RESEARCH ARTICLE

Colorectal Cancer Incidence Trend and Projections in Tunisia (1994 - 2024)

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Abstract

Objectives: The aim of this study was to describe trends of colorectal cancer incidence during the period 1994-2009 and to generate projections until 2024. **Methods:** The North-Tunisia Cancer Registry (NTCR) was the source of data for patients with CRC. This registry lists, since 1994, cases of malignant tumors in people living in North Tunisia, including the District of Tunis, the north east and the north west. Cases were classified using the International Classification of Diseases for Oncology. Data were analyzed using R software and Joinpoint one was employed to analyse trends. Projections were performed using the Age Period Cohort based on poisson regression. **Results:** During the period 1994 to 2009, 6,909 new cases of CRC were registered in Northern Tunisia. The age standardized incidence rate (ASR) increased significantly from 6.4/100,000 in 1994 to 12.4/100,000 in 2009. Trends in CRC incidence was significantly rising with an annual percentage change (APC) of + 3,9% [2.8% -5.1%]. Without effective interventions, the predicted CRC ASR would be 39.3/100,000 [CI 95%: 32,9/100,000 - 48,8/100,000] in 2024. **Conclusion:** The incidence of colorectal cancer is clearly increasing in Tunisia. Strengthening of screening and primary prevention measures is to be recommended.

Keywords: Epidemiology- colorectal cancers- trend- projection- Tunisia

Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide (Alwan, 2011; Boyle and Langman, 2000; Ferlay et al., 2013). However, there is a large variation in CRC incidence in more developed versus less developed countries. Indeed the highest rates are observed in USA, Canada, Australia, New Zealand and Europe (specially in Czech Republic and Slovakia) where the age standardized incidence rate (ASR) is over 40 per 100,000; whereas India, Egypt and central west Africa shows the lowest rates with an ASR less than 5 per 100,000 (Center et al., 2009; Jemal et al., 2011; Siegel et al., 2014). Concerning the incidence trend, we observed a decrease of the incidence in western countries (as in the United States of America) ; while for developing countries, the incidence of CRC increased over time (Al-Jashamy et al., 2015). These differences if CRC incidence trend between developed and developing countries are mainly due CRC screening policies (Johnson et al., 2013; Marmot et al., 2007).

CRC is also a serious health problem in Tunisia ; according to estimations of the International Agency of Research on Cancer (Globocan, 2012), the ASR was 10.9 per 100,000 in 2012, which is a low to medium rate (Ferlay et al., 2013). CRC was included in the screening program as part of the cancer plans 2010-2014 and 2015-2019 (Plan de lutte contre le cancer en Tunisie, 2015-2019). In Tunisia, data on CRC incidence and trends are rare. The last one are back to the period of 2004-2006 (Ben Abdallah et al., 2012). The aim of this study was to provide updated temporal trends in CRC incidence over a 15-year period in Northern Tunisia from 1994 to 2009 and to realize projections until 2024.

Materials and Methods

North-Tunisia Cancer Registry (NTCR) was the source of data for patients with colorectal cancers (Figure 1). This registry was created in 1997; the main data sources for this registry were medical ones of both public and private sectors in the region.

The Northern cancer registry covers 11 governorates involving the district of Tunis (Tunis, Ben Arous, Ariana and Mannouba), the north east (Zaghouan, Bizerte and Nabeul) and the north west (Béja, Kef, Siliana and Jendouba) (Ben Abdallah et al., 2012) (Figure 2). This Northern region shelters 5,035,000 habitants which represent around the half of the Tunisian population (Institut National de la Statistique, 2016). It was a homogeneous population of Arab ethnicity. Contractual physicians visited all sources to collect data using a

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standard data collection sheet. Demographic data of the North Tunisia population were provided by the National Institute of Statistics (INS) (Institut National de la Statistique, 2016).

Regarding codification of tumors, between 1994 and 2003, the first International Classification of Diseases for Oncology (ICD-O-1) was used; CRC correspond to codes 153 and 154. Since 2004, the third International Classification of Diseases for Oncology (ICD-O-3) is used ; the corresponding codes are: C18 - C20. CRC was divided into subsites: Proximal colon which includes the cecum (C18.0), ascending colon (C18.2), the hepatic flexure of the colon (C18.3), transverse colon (C18.4) and the splenic flexure of the colon (C18.5); Distal colon includes descending colon (C18.6) and sigmoid colon (C18.7); and the rectum includes the rectosigmoid junction (C19) and the rectum (C20).

Data were entered using Epi Info software (version 6). Data check was performed periodically, by following some steps: search of duplicates ; identify missing data for mandatory variables (gender, age, place of residence.); search for tumor codes errors, check for inconsistencies regarding gender and site, age and site and finally site and morphology.

Regarding the completeness of the registry, although death certificates could not be used as a source of data, many efforts are made to have satisfactory completeness of the registry, like active method for data collection. The number of sources per case used as an indirect indicator for the completeness of the registry was around 1.1.

CRC incidences were calculated as cases per 100,000 people and age-adjusted to the World Health Organization standard population. Data were analyzed using R software. Categorical data were described by calculating percentages and quantitative data through the calculation of means and standard deviations. Joinpoint software was used to describe trends (The joinpoint analysis of the trends in the age-adjusted cancer incidence and mortality rates allows the user to more accurately interpret changes over time and to determine if those changes are statistically significant). Projections were performed using the Age Period Cohort based on poisson regression.

Results

CRC Incidence trend (1994-2009)

During the period 1994 to 2009, 6,909 new cases of CRC were registered in Northern Tunisia, the age standardized incidence rate (ASR) increased significantly from 6.4/100,000 in 1994 to 12.4/100,000 in 2009 (13.2 in males and 11.5 in females) with an annual percentage change (APC) of +3.9% [2.8% -5.1%] during this period (Table 1). Regarding anatomic site, the increase of ASR was more important for colon cancer (APC= +4.5% [3.1% - 5.8%]) than for rectum cancer (APC= +2.9% [1.6% - 4.2%]) (Figure 3).

For both gender, colon cancer incidence increased significantly with a approximately similar values of APC (+4.6% [2.9% - 6.4%] in males and +4.4 [2.7% - 6.1%] in females). Concerning the rectal cancer, the increase in trend incidence was also significant but more important among males (APC of +3.9% [2.1% - 5.6%] in male versus +1.5 % [0.5% - 3.1%] in females). Considering anatomic colon subsites , the increase of incidence was

Figure 1. Map of Tunisia and Surrounding Countries

Table 1. Colorectal Cancer Incidence Trends According to Site and Gender in Northern Tunisia (1994-2009)

Site of cancer	Gender	APC	APC CI 95%	P
CRC	Both	3.9	2.8 - 5.1	<0.05
	Male	4.7	3.3 -6.1	
	Female	3.2	1.9 - 4.6	
Colon	Both	4.5	3.1 - 5.8	<0.05
	Male	4.6	2.9 -6.4	
	Female	4.4	2.7 - 6.1	
Proximal colon	Both	3.4	2.0 - 4.8	<0.05
	Male	3.3	1.6 - 5.0	
	Female	3.1	0.7 - 5.7	
Distal colon	Both	5	3.6 - 6.5	<0.05
	Male	4.8	1.6 - 8.1	
	Female	3.7	1.6 - 8.1	
Rectum	Both	2.9	1.6 - 4.2	<0.05
	Male	3.9	3.3 - 6.1	
	Female	1.8	1.9 - 4.6	

Figure 2. Map of Tunisia Showing Its Different Governorates

Table 2. Projections of CRC Number and Standardized Incidence Rate Until 2024 in Northern Tunisia

| Site of cancer	Year	Male N	ASR* (per 100 000)	ASR CI 95%	Female N	ASR* (per 100 000)	ASR CI 95%
colorectal	2014	524	20.5	[18.0-22.3]	435	15.1	[12.5-18.8]
	2019	750	24	[23.4-32.8]	610	18.8	[15.7-22.8]
	2024	1073	39.9	[32.9-48.8]	861	22.9	[17.4-27.1]
Colon	2014	322	11.8	[9.7-14.5]	288	10	[8.1-12.5]
	2019	478	15.2	[12-19.5]	426	12.7	[9.9-16.7]
	2024	708	25.8	[19.8-34.2]	631	16.6	[12.3-22.8]
Rectum	2014	202	7.4	[6.0-9.3]	147	5.1	[3.9-7.5]
	2019	272	8.7	[6.7-11.4]	184	5.6	[4.1-8.6]
	2024	365	13.5	[10.0-18.3]	230	6.3	[4.3-10.3]
Proximal colon	2014	97	3.3	[2.4-5.1]	75	2.7	[2.0-4.4]
	2019	138	4.4	[3.1-6.6]	128	3.9	[2.5-6.7]
	2024	199	7.8	[4.7-11.6]	167	6.5	[3.4-10.0]
Distal Colon	2014	225	8.5	[6.5-10.7]	213	7.3	[6.1-10.4]
	2019	340	10.8	[8.3-15.7]	298	8.8	[6.9-12.7]
	2024	510	20.4	[14.2-26.9]	464	15.9	[10.9-21.4]
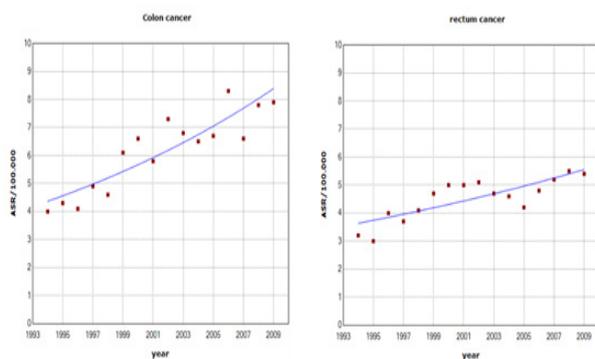
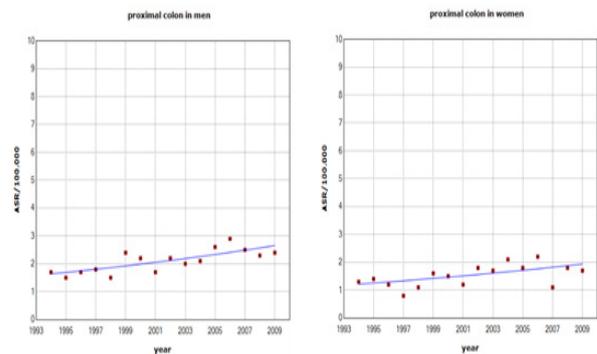Figure 3. Colon and Rectum Trends in Northern Tunisia (1994-2009)

Figure 5. Proximal Colon Cancer Trends According to Gender in Northern Tunisia (1994-2009)

more important in distal than in proximal colon (Figure 4).

Regarding proximal colon, for both gender, there was a significant increase of incidence with approximately a similar values of APC (APC =+3.3% [1.6% -5.0%] in males and APC = +3.1% [0.7 - 5.7] in females) (Figure 5); while for distal colon, the increase of incidence was more important in males (APC =+4.8% [1.6% - 8.1%] in males versus +3.7% [1.6% - 5.9%] in females) (Figure6).
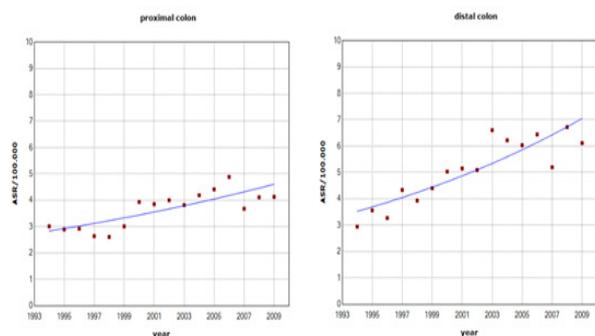
Projection of CRC incidence by 2024

By the year 2024, the predicted CRC ASR would be 39.3/100,000 [CI 95%: 32.9/100,000 - 48.8/100,000] for male and 22.9/100,000 [CI95%: 17.4/100,000 -27.1/100 000] for female. According to colon subsite, predicted ASR would be similar for both genders for proximal colon; however for rectal cancer and with a less degree for distal colon cancer, ASR would be much higher among male
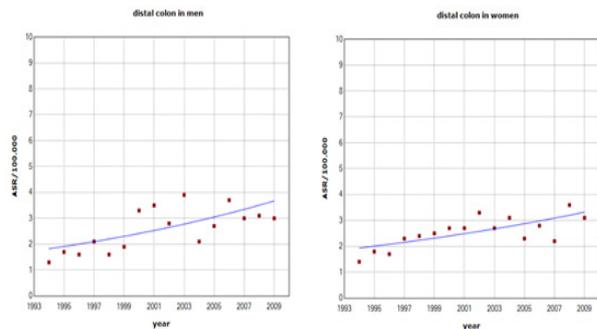

Figure 4. Proximal and Distal Colon Cancer Incidence Trends in Both Genders in Northern Tunisia (1994-2009)

Figure 6. Distal Colon Cancer Incidence Trends According to Gender in Northern Tunisia (1994-2009)

than female (Table 2).

Discussion

According to the results of this study, CRC ASR in Northern Tunisia was of 12.4 in 2009 ; this incidence increased during the period 1994-2009, from 6.4/100,000 in 1994 to 12.4/100,000 in 2009 with a significant APC of +3.9% (4.7% in males versus 3.2% in females). The predicted CRC incidence rate by 2024 should be 28/100 000 for male and 19.6/ 100,000 for female.

Regarding the CRC incidence level, it was largely below the medium rate in the world according to the estimations of Globocan 2012 (17.2/100,000) (Ferlay et al., 2013). Indeed the highest rates are observed in USA, Canada, Australia, New Zealand and Europe (specially in Czech Republic and Slovakia) where ASR is below 40/100 000; while India, Egypt and central west Africa show the lowest rates with an ASR less than 5/100,000. The ASR in other Maghreb countries (Morocco, Algeria and Libya) are also rather close to those reported in this work. Incidence rates were 10.5/100 000 in Morocco (2006-2008 registry) (Tazi et al., 2013) and 11/100,000 in Algeria (2006) (Cherif et al., 2010).

This disparities of CRC incidence in different countries should be explained by the difference in major CRC risk factors levels (obesity, physical inactivity, smoking, high alcohol consumption, a diet high in fat and low in fruits and vegetables) (Aleksandrova et al., 2014; Berghöfer et al., 2008; Cross et al., 2014; Doubeni et al., 2012; Fedirko et al., 2011; Jarosz et al., 2013 ; Ma et al., 2013 ; Schmid and Leitzmann, 2014; Zhu et al., 2015), but also by the magnitude of CRC screening programs (Zavoral et al., 2014).

Modifiable risk factors of CRC were generally associated with the level of economic development which partly explains the highest rates in western countries (Lambert, 2012). In developing countries, as in Tunisia, the observed trend rate could be explained by the epidemiologic transition and the adoption of a westernized life style as dietary habits, physical inactivity, overweight and obesity (Belfki et al., 2013; El Ati et al., 2012). It is relevant to highlight that an upward trend in obesity largely explains the increasing incidence of CRC in Tunisia. In fact, during the period 1980-2005, the prevalence of overweight increased by 67%, and the prevalence of obesity was multiplied by 2.5 times among adults (from 35 to 70 years). During this 25 years, the average BMI of Tunisian adults increased by +2.4 kg / m², but much more in women (+3.2 kg / m²) than in men (+1.4 kg / m²). In 2005, the mean BMI was 28.4 kg/m² for women and 25.3 kg/m² for men (Belfki et al., 2013; El Ati et al., 2012). Among adolescents, the prevalence of obesity, which did not exist in 1996, has already reached 5% in 2005 for both genders. In front of this burden, a national program to fight against obesity is currently in the pilot phase in the governorate of Bizerte in order to be extended to other regions (Belfki et al., 2013; El Ati et al., 2012).

Developed countries, initially experienced an upward trend in the incidence of CRC. Thus, in the Czech Republic and Slowacki, the incidence among men has exceeded the peak observed in the USA, Canada and Australia; this increase was partly due to high exposure to obesity and high prevalence of smoking (60% of males were smokers and 25% of adults were obese) (Berghöfer et al., 2008; Center et al., 2009; Jemal et al., 2011). In Spain also, the incidence of CRC remains high, explained in large part by the high prevalence of obesity (Aleksandrova et al., 2014; Lopez-Abente et al., 2010); moreover there is no national CCR screening program which partly explains that trend still on the rise. Some pilot programs are being developed at a regional level (Zavoral et al., 2014).

Most of Asian countries do not have a CRC screening program which are limited to some pilot programs in Taiwan (through faecal-occult-blood test) and in Hong Kong (through colonoscopy). So that trend on CRC incidence rate still on the rise (Center et all., 2009). Only Japan has had a national CCR screening program since 1992, based on the use of fecal immunological tests (Ross, 2010). Indeed, the trend in the incidence of CRC is decreasing.

According to the results of this study, the increase of incidence was more important for the colon cancer than the rectum one and more important in distal than in proximal colon. This topography is important to precise as distal colon and rectum are more accessible for detection and cancer in these sites have better prognosis than proximal colon (Hoff and Dominitz, 2010; Imperiale et al., 2000; Meguid et al., 2008; Myer et al., 2012; Wong, 2010). A similar trend of CRC incidence was also observed at a national level in the governorate of Sousse in the center of Tunisia during the period 1993-2007 with an APC of +5.3% among males and +2.6% among females (Missaoui et al., 2010).

In the World, this increase of CRC incidence was observed in developing countries where an upward in CRC trend is observed. In the Maghreb countries such as in Algeria , the trend in the incidence of CRC during the period 1996-2010 was clearly on the rise, with a APC of +4.9% (+5.4% in men and +4.5% in women) (Cherif et al., 2015; Cherif et al., 2014). In the Middle East, the incidence rate is increasing such in Iran with an APC of +2.6% between 2004-2011. In Jordan the rates of CRC increased significantly throughout the period between 1996 and 2009 with an APC of 13.7% in men and 12.2% in women (Ismail et al., 2013). In Gulf countries, CRC incidence increased during the period between 1998 and 2007 in both genders ; the total number of newly diagnosed colorectal cancer was multiplied by 2.3 and 2.7, respectively for males and females (Al Hamdan et al., 2009; Alsayyad and Hamadeh, 2007; Arafa and Farhat, 2015). In Asia, Korea has the highest incidence of CRC with an increasing rate (Jung et al., 2013), while Japan is considered as the only country among Asian ones where the incidence begins to decrease during the period from 1995 to 2010 with an APC of -0.4% for colon cancer and +0.1% for the rectum in males and an APC of +0.3% and -3.4% respectively for the colon and the rectum among females (Katanoda et al., 2015; Yang et al., 2004).

However, an opposite trend was observed in developed countries, commonly known with high rates of incidence,

are showing a stable or even declining trends (Ferlay et al., 2013). In most European countries such in Germany the APC is of -1.9 and -3.2 respectively in males and females during 1994-2005 ; in France the APC is of -1.2 in both genders between 1985 and 2005. Likewise, in Czech Republic and in Slowacki, a declining trend is also observed during 1994-2005 (Ferlay et al., 2013). In Canada, the trend is stable with an APC of +1.3% during the period 1996-2000 and of -0.8% between 2000 and 2007 (Kachuri et al., 2013; Mistry et al., 2011; Söderlund et al., 2009). The trend is downward in the United States of America with a significant decrease in the incidence rate between 1998 and 2009 with an APC of -2.3% (-2.6% in men and -2.1% in women) (Howlader et al., 2015; Mateka et al., 2011; Siegel et al., 2014).

This decline of CRC incidence in developed countries should the results of colorectal mass screening programs in these countries.

Even the huge efforts established to reduce the risk factors of CRC in developed countries, only the application of screening programs of this cancer succeeded to inverse the increasing incidence rates of CRC (Brenner et al., 2014; Edwards et al., 2010; Kronborg et al., 1996; Pan et al., 2016). In fact, Germany was the first European country in 1976 to introduce a CRC screening program (West et al., 2009). The Czech Republic was also one of the first countries to launch a national CRC screening program (Zavoral et al., 2014). This should explain the declining trends in these countries. Screening was initially proposed to asymptomatic individuals over 50 years old, through fecal occult blood tests in order to increase the participation rate, colonoscopy screening is now offered as an alternative to faecal-occult-blood test. Several countries in northern Europe (Norway, Sweden, Iceland, Poland, the Netherlands) evaluate colonoscopy screening through a large controlled trial (Aleksandrova et al., 2014). In Australia, a national organized screening program began in 2006, following pilot experiments (2002-2004). This program is based on an immunological test (Foreman, 2009). In Canada, since 2002, the National Committee has recommended a structured and organized screening program for CRC. This screening should be offered to all adults aged 50-74 through the use of the faecal-occult-blood test on a bi-annual basis. In addition, this committee recommends that a colonoscopy or a barium enema or a sigmoidoscopy be performed if the faecal-occult-blood test is positive (Puddu and Tafforeau, 2006). The incidence of CRC in the USA is more decreasing than other developed countries, and the prognosis of this cancer is also better. Screening program in the United States has developed earlier since 1997 and more significantly than in European countries. There is no uniform and generalized screening such in French and British models, but there are several types of programs and several screening alternatives which can be carried out in various ways, even if the colonoscopy is in the front line. Thus, a screening colonoscopy, supported by the Federal Health Insurance Scheme, has been proposed since 2001 to subjects among 65 years and over (Hoff and Dominitz, 2010). The decrease in incidence in the USA is mainly due to the importance given to screening and also to the early

treatment of precancerous lesions of CRC (Al-Jashamy et al., 2015; Richardson et al., 2011). Indeed, priority is currently given to screening to prevent CRC and reduce its mortality.

In Tunisia, a two-year multi-center pilot project was implemented. The target population is men and women aged from 50 to 74 years without any family medical history or personal colorectal cancer who do not suffer from any disabling disease. The screening is done by the faecal-occult-blood test , and if it is positive, a colonoscopy will be performed. Unfortunately, these pilot studies suffer from a low coverage rate. The generalization at national level of this screening would be very beneficial to invert the increasing trend of the CRC in Tunisia. Without a consistent screening program, the predicted CRC incidence rate by 2024 should be 39.3/100,000 for male and 22.9/ 100,000 for female.

In conclusion, CRC incidence in North Tunisia was relatively low in comparison to developed countries; this incidence of CRC observed a significant increase between 1994 and 2009. Without an effective intervention, the ASR for CRC would reach more than the double in 2024.

In order to change this tendency, it's highly recommended to promote primary prevention concerning good eating habits, physical activity and tobacco control, to extend progressively the anti-obesity program to other governorates and most of all to gradually extend the screening of CRC to other health districts, while providing a formal framework for the free provision of services and increasing public awareness of the importance of this screening.

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