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Review Article

Association between *P53* Gene Mutations and Colorectal Cancer in the Iranian Population: A Systematic Review

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Abstract

Background: Colorectal cancer (CRC) is the fourth most common cancer and one of the most significant cancers affecting the Iranian population. This systematic review aimed to investigate the association between mutations in the *P53* gene and CRC.

Methods: We conducted a search of six databases, including; Scopus, PubMed, Web of Science, Cochrane Library, SID, and Magiran up to Aug 10, 2024. Concepts in the search strategy were Iran, P53, and "Colorectal cancer". Original articles written in English or Persian that investigated the association between *P53* gene mutations and CRC in the Iranian population were included.

Results: Out of 313 articles, 17 articles were included in the study. Six case-control studies investigated the association between the codon 72 polymorphism of the *P53* gene and colorectal cancer. Three studies found a significant difference in genotype frequencies of this polymorphism between CRC patients and healthy individuals. Exon 6 was shown to be one of the most common mutated exons in colorectal cancer. Mutations in exon 7 were associated with poor prognosis. The most common type of mutation was G to A mutation from exons 5 to 8 CpG sites.

Conclusion: The present study suggests a potential association between the presence of the Arg allele at codon 72 within the *P53* gene and a heightened susceptibility for developing and metastasizing CRC within the Iranian population. Furthermore, exons 5 to 8 of the *P53* gene suggests that mutations localized at these sites may portend a poor prognosis.

Keywords: Colorectal cancer; *P53* mutation; Systematic review

Introduction

Colorectal cancer (CRC) is one of the most common cancers affecting the Iranian population. Figure 1, shows the incidence rate of CRC in provinces of Iran stratified by sex (1). In 2018, Asia recorded the highest incidence (51.8%) and mortality rates (52.4%) of CRC across all genders and age groups (2). In Iran, CRC is the fourth most common cancer (3). Adenocarcinoma is the predominant histological type of CRC across all regions in Iran (4).

The anticipated increase in CRC incidence emphasizes the necessity for additional research to

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identify risk factors, enhance diagnostic methods and implement screening programs for individuals at higher risk of CRC (4).

APC (Adenomatous polyposis coli), *KRAS* (Kirsten rat sarcoma virus), and *P53* are the three important genes in which mutations lead to the occurrence of CRC (5). The inactivation of the *APC* gene results in the uncontrolled activation of the Wnt pathway, leading to tumorigenesis in most CRC cases (6). *KRAS* mutations reduce the GTPase activity of the protein (7). The mutated KRAS protein becomes unresponsive to GTPase activating proteins (GAPs) and quickly swaps GDP (Guanosine diphosphate) for GTP (Guanosine triphosphate), maintaining its active form (8). The continuous activity of KRAS leads to uncontrolled cell growth and transformation, promoting cancer metastasis and increasing resistance to chemotherapy in various cancers, including CRC (9, 10).

P53 mutation occurs in 34% to 45% of CRC cases (11-13). Most of these mutations usually occur in the DNA-binding domains at exons 5 to 8, mainly in some codons such as 175, 245, 273, and 282, and result in single-base substitutions (12, 14). These mutations, particularly in the hotspot regions of the *p53* gene, result in a protein that loses its function (15). Mutations in *P53* are significantly associated with lymphatic and vascular invasion in CRC patients, and patients with *P53*-mutated CRC exhibit greater resistance to chemotherapy and a weaker prognosis than those without *P53* mutations (12, 16). The precise biological mechanisms underlying these associations remain unclear. However, research conducted by Ahnen et al (17), Elsaleh et al (18), and Liang et al (19), discovered that patients with the wild-type *P53* gene, as opposed to those with the mutant *P53* gene, experience better outcomes from 5FU (5-Fluorouracil)-based chemotherapy. However, these findings are consistent with in-vitro and animal studies (20).

Numerous global studies have examined the relationship between *P53* gene mutations and CRC. However, the findings are often inconsistent. One possible explanation for these discrepancies is the variation in the genotype distribution of the *P53* codon 72 Arg/Pro polymorphism across different geographic regions and ethnic groups (21). General populations in Latin America, United States, and Europe show higher frequencies of the Arg allele compared to the Pro allele. In contrast, African and Asian populations exhibit lower frequencies of the Arg allele (22).

This study aimed to address a gap in the existing research by investigating the frequency of mutations in the hotspot regions of the *P53* gene among CRC patients in Iran. Due to the diverse ethnicities within the Iranian population, there is a lack of comprehensive studies examining these mutations and their association with CRC across different cities in Iran. Given that a comprehensive exploration of the association between *P53* gene mutations and CRC in the Iranian population is yet to be conducted, our intended objective in this study is to take a significant stride toward identifying potential risk and predictive factors in CRC in the Iranian population via a systematic review.

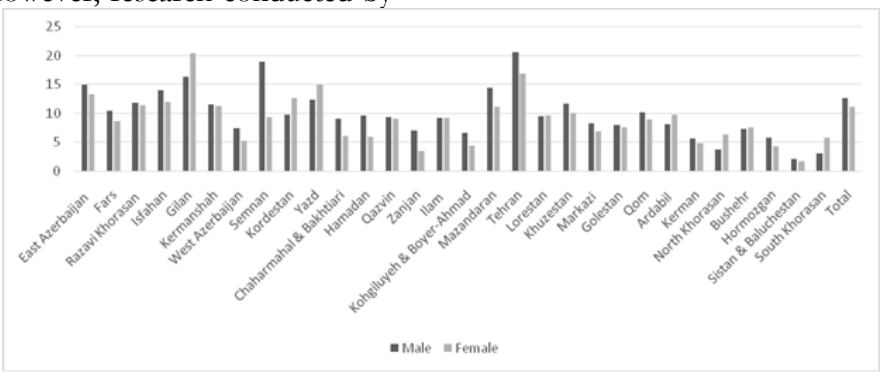

Fig. 1: The incidence rate of CRC in provinces of Iran stratified by sex

Methods

This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23) and aims to examine the potential correlation between *P53* gene mutations and CRC within the Iranian population.

Inclusion criteria

The inclusion criteria for this study were original articles written in English or Persian that investigated the association between *P53* gene mutations and CRC in the Iranian population. All short articles, letters to the editor, conference abstracts, observational studies, review articles, articles with incomplete access, articles studying non-human samples or cell lines, and articles studying non-Iranian specimens were excluded from the study. The quality assessment criteria for each study included: The number of participants, with case-control studies requiring at least 100 participants in each group, and the use of appropriate methods and techniques that are consistent with similar studies conducted in other countries and populations.

Databases and search strategy

The databases of Scopus, PubMed, Web of Science, Cochrane Library, Magiran, and SID were searched to retrieve English and Persian articles. The searches were done without any time limitations and up to Aug 10, 2024. Used concepts in the search strategy were Iran, *P53*, and "Colorectal cancer".

Selection of studies/ Data collection

The retrieved studies based on the search strategy were imported into EndNote references management software. Initially, duplicate articles were identified and removed. Then, the title and abstract of all studies were evaluated based on the inclusion criteria and if needed, the full text of the articles was reviewed. The selection process of the studies was carried out independently by two researchers. Figure 2 shows the procedure for screening and including studies.

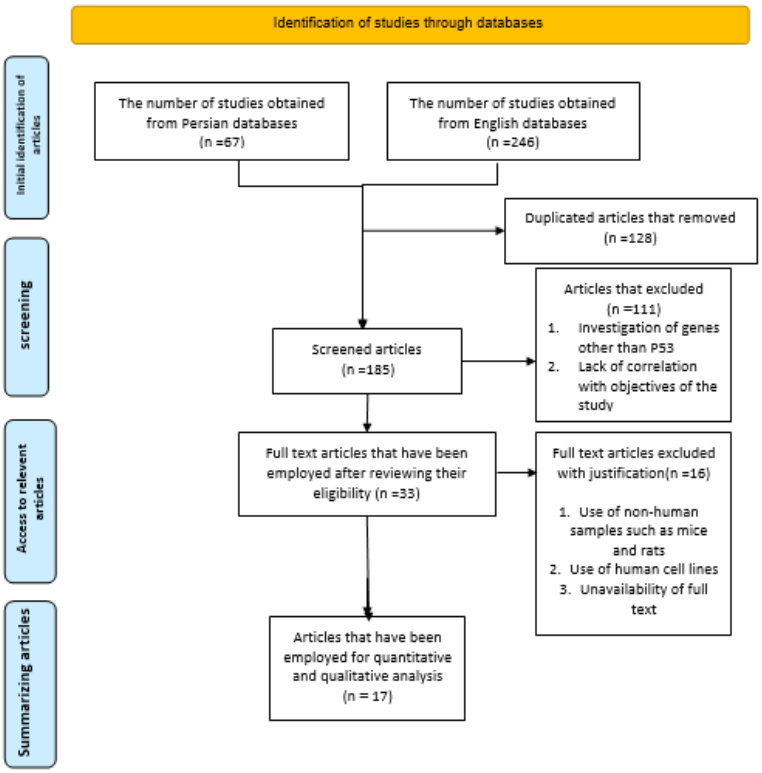

Fig. 2: The procedure for screening and including studies

Data extraction

After the selection of appropriate studies, data collection was systematically conducted in line with the predetermined inclusion and exclusion criteria, utilizing a purpose-specific data extraction form aligned with the study's objectives. The data encompassed the publication year, the name of the first author, the city, the study design, the type of mutation investigated, the number of samples, and a summary of the results. This information aids in addressing questions such as the number of studies conducted on each exon, the number of participants in each study, and the populations examined in each study to achieve the study's objectives.

Results

In the initial review, 313 articles were retrieved and imported into Endnote. After reviewing their eligibility, 17 articles remained, presented descriptively in Table 1.

In the present study, 8 articles specifically focused on the association of codon 72 polymorphisms of the *P53* gene with colorectal cancer, 2 articles examined the association of exon 6 mutations of the *P53* gene with colorectal cancer, one article specifically focused on the association of exon 7 mutations of the *P53* gene with CRC prognosis, 5 articles analyzed mutations in at least two exons out of exons 5 to 8 in CRC patients, and finally, one article generally investigated mutations in the *P53* gene in CRC patients (Fig. 3).

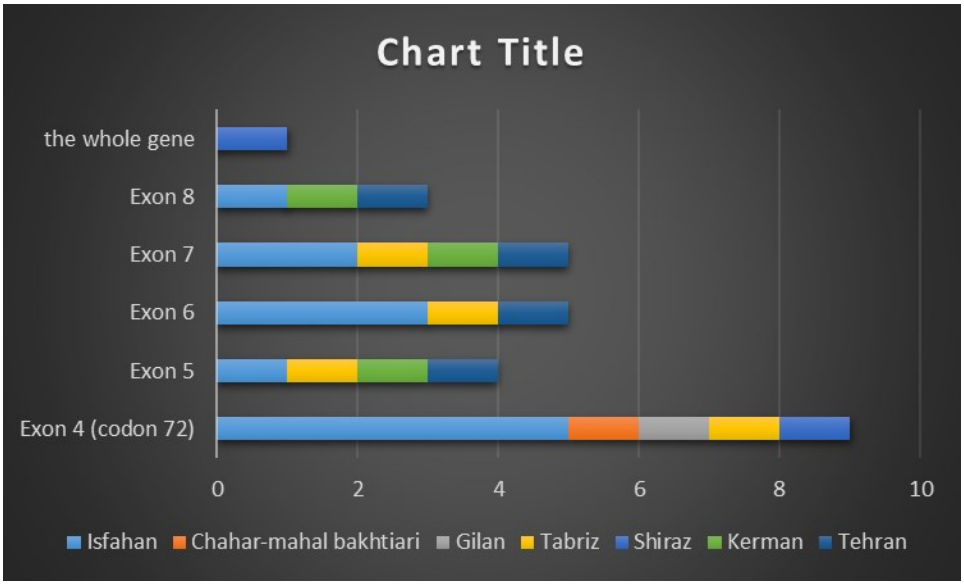

Fig. 3: The number of studies focused on each exon across various regions. The codon 72 polymorphism of the P53 gene is the most extensively researched region, with the majority of studies conducted in Isfahan

Codon 72 polymorphism

Codon 72 is located in exon 4 of the *P53* gene and results in the substitution of Pro with Arg amino acid. Dastjerdi et al. investigated the relationship between codon 72 and sporadic CRC in Isfahan. In comparison to other Asian studies, both observed groups exhibited a more pronounced prevalence of the Arg allele in contrast to Pro allele. Additionally, the frequency of the Arg/Arg genotype was significantly different between the two patient groups compared to the Pro/Pro and Arg/Pro genotypes (24).

The arginine allele is more frequent than the proline allele. The Arg/Arg genotype in the patient group is significantly higher than the healthy

group (25). Doosti et al. showed the same results in the southwest of Iran (26).
Mojtahedi et al. investigated the association of the *P53* codon 72 with gastric and CRC in Shiraz and they did not reveal any statistically meaningful variations in the distribution of genotypes of this specific polymorphism (21).
In Gilan, Iran, a statistically significant correlation was indicated between the presence of the Arg allele and the metastatic nature of colorectal cancer. Furthermore, the Arg/Arg genotype was present in 68.8% of patients with tumors on the left side of the colon (27).
Asadi et al. did not find any substantial discrepancy between the polymorphism and CRC in the Azerbaijani population (28).

Descriptive Analytical Studies of Codon 72 Polymorphism

In Isfahan, the frequency of the arginine allele compared to the proline allele was found to be higher in patients with sporadic CRC and furthermore, a higher incidence of MSI was observed among patients exhibiting the Arg/Pro genotype in comparison to those with the Arg/Arg and Pro/Pro genotypes (29).
Similarly, an exploration of the relationship was conducted between this genetic polymorphism and patients with mucinous and non-mucinous CRC in Isfahan, which revealed that the Pro allele was correlated with advanced stages of non-mucinous colorectal cancer (30).

Exon 6 Mutations

Golmohammadi et al. examined the mutations in exon 6 of the *P53* gene in 80 patients with CRC and their association with *P53* protein expression. In this study, 12 patients had mutations in exon 6, with negative protein expression in two cases and positive protein expression in ten cases, indicating a significant correlation between the mutation in exon 6 and *P53* gene expression (31).
Seven samples out of 40 had mutations in exon 6, with one case in the rectum and the remaining six samples in other regions of the colon (32).

Exon 7 Mutations

In order to explore the mutations occurring in exon 7 of the *P53* gene in patients affected by colorectal cancer, and its potential association with the prognosis of the disease, a research was conducted in Isfahan. By examining 80 samples of colorectal cancer, 4 samples were found to have mutations in exon 7. The survival rate of patients with mutations in this exon was lower than that of patients without mutations. Mutations in exon 7 may be associated with poor prognosis (33).

Mutations in Exons 5 to 8

Lohrasbi et al. conducted a study in Kerman Province to investigate the mutations present in exons 5 to 8 of the *P53* gene in CRC patients and compare them with healthy samples. Two deletion mutations for the first time were observed in codons 140 and 142 in one of the cancer samples, which caused stop codons at positions 169 and 173, respectively. In three cancer samples, a substitution mutation was present, with two occurring in codon 284 and one in codon 184 and in one cancer sample, two different insertion and substitution mutations were present in intron 7, not observed in healthy tissue samples (34).
Mahdavi-Nia et al. investigated these mutations in the north of Iran, and their association with MSI occurrence and *K-ras* gene mutations. Out of 196 patients, they observed mutations in these exons in 87 patients, with 9 samples having 2 mutations in this region, resulting in a total of 96 mutations. Of these 96 mutations, 84 were of the insertion-deletion type, with the most common being G to A mutations in CpG regions (42 of 96). The most frequent codons with mutations in these regions were 248, 213, 245, 175, and 273. In addition, they found an inverse correlation between *P53* gene mutations in the aforementioned regions and MSI occurrence (35).
Gholmohammadi et al. carried out a study with the goal of analyzing mutations in exons 7 and 8 of the *P53* gene in Isfahan. The study included 80 samples of patients with colorectal cancer, of which 9 had mutations in these two exons, 4 of

related to exon 7 and 5 to exon 8. Moreover, analysis of the data revealed no noteworthy correlations between the mutations observed and the location of the tumor in the colon (36).

Gholmmohamadi et al. carried out another research included 61 patients, of which 14 had 21 point mutations in exons 5 and 6 of the *P53* gene, 81% of which were missense mutations and 9.5% were nonsense mutations. Furthermore, two new mutations were observed in the intron between these two exons, one of which was a deletion mutation that caused a frameshift and did not produce any protein product. Additionally, patients with mutations in these exons had a lower rate of recovery (37).

Dayemomid et al. investigated mutations in exons 5 to 7 of the *P53* gene in the colon and stool tissues of 64 patients with colorectal cancer. Overall, 27 point mutations were observed, including 22 missense mutations, 3 nonsense mutations, and 2 silent mutations. However, in the stool examination of these patients, 12 patients were found to have mutations in this region, with a total of 22 point mutations, leading to the conclusion that stool samples can be used instead of colon tissue samples for the detection of mutations in patients with colorectal cancer. In exon 7 and codon 245, the highest number of mutations was observed among the patients, and there was a significant correlation between the stage and histological differentiation of the tumor and the mutations present in the *P53* gene (38).

Mutation Analysis throughout the P53 Gene

Ashktorab et al. examined mutations in genes associated with CRC in Shiraz. Overall, 106 mutations were observed in the *P53* gene, of which 61 were new and had not been previously identified. However, using the Illumina sequencing platform, only 3 mutations were confirmed. Of these 3 mutations, two were located in introns, which are transcriptionally active regions, and the other one was a substitution mutation in a proline-rich region (39).

Table 1: Summary of descriptive characteristics of included studies

Author's Name/ Publication Year	City/ Province	Type of Study	The area under investigation	Sample Number (Case/Control)	Result
Doosti (26)	Isfahan, Chahar Mahal Bakhtiari	CC	Codon 72	140/145	SA
Faghani (27)	Gilan	CC	Codon 72	112/112	NSA
Dastjerdi (25)	Isfahan	CC	Codon72	250/250	SA
Dastjerdi (29)	Isfahan	DA	Codon72	144 patients	Arg/Pro associated with MSI
Dastjerdi (24)	Isfahan	CC	Codon 72	180/180	SA
Asadi (28)	Tabriz	CC	Codon 72	100/100	NSA
Mojtahedi (21)	Shiraz	CC	Codon 72	164/132	NSA
Dastjerdi (30)	Isfahan	DA	Codon 72 Exon 4	Mucinous (46) and non-mucinous (134) adenoma carcinoma	Arg allele associated with mucinous adenoma carcinoma
Golmohammadi (37)	Isfahan	DA	Exon 5, 6	61 patients	Patients with mutations had a lower rate of recovery
Golmohammadi (31)	Isfahan	DA	Exon 6	80 patients	A correlation between the mutation in exon 6 and *P53* gene expression
Golmohammadi	Isfahan	DA	Exon 6	40 patients	Exon 6 is a common mu-

Table 1: Continued …

(32)					tated exons in CRC
Golmohammadi (33)	Isfahan	DA	Exon 7	80 patients	Mutations in exon 7 associated with poor prognosis
Golmohammadi (36)	Isfahan	DA (cross-sectional)	Exon 7, 8	80 patients	NSA
LohrasebiNejad (34)	Kerman	DA	Exons 5, 7,8 Intron 7	43 patients	Found two novel mutations in codons 140 and 142 in CRC patients for the first time.
Dayemomid (38)	Tabriz	DA	Exons 5, 6,7	64 patients	Stool samples can be used instead of colon tissue samples for the detection of mutations
Mahdavinia (35)	Tehran	DA	Exons 5 to 8	196 patients	Significant correlation between G to A mutations in non-CpG regions and MSI occurrence
Ashktorab (39)	Shiraz	DA	The whole gene	63 patients	Found 3 novel mutations in CRC patients

CC: Case-control, DA: Descriptive-analytical, SA: Significant association, NSA: No significant association

Discussion

This systematic review endeavors to scrutinize the potential relationship between polymorphisms and mutations in the *P53* gene with CRC within the Iranian population. Polymorphism codon 72 of the *P53* gene has been studied more than other polymorphisms. Two studies conducted in Isfahan and southwestern region of Iran, have identified a meaningful correlation between the Arg allele and the Arg/Arg genotype, with an increased vulnerability for the development of CRC (24-26). These results were consistent with the studies in Argentina and Italy (40, 41). However, studies in Taiwan, Spain, and China found a significant association between the Pro allele and the risk of developing CRC, in contrast to the aforementioned studies (42-44). This polymorphism also could be a predisposing factor for the incidence of other types of cancer such as oral squamous cell carcinoma in the Iranian population (45). Arg/Arg genotype induces apoptosis more rapidly and suppresses transformation more effectively than the Pro/Pro genotype (46, 47).

In Isfahan, the Arg/Pro genotype is associated with the occurrence of MSI (29), which is consistent with the results of the Sobczuk study on the importance of MSI in sporadic endometrial cancer in Poland (48). There are some explanations for the P53-dependent increase in MSI: Firstly, heterozygosity at *P53* codon 72 might decrease genomic instability at the nucleotide level by either directly or indirectly facilitating repair (29). This is evidenced by the observation that P53 can bind to insertion/deletion loops, which are DNA lesions linked to MSI (49). Another possibility is that the Arg72 allele is more frequently mutated and retained in human tumors that develop in Pro/Arg heterozygotes. In this scenario, the *P53* mutant acts as a stronger inhibitor of p73, a member of the P53 family with an apoptotic function (50). A third possibility is that *P53* heterozygosity might cause an increase in MMR defects (29). However, no correlation was observed between MSI and susceptibility to the thyroid, breast, bile duct, and bladder cancers, respectively, in studies in the USA, Turkey, Greece, and Germany (51-54).

There was a significant association between exon 6 mutations in patients with CRC and the expression of the *P53* gene (31), which is consistent with the results of study in Chile (55). In another study, 7 out of 40 fresh tissue samples from pa-

tients were found to have mutations in exon 6 (32). This is in contrast to the studies in Japan and Ireland, that worked with paraffin samples and observed a lower number of mutations (56, 57). Additionally, considering the high number of mutations in exon 6 observed in the Roa study, which examined fresh tissue samples (55), the influence of fresh tissue samples on the assessment of mutation frequency via molecular testing can be observed.

In 2009, among 80 patients with colorectal cancer, Golmohammadi observed four cases of mutation in exon 7, suggesting that lifestyle differences may be the cause of these mutations (33). However, in Chile, China, and northwestern Iran found a high rate of mutations in this exon among affected patients, which does not match the results of Golmohammadi's study (38, 55, 58). By comparing two articles conducted in Iran, considering the similarity of molecular techniques and the sample used, environmental factors can be referred to as the cause of differences in the results of these two studies. Moreover, the study concluded that mutation in exon 7 is associated with poor prognosis (33), which is consistent with the results of Iniesta's study in Spain (59). The mutation in exon 7 may be linked to increased cancer cell progression, as it is associated with the expression of angiogenesis factors (60, 61), that significantly contribute to the advancement of cancer cell (33).

Five studies investigated the mutations present in at least two exons of exons 5 to 8 of the *P53* gene. Lohrasbi reported two deletion mutations in codons 140 and 142 in these exons that had never been observed in patients with CRC (34), but these deletions had been reported in lung, breast, and ovarian cancers in Tseng, Baumbusch, and Angelopoulou studies (62-64).

Evaluating the *P53* mutation in cancer patients is essential for devising an effective treatment strategy (34). Current chemotherapy and radiotherapy treatments for cancer are entirely reliant on the function of P53, as they activate the intrinsic pathway of apoptosis only when P53 is functioning normally (65). Thus, conducting a genetic test before chemotherapy can aid in achieving a successful treatment outcome (34).

Mahdavinia conducted an empirical analysis to examine the prevalence of mutations in exons 5 to 8 of the *P53* gene among a cohort of 196 CRC patients and observed that the most common mutation was a G-to-A transition in CpG regions (35), which is consistent with Russo, Soussi, and Olivier's studies (12, 66, 67). Additionally, individuals with mutations in this region had a lower recovery rate than those without mutations (37), confirmed by the results of other studies (68-71). It may assist clinicians in understanding the extent of genetic alterations that are recognized for their predictive value in clinical trials.

Dayem Omid investigated the frequency of mutations in exons 5 to 7 of the *P53* gene in tissue samples and compared them with fecal samples from patients with colorectal cancer. Out of 27 mutations in tissue samples, 22 mutations were observed in fecal samples of patients (38), which shows a significant difference compared to the study by Eguchi, who only observed 36% of the mutations present in the tissue in fecal samples (72). The reason for this could be the low number of samples in Eguchi's study.

Finally, a positive correlation was identified between Body Mass Index (BMI) and CRC. Conversely, they observed an inverse relationship between fiber consumption and CRC in the northeast region of Iran (73).

This study has several limitations. Firstly, the systematic review protocol was not registered in the PROSPERO database. Secondly, despite the study's reliability, it did not include the Embase database due to access restrictions, nor did it utilize the Google Scholar database due to its lack of specificity. Lastly, future research should consider conducting a meta-analysis to provide a more robust statistical evaluation.

Conclusion

The current review highlights the potential significance of the Arg codon 72 alleles of the *P53* gene in the development of CRC within the Ira-

nian population, as well as their plausible association with the metastatic nature of this disease.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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We did not receive any financial support for this study.

Conflict of Interest

The authors declare that there is no conflict of interests.

Data Availability

The data underlying this article are available in the article

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