AT vs. GC/GC: OR= 1.292, 95% CI 1.050-1.591, p=0.016), and recessive (AT/AT vs. GC/AT+GC/GC: OR= 1.574, 95% CI 1.037-2.391, p=0.033), but not among PB group.

Heterogeneity test

Based on the results, there was a moderate level of heterogeneity was found between the included studies under two genetic models, i.e., heterozygote (GC/AT vs. GC/GC: I^2=62.11 and PH=0.005) and dominant (AT/AT+ GC/AT vs. GC/GC: I^2=55.56 and PH=0.016). Thus, a subgroup analysis was conducted to explore the predefined possible source of heterogeneity. Subgroup analyses showed that ethnicity was not significant source of heterogeneity in this meta-analysis (Table 2).

Sensitivity Analysis

Sensitivity analyses were performed after sequential

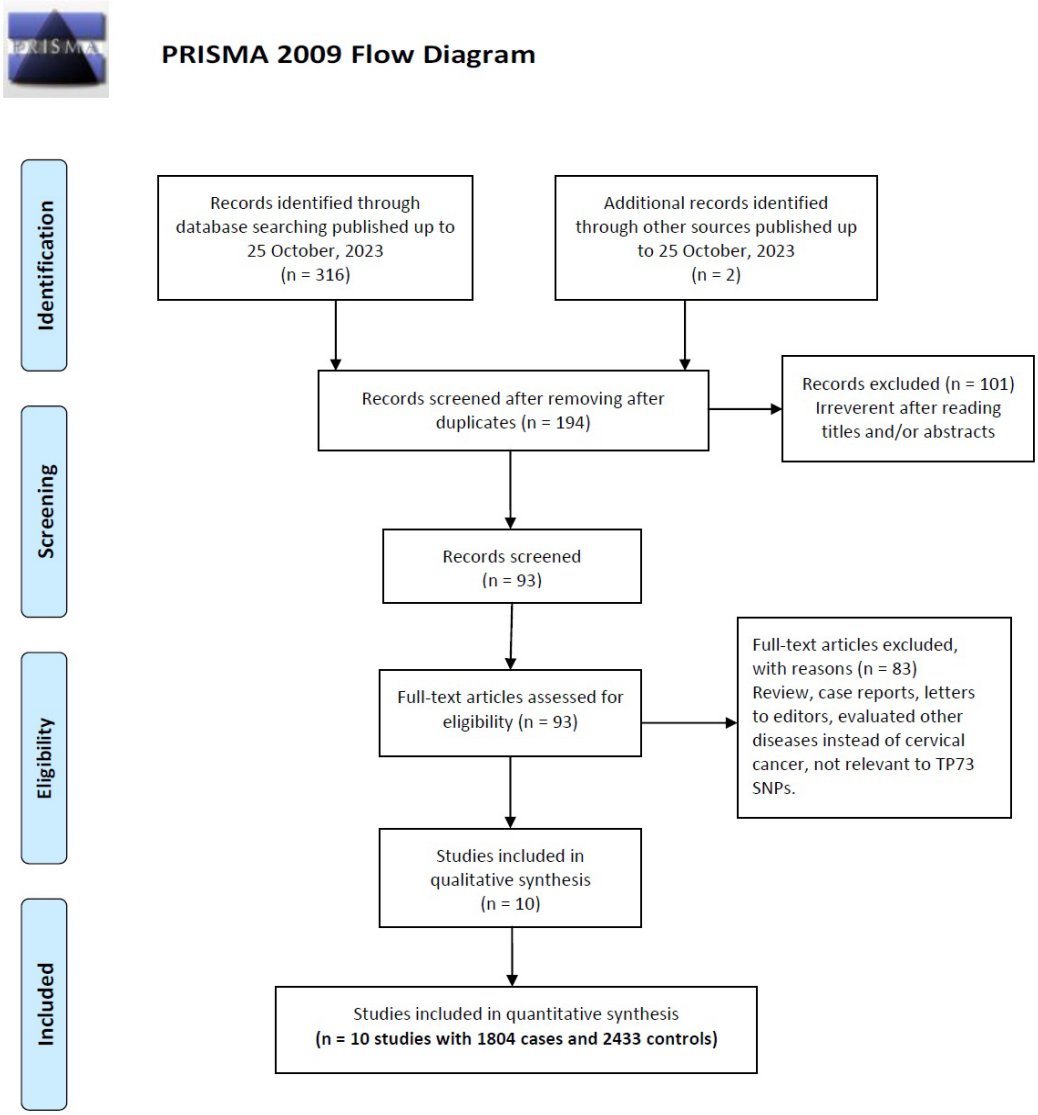

Figure 1. Flow Diagram of the Study Selection Process

removal of each eligible study to examine the influence of a single study on pooled results on pooled data of *TP73 G4C14-A4T14* polymorphism and cervical cancer risk by calculating the ORs before and after exclusion of the article. No outlying study was observed to significantly change the pooled ORs after it was removed which confirmed our results were stable under all five genetic models. Moreover, the test of HWE was conducted in

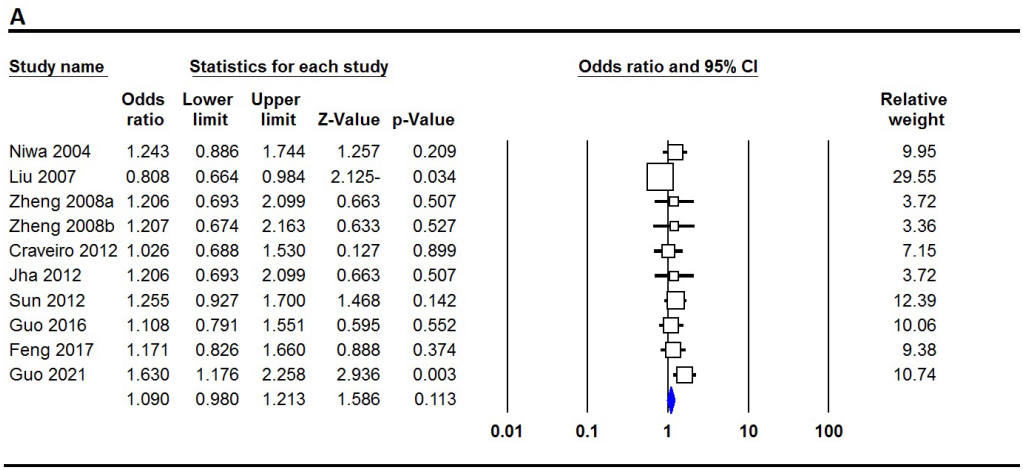

Figure 2. Forest Plots for the association of *TP73 G4C14-A4T14* Polymorphism with Risk of Cervical Cancer. A: allele model

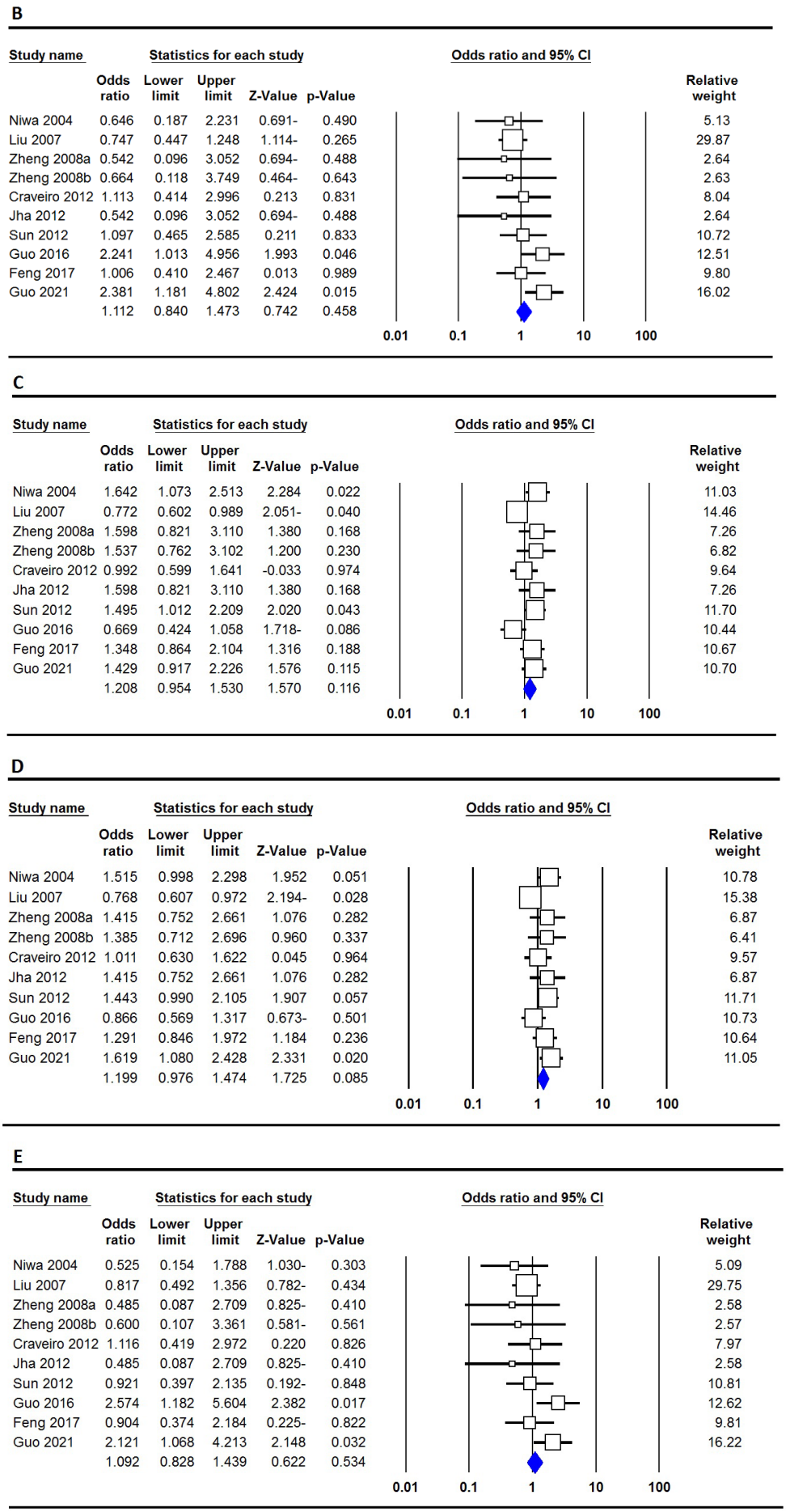

Figure 2. Forest Plots for the association of *TP73 G4C14-A4T14* Polymorphism with Risk of Cervical Cancer. B: homozygote model; C: heterozygote model; D: dominant model; and E: recessive model.

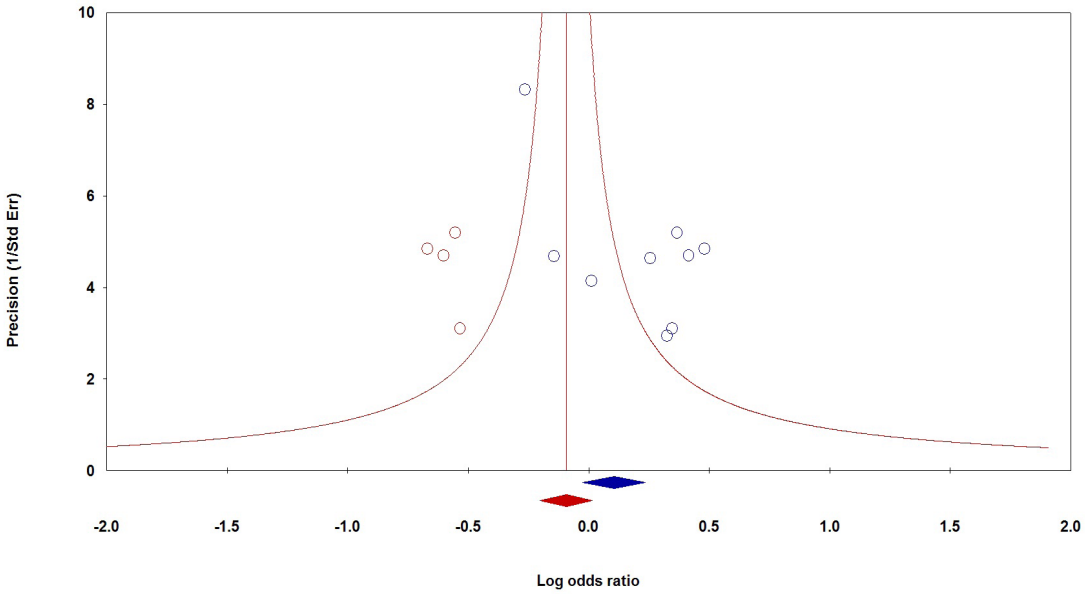

Figure 3. Begg's Funnel Plots of IL *TP73 G4C14-A4T14* Polymorphism with Cervical Cancer Risk for Publication bias Test under the Dominant model. Before (blue) and after (red) ''Trim-and-Fill'' method.

this study, results of which indicate that results remain unchanged.

Publication Bias

The Begg's funnel plot and Egger's test were performed to assess the publication bias. The shapes of the Begger's funnel plots did not show any evidence of publication bias, except under dominant (AT/AT+ GC/AT vs. GC/GC: P_{Beggs}=55.56 and P_{Eggers}=0.016). Thus, we applied the Duval and Tweedie non-parametric ''trim and fill'' method to the publication bias (Figure 3). The results showed that the current meta-analysis with and without ''trim and fill'' did not draw different results, indicating that our results were statistically reliable. Overall, the results suggest this meta-analysis is not affected by publication biases.

Discussion

It is well known that single nucleotide polymorphisms (SNPs) are the most common sources of human genetic variation, which may contribute to an individual's susceptibility to cancer [50, 11, 28]. Here, we have carried out a meta-analysis based on 10 case-control studies with 1804 cases and 2433 controls to obtain a more conclusive result on relationship between *TP73 G4C14-A4T14* polymorphism and cervical cancer. To the best of our knowledge, this is so far the most comprehensive meta-analysis on association between *TP73 G4C14-A4T14* polymorphism and cervical cancer. Pooled analyses indicated that *TP73 G4C14-A4T14* polymorphism was not correlated with cervical cancer in overall and ethnicity. Moreover, when we stratified data by source of controls, we noticed that significant associations between *G4C14-A4T14* polymorphism and cervical cancer were only existed in controls with hospital-based.

Jafrin et al., in a meta-analysis based 55 case-control studies including eight studies on cervical cancer examined the role of TP73 G4C14-A4T14 polymorphism with development of different cancers. Their pooled data revealed that this variant significantly associated with increased risk of cancer, especially in Caucasian and African populations, and specifically predisposes individuals to gynecological, colorectal, oral, and head and neck cancers [27]. In 2018, Meng et al., in a published pooled data based on 36 case-control studies with 9493 cancer cases and 13,157 controls (6 studies on cervical cancer) evaluated the association of *TP73 G4C14-A4T14* polymorphism with susceptibility to different cancer. Their results reveled that this polymorphism causes an upgrade cancer risk, especially in Caucasian population. Moreover, they have shown that G4C14-A4T14 polymorphism might be associated with risk of cervical cancer and colorectal cancer [29]. In 2017, Liang et al., elucidated the role of *TP73 G4C14-A4T14* polymorphism on cervical cancer development by performing a meta-analysis. Their pooled data included a total of 635 cases and 998 control subjects, and showed that *TP73 G4C14-A4T14* polymorphism was associated with susceptibility to cervical cancer [51]. In the same year, Feng et al., in a meta-analysis based on three studies indicated that this variant at TP73 gene might be associated with an increased risk of cervical cancer [25].

Our meta-analysis has some advantages which these advantages strongly guaranteed a more accurate and reliable conclusion. First, we attempted to find as many published studies by means of various searching approaches, which may enhance the authenticity and reliability of the analysis. Second, the well-designed search and selection method significantly increased the statistical power of this meta-analysis and the number of included studies and sample sizes were greatly enlarged than previous meta-analyses. Third, sensitivity analysis also revealed that the our results were not influenced by any individual study. Finally, the subgroup analysis is

sufficient and performed under different subgroups.

In summary, our pooled results revealed that *TP73 G4C14-to-A4T1*4 polymorphism was not associated with an increased risk of cervical cancer globally and among Asian and chinese women. Future studies with large sample size are encouraged to validate our results and to prove the clinical relevance of *TP73 G4C14-to-A4T14* polymorphism in the development of cervical cancer. Moreover, further studies examining the effect of gene-gene and gene-environment interactions may eventually provide a better knowledge.

Author Contribution Statement

Conceptualization: Maryam Motamedinasab, Mojgan Karimi-Zarchi, Zahra Marzbanrad; Data curation: Seyedeh Roghayeh Mirmohammadi, Sepideh Azizi; Formal analysis: Seyed Alireza Dastgheib, Hossein Neamatzadeh; Investigation: Kazem Aghili, Maedeh Barahman; Methodology: Seyed Alireza Dastgheib, Maryam Aghasipour; Supervision: Mohammad Vakili, Ahmad Shirinzadeh-Dastgiri; Validation: Mohammad Vakili, Ahmad Shirinzadeh-Dastgiri, Mojtaba Meybodian; Writing – original draft: Sahel Khajehnoori, Maedeh Barahman; Writing – review & editing: Maryam Aghasipour, Hossein Neamatzadeh.

Acknowledgements

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors. An ethical approval was not necessary as this study was a meta-analysis based on previous studies.

References

1. Karimi Zarchi M, Behtash N, Chiti Z, Kargar S. Cervical cancer and hpv vaccines in developing countries. Asian Pac J Cancer Prev. 2009;10(6):969-74.
2. Hashemzehi A, Karimi-Zarchi M, Parsaeian SF, Asadian F, Golestanpour H, Setayesh S, et al. Association of il-6 -174g>c and -572g>c polymorphisms with susceptibility to cervical cancer and ovarian cancer. Asian Pacific Journal of Cancer Prevention. 2021;22(9):2867-71. https://doi.org/10.31557/apjcp.2021.22.9.2867.
3. Abbaspour S, Abdollahi H, Arabalibeik H, Barahman M, Arefpour AM, Fadavi P, et al. Endorectal ultrasound radiomics in locally advanced rectal cancer patients: Despeckling and radiotherapy response prediction using machine learning. Abdom Radiol (NY). 2022;47(11):3645-59. https://doi.org/10.1007/s00261-022-03625-y.
4. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: A worldwide analysis. Lancet Glob Health. 2020;8(2):e191-e203. https://doi.org/10.1016/s2214-109x(19)30482-6.
5. Kazemi S, Zarei F, Heidarnia A, Alhani F. Improve the cervical cancer prevention behaviors through mobile-based educational intervention based on i-change model: Study protocol for a randomized controlled trial. Trials. 2022;23(1):805. https://doi.org/10.1186/s13063-022-06744-5.
6. Marashi T, Irandoost SF, Yoosefi Lebni J, Soofizad G. Exploring the barriers to pap smear test in iranian women: A qualitative study. BMC Womens Health. 2021;21(1):287. https://doi.org/10.1186/s12905-021-01428-9.
7. Mojahed S, Karimi Zarchi M, Bokaie M, Salimi T. Attitude and knowledge of iranian female nurses about human papilomavirus infection and cervical cancer: A cross sectional survey. J Prev Med Hyg. 2013;54(3):187-90.
8. Farshbaf-Khalili A, Salehi-Pourmehr H, Shahnazi M, Yaghoubi S, Gahremani-Nasab P. Cervical cancer screening in women referred to healthcare centres in tabriz, iran. Niger Med J. 2015;56(1):28-34. https://doi.org/10.4103/0300-1652.149167.
9. Khodakarami N, Farzaneh F, Yavari P, Khayamzadeh M, Taheripanah R, Akbari M. The new guideline for cervical cancer screening in low risk iranian women. Iran J Obstet Gynecol Infertil. 2014;17:8-17.
10. Asadollahi S, Mazaheri MN, Karimi-Zarchi M, Fesahat, Farzaneh. The relationship of foxr2 gene expression profile with epithelial-mesenchymal transition related markers in epithelial ovarian cancer. Klin Onkol. 2020;33(3):201-7. https://doi.org/10.14735/amko2020201.
11. Novin K, Fadavi P, Mortazavi N, Sanei M, Khoshbakht Ahmadi H, Barahman M, et al. Neutrophil-to-lymphocyte ratio (nlr) as a poor predictive biomarker for pathological response to neoadjuvant chemoradiation in locally advanced rectal cancer: A prospective study. Asian Pac J Cancer Prev. 2023;24(1):61-7. https://doi.org/10.31557/apjcp.2023.24.1.61.
12. Akbari A, Khayamzadeh M, Salmanian R, Moradi A, Akbari ME. Epidemiology and survival of cervical cancer in iran based on national cancer registry data (2008-2014). Front Oncol. 2023;13:1132369. https://doi.org/10.3389/fonc.2023.1132369.
13. Karimi Zarchi M, Heydari E, Tabatabaie A, Moghimi M, Kooti W. Diagnostic value of the caretm hpv test in screening for cervical intraepithelial neoplasia grade 2 or worse. Asian Pac J Cancer Prev. 2017;18(3):687-93. https://doi.org/10.22034/apjcp.2017.18.3.687.
14. Farshid S, Alijanpour A, Barahman M, Dastgheib SA, Narimani N, Shirinzadeh-Dastgiri Z, et al. Associations of mthfr rs1801133 (677c>t) and rs180113 (1298a>c) polymorphisms with susceptibility to bladder cancer: A systematic review and meta-analysis. Asian Pac J Cancer Prev. 2022;23(5):1465-82. https://doi.org/10.31557/apjcp.2022.23.5.1465.
15. Vinokurov MA, Mironov KO, Domonova EA, Romanyuk TN, Popova AA, Akimkin VG. The genetic variant rs55986091 hla-dqb1 is associated with a protective effect against cervical cancer. Front Oncol. 2023;13:1207935. https://doi.org/10.3389/fonc.2023.1207935.
16. Karimi-Zarchi M, Tabatabaie A, Dehghani-Firoozabadi A, Shamsi F, Baghianimoghaddam M, Dargahi M, et al. The most common type of hpv in women with atypical squamous cell of undetermined significance (ascus) in pap smear in iran-yazd. Int J Biomed Sci. 2015;11(4):173-5.
17. Alemrajabi M, Khavanin Zadeh M, Hemmati N, Banivaheb B, Alemrajabi F, Jahanian S, et al. Inferior part of rectus abdominis muscle flap outcomes after abdominoperineal resection: A case series pilot study. World J Plast Surg. 2021;10(3):104-10. https://doi.org/10.29252/wjps.10.3.104.
18. Karimi-Zarchi M, Allahqoli L, Nehmati A, Kashi AM,

Taghipour-Zahir S, Alkatout I. Can the prophylactic quadrivalent hpv vaccine be used as a therapeutic agent in women with cin? A randomized trial. BMC Public Health. 2020;20(1):274. https://doi.org/10.1186/s12889-020-8371-z.
19. Sayad S, Ahmadi SAY, Moradi M, Nekouian R, Anbari K, FS. A meta-analysis on diagnostic accuracy of serum hla-g level in breast cancer. Expert Rev Precis Med Drug Dev. 2020;5:109–114.
20. Gelassa FR, Nagari SL, Jebena DE, Belgafo D, Teso D, Teshome D. Knowledge and practice of cervical cancer screening and its associated factors among women attending maternal health services at public health institutions in assosa zone, benishangul-gumuz, northwest ethiopia, 2022: A cross-sectional study. BMJ Open. 2023;13(5):e068860. https://doi.org/10.1136/bmjopen-2022-068860.
21. Brown MA, Leo PJ. Genetic susceptibility to cervical neoplasia. Papillomavirus Res. 2019;7:132-4. https://doi.org/10.1016/j.pvr.2019.04.002.
22. Ramachandran D, Dörk T. Genomic risk factors for cervical cancer. Cancers (Basel). 2021;13(20):5137. https://doi.org/10.3390/cancers13205137.
23. Leo PJ, Madeleine MM, Wang S, Schwartz SM, Newell F, Pettersson-Kymmer U, et al. Defining the genetic susceptibility to cervical neoplasia-a genome-wide association study. PLoS Genet. 2017;13(8):e1006866. https://doi.org/10.1371/journal.pgen.1006866.
24. Ahmadi SAY, Sayad S, Shahsavar F, Nekouian R, Panahi M, Sayad S, et al. Expression of angiogenesis-related genes in a group of iranian cases of breast cancer. Curr Pharmacogenomics Person Med. 2021;17:197–205.
25. Feng H, Sui L, Du M, Wang Q. Meta-analysis of tp73 polymorphism and cervical cancer. Genet Mol Res. 2017;16(1). https://doi.org/10.4238/gmr16016571.
26. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M, Mafakher L. Renal cell carcinoma: An overview of the epidemiology, diagnosis, and treatment. G Ital Nefrol. 2022;39(3).
27. Jafrin S, Aziz MA, Islam MS. Association between tp73 g4c14-a4t14 polymorphism and different cancer types: An updated meta-analysis of 55 case-control studies. J Int Med Res. 2022;50(10):3000605221133173. https://doi.org/10.1177/03000605221133173.
28. Asgari M, Firouzi F, Abolhasani M, Bahadoram M, Barahman M, Madjd Z, et al. The association of p53, ck29, and fgfr3 overexpression with the characteristics of urothelial cell carcinoma of the bladder. Asian Pac J Cancer Prev. 2023;24(9):3125-31. https://doi.org/10.31557/apjcp.2023.24.9.3125.
29. Meng J, Wang S, Zhang M, Fan S, Zhang L, Liang C. Tp73 g4c14-a4t14 polymorphism and cancer susceptibility: Evidence from 36 case-control studies. Biosci Rep. 2018;38(6). https://doi.org/10.1042/bsr20181452.
30. Abbaspour S, Barahman M, Abdollahi H, Arabalibeik H, Hajainfar G, Babaei M, et al. Multimodality radiomics prediction of radiotherapy-induced the early proctitis and cystitis in rectal cancer patients: A machine learning study. Biomed Phys Eng Express. 2023;10(1). https://doi.org/10.1088/2057-1976/ad0f3e.
31. Liu F, Liu L, Li B, Wei YG, Yan LN, Wen TF, et al. P73 g4c14-a4t14 polymorphism and cancer risk: A meta-analysis based on 27 case-control studies. Mutagenesis. 2011;26(4):573-81. https://doi.org/10.1093/mutage/ger018.
32. Razmjoo S, Jazayeri SN, Bahadoram M, Barahman M. A rare case of craniopharyngioma in the temporal lobe. Case Rep Neurol Med. 2017;2017:4973560. https://doi.org/10.1155/2017/4973560.
33. Akbari ME, Akbari A, Nafissi N, Shormeij Z, Sayad S, Rohani Rasaf M, et al. Prognostic factors of recurrence (early and late) and death in breast cancer patients in iranian women. Int J Cancer Manag. 2016;9(6):e5747. https://doi.org/10.17795/ijcp-5747.
34. Cheraghi A, Barahman M, Hariri R, Nikoofar A, Fadavi P. Comparison of the pathological response and adverse effects of oxaliplatin and capecitabine versus paclitaxel and carboplatin in the neoadjuvant chemoradiotherapy treatment approach for esophageal and gastroesophageal junction cancer: A randomized control trial study. Med J Islam Repub Iran. 2021;35:140. https://doi.org/10.47176/mjiri.35.140.
35. Vakili Ojarood M, Khanghah AS, Belalzadeh M. Gangrenous ischemic colitis due to acute promyelocytic leukaemia, and myelofibrosis in a 62-year-old man suffering from esrd; case report. Int J Surg Case Rep. 2021;89:106663. https://doi.org/10.1016/j.ijscr.2021.106663.
36. Gholi-Nataj M, Rafieian S, Barahman M, Shirinzadeh-Dastgiri A, Vakili M, Ershadi R, et al. A meta-analysis for prevalence of lung cancer patients with sars-cov-2 infection during the covid-19 pandemic. Eurasian J Med Oncol. 2022;6:73–82 https://doi.org/10.14744/ejmo.2022.5053.
37. Shirinzadeh-Dastgiri A, Saberi A, Vakili M, Marashi SM. 21-year-old female with pneumothorax and massive air leak following blunt trauma; a photo quiz. Arch Acad Emerg Med. 2022;10(1):e24. https://doi.org/10.22037/aaem.v10i1.1513.
38. Vakili J, Samadi N, Dargah M, Isazadehfar K, Kabar S, Zade A, et al. Comparative analysis of the effects of vasopersin and norepinephrine on the renal function in patients undergoing cabg. Iran Red Crescent Med J. 2018;20:e67026.. https://doi.org/10.5812/ircmj.67026.
39. Amini K, Vakili Ogharood M, Davari M, Ershadifard S, Asadi H. A case of a fractured fragment of tracheostomy tube entering the left bronchus: A case report. J Babol Univ Med Sci. 2021;23(1):393-7. https://doi.org/10.22088/jbums.23.1.393.
40. Davari HM, Rahim MM, Ershadi RM, Rafieian SM, Mardani PM, Vakili MM, et al. First iranian experience of the minimally invasive nuss procedure for pectus excavatum repair: A case series and literature review. Iran J Med Sci. 2018;43(5):554-9.
41. Ghorbani S, Rezapour A, Eisavi M, Barahman M, Bagheri Faradonbeh S. Cost-benefit analysis of breast cancer screening with digital mammography: A systematic review. Med J Islam Repub Iran. 2023;37:89. https://doi.org/10.47176/mjiri.37.89.
42. Niwa Y, Hamajima N, Atsuta Y, Yamamoto K, Tamakoshi A, Saito T, et al. Genetic polymorphisms of p73 g4c14-to-a4t14 at exon 2 and p53 arg72pro and the risk of cervical cancer in japanese. Cancer Lett. 2004;205(1):55-60. https://doi.org/10.1016/j.canlet.2003.11.014.
43. Zheng L. Association of p53 arg72pro polymorphism, p73g4a polymorphism with cervical cancer in xinjiang uygur population. Shihezi Univ. 2006;11:65-89.
44. Liu S, Chan YK, Leung CY, Tsang PCK, Ngan HYS. Genetic polymorphisms of p73 is associated with the risk of cervical cancer. Cancer ReS. 2007;67:3434.
45. Zheng XZ, Yang AQ, Pan XL, Zheng LL, Zhou QY, Li XM, et al. Relationship between p53 arg72pro polymorphism and cervical carcinoma in uigur and han women in xinjiang. Zhonghua Bing Li Xue Za Zhi. 2007;36(8):511-5.
46. Sun L, NG ZZ. Correlation of p73 polymorphisms to genetic susceptibilities to cervical carcinoma and meta-analysis. Basic Clin Med. 2012;32:1421-5.
47. Craveiro R, Bravo I, Catarino R, Teixeira AL, Sousa H, Pereira D, et al. The role of p73 g4c14-to-a4t14 polymorphism in the susceptibility to cervical cancer. DNA Cell Biol. 2012;31(2):224-9. https://doi.org/10.1089/

dna.2011.1294.
48. Jha AK, Nikbakht M, Jain V, Sehgal A, Capalash N, Kaur J. Promoter hypermethylation of p73 and p53 genes in cervical cancer patients among north indian population. Mol Biol Rep. 2012;39(9):9145-57. https://doi.org/10.1007/s11033-012-1787-5.
49. Guo H, Yang S, Xu L, Li D, Tang J, Wang S, et al. Association between the p73 gene g4c14-to-a4t14 single nucleotide polymorphism and risk of cervical cancer by high resolution melting and pcr with confronting two-pair primers in a chinese population. Oncol Lett. 2016;12(1):721-6. https://doi.org/10.3892/ol.2016.4655.
50. Barahman M, Zhang W, Harris HY, Aiyer A, Kabarriti R, Kinkhabwala M, et al. Radiation-primed hepatocyte transplantation in murine monogeneic dyslipidemia normalizes cholesterol and prevents atherosclerosis. J Hepatol. 2019;70(6):1170-9. https://doi.org/10.1016/j.jhep.2019.01.010.
51. Liang X, Chen B, Zhong J. Association of p73 polymorphisms with susceptibilities of cervical carcinoma: A meta-analysis. Oncotarget. 2017;8(34):57409-13. https://doi.org/10.18632/oncotarget.18164.