

RESEARCH ARTICLE

Epidemioclinical Feature of Early-Onset Colorectal Cancer at-Risk for Lynch Syndrome in Central Iran

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Abstract

Background: Colorectal cancer (CRC) is becoming one of the most complicated challenges of human health, particularly in developing countries like Iran. In this paper, we try to characterize CRC cases diagnosed < age 50 at-risk for Lynch syndrome within central Iran. **Materials and Methods:** We designed a descriptive retrospective study to screen all registered CRC patients within 2000-2013 in Poursina Hakim Research Center (PHRC), a referral gastroenterology clinic in central Iran, based on being early-onset (age at diagnosis ≤ 50 years) and Amsterdam II criteria. We calculated frequencies and percentages by SPSS 19 software to describe clinical and family history characteristics of patients with early-onset CRC. **Results:** Overall 1,659 CRC patients were included in our study of which 413 (24.9%) were ≤ 50 years at diagnosis. Of 219/413 successful calls 67 persons (30.6%) were reported deceased. Family history was positive for 72/219 probands (32.9%) and 53 families (24.2%) were identified as familial colorectal cancer (FCC), with a history of at-least three affected members with any type of cancer in the family, of which 85% fulfilled the Amsterdam II Criteria as hereditary non-polyposis colorectal cancer (HNPCC) families (45/219 or 20.5%). Finally, 14 families were excluded due to proband tumor tissues being unavailable or unwillingness for incorporation. The most common HNPCC-associated extracolonic-cancer among both males and females of the families was stomach, at respectively 31.8 and 32.7 percent. The most common tumor locations among the 31 probands were rectum (32.3%), sigmoid (29.0%), and ascending colon (12.9%). **Conclusions:** Given the high prevalence of FCC (~1/4 of early-onset Iranian CRC patients), it is necessary to establish a comprehensive cancer genetic counseling and systematic screening program for early detection and to improve cancer prognosis among high risk families.

Keywords: Colorectal cancer - epidemioclinical feature - lynch syndrome - central Iran

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Introduction

Colorectal cancer (CRC) is the second cause of cancer-related mortality among adult people throughout the world (Bush and Haines, 2009; ACS, 2013). It is being converted to one of the most complicated challenges of human health, particularly in developing countries (Bener, 2011). It seems along with westernization of life style in these countries, such as Iran, CRC will be one of the most important leading causes of cancer death among adults in the world (Pourhoseingholi et al., 2009).

Current information shows CRC is the third common cancer among Iranian adult males and the forth one among the females (excluding skin malignancies) (Mousavi et al., 2008; Kolahdoozan et al., 2010). Its incidence has been increased during the last 3 decades more than 80% according to recent studies (Yazdizadeh et al., 2005; Dolatkahh et al., 2015).

Inheritable genetic factors contribute in incidence of

at least 35% of the new cases (Burt, 2007) and hereditary non-polyposis colorectal cancer (HNPCC) is the most common cause of hereditary CRC (Rybak and Hall, 2011). It is an autosomal dominant condition with about 70- 90% penetrance due to mutation in the mismatch repair genes (Lynch et al., 2009).

Although a prevalence of about 3-5% has been estimated for HNPCC in different studies among western societies, there is just a little information about the prevalence of the disease in Iran (Bavi et al., 2008).

In one study in Tehran hospitals, clinical diagnosis of HNPCC was established in 21 (4.7%) probands (Fatemi et al., 2010). In a recent study in Isfahan (Central Iran), the prevalence was estimated about 2% according to Amsterdam II criteria (Nemati et al., 2011). Since no screening program has been established for hereditary CRC so far in Iranian health system, there is no exact epidemiologic data in this area from general population. So we designed a new study to set up a screening program

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for hereditary CRC in Central Iran. In this article we discuss some epidemiologic data, obtained from a primary screening program based on genetic counseling

Materials and Methods

We designed a descriptive retrospective study to find most detectable samples of HNPCC in central Iran, including Isfahan and Chaharmahal va Bakhtyari provinces (CMB). Our samples included 1659 CRC patients registered in cancer registry unit of Isfahan Provincial Health Center or referred to Poursina Hakim Clinic (PHRC), a famous referral gastroenterology clinic in central Iran, from 2000 to end of 2013. As the population-based cancer registry has been set up in our region since 2006, apparently our study does not cover all CRC patients in Central Iran.

We used being early-onset disease (age at diagnosis ≤ 50 years) and Amsterdam II criteria, consecutively, to primary selection of our samples. This stringent screening method was selected due to our financial limitations. Amsterdam II criteria include: having at least 3 affected members with one of the HNPCC-associated cancers (CRC, other GI cancers, endometrial, renal, breast (according to some resources), Brain, Skin, and pelvic cancers) in at least two successive generations, and one of these three members being a first degree relative of the other two and at least one diagnosed before the age of 50 years. So, we reviewed at first the patients' rolls and selected all probands with age

up to 50 years to call and ask them about family history of cancer. Then all patients with positive family history of cancer and/or their families were invited for genetic counseling and face to face interview. We considered any kind of cancer in addition of HNPCC-associated cancers. The pedigrees were confirmed by interviewing at least 2-3 members of family. We also requested all clinical and paraclinical documents to verify reported malignancies in the probands and their relatives, if were available. Finally, the obtained data was statistically analyzed by SPSS 19 software package (SPSS Inc., Chicago, IL, USA).

Results

We found that 413/1659 (24.9%) of the patients had been affected by early-onset CRC (age at the time of diagnosis ≤ 50). In addition, 213/413 (51.6%) of these probands were male.

Our response rate in follow up was 219/413 (53%) of which in 67/219 (30.6%) the probands had been deceased and their first-degree relatives were responded on behalf of them. Family history was positive for 72/219 probands (32.9%) and among them, we found 53 families (24.2%) with at least three affected members to have any different types of cancer. We classified them as "Familial Colorectal Cancer" (FCC) families.

Overall, 45/53 (85%) of FCC families fulfilled the Amsterdam II Criteria as HNPCC families (45/219 or 20.5% of all CRC cases). Though we invited all of them

Table 1. Frequency of All Cancer Sites in the HNPCC Families in Both Male and Female Patients

tumor site	sex				Total
	male		female		
	frequency	percent	frequency	percent	
colorectal cancer	38	36.5	30	36.1	68
lung cancer	16	15.4	1	1.2	17
gastric cancer	14	13.5	17	20.5	31
small bowel cancer	7	6.7	2	2.4	9
prostate cancer	6	5.8			6
brain cancer	5	4.8	6	7.2	11
hematopoietic cancer	5	4.8	3	3.6	8
hepatobiliary cancer	3	2.9	3	3.6	6
bladder	2	1.9	1	1.2	3
testis cancer	2	1.9			2
thyroid cancer	2	1.9	0	0	2
renal cancer	1	1	0	0	1
skin cancer	1	1	1	1.2	2
bone cancer	1	1	1	1.2	2
pancreas cancer	1	1	0	0	1
breast cancer			12	14.5	12
uterus cancer			5	6	5
nasopharynx	0	0	1	1.2	1
Total	104	100	83	100	187

for genetic testing, just 31/45 (69%) of them were finally included in the next molecular testing stages. Of 14 excluded families, 10 families were omitted because their probands' tumor tissues were unavailable, and 4 others were excluded due to reluctance for incorporation.

Altogether, 31 HNPCC families had 187 cancer patients including 168 HNPCC-associated cancers, with 3-13 affected members in each family, so the affected members in the families were averagely 5.9. Extracolonic cancers were more prevalent among males (M/F=1.3).

Of 31 probands, 16 cases (51.6%) had one parents affected with CRC, 3 had 2 parents affected (9.7%), and 8 in at least one sibling (25.8%).

The most common cancers in male HNPCC families were: CRC (36.5%), lung (15.4%), stomach (13.5%), small bowel (6.7%), and prostate (5.8%); while in females: CRC (36.1%), stomach (20.5%), breast (14.5%), brain (7.2%), and uterus (6%). Of these, stomach with 31.8 and 32.7 percent among males and females, respectively, was the most frequent affected site in HNPCC-associated extracolonic cancers (Table 1,2).

Although, average age at diagnosis in HNPCC probands was 41.3 (range 24-50 years), it was 50.6 (range 2-82 years) for all cancers within 31 HNPCC families. The least average age at diagnosis was related to thyroid, brain, and bone cancers with 16.5, 38.5, and 39.5 years, respectively. While, average age at diagnosis of prostate, pancreas, and lung cancers were 70.2, 70, and 66, respectively. In addition, average age of CRC diagnosis in the families was 48.7.

12/31 (38.7%) of the HNPCC probands, and 120/187 (64.2%) of the all affected members had been deceased. The mean survival length in the HNPCC probands was

8.0 years (range 1-33). It was 5.8 years (range 1-25) in the deceased and 9.4 years (range 2-33) in the live probands after initial clinical diagnosis.

The frequency of tumor pathological stage in which the HNPCC probands had been identified, according to TNM staging system, included: 1/31 (3.2%) stage I, 10/31 (32.3%) stage II, 10/31 (32.3%) stage III, and 10/31 (32.3%) stage IV. Of the live probands, 9/19 (47.4%) were in stage III or IV at diagnosis, while for the deceased probands, it was 11/12 (91.7%). Survival period, distance between age at diagnosis and death, was 10, 4.7, and 2.3 years in deceased probands identified at stage I, III, and IV, respectively. According to tumor pathological reports of the probands, the most common diagnosis had been reported as "well differentiated adenocarcinoma" by 38.7%, and the least one was "non-mucinous adenocarcinoma" by 3.2%.

The most common tumor locations among the 31 probands were respectively: rectum (32.3%), sigmoid (29.0%), and ascending colon (12.9%). (Table 3)

Table 3. Frequency of Tumor Locations in HNPCC Probands

tumor location	Frequency	Percent
ascending colon	4	12.9
transverse colon	1	3.2
descending colon	2	6.5
sigmoid colon	9	29
rectum	10	32.3
cecum	4	12.9
unknown	1	3.2
Total	31	100

Table 2. Frequency of HNPCC-Associated Extracolonic Cancer Sites in the HNPCC Families in Both Male and Female Patients

tumor site	sex			
	male		female	
	frequency	percent	frequency	percent
gastric cancer	14	31.8	17	32.7
small bowel cancer	7	15.9	2	3.8
brain cancer	5	11.4	6	11.5
hematopoietic cancer	5	11.4	3	5.8
hepatobiliary cancer	3	6.8	3	5.8
bladder	2	4.5	1	1.9
testis cancer	2	4.5		
thyroid cancer	2	4.5	0	0
renal cancer	1	2.3	0	0
skin cancer	1	2.3	1	1.9
bone cancer	1	2.3	1	1.9
pancreas cancer	1	2.3	0	0
breast cancer			12	23.1
uterus cancer			5	9.6
nasopharynx	0	0	1	1.9
Total	44	100	52	100

Discussion

I- Epidemiologic features: This study was designed to find most detectable HNPCC families in Central Iran, since there is a lack of data around the issue in our population. Due to our financial limitations and high family size in Iranian population, we used Amsterdam II Criteria as a more specific tool than revised Bethesda guidelines to screen the early-onset at-risk patients (Syngal et al., 2000; Pinol et al., 2005).

In spite of our repeated attempts, we did not succeed to find about 47% of probands. It is due to changing of the patients' phone numbers and addresses after passing too much time.

Overall, 213/413 (51.6%) of the probands with age up to 50 years were male. It is similar to the gender structure of our population, so 51% of the population throughout the Province was male according to 2011 census (on-line available in: www.sci.org.ir). Although CRC incidence rates among most populations are significantly higher in males than in females, there are more differences between Western males and females in these rates than Eastern populations. So, age-standardized CRC incidence rate, during 2008, among males and females in Western European population have been 41.2 and 26.3, and in Western Asian populations 13.1 and 10.1, respectively (Jemal et al., 2011). Apparently, the incidence rate of CRC, particularly in early-onset group, is similar in both male and female among our population according to our results and some similar studies (Kolahdoozan et al., 2010; Dolatkah et al., 2015).

Average age of the HNPCC probands at diagnosis in our population was a bit less than the Western population. This study among other Eastern studies has shown that Early-onset CRC (less than 50 years of age at diagnosis) covers almost one fourth of all CRC cases in the country. This is different from Western countries where the rates of early-onset CRC include less than 10% of all CRC cases (Griffin et al., 1991; Mitry et al., 2001; Yuen et al., 2002; Claes et al., 2005; Yazdizadeh et al., 2005; Ansari et al., 2006; Dolatkah et al., 2015). Given the changing of life style in developing societies like Iran toward westernization, in particular within youth, incident rate of early-onset CRC has been increased in these populations during the recent decades (Fatemi et al., 2010; Safari et al., 2013; Dolatkah et al., 2015).

II- Clinicopathologic features: Prevalence of the FCC and HNPCC families 33% of our probands had a positive family history of cancer among their first or second degree relatives. This is near to other previous studies in Iran (Fatemi et al., 2010; Dolatkah et al., 2015). We considered for FCC families, existence of at least three affected members among the first or second degree relatives. Accordingly, the frequency rate of FCC among the early-onset probands in our study was calculated 24.2%, most of which fulfilled the Amsterdam II Criteria and were reproduced as HNPCC families (20.5%). It is more than previous studies in the Province and other parts of Iran (Yuen et al., 2002; Ansari et al., 2006; Fatemi et al., 2010; Nemati et al., 2011; Dolatkah et al., 2015). Since the proportion of early-onset probands to all CRC patients

has been calculated nearly 25%, the total frequency of HNPCC families according to Amsterdam II Criteria is estimated $0.25 \times 20.5\% = 5.1\%$. However, a portion of the patients older than 50 years are likely related to other unknown HNPCC families which are missed in our study (Jasperson et al., 2010; Nemati et al., 2011). Therefore, it seems the previous report of HNPCC frequency in Isfahan (2%) had been underestimated (Nemati et al., 2011). Meanwhile, given the limitation of our study to not include all CRC cases, a precise estimation of HNPCC prevalence could be impossible. On the other hand, according to the last WHO report about life expectancy (LE) in worldwide countries, LE in Iran was averagely estimated 73.5 years for 2012 which was 2.5 years more than world average (WHO, 2012). Meanwhile, it was about 6.5 years less than the most Western countries. Apparently it could justify the relative high proportion of early-onset CRC patients among Iranian populations.

According to our results, more than 74% of Amsterdam II positive probands had no cancer affected siblings, and there was no cancer history among the parents of about 50%. It shows the importance of complete genetic counseling covering at least three generations of every pedigree (Maserat et al., 2009). A significant portion of these families would be likely excluded from the Lynch

Syndrome after molecular analyses. These cases are usually associated to other hereditary cancer syndromes, a fact that has been confirmed by different studies (Lindor, 2009; Francisco et al., 2011; Dominguez-Valentin et al., 2015).

Colonic and extracolonic malignancies: CRC was the most common cancer among HNPCC families by nearly 36%, compatible with other studies in Iran (Ansari et al., 2006; Fatemi et al., 2010; Dolatkah et al., 2015), but it is much less than another recent study (Nemati et al., 2011). Meanwhile, there are significant discrepancies, 33-78%, between similar studies in other countries (Park et al., 2000; Maul et al., 2006; da Silva et al., 2010; Bansidhar, 2012).

Also we found gastric cancer (GC) as the most common HNPCC-associated extracolonic cancer by 31.8 and 32.7 percent among males and females, respectively, as it is confirmed by others (Fatemi et al., 2010; Nemati et al., 2011). There are, however, distinct discrepancies between Western and Eastern populations over this issue (Bansidhar, 2012). In a Brazilian study, GC was the second most common extracolonic cancer in HNPCC families (da Silva et al., 2010). In addition, several Chinese and Korean studies have presented GC as the most common extracolonic cancer in HNPCC (Park et al., 2000), while in Western populations, the prevalence of GC within HNPCC cohorts is the third or fourth most common cancer (Maul et al., 2006; Bansidhar, 2012). These discrepancies could be related to environmental factors (Vasen et al., 2013).

We also found the lung cancer as the second common cancer after CRC in males (15.4%), among HNPCC families. Although, some authors, in 1990s decade, believed that having HNPCC could even protect the patients against some other malignancies such as lung (Lynch and Chapelle, 1999), some recent studies have shown new presentations of HNPCC and Lynch syndrome

by which our understanding is evolving (Vasen et al., 2013; Steinke et al., 2013). Meanwhile, environmental conditions have significant role in familial clustering of lung cancer (Sun et al., 2007; Brennan et al., 2011). So it might be an interaction between both environmental and genetic factors causes an increase in the incidence the lung cancer (Brennan et al., 2011; Peto, 2001).

Amazingly, the frequency of uterus cancer among female members of the HNPCC families has been less than our prediction according to the previous studies (Park et al., 2000; Maul et al., 2006; Pickhardt et al., 2010; Vasen et al., 2013). It may be due to some specific genetic characteristics of our populations about which more future researches would be helpful.

Given the results, the average age of cancer diagnosis in some organs such as prostate, pancreas, and lung within the HNPCC families have been near to its rate among general population (Sadjadi et al., 2007; Mousavi et al., 2009). Apparently, in these types of cancers environmental and senile factors are dominant, and inheritable genetic factors have likely a little effect to trigger them (Yoder, 2006; Kratzke and Franklin, 2012).

Tumor sites in HNPCC probands: Although right colon has been the most common involved site in CRC patients of HNPCC families, particularly among early-onset of them (Lynch et al., 2009; Nemati et al., 2011), in a recent Iranian study, just 35.4% of CRC patients with positive family history had a tumor in right colon (Fatemi et al., 2010). In our study, right colon was the third common sites after rectum and sigmoid colon, being only 26% of CRC tumors. Future studies could elucidate more information in all parts of Iran.

Survival and mortality rates: Over 13 years cancer registering in PHRC convinces us that more than one third (39%) of our HNPCC probands have deceased during this period. According to different studies, 5-year survival of HNPCC probands has been estimated 55-94% in various populations (Stigliano et al., 2008; Haghghi et al., 2009). It was 82.5% in HNPCC-CRC patients versus 56.4% in sporadic ones according to one study in Iran (Haghghi et al., 2009). HNPCC-CRC probands in our study lived averagely 8.0 years after the first diagnosis. Meanwhile, only 35.5% of them had been clinically identified in TNM stage I or II. Since advanced pathologic stage at diagnosis time is due to diagnostic delays (Mitchell et al., 2008), we expect to identify the patients in more advanced pathologic stage in Iran than most developed countries according to lack of a systematic program for cancer screening in Iranian Health System leading to worse prognosis (Cappell, 2008). Therefore, establishing a systematic screening program to early detection of CRC, particularly

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