Genetics of Colorectal Cancer
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For Jeremy Jass: friend, teacher, scientist
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Contributors

Lisa A. Boardman  Division of Gastroenterology and Hepatology, Mayo Clinic
                  College of Medicine

Roberd M. Bostick  Department of Epidemiology, Rollins School of Public
                  Health, Emory University
                  rmbosti@sph.emory.edu

Graham Casey  Genetic Epidemiology Program, Department of Preventive
              Medicine, USC/Norris Comprehensive Cancer Center

James M. Church  Department of Colorectal Surgery, Cleveland Clinic

James T. Cross  Division of Public Health Sciences, Fred Hutchinson Cancer
               Research Center

Matthew J. Ferber  Department of Laboratory Medicine & Pathology,
                   Mayo Clinic College of Medicine

Steven Gallinger  Department of Surgery, Samuel Lunenfeld Research Institute,
                 Mount Sinai Hospital, University of Toronto
                 Steven.Gallinger@uhn.on.ca

Michael Goodman  Department of Epidemiology, Rollins School of Public
                 Health, Emory University

Joanna Groden  Department of Molecular Virology, Immunology and Medical
               Genetics, The Ohio State University College of Medicine.
               joanna.groden@osumc.edu

Robert Gryfe  Department of Surgery, Samuel Lunenfeld Research Institute,
              Mount Sinai Hospital, University of Toronto
              RGryfe@mtsaini.on.ca

Spring Holter  Dr. Zane Cohen Digestive Diseases Clinical Research Centre,
               Familial Gastrointestinal Cancer Registry, Mount Sinai Hospital,
               University of Toronto
               sholter@mtsaini.on.ca
David Hunter  Department of Epidemiology, Harvard University
david.hunter@channing.harvard.edu

Jeremy R. Jass  Department of Cellular Pathology, St Mark’s Hospital
jeremy.jass@nwlh.nhs.uk

Peter W. Laird  USC/Norris Comprehensive Cancer Center, Keck School of Medicine
plaird@usc.edu

Loïc Le Marchand  Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii
loic@crch.hawaii.edu

Noralane M. Lindor  Department of Medical Genetics, Mayo Clinic College of Medicine
nlindor@mayo.edu

Amy Y. Liu  Division of Public Health Sciences, Fred Hutchinson Cancer Research Center

Serena Masciari  Population Sciences Division, Dana-Farber Cancer Institute

Kara A. Mensink  Department of Laboratory Medicine & Pathology, Mayo Clinic College of Medicine
Mensink.Kara@Mayo.edu

Erin M. Perchiniak  Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University College of Medicine

Elizabeth M. Poole  Division of Public Health Sciences, Fred Hutchinson Cancer Research Center
epoole@fhcrc.org

John D. Potter  Cancer Prevention Research Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center
jpotter@fhcrc.org

Douglas L. Riegert-Johnson  Division of Gastroenterology and Hepatology, Mayo Clinic
riegertjohnson.douglas@mayo.edu

Beatriz Russell  Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University College of Medicine

Julian A. Sanchez  Department of Colorectal Surgery, Cleveland Clinic

Eduard Sidelnikov  Department of Epidemiology, Rollins School of Public Health, Emory University

Sapna Syngal  Familial Gastrointestinal Cancer Program, Dana-Farber Cancer Institute/Brigham and Women’s Cancer Center
ssyngal@partners.org
Brittany C. Thomas  Department of Laboratory Medicine & Pathology, Mayo Clinic College of Medicine
thomas.brittany@mayo.edu

Cornelia M. Ulrich  Division of Public Health Sciences, Fred Hutchinson Cancer Research Center
nulrich@fhcrc.org

Joanne P. Young  Cancer Council, Queensland Institute of Medical Research
Joanne.Young@qimr.edu.au
Introduction

Colorectal cancer (CRC) is among the most common cancers in western populations and indeed, increasingly, all over the world. There are several known modifiable risk factors for CRC and, for a number of well-characterized inherited syndromes where the phenotype includes CRC, germline genetic mutations are known. Polyps with varying histology (but mostly adenomas) are established preneoplastic lesions, the accessibility of which, to endoscopy, allows, simultaneously, effective screening, early diagnosis, and treatment. Endoscopy and histopathology have also facilitated the emergence of an increasingly clear picture of the molecular steps to cancer down several paths.

This volume is focused on the current picture of genetics in CRC – both inherited and acquired – and the ways in which the inherited lesions influence risk directly, as well as how they interact with the environment; the ways in which molecular progression occurs; and the possible insights into prevention, early diagnosis, and treatment that the knowledge of genetics provides.

The book is divided into four parts. In the first section, we describe the epidemiology of CRC, paying particular attention to what is known about behavioral, dietary, and host-related risk factors, and we examine the murine models of CRC which provide useful insights into prevention, progression, and potential therapy.

In Sect. 2, we present overviews of the molecular pathways to CRC, describing in detail the major pathways: the chromosomal-instability pathway involving mutations in the APC gene, the DNA-methylation pathway involving widespread epigenetic alterations, and the DNA mismatch repair pathway with its signature microsatellite instability. Chapter 3 in this section describes, in detail, the relationships between the pathways to progression and pathology.

The third section provides a detailed discussion of the known major and minor CRC syndromes, not only familial adenomatous polyposis and Lynch syndrome, but also MUTYH-associated polyposis (MAP), familial CRC type X, serrated neoplasia of the colon, Peutz–Jeghers syndrome, juvenile polyposis, germline mutations in p53, and BLM-related CRC. The recent association studies involving chromosomes 8q24 and 9p24 are also highlighted.

The final section presents what is known about interactions between polymorphisms in several metabolic and nutrition-related pathways and established environmental risk and protection factors for CRC. Specific chapters focus on
folate-mediated one-carbon metabolism, on genetic variability in NSAID targets and NSAID-metabolizing enzymes, on biotransformation of chemical carcinogens, and on calcium and vitamin D.

CRC continues to provide enormous challenges because of its high incidence and its important contribution to cancer mortality. However, it also contrasts with a number of the other common cancers, inasmuch as we know that early detection, particularly via colonoscopy, reduces incidence considerably. Finally, we also know a great deal about the roles of genetics and the environment in causing and protecting against CRC.