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TOPIC HIGHLIGHT

2016 Colorectal Cancer: Global view

Colorectal cancer in the young, many questions, few answers

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Abstract

At a time where the incidence of colorectal cancer, a disease predominantly of developed nations, is showing a decline in those 50 years of age and older, data from the West is showing a rising incidence of this cancer in young individuals. Central to this has been the 75% increase in rectal cancer incidence in the last four decades. Furthermore, predictive data based on mathematical modelling indicates a 124 percent rise in the incidence of rectal cancer by the year 2030 - a statistic that calls for collective global thought and action. While predominance of colorectal cancer (CRC) is likely to be in that part of the large bowel distal to the splenic flexure, which makes flexible sigmoidoscopic examination an ideal screening tool, the cost and benefit of mass screening in young people remain unknown. In countries where the incidence of young CRC is as high as 35% to 50%, the available data do not seem to indicate that the disease in young people is one of high red meat consuming nations only. Improvement in our understanding of genetic pathways in the aetiology of CRC, chiefly of the MSI, CIN and CIMP pathway, supports the notion that up to 30% of CRC is genetic, and may reflect a familial trait or environmentally induced changes. However, a number of other germline and somatic mutations, some of which remain unidentified, may play a role in the genesis of this cancer and stand in the way of a clear understanding of CRC in the young. Clinically, a proportion of young persons with CRC die early after curative surgery, presumably from aggressive tumour biology, compared with the majority in whom survival after operation will remain unchanged for five years or greater. The challenge in the future will be to determine, by genetic fingerprinting or otherwise, those at risk of developing CRC and the determinants of survival in those who develop CRC. Ultimately, prevention and early detection, just like for those over 50 years with CRC, will determine the outcome of CRC in young persons. At present, aside from those with an established familial tendency, there is no consensus on screening young persons who may be at risk. However, increasing awareness of this cancer in the young and the established benefit of prevention in older persons, must be a message that should be communicated with medical students,

primary health care personnel and first contact doctors. The latter constitutes a formidable challenge.

Key words: Colon cancer; Young age; Rectal cancer; Colorectal cancer; Young patients; Survival; Early onset

Core tip: This review of colorectal cancer in the young focuses on new data that reveal CRC to be more a left sided cancer than previously thought and the predicted rise by the year 2030. The article outlines the genetics of colorectal cancer (CRC) and discusses limitation in current knowledge in establishing a fingerprint for sporadic CRC. Aside from diet in its aetiology, luminal alkalinity and the colonic microbiome may be contributory and require further research. The review discusses the need for increased awareness of CRC in the young and the need for global consensus on screening young people at risk.

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INTRODUCTION

Colorectal cancer (CRC) is now the fourth most common cause of cancer deaths, with 600000 deaths reported worldwide annually - about 8% of all cancer deaths[1,2]. It is the third most common cancer in men and the second most common cancer in women. The sporadic form, known to affect individuals in their fifth and sixth decades of life[3], arises from a pre-existing polyp which progresses to cancer through the adenoma-dysplasia-carcinoma sequence; a pathological process which, in general, takes five to ten years[4], and lends itself to prevention by screening[5,6]. CRC is a disease of developed nations, and screening by faecal occult blood testing and colonoscopy has stemmed its incidence in those over 50 years[6]. By contrast, CRC in the young, was a disease prevalent in the developing world[7-14] compared with Australia, New Zealand and the West, where its prevalence in young individuals was low[11,15,16]. However, more recently, there has been an increase in the number of reports of CRC in the young from the developed world[17-19]. This is of concern because the incidence of rectal cancer has risen by 75% in the last 40 years[20-22], contributing chiefly to the overall rise in cancer prevalence. Furthermore, this disease affects people in the prime of their life, and unlike cancer in older individuals, there is limited knowledge about the aetiology and pathogenesis of CRC in the young. The aim of this review is to present the current status of CRC in the young and to highlight areas for future research.

EPIDEMIOLOGY/PREVALENCE

Historically, CRC in young patients was highest in proportional prevalence from the Asian region. Studies have reported a high young cancer prevalence of 38% in Egypt[7], 18% in Turkey[8], 39% in India[9], 29% in Nepal[10], 23% from Saudi Arabia[11], 19.7% from Sri Lanka[12], 52% from a single institution in Pakistan[13] and 10.1% from Taiwan[14]. Most significantly, a recent study from the United States[19], where the authors evaluated the records of 393241 patients over a 15-years period, revealed an overall decline in CRC by 0.92% - the effect attributed to screening. While this was true for those over 50 years old with CRC, the study observed an alarming increase in CRC in those less than 50 years, specifically, in young patients less than 35 years. Using statistical modelling, the authors predicted an increase in colon cancer by 90% in patients aged 20 to 34 years and 27.7% in those 35 to 49 years old by the year 2030. For rectal cancer, the predicted percentage increase in cancer prevalence for these two age groups was 124.2% and 46% respectively. Gender based analysis of CRC in young patients revealed an equal prevalence in young men and women[22] contradicting the theory that female hormones are protective of colon and rectal cancer. Furthermore, a 1991 study of young patients in North America showed that the disease occurred in 34% more black men and 45% more black women compared with white Caucasian counterparts[23]. Most young patients did not report a family history of CRC; O'Connell *et al*[22] revealed that only 23% of young patients with CRC reported the presence of cancer in a family member.

FAMILY HISTORY

Contrary to previous knowledge, a current estimate of the proportion of CRC likely to have a major hereditary component is between 15% and 30%[24]. The common heritable syndromes in CRC are either familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC)[25-27] known to be found in 2 to 5 percent of all patients with CRC. Familial adenomatous polyposis is defined by phenotype if an individual has multiple colonic polyps, usually over 100, in association with loss of the tumour suppressor gene -the adenomatous polyposis coli-APC gene-located on the long arm of chromosome 5 (5q21)[25]. Most FAP patients will develop CRC by age 40 years, while in a minority, cancer will manifest in the fifth decade or after, due to the presence of the attenuated *FAP* gene. In contrast to FAP, HNPCC, first described by Henry Lynch, is characterised by the presence of fewer colonic polyps or cancer that is indistinguishable from sporadic CRC. In both conditions, which are of autosomal dominant inheritance, family history is of prime importance. For HNPCC, an affected member or members of a family should have had either CRC (Lynch type 1-site specific) or other extra-intestinal cancers (Lynch type 2), in association with

an index patient with CRC. In the absence of definitive genetic testing, a detailed family history was essential and formed the core of the Amsterdam and Bethesda criteria to make a diagnosis of HNPCC[28,29]. Currently, we know that young patients with an underlying genetic syndrome are more likely to have a family history of cancer and present earlier compared with those with no known genetic syndrome, who presented with late stage metastatic disease[30]. Thus, family history must continue to remain an essential component of clinical evaluation in patients with CRC, while it is essential to note that up to 20 percent of patients with a germline mutation in the study reported by Mork *et al*[30] had no family history of CRC.

ANATOMIC DISTRIBUTION

Several studies have reported that CRC in the young is a condition mostly confined to the left colon and rectum; in a retrospective study of young patients, Leff *et al*[31] revealed that 65% of cancers were in the rectum and that 83% of all colon and rectal cancers were distal to the splenic flexure. Kumar *et al*[32] reported that CRC was confined to the left colon and rectum in 67% of their study population Furthermore, O'Connell *et al*[22] in a structured review of 55 studies comprising 6425 patients with young CRC, reported that cancer of the rectum was most frequent (54%). In the most recent publication of the Surveillance Epidemiology and End Result (SEER) study from the United States, dominance of cancer in the left colon and rectum was again mirrored[19].

PRESENTATION

Studies have shown that CRC in young patients presents with three cardinal features of rectal bleeding, abdominal pain and alteration in bowel habit - constipation, altered stool diameter, mucoid rectal discharge[33,34]. In general, CRC diagnosis in young patients was associated with a delay of approximately 6 mo[33]. Physician related delay in diagnosis was chiefly because of a lack of understanding and suspicion of this disease in the young, where symptoms in young patients were considered due to such benign causes as haemorrhoidal disease by first contact physicians and patients alike. Some other factors that may contribute to delay are patients' preference in seeking non-traditional methods of symptom relief, such as Ayurvedha and Chinese medical treatment, in Asia, and because practitioners of allopathic medicine fail to perform a focused rectal examination at the point of first contact. With current worldwide reports of increasing prevalence of young CRC, it is important that we offer young symptomatic patients flexible sigmoidoscopy early, after comprehensive clinical examination, including focused digital rectal examination.

PATHOLOGY

In young patients, CRC is likely to be found in those with a heritable syndrome[28-30] such as FAP and HNPCC. In the Lynch Syndrome, tumours have been known to be predominant in the proximal colon[35,36], but recent research revealed contradictory data where the most frequent site among early onset CRC patients was the distal colon[37]. Of these, between 40 and 60 percent were in the rectum[38,39]. In the WHO classification of tumours[40], HNPCC and sporadic CRC with microsatellite instability have been classified based on the site and microscopic criteria. These are (1) proximally located mucinous adenocarcinomas which are commonly well circumscribed and are moderate-to-well differentiated; (2) proximally located poorly differentiated adenocarcinomas which show failure of gland formation with malignant epithelium arranged in small clusters, irregular trabeculae or large aggregates in well circumscribed tumours; and (3) adenomas in HNPCC indicating features of high cancer risk including villous and high grade intraepithelial neoplasia which display good circumscription and present as polypoid growths, plaques, bulky masses or ulcers rather than diffuse growths or strictures[40]. In a single centre study, mucinous and signet-ring histological subtypes and poor to non-differentiated tumours were frequently seen among the young[38,41,42], and accounted for 41.5% of all tumours[38]. The incidence of tumour *in situ* (Tis) was lower in young patients compared with older patients and may indicate either failure of early detection or rapid progression from adenoma to carcinoma in the young compared with older patients[43]. Other features that suggest more aggressive tumour biology in the young compared with older patients are the higher percentages of patients with lymph node metastasis ($\geqslant$ 4 lymph nodes), distance metastasis and stage Ⅳ disease[41,42].

GENETICS

All colorectal cancers occur from genetic mutations, which are part of a familial syndrome, hereditary syndrome or as sporadic cancer[44]. Frequent among young patients are either FAP, variants of FAP or HNPCC. Historically, in the sporadic subtype, the origin of CRC was attributed to various common or rare genetic alterations that displayed variable penetrance, and remained largely unidentified[45]. It is now estimated that up to 30% of CRC may have a hereditary component, with identifiable genetic aberration, especially if cancer occurs in the young[23,24,30,46]. Next generation sequencing (NGS) is likely to further increase our knowledge of hitherto unidentified chromosome aberrations in association with cancer[47] resulting in such diagnoses as the Li-Fraumeni syndrome, Cowden's disease, Juvenile polyposis and Peutz-Jegher syndrome[46].

Different from germline mutations, somatic mutation, that may be spontaneous or follow contact with luminal carcinogens, may result in genetic alteration of a colonocyte in which control of apoptosis is lost in conjunction with a series of chromosomal changes that create microsatellite instability[43]. In fact, the aetiology and range of hitherto unidentified germline and early onset somatic mutations is likely to be more extensive than

previously understood, which makes our understanding of the pathology in young patients with sporadic cancer even more complex. Essential to our understanding of tumourigenesis is knowledge of preservation of DNA integrity in the intestinal epithelial cell; deep within the base of the intestinal crypt lies the colonocyte stem cell that is covered in a thick layer of mucus. Each stem cell is designed to replicate into a transit amplifier stem cell and an inert stem cell that remains in the protected crypt base, remote from contact with carcinogens that may be present in the lumen of large bowel, thus preserving its DNA intact. In health, upward migration of the amplifier cell will give rise to a functional colonocyte that will shed in 5 to 7 d by genetically determined apoptosis, controlled by the *p53* gene located on chromosome 17 and the mitogen-activated protein kinase pathway (MAPK)[43]. The MAPK pathway, of which KRAS and BRAF proteins are part, regulates cell proliferation, cell differentiation, cellular aging and apoptosis[48]. Programmed colonocyte death prevents the propagation of mutagenic change, and constitutes yet another strategy of preserving intestinal cell DNA integrity[43]. In the adenoma-carcinoma sequence, initialisation of neoplastic change occurs with silencing of the tumour suppressor genes located on chromosome 5 (*APC* gene), followed by serial changes in chromosome 17 (*p53* gene-mutated in colorectal cancer) and chromosome 18 (long arm deletion)[49]. Furthermore, simultaneous activation of the proto-oncogene K-Ras will lead to uncontrolled cell growth[49]. Hence, both germline mutations and somatic mutations may drive colorectal cancer in the young.

Currently, the genetic mechanisms that trigger CRC are grounded in three major pathways; chromosomal instability (CIN), microsatellite instability (MSI) and the cytosine-phosphate-guanine island methylator phenotype pathway (CIMP) pathway[50,51] - mechanisms that create genomic instability, which together with a process that will selectively support mutagenic driver cells, produce colorectal cancer. It is essential in our understanding of this process that none of these pathways is mutually exclusive. However, CIN aberrations, by far, constitute the most common pathway in the development of CRC[52].

CIN pathway

This describes the classical adenoma-dysplasia-carcinoma sequence in which it is thought that tumour formation is a result of progressive and sequential inactivation of tumour suppressor genes and, correspondingly, activation of tumour promoting oncogenes - mutation in the adenomatous polyposis coli (APC) gene being an important initial step in this pathway[52]. Likewise, it is known that mutation of the KRAS oncogene contributes to CIN-associated sporadic CRC in up to a half of such sporadic cancer[53]. Since RAS proteins control signaling in cell differentiation and apoptosis, disruption of such pathways will lead to neoplastic transformation. CIN-associated tumours comprise 75% to 80% of all tumours found in Western populations[54].

MSI pathway

It is known that formation of new strands of DNA may be interrupted by base pair mismatches, *i.e.,* mutations which may be either deletions or insertions. In health, the role of mismatch repair proteins is to bind, remove and repair the region of the mismatch error. In cells with malfunction of mismatch repair proteins, these mutations will tend to accumulate within areas of DNA coding called microsatellites. Such areas of microsatellite instability are the cause of sporadic CRC[55].

CIMP pathway

This pathway of CRC differs fundamentally from CIN and MSI, in that, it causes mutation and epigenetic silencing of genes that control the cell cycle outside the APC control system. This pathway is chiefly associated with a group of protein kinases known as BRAF proteins, and usually occurs due to promoter methylation and silencing of the mut-L homologue 1 gene (MLH-1- short arm of chromosome 3), resulting in microsatellite instability. CIMP associated cancer is frequently found in patients of older age, has a slight female preponderance and is associated with right sided colon cancer, similar to the Lynch syndrome. However, it is rare for patients with Lynch syndrome-associated CRC to have BRAF mutations, which helps differentiate Lynch syndrome associated CRC from sporadic CRC[56]. Thus, it becomes evident that no two colorectal cancers are likely to be the same, and that each will have its own unique characteristic genetic "fingerprint". It is also known that each cancer may have more than one of the aforementioned carcinogenic pathways[57,58], which makes genetic imprinting of sporadic CRC all that more challenging. Furthermore, since CIN and MSI associated CRC is known to respond differently to chemotherapeutic agents and impact on cancer related survival, to enable tumour specific personalized treatments, future standard pathological tumour work-up may have to include such genetic "fingerprinting".

RISK FACTORS

A historic study of tumour genesis in the colon shed light on the alkaline environment in the lumen of the colon which, combined with secondary bile acids, is a promoter of tumour formation[59]. N-nitroso compounds and ammonia, produced from bacterial action upon undigested protein products, and secondary bile acids alter the luminal environment, which affect colonocyte function and deplete oxygen levels in the colonic mucosa, thus favouring tumourigenesis. Furthermore, rapid urbanization with environmental pollution, lifestyle alterations such as reduction in physical activity and change in dietary patterns in young individuals[9,60], may have also contributed to the rising incidence of CRC, although this alone does not explain its disproportionate rise in incidence in previously

low incidence parts of the world[61].

SURVIVAL

Multiple studies of young patients with CRC from cancer registries have shown that, in young patients, 5-year survival did not differ from older patients despite a greater proportion of locally advanced cancer, regional lymph node involvement and less favourable histological types in the young[61-63]. Ruiz *et al*[64] showed an overall survival rate of 69.4% and 67.4% at 5 years for colon and rectal cancer respectively from a cancer registry database in Peru. Likewise, Parc *et al*[63], reporting survival data from the central South Korean cancer registry, revealed a 5-year survival of 66% for young patients with cancer of the proximal colon, 70% for patients with distal colon cancer and 66% in patients with rectal cancer. However, if young patients with CRC present with concomitant metastasis, or in the case of a small proportion of patients with unfavourable histological features (poorly differentiated cancer, signet ring cancer), survival may be poor[65]. Chan *et al*[66] have shown that survival in young patients with a poor prognosis is predictable, and that maximum survival in this group of young patients after surgical intervention is no more than 20 mo.

SCREENING

CRC screening guidelines currently recommend routine screening of individuals from the age of 50 years. The screening tests range from invasive procedures such as flexible sigmoidoscopy and colonoscopy, through imaging investigations such as virtual colonoscopy, to minimally invasive procedures such as faecal occult tests[67].

Although each test has its own different advantages and limitations, colonoscopy - widely regarded as the gold standard - has shown to decrease the incidence of CRC up to 80%. However, it is essential to note that colonoscopy is not a perfect test - studies have shown a miss rate of 6%-12% of adenomas > 1 cm and 5% for CRC[67]. Faecal occult tests have shown promise too; an example being, the faecal immunochemical test which has shown high rates of detection of prevalent CRC in an asymptomatic population[68].

With the rising incidence and mortality of CRC in young patients, effective screening methods must be able to detect these tumours early. Current guidelines suggest that individuals with a family history of CRC or adenomatous polyps, other than FAP, undergo screening earlier than at 50 years. That is, from the age of 40 or 10 years before the youngest cancer affected family member, while those with a family history of FAP undergo screening in adolescence[68]. Population based early-onset CRC screening has not been justified due to low prevalence, cost and potential adverse procedural outcomes outweighing the benefits[17]. To detect early onset CRC, suggestions have been to undertake routine screening from 40 years, instead of 50 years - however, decision analysis models have shown no significant life-year gains for this change[37].

To combat the rising incidence by screening of potential early onset CRC patients, awareness among physicians, primary healthcare workers and the lay public must increase. For the physician, this should begin at the stage of medical school by integration of preventive medicine and longitudinal cancer prevention modules into medical school curriculums - which have shown positive results[69], and will improve the future physician's ability to identify young individuals at high risk.

In terms of young patient awareness, it is imperative that young adults are aware of screening for early onset CRC. A study revealed that university students had very poor knowledge of CRC screening, indicating the necessity for early-onset cancer awareness campaigns[70]. Another feasible plan to improve screening rates is the employment of a well-trained lay cancer-screening navigator; this person's role would involve contacting individuals, discussing the importance of screening for CRC and implementing screening procedures such as faecal tests sent by mail. Although this was a feasible strategy for older patients aged 50 to 74 years[71], it has yet to be determined how effective this strategy would be in younger individuals.

To avoid low screening rates, patients' screening method preferences require consideration. Studies have shown faecal aversion to be one of the chief hindrances to screening participation, and a survey revealed that 78% of participants would prefer to provide a blood sample instead[72]. One such blood test to detect CRC, which requires further development, is the assessment of circulating methylated SEPT9 DNA, and although it is able to detect CRC in an asymptomatic individual, improved sensitivity is required for population screening[73]. A highly sensitive and specific blood test for CRC could very well become the gold standard in the future, and thereby decrease incidence and mortality rates.

CONCLUSION

An epidemic of colorectal cancer in young patients is imminent. Based on better understanding of genetic mechanisms, currently it is estimated that genetic predisposition to colorectal cancer is 30% of all CRC. The figure is likely to be higher in young patients if all young patients with CRC were to have genetic assessment by NGS testing. While the MSI, CIN and CIMP pathways have been isolated and well defined, a number of germline and somatic mutations in CRC are likely to manifest from widespread use of NGS, multiple panel genetic tests. Furthermore, multiple permutations of genetic alterations are likely to show up in individual CRCs, with overlap of previously known syndrome based genetic changes, which will make individual genetic fingerprinting of CRC more complex and perhaps the age of onset of CRC, that is, whether young or older, irrelevant. In lifestyle assessment, populations, such as in Egypt, where consumption of red meat is high seem to have similar proportions of young

patients with CRC compared with predominantly non-meat eating populations, such as is found in India, which further complicates the search for a common lifestyle aetiology. What is common across the world in lifestyle is the growing fast food industry and childhood obesity; more thought and research needs to focus on its contributory role. For the present, the majority of cases of CRC remains sporadic and of multifactorial origin: Diet and nutrition, obesity, the colonic microbiome, smoking, alcohol consumption and hitherto unknown germline or somatic mutation. The role of screening for CRC in young patients is not likely to follow a "one test fits all" policy until we have worldwide genetic data in this group of patients. At present, mass screening by flexible sigmoidoscopy is expensive and may yield low productive rates. However, better education of medical students, primary healthcare personnel and first contact doctors, about the benefit of prevention and early detection of CRC in the young is likely to improve early detection rates in young persons. Whether early detection influences lead-time in such young patients with cancer remains unresolved, as some studies have shown a clear cut-off in survival at around 2 years. It is a formidable challenge to fight the rising incidence and mortality in early onset CRC patients, an effort that will require global co-operation and consensus.

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