EDITORIAL

Colorectal Cancer
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Colorectal cancer in the young

"While colorectal cancer is predominantly a disease of older adults with a median age at diagnosis of 72 years, population-based studies have shown an increase in colorectal cancer in the young."

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Colorectal cancer (CRC) is the most common malignancy in the GI tract and the fourth leading cause of cancer deaths worldwide. In the USA, it is estimated that 103,170 patients will be diagnosed in 2012 and 40,290 will unfortunately succumb to the disease. While CRC is predominantly a disease of older adults with a median age at diagnosis of 72 years, population-based studies have shown an increase in CRC in the young [1,2]. It is estimated that between 2 and 3% of CRCs occur in patients younger than 40 years of age. Studies have indicated varied outcomes in young patients, and it is unclear from the literature whether this group of patients has a worse prognosis than the whole population or different clinical parameters from older adults.

Advances in screening and detection as well as management of CRC over the last three decades have resulted in an improvement in prognosis of the disease [3,4,101]. The proportion of early-stage disease (stages I and II) at the time of diagnosis has increased from 39.6 to 56.6% between the 1970s and 1990s with a corresponding decrease in the proportion of patients with advanced disease (stages III and IV) leading to an improvement in 5-year survival from 33% in the 1970s to 53.3% in the 1990s [5]. More recent postoperative adjuvant studies indicate a 7-year survival of 77% in patients treated with postoperative oxaliplatin-based chemotherapy with the overall 5-year survival at 60% [6].

This editorial summarizes CRC in young men and women.

Decreasing incidence & mortality in CRC

CRC incidence rates in the USA have decreased from 1998 through to 2004 in both males and females, contributing to the total decrease in overall cancer death rates. Death rates for all cancer sites of disease combined decreased by 2.6% per year in males and by 1.8% per year in females from 2002 to 2004 compared with 1.5% per year in males from 1992 to 2002 and

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0.8% per year in females from 1994 to 2002 [101]. There has been a continued decrease of CRC cases and thus incidence rates of 2.8% per year in men and 2.2% per year in women since 1998 [101]. Multiple factors are associated with or contributed to lowered CRC rates, including increased screening in asymptomatic individuals among the 50 years and older population [3,7]. However, screening for individuals less than 50 years of age with average risk potential has not been recommended and is not included in current clinical practice guidelines.

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Increase in incidence in young men & women

In an analysis of data from 13 Surveillance, Epidemiology and End Results (SEER) cancer registries from 1992 through to 2005, an evaluation of young patients with CRC was made utilizing data on trends by sex, race/ethnicity, age, stage at diagnosis and anatomic subsite [8]. These authors noted increases in incidence rates of 1.5% per year in men and 1.6% per year in women from 1992 to 2005 of CRC per 100,000 in young adults between the ages of 20 and 49 years. There were higher rates in non-Hispanic whites in all stages of the disease, and the increase was associated with a higher prevalence of rectal cancer in women and men over this time period. Additional research was suggested as important and necessary to determine the etiology of the change in CRC patterns and to develop potential preventive, diagnostic and interventional strategies. Increasing trends in CRC rates in young individuals have also been noted by other authors [2,3,9].

Prognostic factors in young patients with CRC

Reports indicate that hereditary CRCs occur in 38.4% of patients younger than 40 years old and in 3.5% of individuals older than 55 years [9]. Others have likewise confirmed that hereditary tumors are detected more frequently in young individuals suggesting hereditary factors as etiology rather than dietary and lifestyle [10,11].

Earlier reports indicated a worse survival rate in young patients with CRCs [10,11]. Young patients are more likely to present with advanced- and late-stage disease and higher grade tumors [12]. Approximately 60–67% of young patients with CRC present with stage III or IV diseases with the majority being poorly differentiated or mucinous tumors, having signet-ring cell, infiltrating tumor edge and aggressive histologic grade in the primary tumor [10,13–16]. Distal location and advanced stage of tumor at diagnosis were reported as independent prognostic factors [17]. Liang reported age, type of operation, blood transfusion, histological type, diameter of tumor, invasion, lymphatic invasion and distant metastasis (TNM) stage as predictors of survival in young patients in young patients with colon cancer after surgery [14]. Levi *et al.* reported an increase in second primary CRCs in young patients with a history of CRC [18]. Adloff *et al.* reported virulence but delay in diagnosis and 5-year survival rates being no different in young and old patients. Young patients survived as well as or better than their older patient counterparts. The most frequent symptoms were bleeding and abdominal pain [19].

Siegel *et al.* reported that, at initial presentation of early-onset CRC in patients under 50 years of age with sporadic disease and no obvious history of evidence of known risk factors, it was found that at least 86% demonstrated a history of abdominal symptoms evident by the time of diagnosis. The most common findings were rectal bleeding in 51%, abdominal pain in 32% and change in bowel habits in 18% [8]. The most frequent clinical and laboratory parameters were anemia in 14% and positive fecal occult blood tests in 7% [8]. These authors emphasize that, with the findings of a recent increase in CRC among those aged under 50 years, an adequate evaluation in young patients with abdominal symptoms was necessary to impact this trend. They further imply that early recognition of CRC in patients without known established risks factors requires enhanced clinical awareness and education of providers of these changing trends to allow for aggressive diagnostic evaluation of symptoms and thus treatment at a potentially earlier stage of disease [8].

Owing to the facts related to CRC in younger patients and the varied reports concerning pathological features and prognosis when compared with older patients, we conducted a study to assess pathological features and outcomes of CRC in patients less than 50 years of age using an institutional database and comparing with the SEER on a similar patient population. We evaluated 4595 patients from the Tumor Registry at Thomas Jefferson University Hospital (TJUH; PA, USA) from

1988 through to 2007 and 290,338 cases from SEER from 1988 through to 2004 and compared pathological and clinical findings and outcomes of those less than 50 years of age with those over 50 years. The younger patients had more advanced-stage tumors at the time of diagnosis ($p < 0.0001$), more poorly differentiated tumors ($p_{TJUH} = 0.02754$; $p_{SEER} < 0.0001$), a higher number of mucinous to signet ring cell tumors with 12% to 8.1% in the TJUH data ($p = 0.002916$) and 13.2% to 10.3% in the SEER data ($p < 0.0001$), with a greater preponderance of cases in younger males. Younger patients had fewer proximal tumors, a higher percentage of rectal tumors ($p < 0.001$), and a greater likelihood of positive nodes at all stages ($p_{SEER} < 0.0001$), as well as more frequent development of peritoneal metastases ($p_{TJUH} = 0.3507$), but less frequent lung metastases ($p_{TJUH} = 0.05249$) than older patients. Despite later stages of disease at initial diagnosis and a higher incidence of aggressive pathologic features, and demonstrated earlier metastases, overall survival in the younger patients was better than or equal to those older than 50 years of age. Future research is ongoing to evaluate response to treatment and molecular features among younger and older CRC patients [20].

Mutation status

Berg *et al.* examined the mutation status of five known CRC genes and compared the genomic complexity of tumors from young patients without known CRC inherited or genetic syndromes with older ones in a group of 181 CRC patients, stratified by microsatellite instability status, and identified DNA sequence changes in *KRAS* in 32%, *KRAS* in 16%, *PIK3CA* in 4%, *PIK3CA* in 14% and *TP53* in 53% [21]. Interestingly, *PIK3CA* mutations were not observed in younger patients and *TP53* mutations occurred more frequently than in the older age groups. The total gene mutation index was lowest, although genomic complexity, as determined by copy-number aberrations, was highest, in tumors from the young subjects. While the number of tumors from young patients that were quadruple negative for the four predictive gene mutations (*KRAS_KRAS_PIK3CA_PIK3CA*), tumors from 16% of young versus only 1% of the old patients showed mutations in *PIK3CA*/*PIK3CA* exclusively. The conclusions from this study thereby indicate that different genetic profiles exist in tumors from young and elderly patients with comparable and pathological features, indicating potentially a different genetic risk profile of CRC tumorigenesis in young patients when compared with older ones [21]. Other studies have demonstrated microsatellite instability and other molecular biomarkers as being different in young patients with CRC [22–24].

Race

Sporadic nonhereditary CRC in the USA occurs more frequently and at a younger age in African–Americans, suggesting that there may be potential differences in risk factors contributing to disease development. Deaths from CRC are higher in African–American men and women than in any other racial or ethnic group. While the pathogenesis and etiology of these striking differences are unknown because of the development of colon cancer at a younger age, the American College of Gastroenterology has recommended earlier screening with colonoscopies at 45 years of age rather than the 50 years of age advised in other clinical guidelines. It is assumed that earlier screening may detect colon cancer or other bowel abnormalities at an earlier stage and allow for intervention and improved treatment outcomes [25–28,102,103].

Conclusion

The incidence rates of colon and rectal cancers are increasing in young adults. Tumors in the young population appear to be more aggressive, to present with later stage and more advanced disease at diagnosis, and to have poorer histopathologic features compared with older patients with the disease. Despite more advanced disease at the time of disease diagnosis, response to therapy and overall survival appear similar to older patients with the disease. Early reports indicate genetic mutation profiles that differ from older patients with the disease. These findings indicate a need for healthcare providers to have a heightened awareness of this continuously increasing trend and institute diagnostic evaluation of gastrointestinal symptoms when caring for this young patient population. It is necessary that future research focuses attention on studies to elucidate and delineate factors contributing to the disparate trend and to design and develop potential diagnostic and early detection, interventional, and preventive strategies to address the causes of and reverse the current trend.

"Future research is ongoing to evaluate response to treatment and molecular features among younger and older colorectal cancer patients."

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