Original Article

Non-polyposis Colorectal Cancers in Northeastern Iran: A Familial Approach

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ABSTRACT

Background:
There are no data on familial aggregation of colorectal cancer (CRC) in northeastern Iran. The aim of this study was to determine the prevalence of early-onset CRC and patients suspected for hereditary non-polyposis colorectal cancer (HNPCC) based on the clinical criteria in this area.

Materials and Methods:
Documents were collected from two hospitals in Mashhad regarding 326 inpatients during 2013-2015. Demographics, clinical, and tumor-related features were recorded. Interviews were done to identify cancer in the family up to second-degree relatives.

Results:
326 patients with CRC (48.5% male) were evaluated. The mean age at diagnosis was 55.44±14.85 years, with 91 patients (27.9%) below 45 years old. Eleven (3.4%) patients fulfilled the Amsterdam II criteria and 136 (41.7%) patients met at least one criterion of the revised Bethesda guideline. There was no difference between early- and late-onset CRC regarding the frequency of CRC in 1st degree relatives or tumor site (p=0.73, p =0.64). However, CRC in second-degree relatives and cases suspected for HNPCC were more common in early-onset of the disease (p =0.022, p =0.024). The patients who fulfilled the Amsterdam II criteria had lower mean age and higher frequency of proximal cancer (p =0.03, p =0.048).

Conclusion:
VAs CRC is common in the young population and CRC clustering and patients suspected for HNPCC are also frequently encountered, measures should be taken to CRC screening policy and genetic studies in this area.

Keywords: Familial, Colorectal neoplasms, Northeastern Iran

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INTRODUCTION

Colorectal cancer (CRC) has a profound effect on world health as 1.2 million new cases are diagnosed annually (1). CRC is the third and fourth most prevalent cancer in Iranian men and women, respectively. Over 3500 new cases of CRC are reported annually in Iran with a mortality rate of more than 50%, constituting approximately 6% of cancer deaths(2).

Both the environment and inheritance contribute to the development of CRC, each to a different degree in various patients (3). Only 20-30% of CRC cases can

be attributed to an identifiable inherited cause. The remaining majority (70-80%) occur sporadically without any evidence of inheritance(4).

Amongst the inherited causes of CRC, the autosomal dominant Lynch syndrome (LS) is the most prevalent (3% of diagnosed CRCs)(5-8). In addition to CRC, patients with LS also tend to be at a higher risk of developing other types of malignancies such as tumors of the endometrium and stomach(9).

Patients and family members with germline mutations in a mismatch repair (MMR) gene or deletion in the epithelial cell adhesion molecule (EPCAM) gene with subsequent muts protein homolog 2 (MSH2) loss of expression are known to have LS(10,11).

The risk of developing CRC in LS during the patient's lifetime depends on their sex and the mutated MMR gene(12). In carriers of the MLH1 and MSH2 gene mutations the risk is between 30% and 74%(13).

To identify patients with LS, different strategies have been incorporated, such as clinical criteria, prediction patterns, tumor, germline, and universal testing(14). Those patients and their family members meeting the Amsterdam I or II criteria are considered to have hereditary non-polyposis colorectal cancer (HNPCC). Data on the prevalence of LS and familial aggregation of CRC in Iran have been scarce. Mahdavinia and colleagues reported that 21 probands (4.7%) were clinically diagnosed as HNPCC based on the Amsterdam II criteria(15). Molaei and co-workers showed that immunohistochemical (IHC) staining for MMR proteins was abnormal in 14% of the 343 CRC cases. In the present study the prevalence of HNPCC was estimated to be 5.5% of all CRCs(16). In a recent study done in central Iran, the clinical diagnosis of HNPCC and familial colorectal cancer (FCC) was 2% and 2.9%(17). However, no such studies have been performed in northeastern Iran. Therefore, we evaluated the prevalence of early onset CRC and patients suspected for LS based on the clinical criteria of Amsterdam II and the revised Betheda guidelines.

MATERIALS AND METHODS

We reviewed 326 files of the patients with colorectal adenocarcinoma at two referral centers in Mashhad city, northeastern Iran, between January 2013 and February 2015. Information regarding the history of cancer in relatives of at least second-degree and beyond was obtained by interviewing the patients or, in the circumstance of their death, their siblings/ parents.

Of the 500 patients in the database, 150 patients were unavailable because of change in address and/or phone number and 24 patients refused to be interviewed. The remaining 326 patients with CRC or their close family members were included in the study.

Statistical data, clinical features, and cancer characteristics of every patient were documented via information gathered through archives, pathology reports, and interviews. Such information included, amongst others, sex, age at diagnosis, tumor site, history of CRC or non-CRC in 1st and 2nd degree relatives, and histological features for the revised Bethesda criteria reported by expert pathologists in gastroenterology.

Early-onset CRC was regarded as onset ≤ 45 yr. The Amsterdam II criteria were applied for the diagnosis of patients suspected to have HNPCC(14). However; patients fulfilling the revised criteria of Bethesda were documented, as well(18).

The revised Bethesda guidelines, a 3rd set of clinicopathological criteria, identify those patients for whom it is justified to further investigate LS with microsatellite instability and/or IHC(14).

We used Chi-square test and the Student's t test for statistical evaluation. A p value ≤ 0.05 was considered as statistically significant. The SPSS software version 16 (SPSS Inc., Chicago, IL, USA) was used to analyze the data.

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences. Written informed consent was obtained from patients/family members participating in the study.

RESULT

A total of 326 patients with CRC were studied during 2013-2015. Of them, 158 patients (48.5%) were male. Mean age at diagnosis was 55.44±14.85 years (range: 20-90 yr), with 91 (27.9%) subjects aged≤45 years (Table 1). 24.8% of the patients aged between 40 and 50 years (Figure 1). Eleven (3.4%) patients met the clinical criteria of HNPCC based on the Amsterdam II while 136 (41.7%) patients met at least one criteria of revised Bethesda guideline. 121 patients aged<50 years, 9 patients had positive family history,

Table 1: Demographic characteristics of patients with colorectal cancer

Patients with colorectal cancer	Number (percent)
Age (y)	55.94± 14.85
Sex	
Male	158 (51.5%)
Female	168 (51.5%)
Cancer location	
Proximal	112 (34.4%)
Distal	209 (64.1%)
First degree relatives with CRC	29 (8.9%)
Second degree relatives with CRC	28 (8.5%)
Amsterdam II	11 (3.4%)
Revised Bethesda	136 (41.7%)

Table 2: Colorectal cancer characteristics among young and old patients

	Young onset (≤45)	Late onset (>45)	*p* value
Age	37.82±6.99	63.01±10.45	0.001
Sex			
Male	40 (44%)	117 (50.2%)	0.33
Female	51 (56%)	116 (49.8%)	
Cancer location			
Proximal	29 (32.6%)	82 (35.7%)	0.64
Distal	60 (67.4%)	148 (64.3%)	
First degree relatives with CRC	11 (12.4%)	23 (10.1%)	0.73
Second degree relatives with CRC	16 (17.6%)	17 (7.3%)	0.022
AmsterdamII	6 (6.7%)	5 (2.1%)	0.024
Revised Bethesda	110 (97.3%)	26 (13.4%)	0.001

Table 3: Characteristics of colorectal cancer among patients who fulfill Amsterdam II criteria

Amsterdam II	Yes	No	
Age (y)	43.6 16.54	56.37 14.6	0.038
Sex			
Male	5 (4.5%)	152 (48.7%)	0.92
Female	6 (5.5%)	160 (51.3%)	
Location of tumor			
Proximal	6 (54.5%)	104 (33.8%)	0.046
Distal	5 (45.5%)	204 (66.8%)	

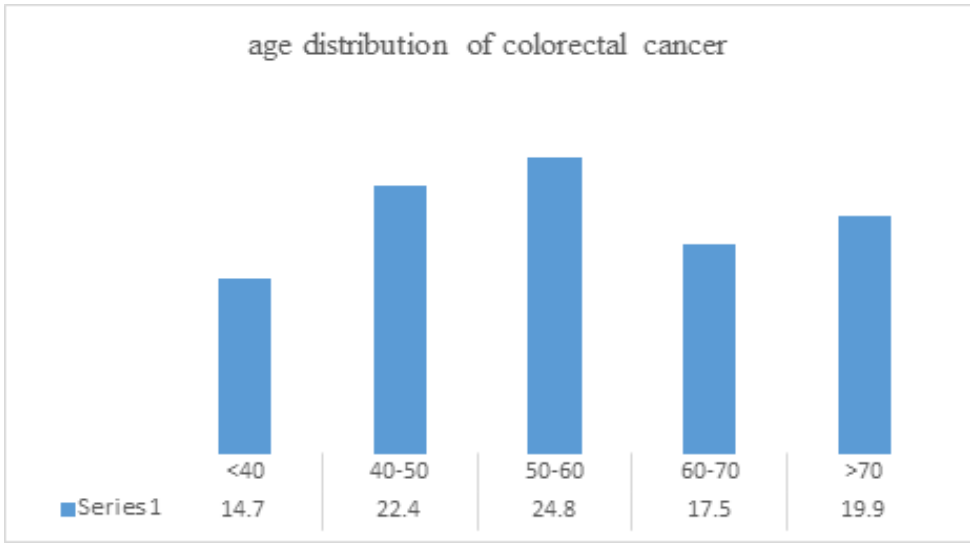

Fig. 1: **Age distribution of patients with**

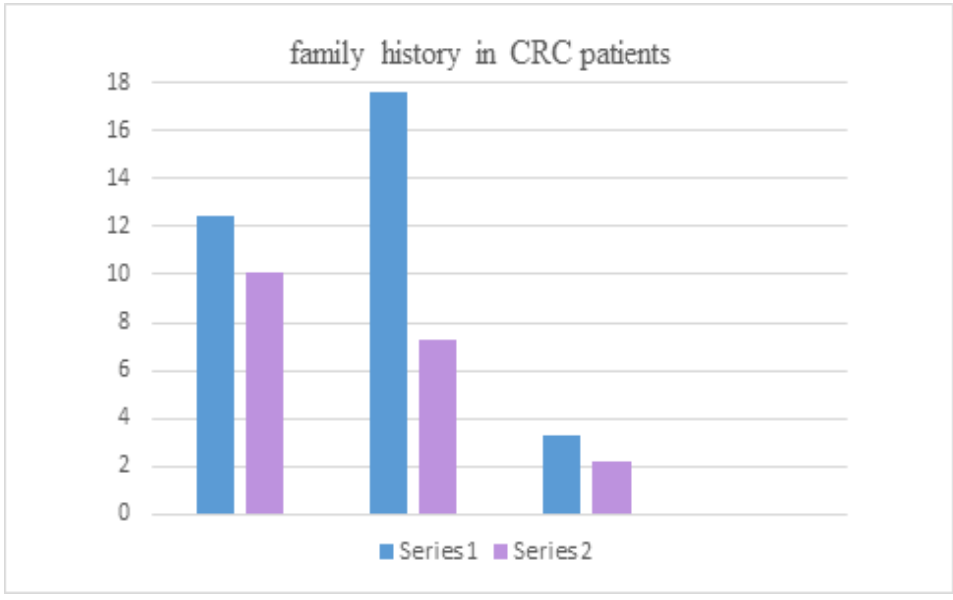

Fig. 2: **Family history in patients with colorectal cance**

6 patients had histological criteria (four mucinous components, two intratumoral lymphocytes).

There was no difference between early- and late-onset CRC regarding family history of colorectal cancer in the 1st degree relatives (FDR) and tumor location (proximal versus distal) (p =0.73 and p =0.64, respectively). However, family history of CRC in 2nd degree relatives (SDR) and cases suspected for HNPCC were found more frequently among those with early-onset CRC (p =0.022 and p =0.024, respectively) (Table 2).

The mean age for patients fulfilling the Amsterdam II criteria was lower than the other patients (43.6±16.5 and 56.37±14.6 years, respectively, p =0.03). In addition, proximal cancer was more prevalent than distal in the former [6 patients (54%) and 104 patients (33.8%), respectively, p =0.048) (Table 3).

Finally, family history of CRC and non-CRC in

FDRs and SDRs was 27% and 22.8%, respectively. The most frequent FDR with CRC was the father. Cancers of the breast, stomach, endometrium, and esophagus were the most commonly found non-CRCs, respectively. Amongst these, mothers [16 cases (4.9%)] and uncles [11 cases (3.4%)] were the most frequently affected FDRs and SDRs, respectively (Figure 2).

DISCUSSION

The results revealed that 3.4% of the patients with CRC in northeastern Iran fulfilled the Amsterdam II clinical criteria for LS, while 41.7% met at least one criteria of revised Bethesda guideline. 121 patients aged<50 years, 9 patients had positive family history, 6 patients had histological criteria (four mucinous components, two intratumoral lymphocytes). The incorporation of the Amsterdam II criteria requires that the patient and their family be evaluated for CRC and other LS-related cancers. The Amsterdam II criteria carry a sensitivity and specificity of 22% and 98% for the diagnosis of LS, respectively(14,18,19). The revised Bethesda criteria, however, identify the need for MSI testing in patients with CRC. The sensitivity and specificity for LS in those fulfilling any one of the revised Bethesda criteria was 82% and 77%, respectively(7).

The Lynch syndrome has been reported to have a prevalence of 2-6% depending on the country(14). According to a study on 406 Finnish patients with CRC, the prevalence of HNPCC based on the Amsterdam II criteria was 1.7%(20). This figure was 3.4-4.5% in northern Italy based on the Amsterdam II criteria(21). In Malaysia, Phaik-Leng and colleagues showed a frequency of 9.9% for deficient MMR (dMMR) amongst patients with CRC(22). In China, the prevalence of HNPCC based on IHC was 2.6%(23).

Variations in the prevalence of HNPCC are most likely the result of genetic and social elements such as marriages between relatives. The first study amongst the few studies performed on LS prevalence in Iran was done in Tehran and was performed on 447 patients with CRC, of whom 21 subjects (4.7%) fulfilled the Amsterdam II criteria(15). This figure was 2.9% and 10.9% in other studies on patients with CRC in central and northern Iran, respectively(17,24). The frequency of abnormal nuclear staining for the MMR proteins in 343 CRC patients was reported to be 14% according to Zali and co-workers, who also reported an estimated figure of 5.5% HNPCC prevalence in Iranian patients with CRC(16).

In northeastern Iran, we found a significant frequency of 3.4% for HNPCC amongst patients with CRC, which is a figure similar to results obtained in other parts of Iran. Utilizing the Bethesda criteria, however, the proportion of our patients requiring genetic testing for HNPCC reached 41.7%. Such a relatively high frequency of cases suspected for HNPCC in the present study must be confirmed by genetic testing.

In line with previous studies, the mean age for those of our patients who met the Amsterdam II criteria was lower than those who did not (43.6±16.5 years and 56.37±14.6 years, respectively)(15,25). In addition, the former group of patients were more likely to have a proximal site of cancer [6 patients (54.5%) versus 104 patients (33.8%), respectively]. Other studies showed a more proximal location for CRC in familial colorectal cancer(1, 15,17,21,24,26).

A characteristic finding in HNPCC and familial adenomatosis polyposis (FAP) syndrome is the early development of CRC compared with the general population(27,28). The mean age at diagnosis for CRC in our study was 55.44±14.85 years (range: 20-90 years). More than a third of our patients with CRC (37.1%) aged≤50 years and 22.4% aged between 40 and 50 years.

In a report by Mahdavinia and colleagues, patients with CRC aged less than 45 years comprised 29% of all CRC cases in Iran(15). Of the 1659 cases with CRC in central Iran, Zeinlian and co-workers reported 413 patients (24.9%) aged less than 50 years at diagnosis(17). Likewise, according to a four-year survey of the national cancer registry, Safayee and others found that a quarter of the patients with CRC aged less than 50 years (29).

Such results from Iran suggest a larger proportion of young patients with CRC than what was found in the West (2-8%)(1,15,30). In CRC with early onset, there was a higher incidence of hereditary forms, of which LS was the most frequent (18%)(27). Based on age, the percentage of MSI tumors in early-onset CRC is between 19.7% and 41.0%(30). Therefore, it is reasonable to conclude that, with the larger young

population in Iran, familial and hereditary syndromes and consequently CRC were more common compared with other countries. According to our findings and others by our Iranian counterparts, the prevalence of HNPCC was remarkable (2.9-10%)(15-17). A common finding among patients with CRC, especially those with early-onset disease, was a positive family history for CRC and non-CRC, though a minority met the Amsterdam II criteria. Overall, almost half (49.8%) of our patients had an either FDR or SDR with established CRC or non-CRC (27% and 22.8% for FDR and SDR, respectively). We did not find any difference between early- and late-onset CRC in terms of family history of CRC in FDR. However, patients suspected for HNPCC and SDR with CRC were found more commonly in our patients with early-onset CRC. These results were in agreement with those obtained previously in Iran. Cai and colleagues reported that 19.6% of CRC cases had a positive family history of CRC in their immediate relatives(23). This figure was 36.8% in patients studied by Nemati and others(17). These numbers were even higher according to the study by Mahdavinia and co-workers, where 53.5% and 43.5% of patients with early- and late-onset CRC had history of cancer in the family up to SDR(28).

Several causative factors may contribute to the high frequency of CRC found in young patients and familial aggregation found in Iran. Amongst others, the young-majority population and environmental exposures during recent years are worth mentioning. However, the most likely cause may be genetic predisposition for CRC, of which HNPCC is the most common (associated with both CRC and non-CRC)(28,31). As a result, the Healthy People 2020 and the National Comprehensive Cancer Network (NCCN) have supported universal screening for LS. The American Gastroenterology Association (AGA) recommends IHC testing for the MMR protein in every patient diagnosed with CRC, suggesting an acceptable cost-benefit ratio(10,14,32-34). Therefore, in a country like Iran with a high prevalence of this syndrome, such testing should be considered as well as further relevant genetic and epidemiological research. If implemented, such screening could lead to a better identification of families inflicted by LS ultimately resulting in a reduction in the rate of LS-related CRC and non-CRC (e.g. breast and endometrial cancers) (14). A less costly means of detecting families with the disease may be through the development of IHC markers able to predict specific gene mutations. The diagnosis and management of patients with multiple tumors consumes both time and money, justifying the need for a proper means of screening and surveillance, which would benefit the patient and the medical care system alike(35).

Nevertheless, defects in MMR-related genes are not always responsible for cases of CRC clustering(34). Based on our findings, although half of our patients had a positive family history of cancer and one-fourth aged below 50 years, only 3.4% met the criteria for LS. Therefore, familial CRC syndrome type X and unknown genetic loci, amongst other hereditary CRC syndromes, may also contribute to the many cases of familial aggregation and early-onset CRC observed in different populations(36-38). Familial CRC results from the interaction of genetic and environmental causes(39). Many low-penetrance have effects on familial CRC(8). In recent genome wide association studies (GWAS), 11 polymorphisms were identified that were statistically associated with CRC. However, with the exception of genetic syndromes such as HNPCC and FAP, these associations were weak, inconsistent, and accounted for few observed familial risks(40,41).

Early-onset CRC has recently been shown to be a heterogenous disease, encompassing both familial and sporadic components. Various molecular alterations seem to play a role in this heterogeneity, distinguishing subgroups specific histopathological and familial features(42-44).

Recently a marked increase in the incidence of CRC was found in the 40- to 44-year-old age group in USA. In 1987, the incidence was 10.7 per 100,000. In 2006, the incidence rocketed to 17.9 per 100,000, showing 67% increase(31). In a recent study on 2055 patients in five provinces of Iran, the incidence of CRC in Iranian men and women were 8.2 and 7.0 per 100,000, respectively. 17% of the cases were younger than 40 years at the time of diagnosis(45). Therefore our result is in line with the recent literature and our younger generation is experiencing an accelerated rate approaching the rates in Western countries. So the burden of the disease will increase dramatically in near future and suggest that we in Iran should think

of younger age (age 40) for screening. Also the high frequency of positive family history of CRC in Iranian patients indicates that a significant number of CRCs in Iran arise in family members and relatives of patients with CRC. It is clear that the familial clustering of CRC is more often seen in younger probands.

Finally, it seems vital to extend genetic and molecular research in this area in order to better recognize the etiology of familial cancer types in Iran. Furthermore, CRC screening at younger age, especially in relatives of patients with CRC, appears to be beneficial, underlining the significance of family history taking in the identification of people at risk.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest related to this study.

REFERENCES

1. Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H. Five common cancers in Iran. *Arch Iran Med* 2010;13:143-6.
2. Sadjadi A, Nouraie M, Mohagheghi MA, Mousavi-Jarrahi A, Malekezadeh R, Parkin DM. Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev* 2005;6:359-63.
3. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. *Cancer Causes Control* 2000;11:579-88.
4. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343:78-85.
5. Aaltonen LA, Salovaara R, Kristo P, Canzian F, Hemminki A, Peltomäki P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *N Engl J Med* 1998;338:1481-7.
6. Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med* 2006;354:2751-63.
7. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med* 2005;352:1851-60.
8. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastroenterology* 2010;138:2044-58.
9. Vasen HF, Wijnen JT, Menko FH, Kleibeuker JH, Taal BG, Griffioen G, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996;110:1020-7.
10. Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genet Med* 2010;12:93-104.
11. Miyaki M, Konishi M, Tanaka K, Kikuchi-Yanoshita R, Muraoka M, Yasuno M, et al. Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. *Nat Genet* 1997;17:271-2.
12. Bonadona V, Bonaïti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011;305:2304-10.
13. Choi YH, Cotterchio M, McKeown-Eyssen G, Neerav M, Bapat B, Boyd K, et al. Penetrance of colorectal cancer among MLH1/MSH2 carriers participating in the colorectal cancer familial registry in Ontario. *Hered Cancer Clin Pract* 2009;7:14.
14. Dinjens WN, Dubbink HJ, Wagner A. Guidelines on genetic evaluation and management of Lynch syndrome. *Am J Gastroenterol* 2015;110:192-3.
15. Mahdavinia M, Bishehsari F, Ansari R, Norouzbeigi N, Khaleghinejad A, Hormazdi M, et al. Family history of colorectal cancer in Iran. *BMC Cancer* 2005 5;5:112.
16. Molaei M, Mansoori BK, Ghiasi S, Khatami F, Attarian H, Zali M. Colorectal cancer in Iran: immunohistochemical profiles of four mismatch repair proteins. *Int J Colorectal Dis* 2010;25:63-9.

17. Nemati A, Rahmatabadi ZK, Fatemi A, Emami MH. Hereditary nonpolyposis colorectal cancer and familial colorectal cancer in Central part of Iran, Isfahan. *J Res Med Sci* 2012;17:67-73.

18. Balmaña J, Balaguer F, Castellví-Bel S, Steyerberg EW, Andreu M, Llor X, et al. Comparison of predictive models, clinical criteria and molecular tumour screening for the identification of patients with Lynch syndrome in a population-based cohort of colorectal cancer patients. *J Med Genet* 2008;45:557-63.

19. Green RC, Parfrey PS, Woods MO, Younghusband HB. Prediction of Lynch syndrome in consecutive patients with colorectal cancer. *J Natl Cancer Inst* 2009;101:331-40.

20. Mecklin JP, Järvinen HJ, Hakkiluoto A, Hallikas H, Hiltunen KM, Härkönen N, et al. Frequency of hereditary nonpolyposis colorectal cancer. A prospective multicenter study in Finland. *Dis Colon Rectum* 1995;38:588-93.

21. Ponz de Leon M, Sassatelli R, Benatti P, Roncucci L. Identification of hereditary nonpolyposis colorectal cancer in the general population: the 6-year experience of a population-based registry. *Cancer* 1993;71:3493-501.

22. Cheah PL, Looi LM, Teoh KH, Rahman NA, Wong LX, Tan SY. Colorectal carcinoma in Malaysians: DNA mismatch repair pattern in a multiethnic population. *Asian Pac J Cancer Prev* 2014;15:3287-91.

23. Cai SJ, Xu Y, Cai GX, Lian P, Guan ZQ, Mo SJ, et al. Clinical characteristics and diagnosis of patients with hereditary nonpolyposis colorectal cancer. *World J Gastroenterol* 2003;9:284-7.

24. Fakheri H, Bari Z, Merat S. Familial aspects of colorectal cancers in southern littoral of Caspian Sea. *Arch Iran Med* 2011;14:175-8.

25. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer. Study of two large midwestern kindreds. *Arch Intern Med* 1966;117:206-12.

26. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005;16: 481-8.

27. Magnani G, Furlan D, Sahnane N, Reggiani Bonetti L, Domati F, Pedroni M. Molecular Features and Methylation Status in Early Onset (≤40 Years) Colorectal Cancer: A Population Based, Case-Control Study. *Gastroenterol Res Pract* 2015;2015:132190.

28. Malekzadeh R, Bishehsari F, Mahdavinia M, Ansari R. Epidemiology and molecular genetics of colorectal cancer in Iran: a review. *Arch Iran Med* 2009;12:161-9.

29. Safaee A, Fatemi SR, Ashtari S, Vahedi M, Moghimi-Dehkordi B, Zali MR. Four years incidence rate of colorectal cancer in Iran: a survey of national cancer registry data- implications for screening. *Asian Pac J Cancer Prev* 2012;13:2695-8.

30. Silla IO, Rueda D, Rodríguez Y, García JL, de la Cruz Vigo F, Perea J. Early-onset colorectal cancer: a separate subset of colorectal cancer. *World J Gastroenterol* 2014 ;20:17288-96.

31. Ansari R, Mahdavinia M, Sadjadi A, Nouraie M, Kamangar F, Bishehsari F, et al. Incidence and age distribution of colorectal cancer in Iran: results of a population-based cancer registry. *Cancer Lett* 2006;240:143-7.

32. Ladabaum U, Wang G, Terdiman J, Blanco A, Kuppermann M, Boland CR, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. *Ann Intern Med* 2011;155:69-79

33. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN.EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009;11:42-65.

34. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol* 2001;96:2992-3003.

35. Jung I, Gurzu S, Turdean GS. Current status of familial gastrointestinal polyposis syndromes. *World J Gastrointest Oncol* 2015;7:347-55.

36. Losi L, Di Gregorio C, Pedroni M, Ponti G, Roncucci L, Scarselli A, et al. Molecular genetic alterations and clinical features in early-onset colorectal carcinomas and their role for the recognition of hereditary cancer syndromes. *Am J Gastroenterol* 2005;100:2280-7.

37. Liang JT, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. *Br J Surg* 2003;90:205-14.

38. Perea J, Rodríguez Y, Rueda D, Marín JC, Díaz-Tasende J, Álvaro E, et al. Early-onset colorectal cancer is an easy and effective tool to identify retrospectively Lynch syndrome. *Ann Surg Oncol* 2011;18:3285-91.

39. Mucci LA, Wedren S, Tamimi RM, Trichopoulos D,

Adami HO. The role of gene-environment interaction in the aetiology of human cancer: examples from cancers of the large bowel, lung and breast. *J Intern Med* 2001;249:477-93.

40. Kiss I, Sándor J, Pajkos G, Bogner B, Hegedüs G, Ember I. Colorectal cancer risk in relation to genetic polymorphism of cytochrome P450 1A1, 2E1, and glutathione-S-transferase M1 enzymes. *Anticancer Res* 2000;20:519-22.
41. von Holst S, Picelli S, Edler D, Lenander C, Dalén J, Hjern F, et al. Association studies on 11 published colorectal cancer risk loci. *Br J Cancer* 2010;103:575-80.
42. Chang DT, Pai RK, Rybicki LA, Dimaio MA, Limaye M, Jayachandran P, et al. Clinicopathologic and molecular features of sporadic earlyonset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. *Mod Pathol* 2012; 25:1128-39.
43. Giráldez MD, López-Dóriga A, Bujanda L, Abulí A, Bessa X, Fernández-Rozadilla C, et al. Susceptibility genetic variants associated with early-onset colorectal cancer. *Carcinogenesis* 2012; 33:613-9.
44. Tezcan G, Tunca B, Ak S, Cecener G, Egeli U. Molecular approach to genetic and epigenetic pathogenesis of early-onset colorectal cancer. *World J Gastrointest Oncol* 2016;8:83-98.
45. Davis DM, Marcet JE, Frattini JC, Prather AD, Mateka JJ, Nfonsam VN. Is it time to lower the recommended screening age for colorectal cancer? *J Am Coll Surg* 2011;213:352-61.