RESEARCH COMMUNICATION

Colorectal Cancer in Young Cambodians

Monirath Hav[1,2]*, Sokha Eav[3], Vutha Ky[4], Claude Cuvelier[1], Sokneang In[5], Rithy Kong[6], Yana Kheang[7], Chakravuth Oung[8], Piet Pattyn[9], Dara Lem[7]

Abstract

Aim: Colorectal cancer (CRC) is a common disease in the older population, but it has become increasingly evident that it is also not infrequent in the young. The aim of this study was to describe the epidemiological, clinical and pathological characteristics of CRC in young Cambodians. Methods: We examined clinical and pathological data from all CRC cases registered in the two reference centres for gastrointestinal tumours in Cambodia between 2005-2010. Age-specific CRC incidence rates were computed using the national population census 2008 data from the National Institute of Statistics. We compared differences in distribution of tumour location, histology, differentiation and UICC/TNM stage in two age groups, namely < 40 and ≥ 40. Results: During this period, there were 356 new CRC cases, of which 29.8% affected patients younger than 40. This proportion is the second highest in the world, with a higher proportion only reported in Egyptian population. The crude incidence was 2.82 and 2.36 per 100,000 in females and males, respectively. Adenocarcinoma was the most common histologic type, and >50% of all tumours occurred in the colon, with no appreciable variation between the two age groups. Mucin-producing and advanced-grade tumours were twice more frequent in the young. Conclusion: The unusually high CRC proportion in the young in our study could be due to referral bias. Nevertheless, together with the continuous exposure to hazardous environmental agents and the prevalent consanguinity in Cambodia, this question warrants further research to advance our understanding of CRC risk factors and perhaps genetic-environmental interactions in CRC epidemiology in young adults.

Keywords: Colorectal cancer - epidemiology - characteristics - young patients - Cambodia

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Introduction

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal (GI) tract. It is the third most common cancer in men and the second most common cancer in women worldwide (Ferlay et al., 2010). CRC is generally thought of as a disease of older persons, with more than 90% of patients being diagnosed after the age of 55 years (Atkin et al., 2010). It is well known, however, that CRC also affects a young population. Recent studies suggested that as many as 7% of patients who developed CRC were under 40 years of age, and this incidence keeps increasing (Meyer et al., 2010; O'Connell et al., 2003; O'Connell et al., 2004). In the United States, between 1992 and 2005, the incidence of CRC in young individuals increased at a rate of 1.5% per year in men and 1.6% per year in women (Siegel et al., 2009).

Select groups of young patients are known to have high CRC risk, such as those with inflammatory bowel disease, hereditary non-polyposis colon cancer and polyposis syndromes of the GI tract (Devroede et al., 1971; Aarnio et al., 1995; Herszenyi et al., 2007; van Lier et al., 2010). In this high-risk population, early screening has been shown to reduce mortality from CRC (Järvinen et al., 1995). For young patients who develop CRC, but have no known predisposing risk factors, late diagnosis and poor outcome may result from clinician's failure to consider the possibility of malignant disease in the differential diagnosis (Gallagher & Zeigler, 1972). Knowledge of high CRC incidence rate in the young population of some countries can, therefore, increase the rate of early diagnosis and improve clinical management of these patients.

Younger age at diagnosis of colorectal cancer is more frequently reported in developing countries, in which the incidence differs significantly from that reported in developed countries (Ajao et al., 1988; Bedikian et al., 1981; Soliman et al., 1997). According to the most recent estimation data from a project of the International Agency for Research on Cancer, GLOBOCAN 2008, CRC is the sixth most common cancer in Cambodia, and approximately 10% of CRC patients are younger than 40 (Ferlay, et al., 2010). To date, there have been no data published on the exact incidence of CRC in Cambodia.

*[1]Pathology Department, [9]Surgery Department, Ghent University Hospital, Ghent, Belgium, [2]Pathology Department, [8]Gastroenterology Department, Calmette Hospital, [3]Oncology Department, [7]Surgery Department, Khmer-Soviet Friendship Hospital, [4]University of Health Sciences, [5]Food Safety and Nutrition, Institute of Technology of Cambodia, Phnom Penh, [6]Surgery Department, Siem Reap Provincial Hospital, Siem Reap, Cambodia *For correspondence: hav_monirath@yahoo.com*

The purpose of this study is to describe the epidemiological, clinical and pathological characteristics of CRC in young Cambodian patients.

Materials and Methods

Clinical and pathological data on all primary colorectal cancer cases diagnosed between 2005 and 2010 were obtained from the database of the Reference Center for Gastro-intestinal Tumours Surgery and Marie Curie Cancer Center, both located in Khmer-Soviet Friendship Hospital in Phnom Penh, the capital city of Cambodia. For diagnosis and mainly for treatment, patients were referred from all provinces in Cambodia and from both private and public hospitals. There are no other centres offering standard CRC treatment in this country. Age-specific colorectal cancer incidence rates per 100 000 were computed based on CRC data in these two centres and Cambodian population census 2008 data from the National Institute of Statistics (http://www.nis.gov.kh/). We compared the difference in distribution of tumour location, histology, differentiation and UICC/TNM stage in two age groups, namely < 40 and ≥ 40 years old. Data are expressed as mean ± SD unless stated otherwise. SPSS 16.0.0 statistical software system (SPSS Inc., Chicago, IL, USA) was used for all analyses. A P value of < 0.05 is considered statistically significant. A study of patient survival was not possible due to very limited follow-up data.

Results

Between 2005 and 2010, there were 356 newly diagnosed CRC cases, of which 106 (29.8%) affected patients younger than 40. The mean age at diagnosis was 49 ± 16 years. Female patients constituted 57% (n=202) of the total CRC cases, with a female-to-male ratio of 1.31. There was no significant difference in sex distribution between the two age groups (Table 1). Calculation of 2005-2010 age-specific incidence rates showed a crude incidence of 2.82 and 2.36 per 100 000 in females and males, respectively. Women had a peak of CRC incidence in the 6th decade followed by a second peak in the 7th decade, whereas men had the highest risk of developing CRC in their 7th decade of life (Figure 1).

For all ages, adenocarcinoma was the most common histologic type, and more than one half of all tumours occurred in the colon, roughly one third of which was found in the right colon. There was no appreciable variation of tumour location between both age groups (Table 1). Mucin-producing and advanced-grade tumours were 2 times higher in proportion in the younger patients (p < 0.001). Advanced stage (III and IV) at diagnosis was observed in a slightly higher proportion in the younger (61%) than in the older (49%) group (Table 1).

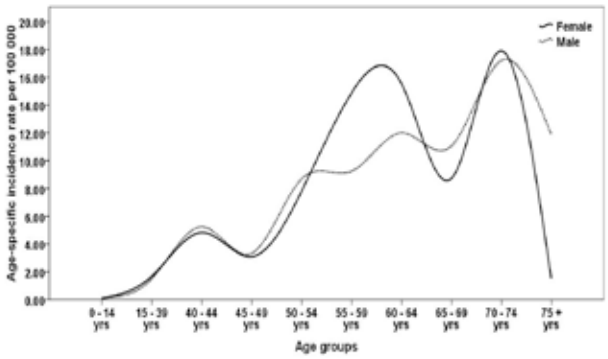

Figure 1. Age-specific Colorectal Cancer Incidence Rates per 100 000

Table 1. Clinical and Pathologic Characteristics of the 356 CRC Cases in this Study

Characteristics	<40	≥40	p value
Gender	106	250	0.332
Female	56 (52.8)	146 (58.4)	
Male	50 (47.2)	104 (41.6)	
Tumour histologic type	106	250	
Adenocarcinoma	97 (91.5)	241 (96.4)	0.054
Non-adenocarcinoma	9 (8.5)	9 (3.6)	
Colon tumour	68	155	-
Adenocarcinoma	60 (88.2)	150 (96.8)	
Carcinoid	0	0	
GIST	0	0	
Leiomyosarcoma	1 (1.5)	0	
Lymphoma	7 (10.3)	5 (3.2)	
Rectum tumour	38	95	-
Adenocarcinoma	37 (97.4)	91 (95.8)	
Carcinoid	0	1 (1.1)	
GIST	0	1 (1.1)	
Leiomyosarcoma	1 (0.8)	2 (2.1)	
Lymphoma	0	0	
Tumour histologic grade	59	146	<0.001
Grade 1 & 2	29 (49.1)	113 (77.4)	
Grade 3 & mucin	30 (50.9)	33 (22.6)	
UICC stage	40	106	0.457
Stage I	6 (15.0)	27 (25.5)	
Stage II	9 (22.5)	27 (25.5)	
Stage III	20 (50.0)	43 (40.6)	
Stage IV	5 (12.5)	9 (8.5)	
Locations	106	250	0.700
Colon	68 (64.2)	155 (62.0)	
Rectum	38 (35.9)	95 (38.0)	
Colon	68	155	0.087*
Descending colon	17 (25.0)	65 (41.8)	
Ascending colon	23 (33.8)	50 (32.6)	
Transverse colon	5 (7.4)	3 (1.8)	
Colon, unspecified	23 (33.8)	37 (23.8)	

* 'Colon, unspecified' excluded from correlation analysis; UICC, Union for International Cancer Control

Discussion

Although CRC is a common disease in the older population, it has been evident since the largest systemic review that the disease is not infrequent in the young (O'Connell, et al., 2004). In this study, CRC proportion in patients aged < 40 (29.78%) is the second highest among the rates reported for CRC in Asia, Europe, USA, the Middle East and New Zealand for the same age group (Figure 2).

Most of the studies on CRC in the young have looked at clinicopathological features of tumours and patients' prognosis and survival. However, very few studies have described the risk factors for development of colorectal cancer at such young age. Among the 3 well documented

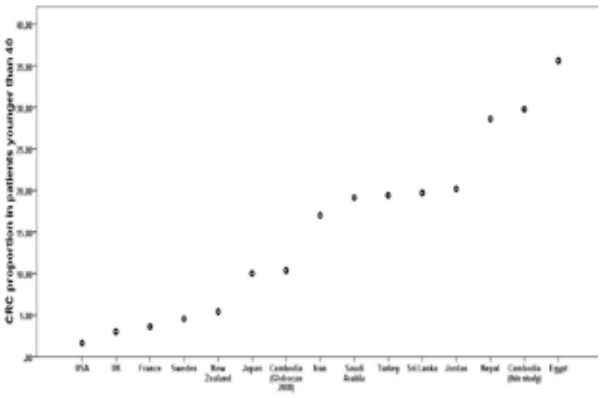

Figure 2. Comparison of CRC Proportions in Patients Younger than 40. USA, New Zealand and different countries in Asia, Europe and the Middle East (Ohman, 1982; Adloff et al., 1986; Okuno et al., 1987; Domergue et al., 1988; Isbister & Fraser, 1990; Griffin et al., 1991; Isbister, 1992; Yilmazlar et al., 1995; Soliman, et al., 1997; de Silva et al, 2000; Singh et al., 2002; Al-Jaberi et al, 2003; Ansari et al., 2006; Ferlay et al., 2010)

categories of predisposing conditions, namely dietary, environmental and genetic, the last has been most frequently found in the young population (Liu et al., 1995).

Two principal forms of hereditary CRC are familial adenomatous polyposis (FAP) and Lynch syndrome. The latter, also called hereditary nonpolyposis colorectal cancer (HNPCC), is a common autosomal dominant syndrome characterized by microsatellite instability and early age at onset of neoplastic lesions in a variety of tissues (e.g., endometrial, gastric, renal, ovarian, and skin). FAP, accounting for < 1% of CRC, is also an autosomal dominant disease classically characterized by the development of hundreds to thousands of adenomas throughout the rectum and colon during the second decade of life. Classic FAP results from a germline APC mutation (McCart et al., 2008). A subset of individuals with clinical features of FAP will instead carry a mutation in the MUTYH gene (Sampson et al., 2005). Individuals with HNPCC and FAP carry about an 80% and 100% chance of developing CRC, respectively (Hampel & Peltomaki, 2000). MacGillivary et al (1991) observed HNPCC in young adults in 2% of their colorectal cancer cases, while FAP was reported in 8.1% (Martin et al., 1981) and 10% (MacGillivray, et al., 1991) of young patients . However, these genetic changes have not been tested in Cambodian CRC.

Family history and parental consanguinity have been demonstrated to be strongly associated with CRC development in the Arab population (Bener et al., 2010). Even though family history of our CRC patients has not been studied, consanguinity, which is also prevalent in Cambodian residents, can be a contributing factor in increasing the risk of early CRC onset in this population.

Colorectal cancer incidence rates are increasing in countries that are undergoing rapid industrialization because of the lifestyle risk factors including diet, physical activity, and obesity which play an essential role in the etiology of the disease. Peters et al. (1989), investigating the diet of individuals under 45 years of age in California, found that deep fried foods as well as barbecued or smoked meats increased the risk of cancers of the caecum and ascending colon in this subset of population. On the contrary, a recent study by our group, which focused on assessment of the overall impact of dietary intake on CRC development, did not confirm lifestyle as a risk factor for CRC in Cambodian population. The study looked at the risks and benefits of dietary intake (i.e., food type, meat doneness level, quantity, frequency and cooking methods) as well as obesity in 941 Cambodians, aged 25 to 65, in 4 different regions including the capital city of Cambodia. Overweight, defined by body mass index (BMI) of 25–29.9 kg/m2, and obesity (BMI ≥ 30 kg/m2) were found only in 13.92% and 2.44%, respectively, in this cohort. Results from this study suggested that dietary habits in this population appeared to be protective against CRC development and that adaptation of western-style diet occurred only in a minority of the study cohort, mainly in those living in the capital city (unpublished data).

Environmental factors such as exposure to pesticides and other chemical substances have been associated with colorectal cancer in young adults. Pratt et al. (1977) investigated a cluster of 13 adolescents with advanced, poorly differentiated CRC. Nine of the 13 patients had a history of exposure to agricultural pesticides and other chemicals used in growing cotton, rice and soybeans on southern US farms. According to the Cambodian population census 2008, about 75% of Cambodians are engaged in agriculture. Highly toxic pesticides belonging to WHO class I + II and banned or restricted by the Cambodian law are widely used in the country (Jensen et al., 2011). This could be one of the factors contributing to the early occurrence of CRC in Cambodian population.

In Cambodia, Schistosoma mekongi is endemic with an estimated total population at risk of 80,000 (Urbani et al., 2002). Unlike the more common species of Schistosoma such as S. mansoni and S. haematobium that are associated with the development of malignant neoplasms (Noeman et al., 1994), no studies have demonstrated the possible role of S. mekongi infection in neoplastic processes.

Regarding tumour location and histology, the findings that more than half of our CRC cases were diagnosed in the colon and that adenocarcinoma was the commonest histologic type are in agreement with most studies (O'Connell, et al., 2004). Right-sided tumours accounted for roughly 30% of all cases. Moreover, we found that mucinous and advanced-grade tumours were twice more frequent in the younger age group than in the older. More than half of our CRC patients presented with advanced disease. This could be explained by the lack of CRC screening in Cambodia. There was no significant difference between the numbers of young and old patients presenting with advanced colorectal cancer, but information on this parameter was available for only 41% of cases.

In summary, we found that approximately 30% of Cambodian CRC patients were younger than 40. For the same age group, this proportion is remarkably higher than that estimated by GLOBOCAN 2008, in which CRC rates in Cambodia were computed based on observed cancer rates in Thailand (Ferlay, et al., 2010). It can be speculated that the unusually high CRC proportion in the young

observed in our study might result from referral bias. Although the two referral centres received CRC patients from all provinces, the unfavorable economic status and attitude of most Cambodians allow us to assume that many old people diagnosed with CRC elsewhere might have refused treatment and that some other patients, particularly those living in along the borders with Thailand and Vietnam, might have gone for treatment in these two countries. Nevertheless, this peculiarly high proportion of early-onset CRC, the continuous exposure to hazardous environmental agents, and the prevalent consanguinity in Cambodia justify further research, which will advance our understanding of the risk factors for the disease in young adults. These studies should investigate environmental exposures, family history, and consanguinity as well as explore gene–environment interactions in colorectal cancer carcinogenesis in this high-risk population.

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