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Review

# Is right-sided colon cancer different to left-sided colorectal cancer? – A systematic review

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**Abstract**

Colorectal cancer (CRC) exhibits differences in incidence, pathogenesis, molecular pathways and outcome depending on the location of the tumor. This review focuses on the latest developments in epidemiological and scientific studies, which have enhanced our understanding on the underlying genetic and immunological differences between the proximal (right-sided) colon and the distal (left-sided) colorectum. The different ways in which environmental risk factors influence the pathogenesis of CRC depending on its location and the variations in surgical and oncological outcomes are also discussed in this review. In the current era of personalized medicine, we aim to reiterate the importance of tumor location in management of CRC and the implication on future clinical and scientific research.


*Keywords:* Colorectal cancer; Subsite; Classification; Environmental exposure; Pathology

## Introduction

In the current era of personalized medicine, colorectal cancer (CRC) is no longer regarded as a single entity. Colorectal cancer research has concentrated on providing more effective treatment, resulting in advancement in the knowledge of the genetic and molecular mechanism of carcinogenesis.

Bufill et al. started describing CRC depending on the anatomical site.[1] This was an attempt to sub-classify CRC as clinical data showed disparities in incidence and outcome between right-sided and left-sided colon cancer. Subsequent research has described the distinct differences in epidemiology, pathogenesis, genetic and epigenetic alterations, molecular pathways and outcome depending on the anatomical site of tumor. Currently, there is a general consensus that anatomical site is an important factor in management of CRC.

In this review, we aim to present the recent findings and discuss the implications for future research in CRC. For the purposes of this review, proximal or right-sided colon cancer (RCC) will consist of cancers of the caecum, ascending and transverse colon up to the splenic flexure, and distal or left-sided colorectal cancer (LCRC) will consist of cancers of the descending and sigmoid colon and rectum, unless specified.

### *Search strategy and selection criteria*

We performed a systematic review with reference to preferred reporting items for systematic reviews and meta-analysis (PRISMA).[2] We identified relevant articles by searching EMBASE, MEDLINE, and Pubmed using a search strategy to identify reports with a combination of controlled vocabulary and text words related to 'colon'

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and 'colorectum' (neoplasia, carcinoma, tumor, metastasis, malignancy), and to 'site' or 'subsite'. Searches and cross-references were carried out using a 'similar articles' function and hand searches of articles identified. We included all adult human studies in English, published between September 1947 and January 2014. We identified all journal articles that assessed colorectal cancer classification by site in relation to prevalence, presentation, genetic, molecular aspects, immunology, environmental factors, and outcomes (long-term survival and oncological outcome). We did not include conference abstracts due to the insufficient data provided. We also manually explored the reference lists of the included studies for additional supporting articles.

Data were extracted by three independent reviewers (GHL, GM, AA). When recent meta-analyses or systematic reviews were identified, the included studies were not reported individually. Meta-analyses were prioritized, when available. To limit the number of references, the most relevant observational studies were selected. Studies discussing pathophysiological mechanisms were assessed in a narrative way, aiming to balance the arguments for and against different genetic, molecular and immunological hypotheses.

## Results

From 394 initial citations, we included 6 meta-analyses, 12 reviews, 62 observational studies and 7 additional supporting articles (see Fig. 1).

### *Anatomical and histological differences*

Anatomically, the right and left colon derives from different embryologic origin – proximal colon from midgut and distal colon and rectum from hindgut. The proximal colon receives its main blood supply from the superior mesenteric artery with its capillary network being multilayered. The distal colon is perfused by inferior mesenteric artery.

An aberrant crypt focus is a cluster of abnormally large colonic crypts, which are considered preneoplastic, and likely to be the precursor of both hyperplastic and adenomatous polyps.[3] The distribution of aberrant crypt foci is denser and more frequent in the rectum compared to the colon.[4] Additionally, crypts in distal colon are significantly longer and larger compared to those in the proximal colon.[5]

The distribution of mucin-associated M1 antigen, which corresponds to the incidence of mucinous carcinomas, is more frequent in the proximal colon compared to distal colon.[6] Mucinous adenocarcinoma of the colon is histologically characterized by abundant pools of extracellular mucin and is associated with microsatellite instability (MSI).[7,8]

### *Epidemiology and patient characteristics*

Historically, the incidence of LCRC has been higher than RCC, and the latest figures reported by the American Cancer Society confirms a higher proportion of LCRC (51%) compared to RCC (42%) in the US.[9]

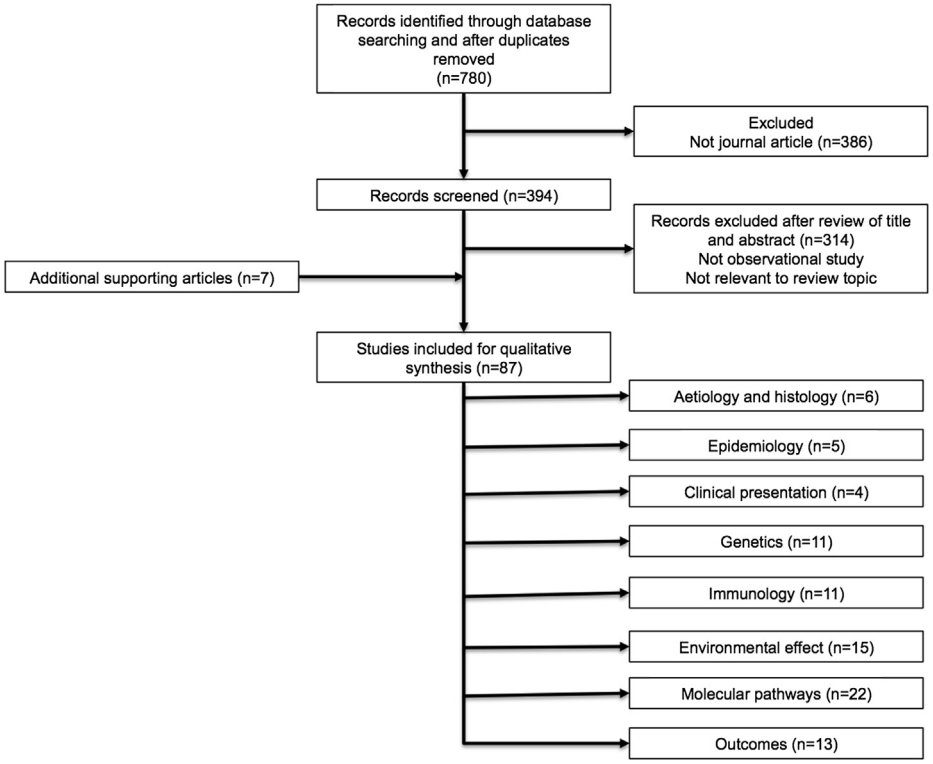


Figure 1. PRISMA diagram.