CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Rising rates of colorectal cancer among younger Iranians: is diet to blame?

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ABSTRACT

Background Colorectal cancer (CRC) is one of the most prevalent cancers in the world. Although the incidence of CRC is currently very low in the older Iranian population compared with Western populations, young Iranians show a rising trend of CRC—that is, the age-adjusted rate is close in the young Iranian population compared with the U.S. population, and the rate in older Iranians is much lower.

Methods To assess a putative relationship between diet and a rising rate of CRC in younger Iranians, a combined text word and MESH heading search strategy identified relevant studies through Google Scholar and MEDLINE.

Results A critical look at diet among Iranians shows major issues that might be raising the risk for CRC. There are also scenarios other than diet for the rise, such as the young age structure of the country. However, the actual scenario is more complex.

Conclusions In Iran, CRC is one of the most common incident cancers and a common cause of cancer death. Primary and secondary prevention—with attention to a healthy lifestyle, physical activity, and screening—should be enhanced in the general population.

Key Words Colorectal cancer, diet, Iran, epidemiology, physical activity, obesity, lifestyle factors

Curr Oncol. 2017 Apr;24(2):e131-e137 www.current-oncology.com

INTRODUCTION

Associated with more than 1 million new cases each year and more than a half million deaths globally, colorectal cancer (CRC) is the 3rd most common cancer in the world[1–3]. It is the 3rd and 4th most common cancer in women and men respectively[4], and it most commonly occurs in the 7th decade of life[5].

The highest CRC incidence rates are seen in Europe, North America, and Oceania. By contrast, the lowest rates are observed in Africa, South America, and Asia[4]. Increases in the CRC incidence rate have been observed in Japan, Singapore, and Israel in recent years[6]. Among Iranians, CRC is the 3rd and 4th most prevalent cancer in men and women respectively. Although the incidence of CRC is currently very low in the older Iranian population compared with Western populations, young Iranians show a rising trend of CRC: that is, the age-adjusted rate is close in the young Iranian population and the U.S. population, but the rate is much lower in older Iranians[7].

Sedentary lifestyles and a diet rich in fat and meat and poor in cereals and fibre, typical of the Western diet, are suggested to be related to the increased incidence of CRC[8,9]. A healthier diet might therefore potentially help lower the incidence of malignancy[10]. To assess the putative relationship between diet and rising rates of CRC in younger Iranians, a combined text word and MESH heading search strategy using the terms "colorectal cancer," "colorectal neoplasm," "colon cancer," "colon neoplasm," "rectal cancer," and "rectal neoplasm" combined with "BMI" or "body mass index," "obesity," "overweight," "alcohol," "physical activity," "exercise," "red meat," "processed meat," "fish," "poultry," "vegetables," "fruits," "diet," "lifestyle" identified relevant studies through Google Scholar and MEDLINE.

RESULTS

Epidemiology of CRC in Iran

Recent epidemiologic studies in Iran have shown rapid growth in the incidence of CRC, and preventive measures

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have yet to be established. Elucidating the epidemiologic trend of CRC in Iran and opting for the most appropriate evidence-based screening method is critical to prevent morbidity and mortality from this lethal and to some extent preventable cancer in the country. According to recently published population-based cancer registry data covering about 22% of the Iranian population, each year more than 51,000 new cases of cancer are diagnosed in Iran, and 35,000 deaths are attributed to cancer. Iran therefore has the second-highest number of cancer deaths in the World Health Organization's Eastern Mediterranean region. According to one study[7], the estimated number of new cases of CRC in Iran is 3641 each year, and 2262 Iranians die of CRC each year, accounting for roughly 6.3% of all cancer deaths in Iran[11].

The first comprehensive study on the incidence and age distribution of CRC in Iran was carried out by Ansari *et al.*[12], who used 5-year data from population-based cancer registries. They found that Iran is still a low-risk country for CRC, particularly in the older population. However, the age-adjusted rates are close in the young Iranian population and the U.S. population (Table I), and the rate is much lower for older Iranians (Figure 1). The study results disclosed a significant increase in the incidence of CRC compared with the previously reported incidence. In Shiraz (southwest Iran), the annual incidence of CRC was seen to sharply increase to 6.92 per 100,000 population in 1990–2000 from 3.96 per 100,000 population in 1970–1980[13]. The incidence of CRC in Tehran, the capital of Iran, was reported to increase dramatically, by 82%, during the period from 1975 to 2005[14]. And according to a recently published pathology-based Iranian national cancer registry study[15], the age-adjusted incidence for CRC in men increased to 8.2 from 5.5 per 100,000.

TABLE I Age-adjusted rates of colorectal cancer per 100,000 population, Iran and the United States[a]

Age group	Iran		United States	
	Men	Women	Men	Women
0–14 Years	0.1	0.1	—	—
15–24 Years	0.6	0.8	—	—
24–34 Years	1.2	1.9	2.9	2.7
35–44 Years	4.8	6.8	10.4	7.9
45–54 Years	17.7	13.2	41.8	32.9
55–64 Years	34.9	27.1	127.1	87.5
≥65 Years	37.3	29.2	355.7	273.9

[a] The U.S. rates were calculated using 5-year age-specific Surveillance, Epidemiology, and End Results data for 1995–1999 and the age structure of the U.S. population during the same years[7] (used with permission from the *Archives of Iranian Medicine*).

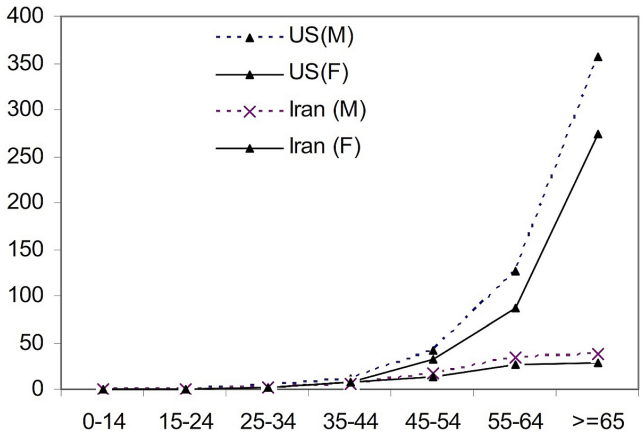

FIGURE 1 Age-adjusted rates of colorectal cancer per 100,000 population, Iran and the United States. The U.S. rates were calculated using 5-year age-specific Surveillance, Epidemiology, and End Results data for 1995–1999 and the age structure of the U.S. population during the same years[7] (used with permission from the *Archives of Iranian Medicine*).

CRC and Red and Processed Meat Consumption by Iranians

Several epidemiologic studies have shown that meat intake is significantly associated with an increased risk of colon cancer[16–18].

In 2007, the World Cancer Research Fund released a report stating that there was convincing evidence of a causal role for red and processed meat in CRC[9]. Also, a quantitative evaluation of 26 cohort studies (111 reports with information about 15,057 people with CRC) examined the association between meat (red meat, processed meat, fish, and poultry) and CRC. The evaluation concluded that, compared with people having the lowest intake of processed meat, those having the highest intake experienced a 20% increased risk for developing CRC. The authors did not observe any apparent association between risk of CRC and consumption of either fish or poultry[19]. Another meta-analysis published in 2013 also observed an elevated risk of colorectal adenoma with intake of red and processed meat[20].

Red meat might be related to the incidence of CRC either directly or indirectly. Frying, grilling, broiling, or cooking meat over coal at high temperatures can lead to the formation of mutagenic and carcinogenic heterocyclic amines through the interaction of muscle creatine with amino acids and to the formation of N-nitroso compounds[21]. Those substances can induce genetic alterations and form DNA adducts characteristic of colorectal tumours. The heme iron content of meats might contribute to colorectal neoplasia by inducing oxidative DNA damage and by increasing endogenous formation of N-nitroso compounds, which are known to be powerful multisite carcinogens[22]. Thus, the greater abundance of heme in darker meats than in white meats could increase the risk of CRC. Many studies have observed a positive association between heme and the development of colonic polyps, adenomas, and CRC[23].

Fish and poultry are alternative sources of protein and have been shown to reduce the risk of colon cancer and adenoma. Mechanisms such as the presence of n-3 polyunsaturated fatty acids, especially in oily fish, and more efficient methylation because of the high methionine content in those foods have been proposed for the protective effect of white meats[24].

In this regard, a preventive diet might involve limitation or avoidance of red or processed meats and consumption of white meat and fish[25]. Although epidemiologic studies have observed a strong association between meat intake

and an increased risk of CRC, it is important to mention that some components of meat are anticancer substances and essential for optimal human health (selenium; zinc; omega-3 fatty acids; vitamins B6, B12, D, and folic acid)[26].

No published official data have reported how much red and processed meat Iranians usually consume, but the traditional Iranian diet rarely includes high consumption of fish because of its high price and lower availability compared with red meat[27], and so most Iranians choose red meat as their first option when choosing meats. Iran is a country in a time of transition, from a traditional to a modern society, and so more modernized lifestyles are being substituted for traditional approaches, suggesting an increase in the incidence of CRC. Fast foods and unhealthy dietary behaviours are emerging in adolescents and families[28,29]. Thus, given low prices, easy access, and more employed mothers than in the past, consumption of processed meat is on the rise among Iranians.

CRC and Fibre, Fruit, and Vegetables

Dietary fibre varies significantly in physical properties and chemical composition, but can be classified according to water solubility, which affects its function in the body and might be relevant to the risk of CRC. Bran fibre is insoluble; fruit and vegetable fibre tends to be more soluble[30]. After observing the low incidence of CRC in African nations whose populations consume a high-fibre diet, the hypothesis that high fibre consumption might reduce the risk of CRC was proposed by Burkitt and colleagues in the 1970s[31].

Cellulose, hemicellulose, and pectin are plant materials that are defined as fibre[32]. Their protective effect against CRC could be explained by the fact that their presence in meals contributes to lower transit time through the gastrointestinal tract, reducing the concentrations of intestinal carcinogens because of increased stool mass, diluting colonic contents, and enhancing bacterial fermentation, which leads to increased production of short-chain fatty acids (acetate, propionate, and butyrate). The latter substances were found to induce apoptosis in CRC cells in rats. Dietary fibre has also been proved to have an anti-inflammatory function, lowering the production of interleukin 6, tumour necrosis factor α, cyclooxygenase 2, and gene expression of inducible nitric oxide synthase. In addition, in an animal model of CRC, short-chain fatty acids interfered with numerous regulators of cell-cycle proliferation and apoptosis such as the beta-catenin, p53, p21, Bax, and caspase 3 genes. Thus, diets high in wheat bran, fruit and vegetables, citrus fruits, cruciferous vegetables, dark green vegetables, onions, garlic, and tomatoes might have a protective effect against colorectal adenomas and subsequently CRC[33].

Fruits and vegetables also contain many potentially protective substances that affect various biochemical pathways. Their benefits can be observed in inhibitory action at early tumour stages or at advanced or metastatic tumour stages[34].

To reduce the risk of chronic diseases, eating 5 servings of fruit and vegetables daily is recommended; yet, according to the data from the National Food Consumption Survey in Iran, Iranians consume fewer fruits and vegetables than the recommendation suggests[35]. With respect to patterns of fruit and vegetable consumption among Iranian adults, a 2007 SURFNCD study revealed that a low intake of fruit and vegetables (fewer than 5 servings daily) was prevalent (87.5%), but also that intake tended to be higher in older age categories[36]. Sabzghabaee *et al.*[37], in a study of a community-dwelling elderly population, found that just one third of the participants achieved World Health Organization recommendations for daily servings of fruits and vegetables. A study of Iranian adolescents revealed the same pattern of insufficient fruit and vegetable consumption among Iranians[38].

CRC and the B Vitamin Family

For DNA methylation, synthesis, stability, and repair, B vitamins, including riboflavin (vitamin B2), pyridoxine (vitamin B6), folate (vitamin B9), cobalamin (vitamin B12), and methionine are essential[39]. Folate deficiency results in genomic hypomethylation and defects in DNA synthesis, both of which can contribute to colonic carcinogenesis. Methionine and folate are required in the production of S-adenosylmethionine, the primary methyl donor, but when methionine levels are low, more folate is used as methyl tetrahydrofolate to form methionine. The lower levels of methyl tetrahydrofolate might affect DNA synthesis[40], which could explain the protective effect associated with higher folate levels for those with low methionine intake. That hypothesis was supported in 2013 by Bassett *et al.*[41] in a prospective cohort study. Interestingly, compared with people having a high methionine intake but low folate intake, those having high intakes of both methionine and folate were observed to have a significantly increased risk for CRC[41].

Pericleous *et al.*[33] showed that the reduction in the CRC incidence in the United States and Canada might be a result of dietary folate supplementation. However, Giovannucci[42] showed how dietary folate, but not folate from supplements, reduced the risk for CRC or adenoma. Giovannucci suggested that folate supplementation could be associated with a higher risk of adenoma recurrence and might even be harmful to patients with a prior history of colon cancer. Low folate levels enhance the invasiveness of colon cancer cells, mediated by activation of the hedgehog SHH ("sonic hedgehog") signalling pathway through stimulation of the nuclear factor κB pathway and promoter hypomethylation, as was reported in recent *in vitro* molecular studies[43]. In a randomized clinical trial, Cole *et al.*[44] found that folic acid supplementation at a dose of 1 mg daily is harmful, causing an increase, by a factor of 2.3, in the total number of colonic adenomas and an increased risk, by a factor of 1.7, for advanced colonic adenomas. Thus, Cole *et al.* suggested that only physiologic levels of folic acid play a protective role and that intense supplementation could lead to progression of small pre-existing adenomas. Moreover, especially in the elderly population, folic acid supplementation at high doses (1000 μg daily) appears to enhance the risk of neoplasms.

Vitamin B6 (pyridoxal phosphate) is an important protective anticancer nutrient that is found in numerous grains, fruits, vegetables. In a meta-analysis of prospective studies, Larsson *et al.* showed a 49% decrease in CRC risk for every 100 pmol/mL increase in the pyridoxal phosphate concentration in serum[45].

To summarize, diets rich in folate might prevent colorectal carcinoma. To assess the increased risk of adenoma recurrence, further studies are required. In Iran, folate comes mainly from the diet because there is no mandatory folate fortification, and use of dietary supplements is uncommon. One study showed that the prevalence of hyperhomocysteinemia and of low serum folate and vitamin B12 is higher in healthy adult Iranians than in other populations[46]. Folic acid supplementation (1 mg daily) is administered to pregnant Iranian women to prevent the development of fetal neural tube defects, and so far, no publications have reported the frequency of CRC in that population.

CRC and Calcium and Vitamin D

Vitamin D, a fat-soluble vitamin, is synthesized mostly endogenously from skin exposure to ultraviolet sunlight. Some comes from the diet as the provitamin cholecalciferol (D3), which is found naturally in oily saltwater fish, liver, and egg yolk. The plant-derived provitamin ergocalciferol (D2) is found in foods such as mushrooms. Food fortification can provide an extra source of vitamin D. The active form of vitamin D, which is synthesized by hydroxylating provitamins in the liver and kidneys, is 1,25-dihydroxyvitamin D3 (calcitriol). The use of calcitriol in experimental studies has been shown to induce differentiation and inhibition of tumour cell proliferation in various types of cancer cells; however, because of the development of toxic hypercalcemia, such use is limited. For those reasons, calcitriol analogues are usually used[47].

Epidemiologic studies show that deaths from CRC are higher in areas with less sunlight. Also, populations consuming higher amounts of fresh fish, shellfish, calcium, and vitamin D have lower rates of CRC[48]. A meta-analysis by Wei *et al.*[49] found an inverse association between circulating levels of 25-hydroxyvitamin D3 and risk of CRC.

In countries in which vitamin D–fortified foodstuffs are available (for example, the United States and some Scandinavian countries), the prevalence of vitamin D deficiency is between 1.6% and 14.8% in various age groups. In countries with an insufficient dietary supply of vitamin D or in which foodstuffs are not supplemented, dietary intake of vitamin D is generally low. According to a study that considered a sample of Tehran's population, the prevalence of severe, moderate, and mild vitamin D deficiency was 9.5%, 57.6%, and 14.2% respectively[50]. Moreover, a multicentre study examining people from various urban areas of Iran in 2008 showed that Iran is a country with a high prevalence of moderate-to-severe vitamin D deficiency and that the prevalence of deficiency is more evident in Tehran[51]. Plus, a work by Bonakdaran and colleagues[52] on participants derived from an urban population in Mashhad (northeast Iran) showed that roughly 80% had vitamin D deficiency at the level of 14.1 ng/mL (range: 8.8–19.0 ng/mL).

CRC and Obesity

In a meta-analysis of CRC risk factors, data from 2309 colon cancer patients and 66,199 CRC patients in twenty-three studies was used to investigate the relationship between body mass index and risk of CRC. Body mass index and CRC were found to be significantly associated (relative risk: 1.10 per 8 kg/m^2)[20].

Like many other developing countries, Iran has been experiencing a rapid phase of urbanization and industrialization in recent decades[53]. Limited studies performed in certain cities in Iran have shown varying prevalences of obesity. However, in a vast country like Iran, with its great diversity of sociodemographic and lifestyle factors in its various provinces, such studies are too small and nationally unrepresentative. Consequently, Kelishadi *et al.*[54] undertook a large population-based survey at the national level as a baseline survey for the first surveillance system of the risk factors for non-communicable diseases in Iran—and, to the best of our knowledge, in the eastern Mediterranean region. They found alarming evidence about the very high prevalence of generalized and abdominal obesity in Iran. Table II shows the data concerning general and abdominal obesity among Iranians. This high prevalence of obesity could also make Iranians more prone to CRC.

CRC and Physical Inactivity

A meta-analysis used data from 5994 colon cancer patients and 5099 CRC patients in twenty-one studies to examine the relationship between physical activity and CRC. Without adjustment for any covariates, a significant negative correlation between CRC risk and physical activity was observed (relative risk: 0.88 per 2 standard score; 95% confidence interval: 0.86 to 0.91)[20].

In developed countries during the past few decades, physical activity levels for both adults and children have steadily declined[55,56]. More than 80% of the Iranian population is physically inactive according to data from three national surveys of Iranian adults[57]. The few local studies performed in Iranian youth showed a similar pattern[58,59]. Those declines in physical activity level are suggested to be a result of more time spent watching television and playing computer games and of a decrease in opportunities for physical activity in schools and communities[60].

CRC and Alcohol Consumption

With respect to alcohol consumption, the pooled estimate for CRC risk from a recent meta-analysis showed a trend toward a positive association, with a relative risk of 1.06 for an increase of 5 drinks weekly (95% confidence interval: 0.91 to 1.23)[20].

According to a World Health Organization report[61], Iran has almost zero alcohol consumption. However, because Iran is an Islamic country, with legal punishment for alcohol consumption, real data about alcohol consumption in Iran is lacking because most people usually deny alcohol use in questionnaires. Thus, because of the lack of reliable data, we cannot draw any conclusions about alcohol consumption and CRC in Iranians.

DISCUSSION

In Iran, patients with early-onset CRC (those less than 40 years of age at the time of diagnosis) comprise roughly one fifth of all CRC patients. That proportion is different from the proportion seen in Western countries, where the rates of early-onset CRC vary from 2% to 8%. Various hypotheses have been proposed for this rise. One proposed hypothesis for the high proportion of CRC cases seen in young Iranians

TABLE II Prevalence of generalized and abdominal obesity by age group[a]

Age group	Weight status (%)					
	Underweight	Normal	Overweight	Obesity	Morbid obesity	Abdominal obesity
15–24 Years	10.8	67.0	17.1	4.0	1.2	4.0
25–34 Years	3.4	50.4	32.3	10.8	3.1	10.8
35–44 Years	2.1	38.6	37.1	16.7	5.4	16.7
45–54 Years	2.1	35.3	37.8	18.5	6.2	18.5
55–64 Years	2.5	38.6	36.6	16.9	5.4	16.9
National estimate	5.7	51.5	28.6	10.8	3.4	10.8

[a] Used with permission from *Public Health Nutrition*[53].

is the young age structure of the country. According to a 1997 census by the Statistical Centre of Iran, approximately 80% of the country's population is younger than 40[12].

Another theory to explain the rising trend is a suggestion, supported by Haghighi and colleagues[62], that the current older generation in Iran was exposed to a low-risk environment when young. Their CRC risk is therefore proposed to be much lower than that for Americans of the same age. The new generation is exposed to a high-risk Westernized environment such that their rate of CRC is similar to that for young Americans. In 1976, after examining large intestines from 801 individuals in Fars Province, Iran, Haghighi *et al.*[62] found a much lower rate of adenomatous polyps in the large bowels of Iranians compared with Americans of the same age—younger and older alike. If their hypothesis is accepted, a cohort effect should soon be evident (that is, within the next 10 years), with the CRC rate in the Iranian population 45–54 years of age also becoming close to the U.S. rate (35 per 100,000 population annually)[12]. In Egypt, where the proportion of young people with CRC is exceptionally high (36%)[63], a genetic predisposition is more possible[64]. A similar unique genetic pattern in the Iranian population cannot be ruled out.

Since the 1979 revolution in Iran, statistics from the Statistical Center of Iran (2007) and a World Bank report (2006) show that, according to nearly all economic indices, living standards have improved dramatically across the entire country. Furthermore, since the mid-1980s, Iran has experienced rapid socioeconomic development, with significant lifestyle changes, such as a transition to a more sedentary lifestyle and to a diet similar to that consumed by Western populations—that is, poor in cereals and fibre, and rich in red and processed meats[7]. A critical look of the Iranian diet and lifestyle in this review article would raise the hypothesis that the rising rate of CRC in the younger generation could partially be attributable to diet. Epidemics of CRC attributable to Westernization have also been reported in other developing countries[65] and might explain the high proportion of young patients with CRC in Saudi Arabia (23%)[66] and Jordan (13%)[67]. Such a hypothesis is further supported by a recent study of cancer incidence rates in Iranian immigrants to British Columbia, Canada. Cancer incidence rates computed from population-based cancer registries in Iran and British Columbia showed a doubling of the CRC incidence among female Iranian immigrants[68].

It is noteworthy that, in East Azerbaijan Province, Iran (bordering West Azerbaijan and Turkey, with Turkish culture), the CRC incidence is showing an increasing trend, especially in women. According to data from one meta-analysis[69], the highest crude rate for CRC was reported from that province, at 11.50 cases per 100,000 men and 9.22 cases per 100,000 women. In Turkey, which borders Iran on the east, CRC is the 7th most frequent cancer in both sexes, with the lowest age-adjusted rates compared with our results for the Turkish cultural provinces in Iran. In Turkey, cancer control programs use education and public awareness campaigns to boost healthy eating habits. In remote parts of Turkey, screening programs for CRC were also introduced, which seem to be successful. Educating people about opting for a healthier lifestyle is thus of great importance. Also, given the young population in Iran and the rising incidence of CRC in that age group, it is recommended that screening start from a younger age[70]. Most patients with this cancer are diagnosed at stage IV, which further clarifies the critical role of on-time screening[71]. Moreover, studies have shown that the burden of CRC has increased in Iran, and the possibility for intervention and effective prevention should be one of the top health priorities for the country[72].

CONCLUSIONS

In Iran, CRC is one of the most common incident cancers and a common cause of cancer death. Primary and secondary prevention, with attention to a healthy lifestyle, physical activity, and screening should be enhanced in the general population.

ACKNOWLEDGMENTS

The authors offer special thanks and acknowledgment to their funders, Reza Radiation-Oncology Charity Center. Sincere thanks also go to Mr. Ebrahim Pouladin for financial support to CRC research.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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