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REVIEW ARTICLE

Proximal shift of colorectal cancer. A persistent phenomenon with multiple causes, patterns and clinical implications

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Summary

A considerable change in the anatomical distribution of colorectal cancer (CRC) towards more proximal sites has been observed in Western countries within the last 6-7 decades. As a result, tumors located proximally to the splenic flexure are now accounting for 30-40% (or even more) of overall CRC cases. This proximal migration is not always representing a true increase of proximal cancer, arising from various combinations of changes in the rates of proximal and distal cancer (e.g. proximal increase with distal stability/reduction, or decline in both sites albeit higher distally etc) in different areas and periods.

Principal potential causes include ageing in Western populations (since proximal cancers are more common among the aged), various potentially site-specific exposures (lifestyle and medical) and systematic screening. Their effect is reflected in the particular shift patterns; for instance, widespread screening in USA has led to an overall CRC decline, more evident distally (for technical, anatomical and morphological reasons). Segmental disparities in particular characteristics (age, gender, morphology) and responses to various exposures are etiologically associated (for the most part) with underlying genetic differences between proximal and distal tumors.

From clinical aspect, proximal shift necessitates a more generalized use of colonoscopy in screening programs. Potential interventions in treatment (segmental patient stratification) and prevention (identification of particular site-specific exposures) require further investigation.

Key words: *colorectal cancer, epidemiology, proximal shift*

Introduction

The anatomical location of CRC has been considered as a clinically significant parameter, influencing the clinical manifestation and the type of surgical resection (both differing between proximal and distal tumors). Further disparities regarding a variety of clinicopathological characteristics (age, gender, stage, grade, histological type and response to chemotherapy) [1-5] are probably attributable to underlying genetic differences between proximal and distal CRCs [5-7], consistent with the heterogeneous and multipathway nature of the disease [8].

In this context, the so called "proximal or rightward shift" (a term describing the change in the anatomical distribution of CRC towards more proximal sites) has been observed within the last decades - mostly in Western countries [9-16]. Notwithstanding some disputing reports [17-19], this trend is persistent, occurring regardless of alterations in overall CRC incidence with time (i.e. increase [10,11], decline [12-16,20] or both variations in succession [21]). The cause behind this phenomenon is rather unclear and probably multifactorial (given that CRC is etiologically associated with both genes and environment [8]), including demographic trends (mostly population ageing) [13,15], several site-specific risk or protective factors (lifestyle and medical) modified with time [8,10,16,20,21] and systematic screening (re-

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Table 1. Current proportion of proximal colorectal cancer in Western countries

Country	*Database [Ref]*	*Proportion (% of overall CRC)*
USA	National [12,13,23]	42 (40-44)*
New Zealand	National [11]	40
Canada	National [16]	37
Sweden	Multicenter [3]	37
Israel	National [22]	34,5
England	Regional [26]	32
Italy	Regional [25]	31
Japan	Multicenter, regional [1,24]	31-32*
France	Regional [10]	27,5

Data derived from recent studies (published within the last 10 years) using a variety of databases.
* Depending on the particular database.
CRC: colorectal cancer.

sulting in a considerably different preventive segmental effect) [12,14,15,20-24].

This review examines the main causes potentially contributing to proximal migration. For this purpose, the shift is categorized into particular patterns, according to the observed combination of changes in the incidence of proximal and distal CRC with time (see next section). Thus, the potential etiological connection of these segmental changes with contemporary or earlier alterations in various modifiable factors (behavioral or medical) is more easily highlighted. In addition, the chronological evolution of proximal shift (since 1940) is briefly described, in relation to the observed variations in overall CRC incidence. Lastly, the clinical implications of this redistribution are summarized, including (but not limited to) the appropriate screening strategy, particularly regarding modality selection (considering the increasing proportion of tumors located beyond reach of sigmoidoscopy). In fact, at least one-third of the detected colorectal malignancies in most Western countries is now proximally originated [11,16,22,24-26]. The corresponding proportion in USA is considerably higher, currently accounting for ~42% of diagnosed CRC cases [12]. (Table 1).

In this study, as proximal are considered lesions of the cecum, ascending and transverse colon, whereas tumors of the descending, sigmoid and rectum are classified as distal. This categorization is based on differences in embryologic origin, blood supply, innervation and function, discriminating proximal from distal segments of the colorectum and providing the biological background for the development of two distinct tumor entities [6,7,27]. Notably, the lack of agreement in the appropriate anatomical division of the colorectum has been considered responsible (in part) for the conflicting results regarding the shift [9,11,18]. Moreover, the wide disparity in the databases of relevant studies (hospital-based [9,17,19,28], population-based [14,29], regional tumor registries [10,15,18,24-26,30] and national registries [11-13,16,21-23,27]) may also account to some degree for some discrepancies. Nonetheless, this variability provides multiple evidence about the existence of the shift among different populations, reveals different epidemiological trends by geographic area and ethnic group observed within particular countries (e.g. New Zealand [11], Italy [18,25] England [19,26] and USA [21,27,28]) and highlights the connection of proximal migration with particular potential causes (such as screening [12,14], aging population [13,15,22], or gender-related factors [16]).

Patterns of proximal shift

The reported combinations of segmental variations in the incidence of CRC with time, resulting in different patterns of proximal shift could be classified as follows:

a) Increase of proximal cancers with reduction of distal cancers [9,10,16,29].
b) Unaltered proximal incidence with reduction of the corresponding distal [13,14,21].
c) Unaltered distal incidence accompanied by proximal increase [22].
d) Reduction in both sites, sharper distally [12,15,23].
e) Increase in both sites, higher proximally [11,24-27,30].

The disparate patterns (Figure 1) probably reflect different geographic trends in both segmental distribution and overall incidence of CRC. Thus, the decline in disease rate observed in USA after 1985 was weaker or not evident for proximal cancer [12-15,21,23]. Conversely, other contemporary Western studies demonstrated a shift type characterized by an increase in overall CRC incidence, being higher proximally [11, 24-26]. Notably, a rather similar pattern had been observed in USA before 1985 [21,27,30].

The change in the type of proximal shift in USA supports the hypothesis of multifactorial cause of this phenomenon (ageing, lifestyle changes, screening). Theoretically, a similar change in the future could be expected in other countries with resembling etiological characteristics of the shift. Moreover, the shift itself may reflect in part a progressively more accurate recording of prox-

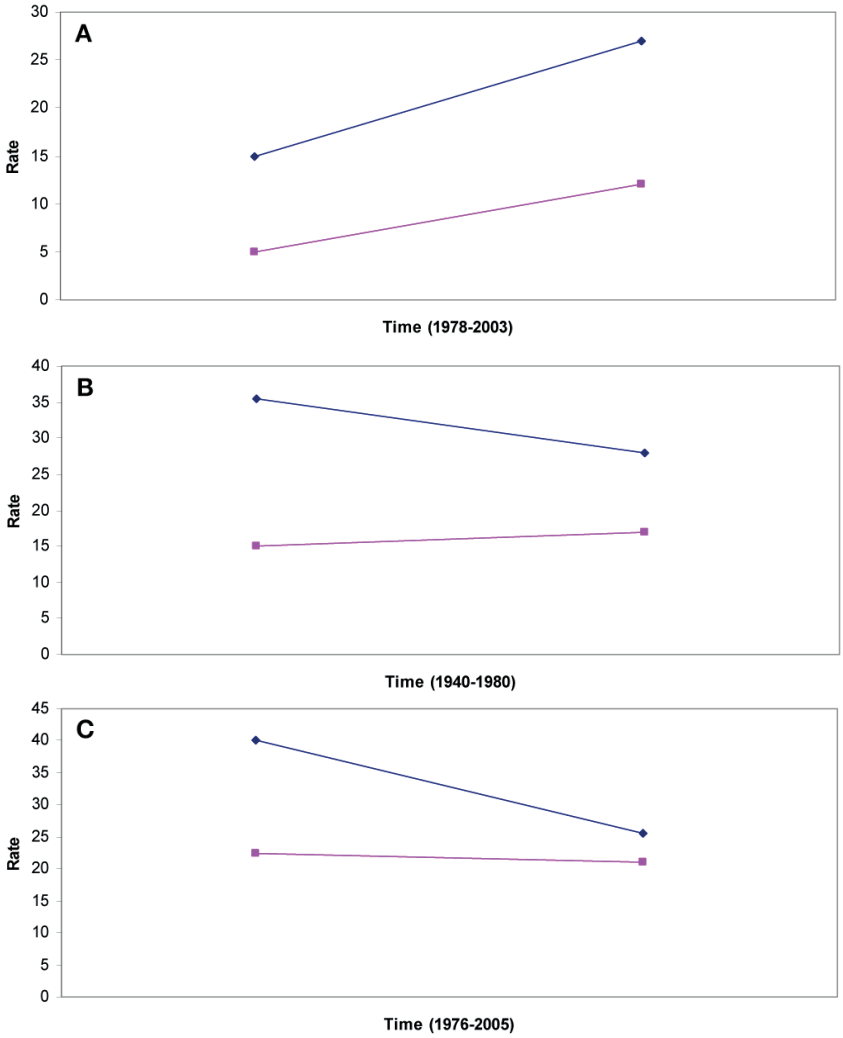

Figure 1. Simplified illustration of the main patterns of proximal shift according to the observed combination of segmental changes in CRC rate with time.
A) Increase in both sites (higher for proximal tumors).
B) Proximal increase / distal decline.
C) Decline in both sites (sharper for distal tumors). Data (incidence rates per 100,000 population in particular time periods) derived from selected studies representative of the corresponding patterns [24,29,35].
Other reported patterns, in particular proximal increase/distal stability and proximal stability/distal decline are not presented here as they are either rarely observed (the former) or considerably resembling to pattern C (the latter).

imal cancer - likely underdiagnosed in the past [26,29,31]. Interestingly, the increase in the incidence of proximal CRC occurred in parallel with the reduction in the frequency of cases designated as "unknown site" [26,30,32] - probably due to diagnostic and surgical improvements [26,29]. Nevertheless, the contribution of this factor to the shift (if any[30]) is probably minor and limited to previous decades - mostly before the 1970s. Since then, the frequency of unspecified cases was consistently very low (<5%) in USA [13,15,21,27,30] and other Western countries [3,9,10,25], although it has remained relatively high in UK and Japan [23,24].

Causes of the shift

Table 2 summarizes the variables potentially involved in the proximal shift of CRC. Most of them are considered as risk or protective factors for the entire colorectum, albeit in a manner favoring the shift (i.e. preferentially increasing proximal or reducing distal tumors) as analyzed in detail in this section. Moreover, their effect probably varies with time, prevailing in certain periods (previous or recent) and modifying accordingly the observed shift patterns.

Demographics

Proximal cancers have been consistently

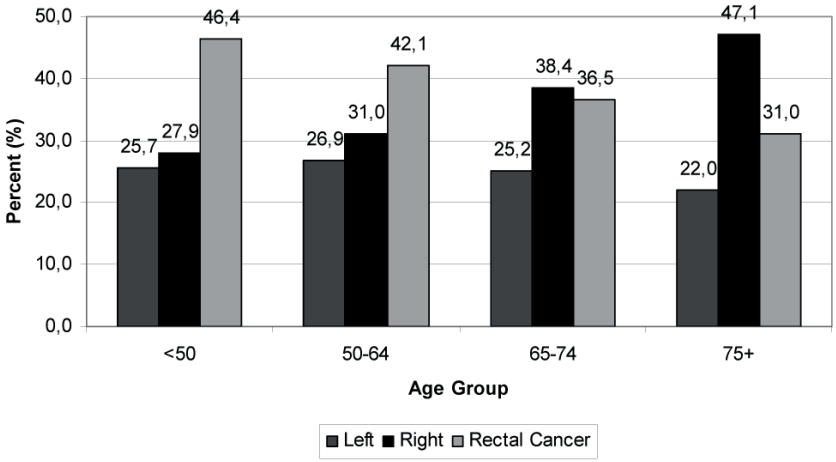

Figure 2. Percentage of CRC cases by subsite and age group, Canada 2004-2006. Proximal (right) and distal (left and rectal) cancers display apparently opposite variation trends in their proportion with advancing age (rise and fall, respectively). Reproduced (after permission) from the Canadian Partnership Against Cancer. Cancer Control Snaphsot #2: Colorectal Cancer Incidence and Mortality. Toronto: 2010 [34].

associated with older age and female gender [1,2,13,23,24,33-35]. Therefore, the shift may be (in large part) a reflection of the aging population, given that proximal CRC accounts for ~50% of cases among elderly in USA and Canada [13,15,34,35]. Conversely, the proportion of rectal cancer is substantially reduced with advancing age (Figure 2). The effect of ageing is more prominent among women [11,16,23-25,35] because of their longer lifespan[22,36] along with their tendency for diagnosis at older age [21,36] likely attributable to the protective role of female sex hormones [16,36] (consistent with both lower incidence [16,18,21,27,34-36] and better outcome [2,16,37] of CRC female patients). The reduction in overall CRC risk observed by the use of hormone replacement treatment (HRT) and oral contraceptives [38] is potentially associated with a protection against estrogen receptor (ER) gene hypermethylation [8]. However, this effect is not clearly site-specific [6,39] despite the reported change in the expression of the particular receptor and its subtypes a and b along the bowel [6,36]. Nevertheless, the progressive increase of the male-to-female cancer incidence ratio across the colorectum, from ~1.1 (cecum) to ~1.7-1.8 (rectum) [16,21,27,36] is indirectly supportive of a stronger hormonal protection against distal tumors [7,16,20].

Table 2. Classification of the potential causes of proximal shift

Variable category	*Specific cause*
Demographic	Ageing populations Hormonal influence (in females) - combined with ageing
Lifestyle	Dietary factors Obesity Physical inactivity Smoking and drinking reduction
Medical conditions	Cholecystectomy Diabetes NSAIDs use HRT use
Diagnostic/preventive procedures	Systematic screening (mostly colonoscopy/sigmoidoscopy and polypectomy)
Other	Increase of CRC family history cases Reduction of unspecified site and stage cases

NSAIDs: non steroidal antiinfammatory drugs, HRT: hormone replacement therapy, CRC: colorectal cancer

Notably, the impact of demographic changes on CRC anatomical distribution is etiologically connected with the distinct genetic mechanisms involved in proximal tumorigenesis [7]; MSI (microsatellite instability) and CIMP (CpG island methylator phenotype) occur predominantly in right-sided tumors, elderly and females [6,7,40]. Therefore, the progressive ageing (especially in women) has led to a selectively higher increase of cancers evolving through these pathways - being preferentially proximal.

Moreover, potential interactions of age and sex with multiple exposures may also influence proximal shift. Cholecystectomy appears to increase the risk for proximal CRC, particularly in women [20,41]. NSAIDs (non steroid antiinflammatory drugs) exhibit a protective effect [20,42], which is likely site-specific (against distal CRC [6,31]) and -also- more prominent among elderly, as they are common users of these agents. In addition, reduction of drinking and smoking,

considered as risk factors for CRC - preferentially for distal (especially rectal) site and male gender [6,36,43]- possibly accounts to some degree for the recorded declining incidence of tumors with this location in USA. Also, dietary risks appear to be stronger proximally for women and distally for men [6,33], fitting with the observed gender predilections for the particular tumor locations. Such sex - and site-specific diet effects (if actually exist), combined with ageing, may contribute to the proximal shift, providing an alternative (or supplementary) explanation for the considerable prevalence of proximal CRC among elderly females [15,34,35] - partially attributable to their prolonging exposure to particular dietary risks. Lastly, advanced age may adversely influence colonoscopic preparation, completion and efficacy [12,22], resulting in lower rates of polyp detection (and subsequent removal) in this particular age group being at the highest risk for developing proximal cancer.

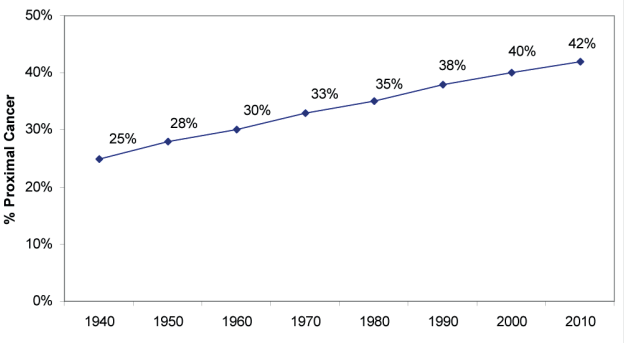

Figure 3. Rising proportion of proximal CRC in USA from ~25% at 1940s to ~42% at 2000s. The illustration (based on published data in relevant studies [13,27,29,30,35,49,67]) is indicative, although not strictly representative of the trend, as none of the particular large databases included the entire US population. Furthermore, earlier studies were based on regional [29,30] or limited national data [67].

Lifestyle alterations

Changes in lifestyle, including meat consumption, high fat and protein intake, hypercaloric diet, obesity and sedentary life, previously observed in Western countries and recently in newly developed areas, are considered responsible for the increase in overall CRC incidence [8,44-47]. The site-specific effect reported for some of these factors [6], selectively promoting tumorigenesis proximally (high fat consumption) [45], distally (high protein and meat intake or high serum albumin, low consumption of fruits and vegetables) [41,45,48] or in the entire colon albeit not the rectum (obesity and decreased physical activity) [8,46], has possibly contributed to the proximal shift [10,24,29]. However, this effect may vary with time, likely becoming weaker in recent years among Western populations, adopting more hygiene lifestyle like reduced intake of fat and calories and increased exercise. Such behavioral changes (also including smoking and drinking reduction), although generally fitting with the declining incidence of CRC in USA [12,49] appear to have a lower specific impact on proximal cancer rate [13,15,21,35], because dietary effects are possibly stronger distally than proximally [27,50,51] and/or because the carcinogenic effect of some previous exposures in the proximal colon (exhibiting a potentially longer latency period) has become evident nowadays, leading to a slower cancer reduction rate in this site [15]. Finally, elimination of particular previous carcinogens (as occurred for nitrosamines in alcohol beverages - through altered beer manufacture) may have had an effect on diminishing distal cancer [20].

Recent data suggested that changes in modifiable factors (excluding screening) accounted for 50% of the decline in CRC incidence between 1975 and 2000 in USA [49], revising previous estimations of an approximately 70% preventive impact of these factors [47]. However, the latter may be still true for other Western countries because of too recent and rather limited implementation of screening programs [10,11,23,44,50]. Nevertheless, despite the convincing evidence for particular exposures regarding overall CRC risk (red and processed meat, obesity, physical inactivity, alcohol and – probably - smoking) [8,49], there is still uncertainty for their exact segmental effect [11,36,50]. Conversely, that the evidence for other CRC risk or protective factors (e.g. fat, fruit and vegetables) is weak, could be explained by the assumption that their effect is largely limited to particular sites and not extended to the entire colorectum.

Common medical conditions

Cholecystectomy has been considered as a factor predisposing to proximal CRC, particularly in women [51], by changing the pattern of intestinal exposure to bile acids [6,51,52]. Cholelithiasis has been also reported as a risk factor for right-sided CRC [41,52], although less consistently [51], likely acting through either the potentially carcinogenic effect of the lithogenic bile or through the improper function of gallbladder (functional cholecystectomy) [52]. In this context, the increase of

Table 3. Impact of various potential causes on proximal shift

Cause	*Type of effect*	*Degree of effect**	
		*Recent (after 1985)***	*Previous (before 1985)***
Demographic			
Ageing of population	Proximal increase	Considerable (particularly among females)	Modest
Sex-related factors (hormonal treatment and oral contraceptives)	Distal fall***	Potentially considerable (protection against distal cancer)	Modest or minor (or even absent before 1960)
Lifestyle habits			
Dietary factors Obesity Physical inactivity	Overall colon cancer increase	Considerable (although relatively attenuated in recent years)	Probably stronger (compared to recent years)
Alcohol and smoking reduction	Distal fall	Possibly modest	Rather minor
Medical conditions			
Cholelithiasis/Cholecystectomy	Proximal increase	Minor (mostly in women)	Minor (mostly in women)
Diabetes/hyperinsulinemia	Proximal increase***	Potentially considerable (hyperinsulinemia is closely related to other lifestyle habits)	Potentially considerable
NSAIDs	Overall CRC decline (preferentially for distal site)***	Modest (increasing use in recent years) considerable in particular risk groups	Minor
Comorbidities	Proximal increase	Unclear (possibly acting through lifestyle changes)	Unclear
Reduction of unstaged and unknown site cases	Proximal increase	Minor (such cases are rarely reported nowadays)	Possibly modest (higher rates of advanced / unspecified disease)
Increase in family history cases	Proximal increase	Minor	Minor
Screening application and polypectomy	Overall CRC reduction (predominantly distal site)	Considerable - widespread application - improvements in technique and experience - lower effect proximally (even with colonoscopy)	Modest - limited application - technical difficulties - lack of effect proximally (with only sigmoidoscopy)

* Characterization of the effect for each particular cause (considerable, modest, minor or unclear) is based on the prevailing opinion among relevant studies.
** 1985 was the initiative year of CRC decline in USA [21].
*** The evidence for site-specific effect is indirect for HRT [16,27,36] and hyperinsulinemia [21,53] and inconclusive for NSAIDs [55].

cholecystectomies observed in USA in the 1970s (particularly in older ages [27]) was possibly among the factors responsible for the subsequent rise in the incidence of proximal CRC. Conversely, the slight fall of cholecystectomies reported after 1980 in this country [20], may account -even barely- for the current decline of proximal CRC rate in USA.

Diabetes mellitus (DM) has been reported - although not consistently [41]- as a risk factor for proximal CRC, [33,53,54], suggesting a different segmental effect of hyperinsulinemia - observed in early DM stages - in tumorigenesis.[21,33] A potential involvement of this mechanism in the proximal shift has possibly taken place through rising rates of chronic hyperinsulinemia accompanying not only sub-clinical diabetes cases but also a large spectrum of risk factors for CRC (Western diet, obesity and lack of physical activity) [21,47,53] exhibiting a potentially site-specific effect [6,45,46]. Indirectly supportive to this assumption is the continuing rise in the rate of proximal CRC in USA, particularly among Blacks (at variance with Whites), a racial group with consistently higher prevalence of diabetes [21].

The use of NSAIDs has been proposed as a factor potentially preventing CRC through reduction of the incidence and the growth of polyps in both

low (general population) and intermediate/high risk groups (history of polypectomy, family history of CRC, familial adenomatous polyposis - FAP) [20,42,55], acting through inhibition of cyclooxygenase (COX-2) [8]. This effect is likely site-specific, as suggested by the reported predilection of COX-2 overexpression for distal and rectal tumors [6,56]. Thus, the rising use of these agents among Western populations in recent years (overdoubled in USA between 1980-2000) [57] has potentially contributed to the shift by reducing distal CRC [31]. Notably, this effect is possibly more prominent among elderly (more commonly consuming NSAIDs, especially for musculoskeletal pain) and men (principal users of aspirin prophylaxis against coronary disease) [20]. However, chemopreventive result is considerably influenced by treatment characteristics (dose, duration, frequency of use and selected drug - aspirin / non aspirin) and risk level (better for advanced adenoma and family history of CRC) [42,55], possibly by interactions with other factors (obesity, HRT) - also changing with time [57], and perhaps by tumor molecular status (COX-2 overexpression) [55,56], hampering an accurate determination of NSAIDs impact on particular anatomic sites.

Other conditions, including congestive heart failure, cerebrovascular disease, chronic pulmonary disease and peptic ulcer have been independently associated with proximal CRC [33]. These links (if actually exist) may contribute to the shift through increasing detection rates of proximal cancers along with rising rates of distal polypectomies, both attributable to the more frequent and easier access to medical services for those patients [33], or even through higher rates of certain exposures (such as fat consumption) incriminated for both CRC (preferentially proximal) and some of the comorbidities (especially the cardiovascular) [47]. In addition, changes in lifestyle habits, usually accompanying diagnosis of these conditions (e.g. smoking stoppage), may also play a role (selectively reducing distal tumors). Indeed, the higher likelihood of distal CRC found in current users of alcohol and tobacco, was not observed in past smokers or was reduced in past drinkers [43].

Genetic susceptibility

The rising CRC rates in previous years have led to a true increase of cases with cancer family history (not necessarily hereditary), currently accounting for at least 10-15% of all CRCs [58]. Their reported predilection for proximal site [28,59] has potentially contributed to the shift [27]. It is possible that some of the factors responsible for the previous rise in CRC rate - and the subsequent increase of family history cases -, may also selectively favor the appearance of proximal disease among high risk individuals. For example, the reported site-specific effect of cholecystectomy, hyperinsulinemia or fat intake may be stronger in this particular group compared to that observed in the general population, implying a higher degree of interaction between host-related (including genetic predisposition) and environmental factors involved in proximal tumorigenesis [27,51]. Notably, some of the major host-related risk factors for CRC (age, personal and family history, chronic inflammatory disease [11,49]) are preferentially associated with proximal disease [15,27]. Nonetheless, the impact of genetic susceptibility on proximal migration is probably minor, as indicated by the relatively stable proportion of proximal cancer in the last 30-40 years in various countries among cases younger than 60 years of age [11,22,35,50] (i.e. those with the expected higher frequency of familial cancer - by definition characterized by earlier onset [58]).

Disease stage

Stage variations over time, particularly changes in the frequency of advanced CRC, may influence proximal shift; several reports [1-3,12,14,33,35] have consistently shown a tendency of proximal tumors to present at a more advanced stage, and higher grade as well [1-3,5]. Notably, a recent study revealed higher frequency of disseminated disease with peritoneal carcinomatosis in the proximal colon [2]. In the past, such cases would be largely considered as CRC of unknown site - a category predominantly including tumors with proximal origin [26,31]. Diagnostic and screening improvements, progressively allowing CRC detection at earlier stages [12,14,21,22,49], have substantially reduced unstaged cases (from 6-7% to ~2% between 1975 and 2006 in USA [49]), potentially yielding higher rates of proximal cancers and thus contributing (even slightly) to the shift [31]. Interestingly, the contemporary reduction in the proportion of late stage [49], was found to be more pronounced for proximal CRC, particularly during the 2000s [12], indicating a parallel shift towards early stage and proximal site - attributable to the recently increased colonoscopy utilization [12,35] (see below).

Screening

The wide use of colonoscopy is considered a factor substantially influencing the shift [12-15,22-25,35]. Endoscopic polypectomy has led to a considerable reduction of CRC incidence [20,49], more evident distally [13-15,20,21,23], because the procedure is easier in this site (in terms of adequate bowel preparation and required duration and technical skill for complete polyp detection and removal [12,23,37,60]) or because of the more frequent selection of sigmoidoscopy instead of total colonoscopy (for lower cost and fewer complications) [23,44,49].

Disparate biological characteristics of tumors according to their anatomical site may also influence colonoscopic efficacy, leading to a higher miss rate in the proximal segment [7,12,23,37,60,61]; the rapid progression of some proximal lesions (MSI cases - probably because of their higher mutational rate [8,40] - and those with nonpolypoid origin, considered to appear a higher malignant potential [60-63]), increases their likelihood of escaping detection, due to a smaller time-window of opportunity [60,61]. By contrast, recent data suggested a slower evolution for most proximal lesions, consistent with their delayed clinical onset (i.e. at an older age) [23]. However, this may also contribute to the lower effectiveness of colonoscopy for this site due to higher rates of inadequate preparation and/or intolerance to the procedure in older patients [12,22]. Additionally, advanced age could be considered as a potential limitation for screening colonoscopy in asymptomatic individuals with average risk for CRC owing to the increased complications in older patients [22, 49]. Morphological characteristics (smaller size and nonpolypoid or serrated morphology), more commonly accompanying proximal precursor lesions [1,7,37,61-63], may also considerably account for the difficulty in their colonoscopic detection.

In USA, screening in asymptomatic individuals has been widely implemented since the 1980s [49], leading to a decline of CRC incidence, particularly for distal lesions - being within reach of sigmoidoscopy (i.e. the initially prevailing screening modality) [14,20]. The growing application of colonoscopy has resulted in a stabilization [14,21] and - more recently - in a reduction of proximal CRC rate [12,15,35,49], consistent with the reported considerable reduction in CRC risk and mortality after colonoscopy for both tumor sites [64,65]. However, this reduction was consistently greater distally than proximally (77 vs 56% [64], 76 vs 42% [65]), probably due to the aforementioned reasons.

Genetic differences - The ultimate cause

The site-specific effect of the various causative factors of proximal shift could be explained - for the most part - by the concept of two biologically and genetically distinct disease entities (proximal and distal) [6,7] responding to different exposures (or responding differently to the same exposures) [29].

The differences existing between proximal and distal colon in embryologic origin (midgut vs hindgut), blood supply (superior mesentery vs inferior mesentery artery), innervation (vagus vs S2-S4), function (absorption vs storage) and other factors (transit time, fermentation, metabolism of bile acids, pH level, hormone receptors and gene expression pattern) provide the internal environment required for the development of genetically and phenotypically different tumors [6,7,27,36,51]. Therefore, it is not surprising that cells of two virtually different organs [7] exhibit disparate sensitivity to risk and protective factors, resulting in distinct tumorigenic pathways for the development of tumors located proximally (MSI, CIMP) or distally (CIN - chromosomal instability) [6]. In this context, particular demographic (older age and preferentially female gender), morphological (smaller size and nonpolypoid or serrated appearance) and clinicopathological (higher stage and grade) characteristics accompanying proximal lesions (cancers and/or polyps), potentially accounting for the proximal shift (as previously analyzed), are probably attributable to the underlying genetic mechanisms [1,6,7]. The validity of this concept is basically retained, even under recent perspectives supporting a gradual rather than an abrupt change (at a discrete point, i.e. the splenic flexure) of tumor molecular characteristics throughout the colorectum and emphasizing in disparities existing among particular colonic subsites [66].

Variation of causes with time and chronological evolution of proximal shift

As indicated in Table 3, screening (predominantly reducing distal cancer) and ageing (preferentially increasing proximal cancer) appear as the main causes of proximal shift in recent years, whereas the effect of behavioral factors - although considerable - may be relatively attenuated compared to previous years [12-15,49]. Conversely, Western lifestyle was probably the principal cause in the past, as supported by the observed

increases in fat and energy intake, obesity and sedentary behavior [20], leading to an increase of overall CRC incidence [47] (becoming more pronounced proximally with time [27,30] because of site-specific environmental effects on tumor initiation, growth and malignant transformation [10,23]). Ageing (less prominent in the past) and earlier diagnostic modalities, such as proctosigmoidoscopy, allowing the detection and removal of distal polyps, had a rather supplementary role [9,27,30,32].

Historically, the evolution of proximal shift in USA could be roughly divided into three time periods with distinct patterns of segmental distribution. The initial period (1940-1960) was characterized by a considerable increase of the colon-rectum cancer ratio [67], as a result of the rising colon (overall) and the virtually unchanged rectal cancer rates - indirectly resulting in a redistribution towards more proximal sites [30, 67]. In the next period (1960-1985), a persistent rise of colonic cancer (more evident proximally [27,30]), accompanied by a parallel slight reduction of rectal cancer, was observed. Finally (after 1985), the recent shift pattern is characterized by a progressive reduction in overall CRC rate, more prominent distally [12,13,15,21,35,49]. Notably, the proportion of proximal cancer during the entire period 1940-2010 was increased from ~25% [29-31] (or even lower [67]) to ~42% [12,33,35,49] (Figure 3). Conversely, the corresponding rectal proportion fell from ~50% [30,67] to ~28% [35,49], thus reversing the classic state that rectal examinations reveal about half of CRCs.

This chronological sequence was also observed in other Western countries [9,16,24-26,32,50], although the last step (reduction in both sites) has not (yet) been ascertained, mostly because of less systematic screening application [10,44,50] and relative persistence of hazardous behaviors. However, recent data from Canada [16,34] and Japan [24] indicated a relative stabilization of overall CRC rate, accompanied by a deceleration of proximal increase along with a suggestion of declining distal cancer rate. By contrast, in newly developed areas the appearance of the shift is rather inconsistent [68-71] despite the recorded increase in overall CRC incidence [44]. For instance, proximal shift has been reported in China [68], albeit not in East Germany [69], Turkey [70] or Hungary [71]. Nonetheless, an increase of colon and a decline of rectal cancer was almost consistently noted following the temporal pattern of CRC redistribution accompanying overall disease incidence rise [8,18,27], indirectly suggesting a possible initiation of proximal migration, in line with the previously described sequence in USA. This pattern is probably associated with the "Westernization" of those areas [44] and the fact that colon cancer is highly sensitive to environmental changes [8]. In Greece, nationwide published data for proximal shift are lacking. Results from hospital-based studies are conflicting [17,72-76]; some support the presence of the shift, either directly (indicating an increase of proximal cancer frequency over time) [17,74] or indirectly (reporting a high current proportion of proximal cancer) [75,76]. However, others dispute this trend [72,73]. These discrepancies may reflect disparities in various exposures and screening among particular Greek territories.

On this basis, demographic, lifestyle, screening (and other medical) changes, progressively taken place since 1940s in Western countries, selectively promoting the development of proximal tumors and/or preventing that of distal cancers, resulted in the proximal shift, modifying the pre-existing anatomical distribution of CRC. However, "populations are dynamic and risk factors such as obesity, NSAIDs and HRT use exist in a shifting (with time) context", interacting with each other and modifying their effect [57]. Therefore, different alterations in relevant factors may favor an opposite trend - as suggested by the recent increase in the incidence of CRC among cases <50 years of age in USA and Norway, particularly those with distal tumor site [12,49,50], likely attributable to earlier lifestyle exposures (poor diet, drinking and smoking) [43,50] along with the lack of protective/preventive medical factors (screening, NSAIDs) for this age group [49]. Perhaps, a similar rise of distal cancer rate particularly in older women should be expected in the next years, as a result of the recent considerable reduction in HRT use due to their adverse effects [16,57].

Clinical implications

A realistic (although not ideal) screening proposal for low risk individuals, considering current epidemiological trends (including proximal shift), modality efficacy, cost and health service level, would select colonoscopy as main tool for ages >50 years [12,44,49], leaving sigmoidoscopy (coupled with fecal occult blood test / FOBT) or fecal immunohistochemical test / FIT) for younger ages (to date virtually unscreened). For countries with limited financial sources, sigmoidoscopy/FOBT for ages <70 years and colonoscopy thereafter (for

medically fit individuals) [22,23] may represent an acceptable strategy. Application of sigmoidoscopy (plus FOBT) as first-line investigation and colonoscopy for follow-up could be another alternative option for areas without evidence of proximal shift [19]. Computed tomographic colonography (instead of colonoscopy) could be used for particular subgroups (e.g. for follow-up of those with detected polyps and – perhaps – for the elderly) [49]. Further research is necessary before establishing specific screening policies for particular risk subgroups, e.g. diabetics, drinkers and smokers [41,43,53].

The impact of proximal shift potentially extends to treatment field. Chemotherapy for stage II disease is currently implemented only for rectal tumors [7,66]. The exclusion of their proximal counterparts is likely justified by the observed overrepresentation -among them - of particular patient subgroups with either favorable outcome (females, MSI cases [37,40,66]) or intolerance and lower response to chemotherapy (elderly [77,78]). Current clinical research examines the efficacy of chemotherapy and targeted therapy by tumor molecular status. For instance, the ECOC-E5202 trial investigates response to 5-fluorouracil-based treatment in stage II CRC cases according to MSI status [66]. Confirmation of the predictive role of MSI would –theoretically - allow the identification of the best candidates for this particular treatment. However, financial, technical (assay validity and availability, insufficient tumor material) and other parameters may hamper a generalized implementation of MSI evaluation, especially for economically weaker populations [66]. Therefore, considering the strong predilection of this marker for proximal disease [6,40], tumor site could guide patient selection for MSI test (virtually excluding distal/rectal tumors displaying MSI positivity in only 2-3% of the cases [6,40,66]).

From the preventive aspect, some favorable behaviors decreasing overall CRC risk, such as healthy diet, drinking and smoking reduction, appear to confer lower protection against proximal disease. Identification of exposures specifically promoting or suppressing the development of proximal tumors (for example, particular fruits and vegetables [48]) could be an optimal and – hopefully - feasible preventive goal. Moreover, elucidation of NSAIDs preventive (and perhaps therapeutic) role in particular sites [55,79] appears as a more demanding, however promising objective.

Lastly, the impact on disease outcome is rather unclear. Although generally worse for proximal tumors [2,37,78], survival varies by site in a complex and stage-dependent pattern (worse proximally for disease stages I and III, albeit not for stage II) [2,66]. While location appears as a modest to minor prognostic determinant [2,37,78], the fact that other factors adversely influencing survival (older age, advanced stage, poor grade, higher co-morbidity rate) [2,37] are more commonly accompanying proximal cancers [1-3,5,33,78] suggests a potentially considerable contribution of proximal shift to CRC mortality.

Conclusion

Proximal shift of CRC is a phenomenon of the last 60-70 years which varies with time and geographic area, following corresponding variations of the main causative factors (lifestyle alterations, aging populations, screening application). The site-specific effect of these causes resulting in the disproportional change of the anatomical distribution of CRC towards move proximal sites, is largely attributable to the fact that proximal and distal tumors are genetically and biologically distinct disease entities, differently responding to various exposures. From the clinical aspect, implementation of systematic screening programs including broad application of total colonoscopy along with technical improvements (facilitating visualization of small nonpolypoid lesions) is the rational adjustment against the rising proportion of proximal lesions. Other potential interventions in CRC treatment and prevention, specifically targeting proximal cancer, require further investigation.

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