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Increased Incidence of Colorectal Cancer in Young People (Less Than 40 Years Old) Over the Last Ten Years

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ABSTRACT

Background: Colorectal carcinoma is a disease of older people, with around 90% of patients being over 55 years old, and it is relatively uncommon in patients younger than 40 years, if we exclude populations with hereditary syndrome. **Objective:** To present our current knowledge of colorectal carcinomas in patients under 40 years of age. **Methods:** The most relevant papers about colorectal carcinoma in young patients published and indexed on PubMed in the last 20 years were reviewed. Articles were chosen to include those studies that examined patients under 40 years old. **Conclusions:** Colorectal cancer in young people appears to be a distinct disease, characterized by biological aggressiveness, with unique features such as localization, adverse histologic factors, not associated with prior or concomitant adenomas, advanced stage at diagnosis, and generally worse prognosis. (J CANCEROL. 2014;1:16-22)

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INTRODUCTION

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract and is the third leading cause of cancer death and the third most common cancer in the USA. For 2013, the estimate of new cases of CRC in the USA is around 70,000, and estimated deaths caused by this disease are around 25,000[1]. Traditionally, CRC is considered a cancer of older people, taking into account that around 90% of CRC patients are over 55 years old[2-4]. However, while overall incidence rates have been declining since the mid-1980s, the incidence of CRC in young people (especially 20-39 years old) has increased over the last 10 years[5,6].

The aim of this review is to characterize the clinically relevant issues regarding colorectal cancer in the younger population.

METHODOLOGY

For the purpose of this review, we refer to a young CRC patient as one who is under 40 years of age at the time of cancer diagnosis. We excluded populations with characteristic hereditary syndrome with significant risk of CRC at a young age.

We obtained the data from the most relevant papers published and indexed on PubMed in the last 20 years; a literature search was performed using combinations of key words including: age, colon, rectal, colorectal, cancer, young, and incidence. Incidence rates were stratified by age, sex, race/ethnicity, tumor location, histopathology, clinical and molecular characteristics, as well as the prognosis.

EPIDEMIOLOGY

In the USA, around 6-7% of all CRCs are diagnosed before 40 years of age[2]. Siegel, et al. reviewed a SEER database for trends from 1999 to 2005 and found that the incidence of CRC has increased in people less than 50 years old. The group that shows the most striking increase was the 20-29 year old group, with incidences of 5.2 and 5.6% per year for men and women, respectively. Meanwhile, for the 30-39 year old group, the incidence was 3.0%[6]. In contrast, in patients > 50 years old the incidence is declining by about 2% per year in both sexes[1,5]. This declining tendency has been attributed to colonoscopy screening and treatment of premalignant lesions. However, people under 50 years of age rarely are included in CRC screening programs.

The increased incidence is similar between ethnic groups. For young non-Hispanic whites, it is about 2.0% per year, while in Hispanics it is 2.7% per year[6]. But this is not true for Asian/Pacific islanders and blacks where the incidence is higher[3]. In terms of gender distribution, there are similar distributions between males and females in young CRC patients; the male/female ratio tends to be 1:1 in most reports[2,3,7].

The frequency of CRC in young people outside of the USA varies widely; France shows a prevalence of 3.1%, Australia 5%, and Denmark 2.5%. On the other hand, an Egyptian population showed a prevalence of 35.6%, the highest prevalence reported in the literature; interestingly, meanwhile, the general incidence of CRC is lower in Egyptian compared with US populations ($5.5/10^5$ vs. $50.8/10^5$). In young Egyptians, the CRC incidence is 1.3 per 100,000 persons, which is clearly higher than in younger US patients[7,10]. Other Asian studies (institutional reports) showed similar trends in patients less than 40 years of age, with a prevalence of 19.5-28.6%, which is clearly higher than that in the USA[11-13]. In Mexico at the National Cancer Institute we reported an incidence of 22.8%[14]. It is unknown why these countries had higher frequencies; however, it should be taken into account that these reports constitute institutional experiences and do not represent exactly the national prevalence in the populations mentioned above. Figure 1 shows the prevalence in different countries[6-10,14].

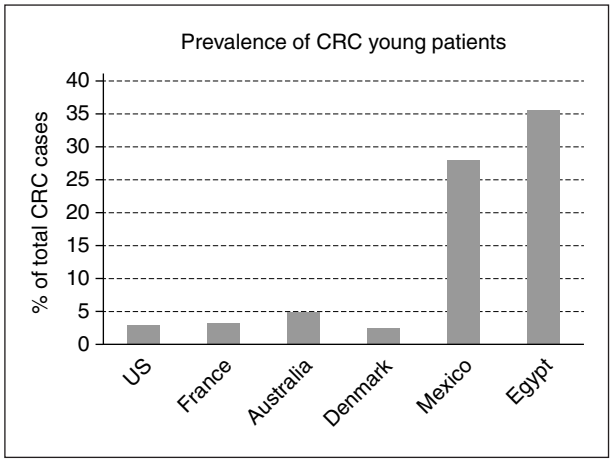

Figure 1. Prevalence of colorectal cancer in young patients in different countries[6-10,14].

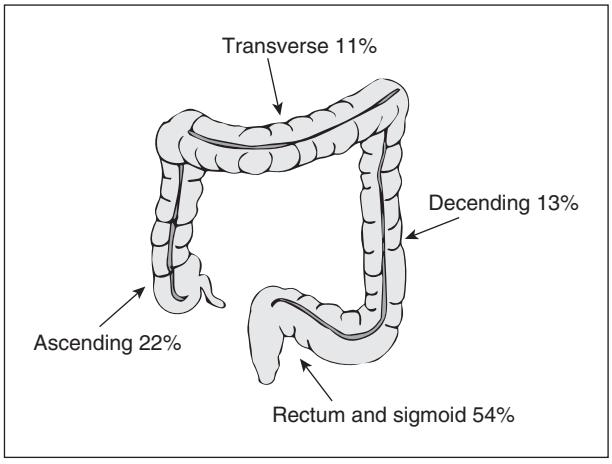

Figure 2. Localization of CCR in young people.

TUMOR LOCATION

Colorectal cancer in young people is generally considered a "left-side" disease. Different population reports showed that sigmoid colon and rectum are the preferred locations in this age group[2,6,7,15]. A report analyzed 39 articles that include CRC patients under 40 years in different populations and shows the following locations: ascending (cecum, ascending colon, hepatic flexure), 22%; transverse colon, 11%; descending (splenic flexure, descending colon), 13%; and rectum and sigmoid region, including the rectosigmoid junction, 54%, confirms this tendency[2] (Fig. 2).

HISTOPATHOLOGY

The most frequent subtype of colorectal carcinoma is intestinal (tubular) adenocarcinoma, so called "adenocarcinoma not otherwise specified (NOS)" in all studied groups[2,6,7,12]. The incidence of mucinous adenocarcinoma and signet-ring cell is higher compared with older populations. Moreover, high-grade carcinomas are more prevalent in younger people compared with older patients[2,16,17].

The relative frequency of histologic subtypes described in this population is as follows: mucinous adenocarcinoma, 21% (range 3-69%); signet-ring cell carcinoma, 3% (range 1.7-11.1%); and poorly differentiated adenocarcinoma, 27% (range 8-54%)[2].

CLINICAL CHARACTERISTICS

Colorectal cancer in young people more frequently presents as an advanced disease at the time of diagnosis, conferring a dismal prognosis. According to a SEER database report, 62.4% of young CRC patients present as regional or distant disease (21.9 and 40.5%, respectively)[3]. A review of Medline literature found that the two most common symptoms were rectal bleeding (46%) and abdominal pain (35%), followed by weight loss (35%) and change in bowel habits including constipation and diarrhea (32%)[2].

MOLECULAR CHARACTERISTICS

The information about the molecular characteristics of CRC in young patients is limited. Chang, et al. performed one of the largest molecular studies

in this population, in which 55 sporadic, microsatellite-stable CRC cases aged < 40 years that had been surgically resected between 2000 at 2010 at an academic center in the USA were compared to 73 consecutive microsatellite-stable cases aged > 40 years. As described previously, in this series left tumors (sigmoid colon and rectum) were more common than right tumors ($p < 0.007$); signet-ring cell differentiation is more frequent (13 vs. 1%; $p = 0.02$) and also perineural invasion and venous invasion are more common in young people (29 vs. 11% and 22 vs. 6%, respectively; $p = 0.009$). Other features that were distinct included fewer tumors with an obvious adenoma precursor (35 vs. 53%; $p = 0.3$) with non-significantly fewer cases harboring *KRAS* mutations (4 vs. 15%; $p = 0.13$). Considering that CRC in young people is predominantly located in the left-side colon, *BRAF* mutations were absent in this report. Other molecular characteristics were evaluated including expression of E-cadherin, b-catenin, and *P16*; none of those were more common in young patients compared with the older group[16].

In other series, Yantiss, et al. compiled a study group of 24 patients < 40 years of age with CRC, and 45 patients > 40 years of age served as controls. In the group < 40 years old, 22 patients had sporadic CRC, one patient had CRC related with ulcerative colitis, and another had hereditary nonpolyposis CRC. The tumors were immunohistochemically stained for markers including *MLH-1, MSH-2, MSH-6,* b-catenin and others, and also assessed for microsatellite instability and mutations in b-catenin, *APC, EGFR, PIK3CA, KRAS*, and *BRAF*. Ninety-two percent of tumors from young patients occurred in the distal colon ($p = 0.006$), particularly the rectum (58%; $p = 0.02$), and 75% were stage III or IV. Tumors from young patients showed more frequent lymphovascular (81%; $p = 0.03$) and/or venous (48%; $p = 0.003$) invasion, an infiltrative growth pattern (81%; $p = 0.03$), and a-Methylacyl-CoA expression (83%; $p = 0.02$) compared with controls. The *EGFR, PIK3CA* and *BRAF* mutations are uncommon in young patients (0, 4, and 8%, respectively). The *KRAS* mutation was slightly more frequent (25%); however, none of these mutations were significantly more common in young groups compared with older groups[18].

Liang, et al. described the clinical and molecular characteristics of 139 young CRC patients (< 40 years) and did a comparison between them and a group of patients older than 60 years (n = 339). Patients with familial adenomatous polyposis (FAP), attenuated FAP, and chronic ulcerative colitis were excluded. The authors found that the younger patients with CRC had more mucin-producing (14.5 vs. 4.7%; $p < 0.001$) and poorly differentiated (7.2 vs. 3.3%; $p = 0.015$) tumors, a higher incidence of synchronous (5.8 vs. 1.2%; $p = 0.007$) and metachronous (4.0 vs. 0.6%; $p = 0{\cdot}023$) CRC, and more advanced tumor stage ($p < 0.001$) than older patients; with respect to molecular characteristics, there was no significant difference between the younger and older patients in codon 12 and 13 mutations of the *KRAS* gene and loss of heterozygocity of the deleted in colorectal cancer *(DCC)* gene. However, the percentage of tumors with *P53* overexpression was significantly lower (38.9 vs. 53.2%; $p = 0{\cdot}023$) among younger patients. This report did not exclude patients with hereditary nonpolyposis CRC and that could be an explanation for the finding of a significantly higher percentage of tumors in younger patients with high microsatellite instability (29.4 vs. 6.3%; $p < 0{\cdot}001$)[17]. In a preliminary analysis of CRC cases in a patient database at the MD Anderson Cancer Center for the period 2003 to 2011, we found a frequency of *KRAS* mutations (exon 12/13) of 14% in young people (< 40 years) compared with 33% in patients ≥ 65 years ($p = 0.08$). When other mutations were analyzed, such as *NRAS, BRAF*, CpG, and *PTEN* loss, there were no significant differences between younger and older controls except for *PTEN* loss (28 vs. 11%; p = 003).

The observation of significant differences in the frequency of *PTEN* loss in the young onset exhibited a slightly lower *KRAS* mutation rate, with differences

consistent with those that have been reported in Middle Eastern populations[19,20.]

Antelo, et al. provided evidence of high levels of LINE-1 hypomethylation (a surrogate of genome-level hypomethylation associated with increased chromosomal instability) in cases ≥ 50 years of age, arguing that LINE-1 hypomethylation is a feature of a pathologically distinct subtype of CRC that is more common in younger cases. LINE-1 hypomethylation has been associated with activation of *MET, RAB3IP,* and *CHRM3* oncogenes[21]. In other studies, overexpression of several microRNA species (e.g. miR-21, miR 20a, miR-181b, and mIR 203) has been reported in tumors from younger compared to older patients[18].

PROGNOSIS

As discussed previously, compared with older adults, there is a propensity in young patients towards more advanced stage (stage III and IV) at presentation, thus influencing overall prognosis. One survey of the SEER database between 1991 and 1999 demonstrated that the overall five-year cancer-specific survival was significantly worse for the young adults compared to an older group (61.5 vs. 64.9%; p = 0.015)[22]. However, when adjusted for stage at presentation, outcomes were similar. Survival was in fact significantly better for young adults with stage II disease (88.6 vs. 82.7%; p = 0.01), equal for stage III disease (58.9 vs. 57.2%; p: not significant), and significantly better for stage IV disease (18.1 vs. 6.2%; p = 0.001)[29]. Other reports have showed similar stage-adjusted survival[23,24].

O´Connell, et al. showed that the average overall five-year survival for patients < 40 years old with CRC was 33.4% (range 0-60%). Also, they reported the prognosis according to histology: for mucinous tumors it was 24.7% (range 11.3-41.6%), and for poorly differentiated tumors it was 25.5% (range 11.8-35%). Young patients with Duke's A stage cancer had an average adjusted five-year survival rate of 94%; B, 76.5%; C, 39%; and D, 6.8%[2]. Similar outcomes have been reported in rectal cancer as well[25].

FUTURE DIRECTION

Although CRC is rare in young adults, the incidence increases significantly in the third and fourth decade of life, underscoring its importance in this age group.

Despite advances in early detection and treatment of premalignant lesions, the incidence of CRC in patients < 40 years old has increased in the last years. This tendency has been corroborated in other non-US populations including non-Western countries[7-13]. The explanation of this phenomenon is not clearly known.

The increasing epidemic of obesity could explain the increase of CRC in young people; obesity is a major risk factor for CRC in men and also a stronger risk factor in women, especially in premenopausal women[26-29]. We noted that in the past three decades, the prevalence of obesity has increased markedly among individuals of all ages and racial/ethnic groups in the USA, which may have contributed to the overall increase in CRC incidence rates among young adults[30,31].

However, as we mentioned previously, CRC in young people affects predominantly sigmoid colon and rectum, but why obesity preferably influences the occurrence of left-side colon tumors in this population is unknown. Also, there is a global tendency to increasing incidence of right-colon cancer that some authors also have attributed to the increase in obesity. How adiposity affects right or left colon tissue depending on the age also remains unknown[32,33.]

Diabetes mellitus (DM) has been increasing dramatically, especially in young people and that also could explain the increasing incidence in CRC, considering that DM has been established as a factor for developing colon neoplasms[34,35].

Another possible explanation for the increasing incidence of CRC among young patients could be the change in alimentary habits. In some Asian countries, the increasing incidence of CRC in young patients has been attributed to "Westernized" diet or lifestyle; the increasing consumption of fast food (containing processed and red meat, a risk factor for CRC) and less consumption of milk products (containing calcium, a protective factor for CRC) in young populations that has been observed in the last decades in the USA coincides with the increase in CRC incidence[20,36-39]. Other risk factors for CRC, such as tobacco use and alcohol consumption, are unlikely to be related with an increase of CRC incidence in young people because, for example, there has been a decrease of alcohol consumption in recent decades and the latency time for these substances are usually prolonged[40-42].

The knowledge about molecular features in young microsatellite-stable CRC patients is limited and only permits us to give a general description; early-onset CRC is not frequently associated with precursor adenomatous or serrated lesions and does not appear to frequently harbor activating *BRAF* or *KRAS* mutations, suggesting that the molecular events in tumor development differ in this patient population, with it being necessary to expand the molecular profiling to other cell signal pathways[16,17,19-21]. Further molecular analysis is necessary to fully elucidate the potential molecular changes that lead to early-onset CRC.

Despite this significant increase in incidence and the concern about the effects on an important sector of society in terms of productivity, currently there are no large-scale efforts directed at understanding the biological or molecular landscape of CRC in young patients for tailoring their treatment, nor efforts directed towards clinical trial opportunities at the community level and there is poor participation of young CRC populations enrolling in clinical trials.

Colorectal cancer in young people has unique features such as localization: these tumors have a striking predilection for the sigmoid colon and rectum, predominance to demonstrate adverse histologic factors, including signet ring cell differentiation, mucinous differentiation, venous invasion, and perineural invasion, unassociated with prior or concomitant adenomas, with advanced stage at diagnosis and generally worse prognosis[2,16,43]. There is an increasing tendency to see younger CRC patients in gastrointestinal oncology services and unfortunately with limited options for treatment, and this is a real challenge in oncology practice.

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