# Ovarian Cancer

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# OVARIAN CANCER

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**McGraw-Hill, Inc.**
**Health Professions Division**
New York St. Louis San Francisco Auckland Bogotá Caracas
Lisbon London Madrid Mexico Milan Montreal New Delhi
Paris San Juan Singapore Sydney Tokyo Toronto

1234567890 HALHAL 98765432

ISBN 0-07-054204-X

This book was set in Century Schoolbook by
Compset, Inc.
The editors were Jane E. Pennington and
Lester A. Sheinis;
the production supervisor was Clare Stanley;
the cover designer was Barolini Graphic Design;
the indexer was Jerry Ralya.
Arcata Graphics/Halliday was printer and binder.

**Library of Congress Cataloging-in-Publication Data**

Ovarian cancer / editors, Stephen C. Rubin, Gregory P. Sutton.
p. cm.
Includes bibliographical references and index.
ISBN 0-07-054204-X
1. Ovaries—Cancer. I. Rubin, Stephen C. II. Sutton, Gregory P.
[DNLM: 1. Ovarian Neoplasms. WP 322 0963]
RC280.080883 1993
616.99'465—dc20
DNLM/DLC
for Library of Congress 92-48792
CIP

To our families

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# PREFACE

Ovarian cancer is the leading cause of death in women with gynecologic malignancies. Although it accounts for only about 27 percent of new gynecologic cancer cases each year in Western countries, this deadly disease kills more women than all other gynecologic malignancies combined. By this measure, ovarian cancer is surely the most important problem in gynecologic cancer today.

Ovarian cancer is a disease that exemplifies the importance of the multimodal approach to the treatment of cancer, requiring the input of gynecologic oncologists, medical oncologists, radiotherapists, pathologists, basic scientists, nurses, and social workers. In this text we have brought together in a single volume the nation's leading experts on ovarian cancer to produce an authoritative multidisciplinary reference on the subject. The book begins with a section on the basic science of ovarian cancer, addressing the latest data in the areas of genetics, growth factors and oncogenes, chemotherapy resistance, and immunobiology. This is followed by separate chapters on the histopathology of the three main types of ovarian cancer: epithelial, germ cell, and sex cord-stromal tumors. The third and largest section of the book addresses in detail the clinical aspects of ovarian cancer, opening with chapters on epidemiology and familial ovarian cancer, followed by chapters covering all aspects of the surgical, chemotherapeutic, and radiotherapeutic management of ovarian cancer, including the latest in investigational approaches, and closing with chapters on quality-of-life issues and new surgical approaches.

Our contributors, to whom we are grateful, have adhered to a tight production schedule to allow timely publication of the most current material. We hope that this book will prove to be a valuable reference for all who treat ovarian cancer patients and that it will be of use in our common quest for improving the care of women with this disease.

# ACKNOWLEDGMENTS

Many people have played important roles in the preparation of this text. The editors would like to acknowledge in particular the essential contribution of Jane E. Pennington, Ph.D., senior medical editor at McGraw-Hill, who guided this project from its inception. We are also grateful for the tireless efforts of Tracy McDonough, Guillermo Metz, and Denise Haller, editorial assistants of the Gynecology Service at Memorial Sloan-Kettering, and Shirley Antonek, administrative secretary at Indiana University.

# OVARIAN CANCER

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## PART 3 CLINICAL ASPECTS OF OVARIAN CANCER

# Part 1

# BASIC SCIENCE OF OVARIAN CANCER

# 1

# GENETICS AND OVARIAN CANCER

**Fred Gilbert**

Cancer is a genetic disease, the result of an accumulation of gene changes that alter the growth and proliferative capacity of the cells in which they occur. Cancer can be sporadic or familial. Sporadic cancers appear as isolated events in a family pedigree; the gene changes required for tumorigenesis occur only in the somatic target cell itself—for example, in a retinoblast, in retinoblastoma, or in an ovarian epithelial cell in ovarian cancer. In familial cases, at least one of the required gene changes has occurred in a germ cell (sperm or egg) and has been transmitted to a second generation; only when the necessary additional gene changes have occurred in a somatic target cell already carrying the inherited gene change will that cell become transformed.

Sporadic cancers are not associated with any increase in recurrence risk of the same cancer in relatives of an affected individual. The genetic contribution to familial cancers can be dominant, recessive, or sex-linked (Fig. 1–1). The familial cancer category may encompass as many as 200 separate disorders.[1] With the exception of a group of recessively inherited disorders (primarily, DNA repair defects) and rare sex-linked immune deficiency syndromes, the majority of inherited gene changes predisposing to the development of cancer are transmitted from parent to child in successive generations, in a dominant fashion (Tables 1–1, 1–2).

It is important to remember that unlike most other dominant disorders, in the dominant disorders associated with cancer the inheritance of a single gene change is not, by itself, sufficient to produce the cancer. In neurofibromatosis type 1, for example, all affecteds will have mutations in the NF1 gene (mapped to chromosome 17), most patients will demonstrate one or more of the phenotypic manifestations diagnostic of the disorder (including café-au-lait spots and neurofibromas), but only some will develop the cancers associated with neurofibromatosis (including fibrosarcoma and brain tumors).[2] Dominant inheritance, in the context

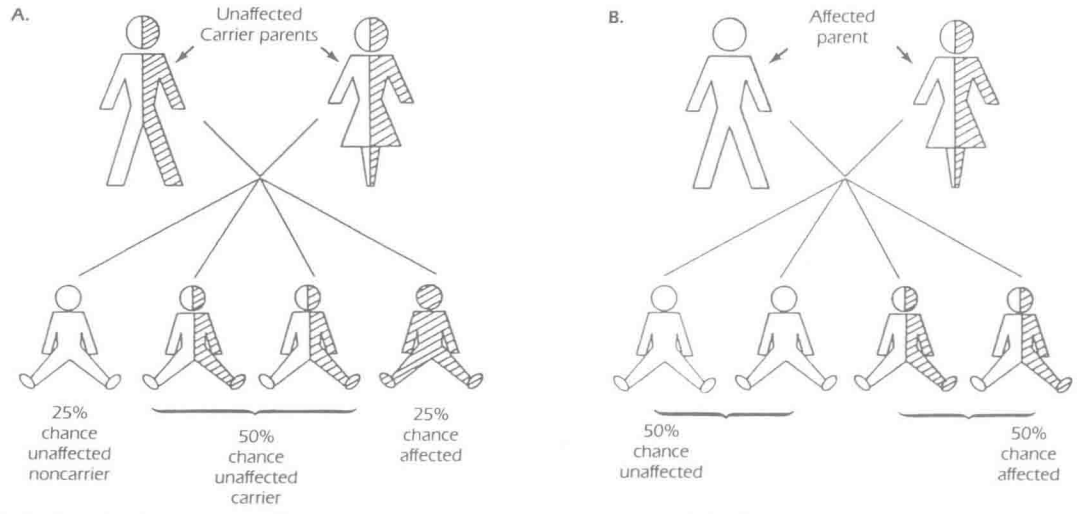


**FIG. 1–1.** *Two basic patterns of inheritance.* **A.** Autosomal recessive, with both parents as carriers, 1 in 4 chance for an affected. **B.** Autosomal dominant, with one parent as affected and 1 in 2 chance for affected child.

**TABLE 1–1. Genetic Syndromes in Which Cancer Is Associated (Examples)**

| Diagnosis | Inheritance[a] | Cancers reported (examples) |
|---|---|---|
| Wiskott-Aldrich syndrome | XLR | Lymphoma, leukemia |
| Xeroderma pigmentosum | AR | Skin, leukemia |
| Fanconi anemia | AR | Leukemia, hepatoma, skin |
| Ataxia-telangiectasia | AR | Leukemia, lymphoma, colon |
| Bloom syndrome | AR | Leukemia, colon |
| Werner syndrome | AR | Leukemia, sarcoma, breast |
| Von Hippel-Lindau disease | AD | Brain, kidney |
| Beckwith-Wiedemann syndrome | AD | Wilms' tumor, hepatoma |
| Neurofibromatosis, I, II | AD | Sarcoma, brain |
| Tuberous sclerosis | AD | Brain, kidney, sarcoma |
| Basal cell nevus syndrome | AD | Skin, brain, OVARY |
| Cowden syndrome | AD | Breast, colon, OVARY |
| Gardner syndrome | AD | Colon, brain, OVARY |
| Peutz-Jeghers syndrome | AD | Colon, OVARY |

[a] XLR-sex-linked recessive, AR = autosomal recessive, AD = autosomal dominant.

of cancer, refers to the transmission of a predisposition gene change from generation to generation, not necessarily to the development of cancer.

The fact that the additional gene changes required for malignant transformation are very likely to occur in the target cells as they divide over time, means that *penetrance* (referring to the proportion of offspring of a known gene carrier that express a specific phenotype [cancer, for example, in the cancer family syndromes]) is high, but not the