



Distribution of colorectal polyps: Implications for screening



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A B S T R A C T

Keywords:

Colorectal adenomas
Screening
Proximal colon
Sigmoidoscopy
FIT
Colonoscopy

Background: During the last decades data from different studies reported modifications of the topographic distribution of colorectal cancers (CRCs), with an increased frequency of tumours in proximal colonic segments. Given the documented link between adenomas and CRC, a proximal migration of adenomas over time could be expected as well.

Aim: To evaluate available evidence about the prevalence of adenomas and of sessile serrated polyps across colonic segments, the changing trends in their distribution across the colon and the diagnostic performance of screening tests currently adopted in population based screening programs for lesions located in different colonic segments.

Methods: Literature search on PubMed, Embase, and Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects with reference to preferred reporting items for systematic reviews and meta-analysis (PRISMA), considering all adult human studies in English, published between January 2000 and February 2017.

Results: Cross-sectional analysis of endoscopy and pathology data-bases are consistently showing a trend toward an increase with age of the proportion of adenomas located in the proximal colon.

Several observational studies analysed the site distribution of adenomas, testing the hypothesis of a proximal shift of these lesions, and most of them reported an increase in the proportion of right-sided adenomas over time, although a similar trend was not confirmed by others. Also the quality of the retrieved evidence was low. Both endoscopy and FIT are showing a different level of sensitivity for lesions arising in different colonic segments, depending also on screenees characteristics.

Conclusion: Available evidence is supporting the hypothesis of an increase in the proportion of right-sided adenomas with age, while a similar increase has not been reported for SSP/A, at least among subjects aged 50 or older. The trend toward a proximalization of colorectal adenomas over time, reported by some authors, likely results from improved diagnostic performances and/or the process of population ageing.

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Introduction

Most colorectal carcinomas (CRCs) are presumed to arise from pre-malignant polyps. Approximately 70% grow from adenomatous polyps, progressing from early low-risk lesions to advanced adenomas (size ≥ 10 mm, or high-grade dysplasia, or villous component $> 20\%$) and eventually to CRC, over a period of 10–15 years (the well-characterized chromosomal instability pathway, [1]). Based on strong evidence, derived both from molecular and epidemiological studies, accumulated over the past two decades, an important role is now recognized for the serrated neoplasia pathway, accounting

for approximately 30% of CRCs [2], and in particular for a high proportion of lesions located in the right colon.

In recent years the removal of adenomatous polyps, in particular advanced adenomas, has been proposed as the most relevant target for screening interventions [3]. Indeed, the association of adenoma detection with the reduction of CRC incidence and mortality is now proven by the results of the randomized trials (RCTs) of sigmoidoscopy (FS) screening [4–7]. This same mechanism can explain the observed CRC incidence reduction with sensitive gFOBT [8], or with FIT [9], attributed to endoscopic removal of advanced adenomas detected among subjects with a positive test result.

During the past decades several reports described a trend toward an increased frequency of tumours in proximal colonic segments [10–12]. It remains unclear whether the observed shift may results from a true increase in the incidence of right-sided lesions,

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possibly related to a change in the risk factors, or whether it just reflects easier access to TC and improved quality of the diagnostic process, eventually combined with population ageing. Studies analysing TC data-bases are generally reporting an increase in the proportion of proximal lesions, attributed to proximal shift of CRC, while those analysing time trends of CRC incidence, based on data from large population cancer registries, are attributing the proximal shift to the process of population ageing [13,14], which is combined, in some jurisdictions, to a decreased prevalence of distal CRC, [13,15].

Most data concern the proximal shift of CRC, but, given the documented link between adenomas and CRC, a proximal migration of adenomas over time could be expected as well.

The publication of the results of the RCTs of 'once-only' FS screening, showing a significant reduction of CRC incidence and mortality [4–7], contributed to raise the interest on this issue. Although different criteria have been adopted in those RCTs for classifying individuals at increased risk for proximal neoplasia, based on distal findings, subjects with negative FS, or with low-risk distal lesions, were not referred for TC. Therefore, it is clear that a trend towards an increase of the incidence of proximal CRCs would tend to reduce the protective effect of FS.

The aim of this review is to evaluate available evidence about the prevalence of adenomas and sessile serrated polyps (SSA/P) across colonic segments, the modification of their topographic distribution across the colon and the diagnostic performance of screening tests currently adopted in population based screening programs for lesions located in different colonic segments.

Methods

We performed a literature search on PubMed, Embase, and Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects with reference to preferred reporting items for systematic reviews and meta-analysis (PRISMA) [16]. We considered all adult human studies in English, published between January 2000 and February 2017. The related articles were also scrutinised and the reference lists of the included studies were manually explored for additional supporting articles. Meta-analyses were prioritised and, when recent meta-analyses, or systematic reviews, were identified, the included studies were not reported individually. Conference abstracts were excluded. The details of the search strategy and the PRISMA flow diagram are reported in Appendix 1.

Reports of studies conducted among people younger than 50, or among high-risk subjects (positive family history for CRC, or personal history of CRC, adenomas, inflammatory bowel disease) were excluded, as these subjects would not be targeted by screening interventions.

Only FIT has been considered when assessing performance of fecal tests, as it has been recommended as the test of choice for mass screening interventions [17] and most population programs, which have been offering screening with gFOBT, are now planning to adopt FIT [18]. Moreover, comparative studies documented a higher sensitivity for advanced adenomas of FIT as compared to gFOBT [17].

FS performance was assessed based on the results of the published trials and of studies simulating the yield of FS screening among subjects undergoing screening TC.

Results of the bibliographic searches

After removing duplicates, 1132 articles were found, 71 were considered potentially relevant and acquired in full text and 50 [12,19–67] of them were included in this review. Ten additional papers [68–77] were added following scrutiny of related articles.

Results

Anatomical distribution of adenomas and SSA/P

Descriptive data about the distribution of adenomas and SSA/Ps have been reported by cross-sectional studies analysing TC and/or pathology databases (Table 1).

The prevalence of proximal adenomas varied between 24% [19] and 54% [20] among Hispanic and Caucasian subjects, aged ≥ 50 years, undergoing screening, surveillance, or diagnostic TC, in US academic centres [19–21]. The proportion of isolated proximal adenomas varied between 28% and 39% and it was similar in the two groups.

No difference between Caucasian and Hispanic patients was reported from a survey of the CORI data-base, analysing the distribution of large (≥ 10 mm) adenomas [22]: the prevalence of these lesions was 6% over the entire colon and 3% when considering only the proximal segments.

The proportion of right-sided polyps (including hyperplastic and adenomatous polyps) was 69.9% among US adults (age ≥ 50) who underwent TC between 2002 and 2012, according to a descriptive report, based on a regional pathology registry. Isolated right-sided polyps exceeded 55% of proximal lesions, both among men and among women, already at age 50–59. No information were however available about patients race/ethnicity, or about indications for the exams, while some patients were likely included more than once, if they had undergone repeat TCs over the 10-year period [23].

A higher prevalence of proximal hyperplastic and adenomatous polyps among African Americans, as compared to Caucasians, was reported from a cross-sectional review [24] of the charts of patients who had polyps excised at TC, in a US health care centre over a 3-year period. Indications for TC included screening, post-polypectomy surveillance, or diagnostic assessment following a positive screening test result (gFOBT or FS).

Other surveys of endoscopy reports from Australia and Spain showed lower prevalence figures (<25%) for proximal adenomas among older adults [25,26].

Cross-sectional surveys from Asia [27–29] showed as well a higher prevalence of distal adenomas, making up about 65% of all adenomas detected among asymptomatic subjects aged ≥ 50 years.

The findings of a recent study [30] comparing prevalence, histology, site distribution and shape of colorectal neoplasia in patients aged 50 to 69, undergoing TC screening in two teaching hospitals, in South Korea and US, would support the hypothesis of different patterns of adenoma distribution between Asian and US subjects. Although the overall prevalence of colorectal neoplasia was similar, South Korean screenees showed a lower risk of proximal neoplasia and flat adenomas, compared with their U.S. counterparts.

Among serrated lesions, SSA/P (with and without dysplasia) and traditional serrated adenomas (TSA) are considered pre-malignant lesions, while hyperplastic polyps (HPs) are generally considered of less clinical importance, especially if diminutive and located in the distal colon. TSAs represent <1% of serrated lesions and they are mainly located in the distal colon, while SSA/Ps account for 20–35% of all serrated lesions and they are mainly located in the proximal colon, usually showing a flat, or sessile, morphology [71].

In an average risk cohort of subjects undergoing TC screening in two US academic centres, between 2000 and 2009, the proportion of exams with at least one proximal serrated polyp (including HP, TSA and SSA/P) was 13% [31]. A recent prospective analysis of TC findings from an academic centre with high adenoma detection rate (ADR) and experienced gastrointestinal pathologists, reported

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