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Prevalence of hereditary nonpolyposis colorectal cancer in patients with colorectal cancer in Iran: a systematic review

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ABSTRACT

Introduction: Colorectal cancer (CRC) is the third leading cause of cancer deaths in the world, and hereditary factors and family history are responsible for the incidence and development of the disease in 20 to 30% of cases. Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is the most common hereditary form of CRC that is inherited in an autosomal dominant manner. This study consisted of a systematic literature review of research articles that described the prevalence of HNPCC in Iranian patients with CRC.

Methods: A systematic literature search was conducted in the PubMed, Scopus, IranMedex, and Google Scholar databases to identify relevant articles that describe HNPCC or Lynch syndrome in patients with CRC in Iran. For this purpose, a keyword search of the following terms was employed: (((Hereditary nonpolyposis colorectal cancer OR HNPCC OR Lynch syndrome)) AND (colorectal cancer OR familial colorectal cancer OR colon cancer OR rectal cancer OR bowel cancer)) AND IRAN. All eligible documents were collected, and the desired data were qualitatively analyzed.

Result: Of the 67 articles that were found via the initial database search, only 12 were deemed to be of relevance to the current study. These articles included a total population of 3237 and this sample was selected and qualitatively analyzed. The findings of the review revealed that the frequency of mutation in MLH1, MSH2, PMS2, and MSH6 genes varied between 23.1% and 62.5% among the studied families. This indicated that HNPCC is linked with up to 5.5% of the total cases of colorectal cancers in Iran.

Conclusion: The results of this study revealed that the hereditary form of HNPCC or Lynch syndrome is significantly high among patients with CRC in Iran.

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Introduction

Colorectal cancer (CRC) is the third leading cause of death from cancer in the world. It is the third most common cancer in women and the fifth most frequently reported malignancy among men in Iran (1). The prevalence of CRC is approximately 6 to 7.9 in each 100,000, and is the 4th most frequent cancer in Iran (2,3). About 70 to 80% of colorectal cancers are sporadic; however, genetic factors are involved in the remaining 20 to 30% (4). Hereditary nonpolyposis colorectal cancer (HNPCC), which is also known as Lynch syndrome, is an autosomal dominant genetic disorder that is

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the most common hereditary colorectal cancer syndrome. The prevalence of this syndrome varies from 1 to 6% in different countries; however, on average, 3% of newly diagnosed CRC patients have Lynch syndrome (5). HNPCC is thought to be associated with an increased risk of the incidence of several malignancies, wherein colorectal and endometrial cancers are of great importance (6).

Mutations in DNA mismatch repair (MMR) genes are widely regarded as one of the major causes of Lynch syndrome (7). The syndrome can be detected in colon biopsy specimens by two conventional methods: Microsatellite Instability Testing (MSI), which has a sensitivity of 85%, and a immunohistochemistry (IHC) of the tumor, which can provide evidence of a lack of MMR proteins (MLH1, MSH2, MSH6 and PMS2) and has a sensitivity of 83% (8). It is widely accepted that MSI represents a suitable method for evaluating different types of cancers such as stomach, breast, lung, thyroid, prostate, uterus, ovarian, head and neck, and especially colorectal cancer (9). Furthermore, research has also demonstrated an association between immunohistochemical analyses of MMR protein and MSI molecular investigation in patients with colorectal cancer (10). MMR proteins are a group of enzymes that are mostly found in the nucleus of all proliferating cells, cells that participate in the repair of base-base mismatch and play a major role in maintaining genomic stability (11).

CRC cancer in people aged below 40 are found in almost one fifth of all malignancy cases in Iran (3,12). According to the latest guidelines for Lynch syndrome, all CRC tumors should be evaluated for Lynch syndrome by IHC or MSI. This is of particular importance for patients under the age of 70 years old (12). For this purpose, biopsies of patients with colorectal cancer can be analyzed in terms of MMR proteins by IHC. Therefore, it may be possible to prevent the onset of cancer by screening the related common mutations as well as the prevalence of Lynch syndrome in patients with CRC, and to identify family members who may be at risk. So far, very limited studies on familial colon cancer have been conducted in Iran. This study aimed to address that gap in understanding by conducting a systematic review of existing literature in which the prevalence of HNPCC or Lynch syndrome has been evaluated among CRC patients in Iran.

Methods

Literature search strategy

A systematic literature search was performed to investigate the prevalence of HNPCC or Lynch syndrome in patients with CRC in Iran. For this purpose, we searched PubMed, Scopus, IranMedex, and Google Scholar databases independently for "hereditary nonpolyposis colorectal cancer" and "familial colorectal cancer" as key terms in the title, keywords, and article abstracts. Following that, the search method (((Hereditary nonpolyposis colorectal cancer OR HNPCC OR Lynch syndrome)) AND (colorectal cancer OR familial colorectal cancer OR colon cancer OR rectal cancer OR bowel cancer)) AND IRAN was used to conduct the literature search in PubMed, IranMedex, and Google scholar. The search was then further refined by restricting the records to literature that described studies on the Iranian population. We used a similar search method to find relevant articles in the Scopus. For this purpose, using the following strategy TITLE-ABS-KEY (hereditary nonpolyposis colorectal cancer syndrome OR HNPCC OR Lynch syndrome) AND (LIMIT-TO (AFFILCOUNTRY, "Iran")) AND (LIMIT-TO (DOCTYPE, "ar")),"Hereditary nonpolyposis colorectal cancer" was searched and then the "colorectal cancer" was searched within the results. The records were then limited to studies that had been conducted in Iran. Along with the electronic data¬base search, reference lists of previously collected articles were also searched to include other potentially relevant studies.

Eligibility criteria

No time and/or language limitations were defined for the collection of potentially relevant articles during the processes of search and study selection. Hence, all documents that were deemed to be relevant to the main purpose of this study wherein the prevalence of HNPCC or Lynch syndrome had been investigated in an Iranian population with CRC were included in this review and used for further analysis. For this purpose, and to collect all available published data, articles that described different study methodologies were included in this survey. However, to avoid any misconceptions, only those articles with English and Persian languages were selected for further evaluation. Articles that were deemed to be irrelevant to the objectives of the current study were excluded in the first step of article selection. Likewise, conference abstracts or presentations, letters, case reports, review articles, and meta-analysis were also excluded from the additional assessment. As too were duplicate documents as well as articles that were deemed to lack data sufficiency. Hence, according to the above-mentioned process, the inclusion criteria in this survey consisted of all articles wherein the prevalence of HNPCC or Lynch syndrome had been studied in an Iranian population with CRC.

Data extraction

All relevant information, including the author's name, publication date, sample size, and territory of the studied population, as well as the total number of participants enrolled in the selected literature, were extracted. Other required and informative data, including target population, demographic records of studied patients, methods of assessment, type of study design, and the key findings of the included studies, were extracted and used for further analysis based on the main purpose of this study. All processes, including the literature search methodology and study selection, as well as data processing and analysis, were performed according to the PRISMA checklist 2009 (13). Two investigators independently identified all potentially eligible articles among the collected documents extracted the relevant data. Any disagreements between the investigators were resolved before further data processing.

Studied variables

Different methods, including MSI testing, fluorescent multiplex polymerase chain reaction, clinical evaluation of patients, colonoscopy, high-performance liquid chromatography (HPLC), and real-time PCR, have previously been used to clinically evaluate patients. Other methods, such as statistical analysis for the incidence and prevalence of HNPCC or Lynch syndrome in all studied family members, as well as the assessment of allelic variation, have also been used to assess HNPCC prevalence among CRC patients. The studied variables in the included documents involved mononucleotide markers including BAT-25, BAT-26, MON0-27, NR-21 and NR-24, polymorphisms of MLH1, MSH2, PMS2, and MSH6 genes and immunohistochemical analysis. Other desired variables that were extracted and compared included survival rate, grade of tumor, the numbers of observed tumors, and distribution of tumors.

Results

Literature search results

Of the 64 articles that were collected via the database search, 21 potentially eligible documents were found in PubMed, 19 in Scopus, 20 in IranMedex, and 4 in Google Scholar. Three additional potentially relevant documents were also identified through manual reference list screening of the previously included literature. Of the collected articles, 38 studies were excluded after the title and abstract screening process because they were deemed to be irrelevant to the study objectives. After limiting the records to those studies that were conducted on the Iranian population, seven additional documents were also excluded from the collected document pool. Moreover, ten documents, including three review articles and two articles with inadequate data, were further excluded from an additional assessment. Finally, the full text of 12 eligible articles wherein the prevalence of HNPCC had been investigated among Iranian CRC patients and met the defined inclusion/exclusion criteria were collected and used for data extraction. The process of document selection is illustrated in Figure 1.

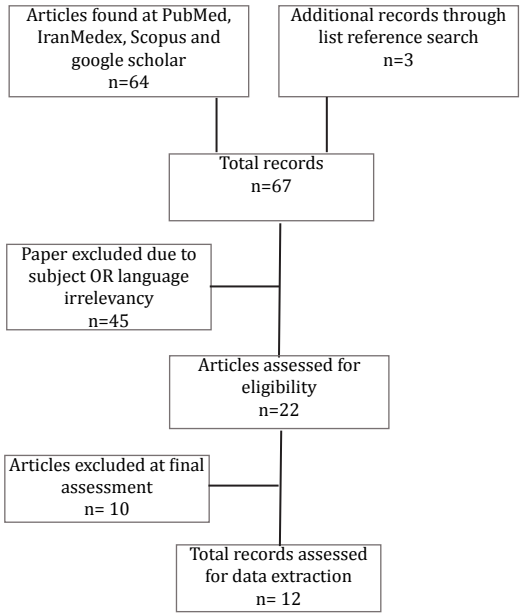

Figure 1. Flowchart of the literature search and strategy for the selection of relevant documents

General information of the included articles

A total of 12 articles that covered a total population size of 3237 were included and evaluated as part of this research. The population size in each respective article ranged from 49 to 1456 patients in the cross-sectional study. The number of patients had not been reported in one study wherein the study had been conducted on 32 HNPCC Iranian families. All the selected literature described both male and female patients. Of these populations, 1458 were male and 1435 were female; in addition, the gender ratio of 344 patients had not been reported. The age of patients enrolled in the included literature also varied from 13 to 90. The dates of the literature ranged from 2005 to 2015, indicating that little information may be available on the subject. Among the included studies that were used for data analysis, six were cross-sectional studies, three retrospective studies, one comparative study, one postmortem study and one case control study. A general overview of the studies that were included in this research is summarized in Table 1 in the chronological order of their publication date.

Table 1. General information of the included studies

NO	Author Year Reference	Province	Study Design *	Gender Ratio	Number of Participants
1	Zeinalian 2015 (14)	Isfahan, Shahre-kord	RS	-	186
2	Homayouni 2014 (15)	Isfahan	CSS	-	80
3	Mokarram 2014 (16)	Shiraz	CCS	48/40	88
4	Nemati 2012 (17)	Isfahan	CSS	755/701	1456
5	Zali 2012 (18)	Tehran	CSS	55/39	94
6	Fakheri 2011 (19)	Mazandaran	RS	152/141	293
7	Haghighi 2010 (20)	Tehran	CSS	-	78
8	Molaei 2010 (21)	Tehran	CSS	187/156	343
9	Galehdari 2009 (22)	Mashhad	PMS	20/29	49
10	Haghighi 2009 (23)	Tehran	CS	60/61	121
11	Salehi 2009 (24)	Isfahan	CSS	-	32 families
12	Mahdavinia 2005 (25)	Tehran	RS	181/268	449
*RS: Retrospective study;CSS: Cross-sectional study; CCS: Case- control study; CS: Comparative study; PMS: Postmortem study.				Male: 1458 Female: 1435	Total: 3237

Study findings

The results of this survey revealed that the occurrence of HNPCC in patients with CRC is of interest. According to the results of research studies that reported the frequency of mutation in NR-27, NR-21, NR-24, BAT-25 and BAT-26 of MLH1, MSH2, PMS2, and MSH6 genes within the studied families, the rate of polymorphisms was between 23.1% and 62.5% in the studied population. This indicates that the prevalence of Lynch syndrome is rather high (20,24). In some studies, the prevalence of HNPCC was estimated to be between 2.0% and 5.5% among the total colorectal cancers in Iran (17,21). According to the results of the included documents, the number of MSI-positive patients varied from 15% to more than 30% young onset CRC (15,16). The studies also revealed that there were variations in the distribution of tumor sites between the patients with and without a family history of CRC. The findings also demonstrated that the family history of CRC can be up to 53.5% among the studied population in the selected literature (25). The main findings of the documents included in this survey are presented in Table 2.

Discussion

It is widely acknowledged that patients with HNPCC are at a greater risk of developing CRC, even at an early age. Early detection of HNPCC can mitigate this risk and allow the implementation of preventive approaches for patients who are at higher risk of CRC in order to potentially reduce the morbidity and mortality of the disease (26). Epidemiological data shows that about 160,000 patients with CRC are added to the world population each year, and it is estimated that 7% of these patients are diagnosed with HNPCC. Moreover, since MSI is

Table 2. Main findings of included literature

NO	Author Reference	Methods *	Variables	Findings ®
1	Zeinalian (14)	MSI test, FM-PCR	BAT-25, BAT-26, MON0-27, NR-21, NR-24	MSI is a mutational signature that is the hallmark of Lynch syndrome.
2	Homayouni (15)	PCR	BAT-26 of MSH2	The use of BAT-26 alone would be sufficient to identify HNPCC-associated MSH2 gene.
3	Mokarram (16)	MSI test, Allelic variation, HPLC, Real-Time PCR	BAT-26 and BAT-25	Due to the high percentage of MSI+ CRC in Iran, screening of this type of CRC is imperative.
4	Nemati (17)	Clinical tests	Numbers of tumors	The frequency of HNPCC and FCC among CRC patients in society is relatively high.
5	Zali (18)	MSI test	MLH1, MSH2, MSI-H	The pattern of MMR mutations in MLH1, MSH2, MSI-H genes differs among Iranian patients.
6	Fakheri (19)	IHCT	Tumor location	Frequency of early-onset CRC and familial syndromes were high.
7	Haghighi (20)	Colonoscopy, PCR	NR-21, NR-24, NR-27, BAT-25 BAT-26	BAT25 and NR-21 provide well diagnostic assistance in colorectal cancer.
8	Molaei (21)	IHCT and clinical tests	MLH1, MSH2, PMS2, and MSH6	Prevalence of HNPCC in Iran was high in the total colorectal cancers.
9	Galehdari (22)	IHCT, MSI test, PCR	BAT25 and BAT26	MSI frequency is considerably lower, compared to other findings.
10	Haghighi (23)	Statistical and clinical tests	Survival, and Grade of tumor	Survival of colorectal cancer in patients with HNPCC is better than sporadic colorectal cancer patients.
11	Salehi (24)	PCR	Mutations of MLH1 and MSH2	The mutation rate in the studied population was very high.
12	Mahdavinia (25)	Clinical tests	Distribution of tumor	Family history of cancer up to second-degree relatives was observed.

* MSI: Microsatellite instability, FM-PCR: Fluorescent multiplex-polymerase chain reaction, HPLC: High-performance liquid chromatography, IHT: Immunohistochemical tests.
® HNPCC: Hereditary nonpolyposis colorectal cancer, CRC: Colorectal cancer.

demonstrated in about 70 to 90% of HNPCC cases, MSI testing of MMR genes can represent a useful diagnostic tool for accurately diagnosing patients with HNPCC among CRC patients (27). On the other hand, since the polymorphism at NR-27, NR-21, NR-24, BAT-25 and BAT-26 codons of MLH1, MSH2, PMS2, and MSH6 genes may be indicative of HNPCC, the definite frequency of Lynch Syndrome among patients with CRC may be manifested by a high incidence of mutations, especially in these regions. However, the type and region of mutation along with the genes that are involved in HNPCC may differ in different geographical areas. Therefore, the frequency and the site of mutations may also differ in terms of the MSH2 gene (28,29). Research has demonstrated that T and G deletion at a 2586 and 2556 position of exon 15 in the MSH2 gene respectively as identified mutations may also be associated with the occurrence of HNPCC (24). Furthermore, the findings of one study on colorectal carcinomas among a group of patients from Iran and Italy revealed that K-ras mutations can be considered to represent a key step in the progression of CRC (30). The application of MSI testing

and molecular methods in almost all of the studies included in this literature review revealed that the prevalence of Lynch syndrome is relatively high in the studied Iranian population.

The results of this study indicated that the prevalence of Lynch syndrome is considerably high among the members of the Iranian population who have CRC. In one study, the prevalence of HNPCC and familial CRC was estimated to be up to 5.5% and 2.9%, respectively, which was almost consistent with the reports of other included literature (17,21). The reported prevalence of HNPCC in different populations varied between 0.3 and 13% (31,32). Epidemiological data also indicated that the frequency of mutations in the hMLH1 and hMSH2 genes was 15.44%, 20.43% and 15.43% in Asian, American, and European populations respectively (33). As previously described, the early onset of hereditary CRC, as well as other cancers, is the most important feature of HNPCC (19). A study involving one Iranian family found that several members of the family were affected by HNPCC-related cancers (34). Although the results indicate that genetic variation can lead to an increased risk of CRC, especially in patients with Lynch syndrome, additional factors, such as obesity, may also be associated with a considerably high incidence of HNPCC. This indicates that it is important to monitor other non-genetic factors when attempting to conduct an early diagnosis of family members (35).

Insufficient published data reporting the prevalence of HNPCC among patients with CRC within the Iranian population, and the small sample size of some articles, were the most important limitations in the current study. Therefore, to obtain more reliable data, several multicenter studies that involve a larger study population wherein the samples are collected from populations in different parts of the country should be conducted. That said, the results of the articles included in this review did indicate that a high prevalence of HNPCC may represent one of Iran's most challenging issues in recent years.

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Conclusion

The results of this survey showed that, within the studied families in Iran, HNPCC is more prevalent in cases of CRC, particularly in patients with a family history of CRC. The systematic review also indicated that the frequency of mutation in MLH1, MSH2, PMS2, and MSH6 genes was high in the studied population.

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Conflict of Interest

The authors declare no conflict of interest.

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