Increasing incidence of colon cancer in patients <50 years old: a new entity?

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Colorectal cancer (CRC) is the third most common cancer type in humans, the fourth most common cause of death because of cancer, and the second most common cancer type in terms of the number of individuals living with cancer 5 years after diagnosis worldwide, almost 694,000 people die from CRC annually. As it is expected is more frequent in older patients (patients older than 70 years old than in young patients (patients younger than 40 years old). The incidence of CRC in young adults is rising the last years and this fact arises the question; is this coincidence or is young adult CRC a real epidemy. In our current commentary we try and elucidate based on current data whether disease on young individuals is a new entity.

Keywords: Colon cancer; gastrointestinal (GI); Lynch syndrome

Submitted Mar 19, 2016. Accepted for publication Mar 24, 2016.
doi: 10.21037/atm.2016.04.13
View this article at: http://dx.doi.org/10.21037/atm.2016.04.13

Introduction

Colorectal cancer (CRC) is one of the most common types of cancer in both women and men and more specifically the third most common type of cancer in all age groups. As it is expected is more frequent in older patients (patients older than 70 years old than in young patients (patients younger than 40 years old) (1). The incidence of CRC in young adults is 2% of all the cancer cases. On the contrary this percentage in older people is around 6% of the cases (2). Despite the fact that the percentage of CRC in young adult seems to be low, this type of cancer is the fourth more common cause of cancer-provoked death in young adults (2,3).

The incidence of CRC in young adults is rising the last years and this fact arises the question; is this coincidence or is young adult CRC a real epidemy and what is the cause of this rise?

Discussion

We can divide CRC in young patients in hereditary and sporadic forms (4). Hereditary nonpolyposis colorectal cancer (HNPCC) is the most common form of hereditary CRC accounting 2–5% of all colorectal carcinomas. HNPCC is divided into Lynch syndrome I (familial colon cancer) and Lynch syndrome II [HNP/CC associated with other cancers of the gastrointestinal (GI) or reproductive system]. The increased cancer risk is due to inherited mutations that degrade the self-repair capability of DNA (5). Patients with HNPCC present CRC at an earlier age than in the general population combined with an increased risk of other cancers, such as endometrial, ovarian, stomach, cancer and malignant neoplasms of the small intestine, the hepatobiliary tract, pancreas, upper urinary tract, prostrate, brain, and skin (5,6).

Screening and epidemiological data

Although Screening for CRC can reduce incidence by preventing cancer occurrence through the detection and removal of precancerous polyps (7) is not performed as routine in patients under 50 years old without any family

record because of the low incidence of CRC in general population (8). According to study of O'Connell about CMC limited to ages 20 to 39 years there was an increase in incidence from 1973 to 1999 for all races combined (9). Another study of Siegel reports the trends in CRC incidence rates between 1992 and 2005 among young adults (ages 20 to 49 years) by sex, race/ethnicity, age, stage at diagnosis, and anatomic subsite (8). According to this study obesity seems to a major risk factor for CRC in men and, to a lesser extent, for colon cancer in women (10). However, there is a difference in the way obesity affects premenopausal and postmenopausal women (11). In fact obesity has been proven to be a stronger risk of CRC in premenopausal, compared with postmenopausal, women (12). Additionally this study of Siegel *et al.* reports that CRC incidence rates among non-Hispanic White people seem to have been increased for left-sided tumors (distal and rectal) but not for right-sided tumors (proximal) (8).

Molecular facts

Young adult patients with CRC have a poorer prognosis and a more aggressive disease in comparison with older patients suffering from the same clinical entity (2,13,14). This is due to the difference of the histologic type. More specific in the histological examination of those specimens is observed a great frequency of mucinous tissue, signet ring cells combined with microsatellite instability-high (MSI-H) and mutations in the mismatch repair (MMR) genes (15). These types of mutations indicate that the main pathophysiological reason (in molecular basis) that leads to this malignancy in young ages is the 'mistakes in gene transcription' (2). There is a recent study in the Cancer Genome Atlas providing us the most common gene mutations (2,16). These mutations can occur either in specific genes or in gene sets (17). One of the genes that are proven to be overexpressed in CRC is the insulin growth factor 2 gene (18).

HNPCC follows an autosomal dominant way of inheritance and is the phenotypic result of defect in the MMR proteins system (19). Additionally, in the vast majority (approximately 90%) of CRCs in HNPCC patients a MSI-H is present, fact that means that in HNPCC families or atypical HNPCC families there are at least two or more genes mutations, which are responsible for this phenotype. In order to be more specific, MMR genes normally produce proteins that identify and correct sequence mismatches that may occur during DNA replication. In fact what really happens is that a mutation inactivating an MMR gene leads to the accumulation of cell mutations (20,21). Seven different distinct MMR genes have been identified and are thought to be responsible for this entity including the hMLH1 located on band 3p22, the hMSH2 and hMSH6 located on band 2p16 as well as hPMS1 on band 3p32 and hPMS2 on band 7q22 (22).

These germline mutations are in their majority inherited but may also arise spontaneously or de novo in a new generation. Because of the poor screening in these young ages, these patients are often identified only after developing colon cancer early in life (23,24). As the phenotypic expression of HNPCC requires inactivation of both alleles, germline mutations of one allele I order to be expressed must be accompanied by somatic inactivation of the wild-type allele. Inactivation may result from deletions, mutations, or splicing errors occurring anywhere throughout the gene. Mutations that lead to protein truncation account for most inactivating hMLH1 and hMSH2 mutations. Failure to correct replication errors results in genomic instability (22). Although there is no polyposis described in HNPCC, HNPCC-associated CRCs are believed to rise from preexisting discrete proximal colonic adenomas. It has been described that affected individuals have a propensity to develop predominantly right-sided, flat adenomas at a young age (22). The possibility of developing adenomas in patients with Lynch syndrome is the same with the general population with the only difference that in case of Lynch syndrome these adenomas are more likely to progress to cancer as the carcinogenetic process progresses much more rapidly in these patients (in 2–3 years) in comparison with patients with sporadic adenomas (8–10 years). Another category is the one of synchronous (primary tumors diagnosed within 6 mo of each other) and metachronous colorectal tumors (primary tumors occurring more than 6 mo apart) (22).

These types of tumors are found to be more common among patients with Lynch syndrome. More specifically, an individual with an HNPCC mutation who does not undergo a partial or total colectomy after the first mass is diagnosed as malignant has an estimated 30–40% risk of developing a metachronous tumor within 10 years and a 50% risk within 15 years. On the other hand in general population, the risk is 3% in 10 years and 5% within 15 years (25).

Conclusions

There is a significant increase in CRC in young patients. The outcome of CRC treatment depends strongly on stage at diagnosis. As the clinical practice guidelines suggest

that patients with inflammatory bowel disease, polyposis syndromes, a known genetic predisposition, or a personal or family history of adenomatous polyps or CRC are the only patients who begin screening before age 50 years (1), the early recognition of CRC in patients under age 50 without these risk factors requires clinical awareness and aggressive pursuit of symptoms. There is no specific biological marker for young adult CRC apart from MSI, which is also associated with Lynch syndrome (2). Because of the increasing incidence of CRC in adults younger than 50 years old and the lack of our knowledge and experience in the early diagnosis of this entity it is crucial for the whole physician community to be in awareness and for the scientific community to discover and develop biological and molecular markers in order to perform a quick screening of the general population with symptomatology which could be the primary expression of the malignancy mentioned above.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Karanikas M, Esebidis A. Increasing incidence of colon cancer in patients <50 years old: a new entity? Ann Transl Med 2016;4(9):164. doi: 10.21037/atm.2016.04.13

