In the memory of
Dr. Eldon J. Gardner

Joji Utsunomiya Henry T. Lynch (Eds.)

Hereditary Colorectal Cancer

Proceedings of the Fourth International Symposium on Colorectal Cancer (ISCC-4)
November 9-11, 1989, Kobe JAPAN

With 97 Figures

Springer Japan KK

Joji Utsunomiya, M.D.
Professor and Chairman
Second Department of Surgery
Hyogo College of Medicine
1-1 Mukogawa-cho, Nishinomiya
Hyogo, 663 Japan

Henry T. Lynch, M.D.
Professor and Chairman
Department of Preventive Medicine
Creighton University School of Medicine
Hereditary Cancer Center
California at 24th Street
Omaha, NE 68178, USA

ISBN 978-4-431-68339-1 ISBN 978-4-431-68337-7 (eBook)
DOI 10.1007/978-4-431-68337-7

Originally published by Springer-Verlag Tokyo 1990
Softcover reprint of the hardcover 1st edition 1990

Foreword

Since the success in chemical induction of cancer in rabbit's ear skin by K. Yamagiwa in 1915, oncologists of the world have come to believe that they can only solve their problems by means of animal experimentation. The importance of environmental factors became more evident in 1935 when T. Yoshida and T. Sasaki introduced azodye hepatocarcinogenesis in rats. In the domain of the gastrointestinal tract, T. Sugimura has more recently accumulated enough evidence to indicate that locally active chemical mutagens are carcinogenic.

In contrast, principal approaches to colorectal tumors have been quite different: emphasis has been placed on gene identification. Long before cancer of the large bowel was recognized, importance of the roles of adenomatosis coli and its familial occurrence attracted the attention of epidemiologists and geneticists. Morphological characterization and analysis of hereditary trends of human material have already had a long history, and recently detailed analysis of genetic material has become feasible in the wake of rapid development in our knowledge of the oncoviruses, oncogenes, suppressor genes, chromosomal and DNA mapping, molecular mutation and so on. It is true that in colorectal pathology, and in no other field, these areas of research have been explored more extensively and decisively. The identification of previously ill-defined lesions such as precancers and benign neoplasms have been improved because sequential changes can be observed in multiple samples spread over a wide area and followed up in due course.

Multidisciplinary approaches with close cooperation of surgeons, pathologists, molecular biologists, geneticists, and epidemiologists among others, have contributed greatly to recent developments and will surely continue to do so in the immediate future. The organization of the present conference and gathering of global experts owe much to the efforts of Prof. J. Utsunomiya who has dedicated many years to the compilation of genetic-epidemiological data in Japan, especially with reference to the adenomatosis. This publication coedited by Prof. J. Utsunomiya and Prof. H.T. Lynch represents another step foreward toward solving remaining problems in this field.

Kunio Oota, M.D.
President, Japanese Association
of Medical Sciences

Preface

Three International Symposia on Colorectal Cancer, organized under the Chairmanship of Dr. Sydney J. Winawer, and held at New York (1979). Washington (1981), and Boston (1983) respectively, had the following topics as their themes: (1) Prevention, Epidemiology, and Screening, (2) Risk Factors and Screening, and (3) Policy for Prevention.

As a sequel to this series of meetings, we had the opportunity of organizing the Fourth International Symposium on Colorectal Cancer, held in Kobe, Japan, on November 9–11, 1989 with the specific theme of "Hereditary Colorectal Cancer." This topic is very timely, because of the imminent convergence of the fields of clinicoepidemiology and molecular genetics: the knowledge of colorectal cancer, accumulated through patient and persistent observations over many decades, has now reached a level at which the merging of incisive ideas and updated technology developed recently in molecular genetics promises to spark breakthroughs in major problems in cancer.

Under the term "Hereditary Colorectal Cancer," we include the presently recognized heritable conditions known to be predisposed to colorectal cancer, which can be roughly classified into the polyposis syndromes and hereditary nonpolyposis colorectal cancer (HNPCC). We have particularly focussed upon: (1) identification, surveillance, and management of HNPCC especially; (2) chemoprevention in theory, research, and practice; and (3) clinicopathological and cytomolecular aspects for better understanding of the etiology and pathogenesis of the conditions; these aspects include: (a) clinical spectra; (b) histopathological diversity; (c) genetic heterogeneity; (d) genetic markers and linkage studies; (e) markers for presymptomatic diagnosis; and (f) cloning and characterization of relevant gene sequences.

The aim of the symposium was to create and maintain an active workshop spirit throughout the meeting in order to generate in-depth discussions between experts in the range of disciplines which have impact upon the field. Spontaneity was encouraged so that new frontiers of knowledge might be developed freely in an intellectually challenging atmosphere.

The three-day symposium began with two plenary sessions which included 10 "state-of-the-art" lectures. This was followed by the workshops, which comprised 75 papers in 6 sessions, organized as two parallel series: one focussed upon genetic epidemiology and clinical features,

while the other delved more heavily into basic science, particularly biomolecular genetics and pathology. Finally, these workshops were summarized by the respective chairpersons, with the primary intent of forecasting future research.

The program and content of this meeting were planned after painstaking discussions among the members of the several planning committees. These interdisciplinary interactions representing diverse fields contributed to the truly eclectic atmosphere which permeated the meeting. The symposium was attended by 70 distinguished speakers from an array of disciplines, including 18 from medicine, gastroenterology, and radiology, 18 from medical and biomolecular genetics, 16 from surgery and gynecology, 10 from pathology and biology, and 4 from epidemiology and biostatistics. These colleagues are from 15 different countries: 25 from the United States, 15 from Japan, 7 from the United Kingdom, 5 from Italy, 3 from the Netherlands, 2 from Denmark, and 1 each from Australia, Canada, Finland, France, Greece, Israel, New Zealand, Poland, and Sweden. Approximately 50 observers, mainly Japanese, joined in active discussion throughout the symposium.

This symposium was dedicated to the memory of Dr. Eldon J. Gardner, who contributed so much during most of his lifetime to the study of hereditary colorectal cancer. Dr. Gardner passed away during the period of conception of this symposium, and his contributions are greatly missed.

Joji Utsunomiya
Henry T. Lynch

Organization of the Fourth International Symposium on Colorectal Cancer

International Committee:
Chairman: Joji Utsunomiya, Japan
Co-chairman: Henry T. Lynch, USA

Sidney J. Winawer, USA	Bruce M. Boman, USA
Paul Rozen, Israel	Martin Lipkin, USA
Sir Walter F. Bodmer, UK	Yusuke Nakamura, Japan
Giuseppe Cristofaro, Italy	Stig Kullander, Sweden
P. Meera Khan, The Netherlands	Raymond L. White, USA

Local Organizing Committee:

Shozo Baba	Takesada Mori	Akira Tonomura
Junichi Furuyama	Tetsuichiro Muto	Kei Takebe
Shinzo Isojima	Masao Sasaki	Ryukichi Tobe
Keiichi Kawai	Takehiko Sasazuki	Masayuki Yasutomi
Kozaburo Kimura	Takashi Shimoyama	Yutaka Yoshida
Yoshio Mishima		

Local Consultant Board:

Takeshi Hirayama	Kyoichi Nakamura	Takashi Sugimura
Shuji Kimura	Yasuaki Nishizuka	Shuji Tsuchiya
Isamu Kinoh	Kunio Oota	Hidenobu Watanabe
Goro Kosaki	Haruo Sugano	

Sponsored by:
The International Committee or ISCC-4 at Hyogo College of Medicine

Co-sponsored by:
WHO Collaborative Center for Prevention of Colorectal Cancer at Memorial Sloan-Kettering Cancer Center, New York, USA

Imperial Cancer Research Fund London, UK
Creighton University, Omaha, USA
University of Utah Medical Center, USA
Dutch Colorectal Genetics Group, University of Leiden Medical Center, The Netherlands
The Hereditary Gastrointestinal Cancer Prevention Center, Brindisi, Italy
Japanese Association of Medical Sciences
Japanese Research Society for Colorectal Cancer

List of Contributors*

NIKI AGNANTIS, M.D.
National Hellenic Research Foundation, Biological Research Center,
48, Vas, Constantinou Avenue, Athens 11635, Greece

SHOZO BABA, M.D.
Second Department of Surgery, Hamamatsu College of Medicine,
3600, Handa-cho, Hamamatsu-shi, Sizuoka-ken, 431-31 Japan

LUCIO BERTARIO, M.D.
Institution Nazionale per lo Studio e la cura dei Tumori,
Via Venezian 1, 20133 Milan, Italy

TIM BISHOP, PH.D.
Genetic Epidemiology Laboratory, Imperial Cancer Research Fund,
3K Springfield House, Hyde Terrace, Leeds LS2 9LU, UK

SIR WALTER BODMER, PH.D.
Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields,
London WC2A 3PX, UK

C. RICHARD BOLAND, M.D., PH.D.
Department of Internal Medicine, University of Michigan,
Medical Center, Veterans Administration Hospital,
3912 Taubman Center, Box 0362, Ann Arbor, MI 48109-0362, USA

BRUCE M. BOMAN, M.D., PH.D.
Creighton Cancer Center, Department of Medicine, Creighton
University School of Medicine, The Hereditary Cancer Center,
Criss III, Room 353, California at 24th Street, Omaha, NE 68178, USA

PHILIP BRALOW, M.D.
Graduate Hospital, University of Pennsylvania, Graduate Hospital,
Philadelphia, PA 19146, USA

PANTALEO BUFO, M.D.
Instituto di Anatomia e istologia Patologica, Bari University,
70100 Bari, Italy

*First-mentioned author only

STEFFEN BÜLOW, M.D., PH.D.
The Danish Polyposis Register, Deptartment of Surgery, Gastroenterology, Hvidovre University Hospital, DK 2650, Hvidovre, Denmark

RANDALL W. BURT, M.D.
Department of Medicine, Division of Gastroenterology, University of Utah, 4R118 Medical Center, Salt Lake City, UT 84132, USA

MITSURO CHIBA, M.D.
First Department of Internal Medicine, University of Akita, 1-1-1, Honmichi, Akita, 010 Japan

JAMES CHURCH, M.D., CH.B.
Department of Colorectal Surgery, Desk A-111, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA

GIUSEPPE CRISTOFARO, M.D.
Hereditary Gastrointestinal Cancer Prevention Center, Via de Terrible 9, 72100 Brindisi, Italy

JEROME J. DECOSSE, M.D., PH.D.
Department of Surgery, Hospital Cornell Medical Center, Cornell University Medical College, 525 E 68 Street, New York, NY 10021, USA

EMILIO DI GIULIO, M.D.
Institute of Surgery, University of Rome "La Sapienza", Viale Regina Elena 324, 00161 Rome, Italy

DAVID L. ERNEST, M.D.
University of Arizona, 1515, N. Campbell Avenue, Tucson, AZ 85724, USA

ANDREW P. FEINBERG, M.D., M.P.H.
Howard Hughes Medical Institute, University of Michigan Medical Center, MSRBI Room 4520, 1150 W. Medical Campus Drive, Ann Arbor, MI 48109, USA

ROBERT J. FITZGIBBONS JR., M.D.
Department of Surgery, Creighton University School of Medicine, The Hereditary Cancer Center, 601 N. 30 Steet, Omaha, NE 68131, USA

EILEEN A. FRIEDMAN, PH.D.
Department of Gastroenterology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 244, New York, NY 10021, USA

ANNA-MARIA FRISCHAUF, PH.D.
Molecular Analysis of Mammalian Lab., Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, UK

GERRIT GRIFFIOEN, M.D.
Department of Gastroenterology, University Hospital,
Rynsburger Weg 10, 2333AA, Leiden, The Netherlands

STANLEY R. HAMILTON, M.D.
Department of Pathology and Oncology Center, The Johns Hopkins
Medical Institute, Baltimore, MD 21205, USA

LEMUEL HERRERA, M.D., M.AQ., F.A.C.S.
Roswell Park Memorial Institute, State University of N.Y at Buffalo,
666 Elm Street, Buffalo, NY 14263, USA

TAKESHI HIRAYAMA, M.D.
Institute of Preventive Oncology, 1-2, Ichigaya Sadohara-cho,
Shinjuku-ku, Tokyo, 162 Japan

TATSURO IKEUCHI, M.D.
Tokyo Medical and Dental University, Medical Research Institute,
1-5-45, Yushima, Bunkyo-ku, Tokyo, 113 Japan

TAKEO IWAMA, M.D.
Tokyo Medical and Dental University, The Research Center for
Polyposis and Intestinal Disease, 1-5-45, Yushima, Bunkyo-ku,
Tokyo, 113 Japan

JEREMY R. JASS, M.D.
University of Auckland School of Medicine, Private Bag, Auckland,
New Zealand

P. MEERA KHAN, M.D., PH.D.
Human Genetics Institute, University of Leiden, Sylvius Laboratories,
Wassenaarseweg 72, P.B. 9503, 2300 RA Leiden, The Netherlands

YOUNG S. KIM, M.D.
Gastroint. Research Laboratory, University of California,
Medical Center, 4150 Clement Street, San Francisco, CA 94121, USA

LEVY KOPELOVICH, PH.D.
VA Medical Center, Bay Pines, Florida, University of South Florida,
College of Medicine, Research Service (151), Bay Pines, FL 33504, USA

PIOTR KROKOWICZ, M.D.
Newton Street 16a/4260-161, Poznan, Poland

STIG KULLANDER, M.D.
Department of Obstetrics and Gynecology, University of Lund,
Malmo General Hospital, Malmo, Sweden

STEPHEN J. LANSPA, M.D., F.A.C.P.
Department of Medicine-Gastroenterology, Creighton University,
School of Medicine and Hereditary Cancer Consultation Center,
California at 24th Street, Omaha, NE 68178, USA

BERNARD LEVIN, M.D.
Gastrointestinal Oncology, MD Anderson Cancer Center,
The University of Texas, 1515 Holcombe, Blvd., Houston, TX 77030,
USA

MARTIN LIPKIN, M.D.
Memorial Sloan Kettering Cancer Center, Cornell University Medical
College, 1275 York Avenue, New York, NY 10021, USA

HENRY T. LYNCH, M.D.
Department of Preventive Medicine, Creighton University School of
Medicine, The Hereditary Cancer Center, California at 24th Street,
Omaha, NE 68178, USA

JANE F. LYNCH, B.S.N.
Department of Preventive Medicine, Creighton University School of
Medicine, The Hereditary Cancer Center, California at 24th Street,
Omaha, NE 68178, USA

PATRICK M. LYNCH, M.D.
Department of Gastroenterology, MD Anderson Hospital and
Tumor Institute, 1515 Holcombe Blvd., Houston, TX 77030, USA

FINLEY MACRAE, M.D., F.R.A.C.P., M.R.C.P.
Department of Gastroenterology, The Royal Melbourne Hospital,
Post Office, Royal Melborne Hospital 305D, Victoria, Australia

PIETRO L. MINGAZZINI, M.D.
Department of Biopathology, University of Rome "La Sapienza",
Viale Regina Elena 324, 00161 Rome, Italy

YOSHIO MISHIMA, M.D.
Second Department of Surgery, Tokyo Medical and Dental University,
1-5-45, Yushima, Bunkyo-ku, Tokyo, 113 Japan

MICHIKO MIYAKI, M.D.
The Tokyo Metropolitan Institute of Medical Science,
3-18-22, Honn-Komagome, Bunkyo-ku, Tokyo, 113 Japan

TETSUICHIRO MUTO, M.D.
First Department of Surgery, The University of Tokyo,
7-3-1, Hongo, Bunkyo-ku, Tokyo, 113 Japan

YUSUKE NAKAMURA, PH.D.
Cancer Institute, 1-37-1, Kamiikebukuro, Toshima-ku, Tokyo,
170 Japan

TOMIO NARISAWA, M.D.
First Department of Surgery, University of Akita, 1-1-1, Honmichi,
Akita, 010 Japan

CHRISTOS PARASKEVA, PH.D.
Department of Pathology, The Medical School, University Walk,
Bristol BS8 1TD, UK

GLORIA M. PETERSEN, PH.D.
Division of Medical Genetics, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048-1869, USA

PAUL ROZEN, M.B., B.S.
Department of Gastroenterology, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel

TAKEHIKO SASAZUKI, M.D.
Kyushu University, Medical Institute of Bioregulation, 3-1-1, Maide, Higashi-ku, Fukuoka, 812 Japan

PETER SCHLAG, M.D.
Chirurgische Universitätsklinik, Im Neuenheimer Feld 110, 6900 Heidelberg, Federal Republic of Germany

SILVANO SENATORE, M.D.
"Di Summa" Brindisi Hospital, 72100 Brindisi, Italy

JOAN SLACK, D.M., F.R.C.P.
Royal Free Hospital School of Medicine, Pond Street, Hampstead, London NW3 2QG, UK

THOMAS SMYRK, M.D.
Department of Pathology, Creighton University School of Medicine, 601N 30th Street, Omaha, NE 68131, USA

ELLEN SOLOMON, PH.D.
Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2A 3PX, UK

JENS O. SØNDERGAARD, M.D.
Department of Surgical, Gastroenterology, Hvidovre University, OK 2650, Hvidovre, Denmark

HARTLEY S. STERN, M.D., F.R.C.S.(C)
Mount Sinai Hospital, Suite 1225, 600 University Avenue, Toronto, Ontario, M5G 1X5, Canada

HIDEHO TAKADA, M.D.
Department of Surgery, Kansai Medical University, 1, Fumizono-cho, Moriguchi, Osaka, 570 Japan

GILLES THOMAS, M.D.
The Institute Curie, 26, Rue D'Ulm, 75231, Paris, CX5 France

CARLI M.J. TOPS, M.SC.
Human Genetics Institute, Silvius Lab., University of Leiden, P.B. 9503, 2300 RA Leiden, The Netherlands

YOSHIYUKI TSUJI, M.D.
Department of Obsterics and Gynecology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663 Japan

KYOSUKE USHIO, M.D.
National Cancer Center, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104 Japan

JOJI UTSUNOMIYA, M.D.
Second Department of Surgery, Hyogo College of Medicine,
1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663 Japan

HANS F.A. VASEN, M.D.
Foundation for the Detection of Hereditary Tumors,
P.O. Box 12009, 3501 AA Utrecht, The Netherlands

BERT VOGELSTEIN, M.D.
Research Laboratories, Room 109, Johns Hopkins Oncology Center,
424 N. Bond Street, Baltimore, MD 21231, USA

MICHAEL J. WARGOVICH, PH.D.
Section of Gastrointestinal Oncology and Digestive Diseases,
Box 78, MD Anderson Hospital and Tumor Institute,
1515 Holcombe Blvd., Houston, TX 77030, USA

HIDENOBU WATANABE, M.D.
First Department of Pathology, Niigata University, 754, Ichiban-cho,
Asahimachi-dori, Niigata, 951 Japan

PATRICE WATSON, PH.D.
Department of Preventive Medicine, Creighton University School of
Medicine, The Hereditary Cancer Center, California at 24th Street,
Omaha, NE 68178, USA

RAYMOND L. WHITE, PH.D.
Howard Hughes Medical Institute, University of Utah,
631 Wintrobe Bldg., UUMC, Salt Lake City, UT 84132, USA

RODGER J. WINN, M.D.
Department of Medicine, The University of Texas, MD Anderson
Cancer Center, TX 77030, USA

ANDREW H. WYLLIE, M.D.
Department of Pathology, University Medical School, Teviot Place,
Edinburgh EH8 9AG, UK

Table of Contents

Chapter 1: General Aspects of Hereditary Colorectal Cancer

The Concept of Hereditary Colorectal Cancer and the Implications of Its Study
J. Utsunomiya 3

Historical and Natural Cancer History Facets of the Lynch Syndromes
H.T. Lynch, S.J. Lanspa, T.C. Smyrk, R.J. Fitzgibbons Jr., P. Watson, B.M. Boman, J.F. Lynch, G. Cristofaro 17

Eldon Gardner Memorial Lecture: Genetic Mapping and Allelic Heterogeneity of the Familial Polyposis Gene
M. Leppert, Y. Nakamura, R. Burt, J.P. Hughes, W. Samowitz, S. Woodward, E. Gardner, J.-M. Lalouel, R. White 27

Hereditary Colorectal Cancer: A Commentary
W.F. Bodmer 37

Chapter 2: Identification, Surveillance, and Management of Polyposis Syndrome

Summary of Chapter 2: Identification, Surveillance and Management of Polyposis Syndrome
S. Bülow 45

Familial Adenomatous Polyposis Study: The Report of the Leeds Castle Polyposis Meeting
J.J. DeCosse 51

Surveillance of Danish Families with Adenomatous Polyposis: Results of the Danish Polyposis Register
S. Bülow 55

Value of Registration in the Identification and Surveillance of Familial Adenomatous Polyposis in the Netherlands
G. Griffioen, H.F.A. Vasen, F.C.A. den Hartog Jager, F.M. Nagengast, H.W. Verspaget, P.M. Khan, C.B.H.W. Lamers, E.A. van Slooten 57

Current Status of the Registration of Familial Adenomatous Polyposis at the Polyposis Center in Japan
T. Iwama, Y. Mishima, J. Utsunomiya 63

Management of Familial Polyposis in Poland
P. Krokowicz 71

The Probability of Developing Familial Adenomatous Polyposis: Combining the Diminishing Risks with Age with Negative Screening at Advancing Age and Linked Gene Markers
J. Slack 75

Follow-up Study of Associated Tumors in Cases of Familial Adenomatous Polyposis
K. Ushio 81

Retinal Pigmentations in Familial Adenomatous Polyposis, and Linkage Study on Gene Probes on Chromosome 5q
S. Baba, M. Tsuchiya, H. Machida, M. Yamada 91

Congenital Hypertrophy of the Retinal Pigment Epithelium: A Clinical Marker for Familial Adenomatous Polyposis
A. Romania, F. Heyen, D. Jagelman, J. Church, Z. Zakov, I. Lavery, V. Fazio, E. McGannon, J. Oakley 97

Chapter 3: Identification, Surveillance, and Management of Hereditary Nonpolyposis Colorectal Cancer

Summary of Chapter 3: Identification, Surveillance and Management of Hereditary Non-polyposis Colorectal Cancer
R.W. Burt 103

Hereditary Nonpolyposis Colorectal Cancer and Tumorigenesis in the Human Body
K. Ushio 107

Colonoscopy Findings in a Series of Patients with Hereditary Colorectal Cancer
S.J. Lanspa, H.T. Lynch, T.C. Smyrk, R.J. Fitzgibbons Jr., P. Watson, J.X. Jenkins 115

Extracolonic Cancer in Hereditary Nonpolyposis Colorectal Cancer
P. Watson, H.T. Lynch 119

Endometrial Cancer as Heterogenic Picture of HNPCC: Population-Based Studies in Sweden
S. Kullander 127

A Monoclonal Antibody C12 Against Endometrial Carcinoma, Recognize Polyfucosyl Lactosamine-Bearing Glycoprotein
Y. Tsuji 131

A Pedigree of Cancer Family Syndrome with an Aggregation of Transitional Cell Cancer of the Urinary Tract
M. CHIBA, Y. OHYAMA, O. MASAMUNE, T. KATO, K. SATO, T. NARISAWA, K. SOGA, R. KOIZUMI 135

Screening for Hereditary Non-polyposis Colorectal Cancer in the Netherlands
H.F.A. VASEN, F.C.A. DEN HARTOG JAGER, F.M. NAGENGAST, F.H. MENKO, G.J.A. OFFERHAUS, G. GRIFFIOEN 143

The Risks of Colorectal Cancer and the Frequency of Recognised Family Cancer Syndromes in 550 Sequential Referrals for Family Risk of Colorectal Cancer
J. SLACK 151

The Incidence of Colorectal Cancer Among First Degree Relatives of Patients with Colorectal Cancer
J.O. SØNDERGAARD, S. BÜLOW, E. LYNGE 157

Genetics of Adenomas
R.W. BURT, D.T. BISHOP 159

Surveillance of High Risk Individuals with Family History Using Guaiac Test (Hemoccult II)
L. BERTARIO, P. SALA, P. SPINELLI, L. GENNARI, G. BALLARDINI, M. VIDALE 163

Studies on Relatives of Sporadic Colorectal Cancer Patients
P. ROZEN, Z. FIREMAN, E. RON 169

Managing Surveillance for Colorectal Cancer: The Importance of Microcomputers
F.A. MACRAE, D.J.B. ST. JOHN, E. MUIR, S. MCPHERSON 175

Hereditary Non-polyposis Colorectal Cancer: The University of Texas MD Anderson Cancer Center Experience
P.M. LYNCH, R.J. WINN, M.J. WARGOVICH, B. LEVIN 185

Medical/Legal Concerns in the Management of Patients from Lynch Syndromes Kindreds
G. CRISTOFARO, E. DI GIULIO, P.L. MINGAZZINI, P. BUFO, S. SENATORE, P.M. LYNCH, P. WATSON, J.F. LYNCH, H.T. LYNCH 193

The Research Nurse/Family Contact Person and Hereditary Colon Cancer
J.F. LYNCH 203

Surgical Strategies for Management of the Lynch Syndromes
R.J. FITZGIBBONS, H.T. LYNCH, S.J. LANSPA, T. SMYRK, B. BOMAN, J. LYNCH, P. WATSON 211

An Attempt for Identification of Hereditary Nonpolyposis Colorectal Cancer in Japan
T. Sakiyama, Y. Sakanoue, Y. Miki, M. Kusunoki, J. Utsunomiya 219

Chapter 4: Chemoprevention of Colorectal Cancer

Summary of Chapter 4: Chemoprevention of Colorectal Cancer
M. Lipkin, P. Rozen 227

Primary and Secondary Chemoprevention of Colorectal Cancer
S.P. Bralow 231

Chemoprevention of Large Bowel Cancer in Animal Models and Its Possibility in Humans
T. Narisawa, M. Takahashi, N. Kusaka, Y. Yamazaki, H. Koyama, H. Kotanagi, Y. Fukaura 239

Inhibitory Effect of Eicosapentaenoic Acid on Colon Carcinogenesis
H. Takada, T. Minoura, T. Takata, M. Sakaguchi, K. Yoshioka, M. Yamamura, K. Hioki, M. Yamamoto 249

Life Styles and Cancer of the Sigmoid Colon with Special Reference to the Role of Alcohol Consumption
T. Hirayama 257

Calcium Regulation of Colon Epithelial Cytokinetics in High Risk Subjects for Colon Cancer: Application of New Proliferation Markers
M.J. Wargovich, B. Levin, P. Lynch, H. Sumiyoshi, A. Baer, G. Isbell, P.-J. Hu, L. Roubein, R. Winn 265

Ornithine Decarboxylase (ODC) and S-Adenosylmethionine Decarboxylase (AdoMetDC) as Markers of Human Colonic Neoplasia
L. Herrera, N.J. Petrelli, G. Vial 271

Dietary Fiber or Piroxicam as Potential Cancer Prevention Agents: Effects on Rectal Epithelial Cell Proliferation in Humans at Increased Risk of Colon Cancer
D.L. Earnest, D.S. Alberts, L.J. Hixson, F.L. Meyskens 275

Long-Term Effects of Dietary Calcium on Risk Markers for Colon Cancer in Familial Polyposis Patients
H.S. Stern, R.C. Gregoire, H. Kashtan, T. Berk, W.R. Bruce 283

Chemoprevention Using Wheat Fiber and Vitamins C and E in Patiants with Familial Adenomatous Polyposis
J.J. DeCosse, J.S. Jacobson 293

Orinithine Decarboxylase (ODC) and S-Adenosylmethionine Decarboxylase (AdoMetDC) as Markers in Human Colonic Neoplasia
L. Herrera, N.J. Petrelli, G. Vial 301

Chemoprevention Trials in Patients with Familial Adenomatous Polyposis (FAP) at Roswell Park Cancer Institute
L. Herrera, T.M. Speers 307

Chapter 5: Clinicopathological Aspects of Hereditary Colorectal Cancer Syndrome

Summary of Chapter 5: Clinicopathological Aspects of Inherited Colorectal Cancer Syndromes
S.R. Hamilton 315

Pathology of Gastroenteric Lesions in Familial Adenomatosis Coli
H. Watanabe, M. Iida, M. Iwafuchi, Y. Ajioka, Y. Noda, T. Motoyama 321

The Peutz-Jeghers Syndrome and Malignant Tumor
T. Iwama, H. Ishida, M. Imajo, K. Takemura, N. Aoki, Y. Mishima 331

Histogenesis of Gastrointestinal Carcinoma in Peutz-Jeghers Polyp
H. Watanabe, Y. Ajioka, M. Iwafuchi, T. Motoyama, N. Ishihara, J. Hitomi 337

Pathology of Polyposis Syndromes with Special Reference to Juvenile Polyposis
J.R. Jass 343

Clinicopathologic Features of Flat Adenoma of the Large Bowel
T. Muto, M. Adachi, K. Sugihara, T. Sawada, T. Masaki, Y. Morioka 351

Histologic Features of Hereditary Nonpolyposis Colorectal Carcinoma
T.C. Smyrk, H.T. Lynch, P.A. Watson, H.D. Appelman 357

Crypt Atrophy of Colorectal Mucosa in Lynch Syndromes I and II: Its Characteristics and Meaning, Preliminary Observations
P. Bufo, F. Frassanito, H. Müller, G. Cristofaro, S. Senatore, H.D. Appelman, H.T. Lynch 363

Cellular Immune Response in Lynch Syndrome II on Gastrointestinal Biopsy
S. Senatore, M. Longo, G. Cristofaro, G. Capano, M. Tancredi, F. Deta, C. Blasi, S. Rinaldi, P. Bufo, E. di Giulio, H.T. Lynch 369

Glycoconjugate Expression in Familial Colorectal Cancer: Polyposis Syndromes and Hereditary Nonpolyposis Syndromes
C.R. Boland 377

Carbohydrate Associated Antigens in Neoplastic and Preneoplastic Colon
Y.S. Kim 387

Interphasic Nucleolar Organizer Regions in Colorectal Dysplastic and Neoplastic Lesions
P.L. Mingazzini, L. Scucchi, D. di Stefano, A.F. Malchiodi, F. Ciaralli, M. Falchi, G. Cristofaro 393

Cultured Skin Fibroblasts from Hereditary Colorectal Cancer Patients: Susceptibility Mechanisms, Genetics, and Biomarkers
L. Kopelovich 399

Chapter 6: Cytomolecular Aspects of Polyposis

Summary of Chapter 6: Cytomolecular Aspects of Polyposis
P.M. Khan 413

Two Cases of Familial Adenomatous Polyposis Associated with Mental Retardation
M. Chiba, R. Ito, O. Masamune, T. Waga, S. Sato 417

Pedigree Analysis of Susceptibility to Colonic Adenomas
D.T. Bishop, L.A. Cannon-Albright, R.W. Burt, M.H. Skolnick 423

Genetic Linkage Study of Juvenile Polyposis: Preliminary Analysis
G.M. Petersen, J. Brown, X. Bu, R.S. Sparkes, Y. Nakamura 431

Linkage Studies on Familial Adenomatous Polyposis in the Netherlands
C.M.J. Tops, C. Breukel, J.T. Wijnen, H.M. van der Klift, I.S.J. van Leeuwen-Cornelisse, H.F.A. Vasen, G. Griffioen, F.C.A. den Hartog Jager, C.B.H.W. Lamers, P. M. Khan 433

Genetic Counseling for Familial Adenomatous Polyposis with Chromosome 5q Linkage Information
G.M. Petersen, T. Shohat, J. Brown, Y. Nakamura 441

Allele Loss and Kras Mutation Involved in the Development of Colorectal Tumors in Patients with Familial Adenomatous Polyposis
M. Miyaki, M. Seki, M. Okamoto, C. Sato, K. Tanaka, A. Yamanaka, M. Koike, T. Mori, J. Utsunomiya, T. Iwama ... 445

Status of the APC Gene in Familial and Sporadic Colorectal Tumours as Determined by Closely Flanking Markers
A.H. Wyllie, P. Ashton-Rickardt, M.G. Dunlop, Y. Nakamura, J. Piris, C. Purdie, C.M. Steel, C.C. Bird 453

Strategies for Cloning the Gene for Adenomatous Polyposis Coli
L. Varesco, H. Thomas, J.R.T. Ward, E. Solomon, A.-M. Frischauf 457

Genetic and Molecular Analysis of Familial Polyposis Coli
T. Sasazuki, K. Sugio, M. Sasaki, Y. Yanagawa, K. Urabe 461

Searching the Gene Responsible to Familial Polyposis Coli (FAP)
Y. Nakamura, J. Wasmuth, R. White 469

Chapter 7: Cytomolecular Aspects of Colorectal Cancer

Summary of Chapter 7: Cytomolecular Aspects of Colorectal Cancer
Y. Nakamura, R.L. White 475

Genetic Alterations in Colorectal Tumors
K.R. Cho, B. Vogelstein 477

Ras and c-*myc* Oncoprotein Expression in Human Colorectal Tumors
N.J. Agnantis, D.A. Spandidos 483

Molecular Analysis of the Retinoblastoma (Rb) Gene in Human Colorectal Carcinomas
R. Gope, M.A. Christensen, A. Thorson, H.T. Lynch, T. Smyrk, M.L. Gope, B.M. Boman 489

Cellular and Molecular Events Involved in Tumour Progression in Colorectal Carcinogenesis:
A Study of the Adenoma Carcinoma Sequence In Vitro
C. Paraskeva, S. Finerty, S. Harper, A.C. Williams 497

Genetic Alterations in Colorectal Cancers in Correlation to Clinical Parameters
M. Schwab, S. Brüderlein, K. van der Bosch, A. Weith, I. Leister, C. Cziepluch, L. Amler, P. Schlag 509

Clinical and Pathological Associations with Molecular Genetic Alterations in Colorectal Carcinoma
S.R. Hamilton, S.E. Kern 517

A Subset of Genetic Alterations Distinguish Distal from Proximal Colorectal Cancer
S. Olschwang, O. Delattre, H. Leroy, Y. Remvikos, T. Melot, D.J. Law, A.P. Feinberg, G. Thomas 519

Chromosome 5 Deletions as a Means of Defining the APC Region
H. Thomas, L. Varesco, A.-M. Frischauf, E. Solomon 529

Cytogenetic Studies on Colon Carcinomas and Adenomas from Patients with Familial Polyposis Coli
T. Ikeuchi, M.A. Yoshida, T. Iwama, M. Miyaki, I. Okayasu, A. Tonomura 533

The DiFi Rectal Carcinoma Cell Line from a Familial Adenomatous Polyposis Patient: An In Vitro Model System to Study Genetic Changes in Colorectal Cancer
B.M. Boman, M. Olive, S. Untawale, M. Blick, S. North, G. Gallick, G. Dolf, M.J. Siciliano, L.D. Roubein, H. Fritche, G. Thomas, S. Pathak, D.M. Wildrick, B. Levin 541

Dietary Fat Diglycerides Activate by Tyrosine Phosphorylation a pp63 Membrane Protein Only in Colon Tumors and not in Normal Colonocytes, Leading to Selective Biological Effects
E.A. Friedman 549

Overview and Epilogue
H.T. Lynch, J. Utsunomiya 555

Author Index 573