

Noninvasive Molecular Markers in Gynecologic Cancers



Edited by
Debmalya Barh
Mehmet Gunduz



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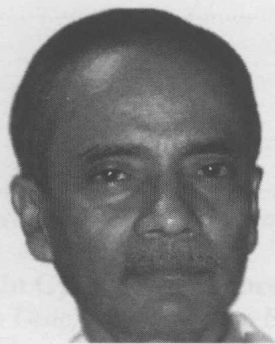
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Dedicated to Deb's Maternal Uncle, Dr. S. Samanta, MBBS, DTMH,

a brave fighter against Non-Hodgkin's Lymphoma at 65 years.

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Foreword

Gynecologic cancers are major causes of death in women worldwide. In practice, screening and early diagnosis provides an opportunity for better treatment and management and, thus, improves the prognosis and survivability. This book covers all the subsections of gynecologic cancers with the focus on noninvasive biomarkers. Biomarker identification and its critical usage for the early detection of cancer have accelerated in recent years, and the clinical use of noninvasive biomarkers seems to be especially promising. Thus, the topic has a wide appeal to basic scientists, clinical researchers, and physicians (especially from oncology and gynecology).

This *Noninvasive Molecular Markers in Gynecologic Cancers* book by Dr. Barh and Dr. Gunduz is a timely and valuable contribution to the field of gynecologic oncology. Chapters in this book cover all gynecological cancer types (ovarian, cervical, uterine, vaginal, fallopian tube, and vulvar cancers), from different perspectives. For readers' benefit, the book has also included breast cancer. After giving general information about the disease, identified biomarkers are presented in each chapter. The general information in each chapter about disease epidemiology, clinical features, diagnosis, treatment and prognosis will educate non-clinical readers about these particular cancers. The biomarker part of each chapter comprises the results of considerable amounts of research studies along with used, upcoming, and novel non-invasive molecular markers from various classes. Therefore, this book is a useful guideline for clinical researchers and basic scientists to have the overall idea of the non-invasive markers in various gynecologic cancers to be used clinically and also help us to find new and novel ones.

I certainly find this book fascinating and intellectually stimulating and I believe that there are a lot of scientific people and clinicians who will have the similar feelings about the book. I would like to thank all authors and editors for their all efforts to develop this highly useful book.

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Preface

Cancers that affect women's reproductive organs are collectively referred to as gynecologic cancers and are named according to the part of the body that is affected. Ovarian, cervical, uterine, vaginal, and vulvar cancers are the five main cancers that constitute the group. However, fallopian tube cancer, which is very rare, can also be included in this group. According to various reports, cervical cancer is the second most common cancer in women after breast cancer, and cumulatively both these cancers contribute over 40% of cancer-specific deaths in women worldwide, whereas ovarian and uterine cancers cause 10%–15% of all cancer-associated deaths. From this, we can conclude that gynecologic cancers along with breast cancer contribute to more than 50% of all cancer-associated deaths in women.

Early detection is critical for any given cancer. With the advent of the latest omics technologies, molecular markers in combination with conventional diagnostic and screening methods are emerging as next-generation early diagnostic and prognostic strategies that can allow early-stage diagnosis, resulting in more effective treatment and patient care and, in turn, increased rate of survival. The current trend in diagnosis is slowly shifting from invasive (tissue biopsy based) to minimally invasive or noninvasive (blood, serum, urine, and saliva) methods to avoid complications related to biopsy and other associated patient discomforts. Furthermore, obtaining samples noninvasively is easy and less time consuming. Moreover, molecular markers obtained noninvasively that are currently in use or under development show better sensitivity and specificity as compared to conventional markers obtained through biopsy.

Although there are several books available on various aspects of gynecologic cancers, none have documented the noninvasive molecular biomarkers that are under development or precisely used for screening, early diagnosis, prognosis, and/or therapy for cancers in female reproductive organs. This book, *Noninvasive Molecular Markers in Gynecologic Cancers*, is the first of its kind to fill this gap and to provide a ready-made resource that not only provides information on noninvasive molecular diagnostic biomarkers for gynecological cancers but also accounts for the epidemiology, clinical features, conventional diagnosis, treatment, and prognosis for these cancers. Each of these cancer types has unique signs and symptoms, risk factors, and molecular profile, and therefore requires different prevention strategies. A common factor in all of these cancers is risk, which increases with age and in some cases is associated with genetic predisposition or heritability. Different features of each cancer are explained in detail in dedicated chapters, where general information, epidemiology, clinical features, and biomarkers are given. Breast cancer is also included in the spectrum of cancers specific to women to make this book more complete and beneficial to the target audience: clinicians, oncologists, gynecologists, pathologists, radiologists, medical students, and researchers in biomarkers and targeted drug discovery.

Before the in-depth molecular investigation of gynecologic cancers, etiopathogenesis and clinics of these cancers should be known. To make the book more user-friendly, the 18 chapters are organized into six sections. In Section I, general topics are discussed. In Chapter 1, Dr. Kaygusuz and colleagues present an overview of gynecologic cancer in a compact but comprehensive way. In Chapter 2, Dr. Oznur's group gives a detailed account on early cytogenetic markers for gynecologic cancers.

Section II deals with breast cancer and includes Chapters 3 through 6. In this section, breast cancer biomarkers are investigated from different aspects. In Chapter 3, early molecular biomarkers in breast cancer are presented by Dr. Kaul-Ghanekar et al. Dr. Calomarde's group has specifically described clinical and molecular diagnostic and prognostic markers for invasive breast cancer in Chapter 4. Dr. Yilmaz and colleagues, in Chapter 5, have provided details on biomarkers in familial breast cancer. In the last chapter in this section, Chapter 6, Dr. Hasan's group summarizes the epigenetics of breast cancer and the influence of nutrients for methylation on this cancer.

In Section III, Chapters 7 through 9 deal with cervical cancer. Dr. Kaul-Ghanekar et al. provide a detailed account from the epidemiology to molecular markers of cervical cancer. In Chapter 8, Dr. Serrano's group presents the possible use of HPV, p16, Ki-67, and E6/E7 markers in cervical cancer. In Chapter 9, Dr. Kunos et al. summarize the biomarkers of nucleotide metabolism in cervical cancer.

In Section IV, Chapters 10 through 13, ovarian cancer is investigated from various aspects. In Chapter 10, Dr. O'Toole's group comprehensively presents various noninvasive early biomarkers in ovarian cancer. Dr. Oznur et al. have discussed biomarkers for ovarian endometrioid carcinoma in Chapter 11. In Chapters 12 and 13, two important biomarkers (CA125 and He4) in ovarian cancer are discussed by Dr. Bouanene et al. and Dr. Abehsera et al., respectively.

Section V, Chapters 14 through 16, discusses uterine and fallopian tube cancers. In Chapter 14, Dr. Nas and colleagues present molecular biomarkers for endometrial cancer, and in Chapter 15, Dr. Buery and Dr. Gunduz summarize biomarkers in uterine mesenchymal tumors. Chapter 16 by Dr. Peitsidis gives a detailed account on various aspects of fallopian tube carcinoma, including noninvasive early markers.

Finally, in Section VI, Dr. Ocak et al. and Dr. Iaconi et al. describe noninvasive early markers associated with vaginal (Chapter 17) and vulvar (Chapter 18) cancer, respectively.

Leading international experts have authored these topics and each chapter is organized with a uniform structure: outline, abstract, detailed information for each title under outline, future perspectives, and references. A sufficient number of illustrations are included to support each topic. This basic structure makes understanding the topics easier. Almost all of the knowledge about all gynecological cancers and their biomarkers has been covered in this book.

We do hope this book will be a useful resource and a reliable and valuable reference on gynecological cancers that will help physicians manage early detection of any given gynecologic cancer and will motivate further research to find more noninvasive biomarkers. We also highly appreciate our readers' valuable comments on further improvements to the contents.

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Editors

Editors



Debmalya Barh, MSc, MTech, MPhil, PhD, PGDM, is the founder of the Institute of Integrative Omics and Applied Biotechnology (IIOAB), India, a first-of-its-kind virtual global platform for multidisciplinary research and advocacy. He is a biotechnologist and active researcher in integrative *omics*-based biomarkers, targeted drug discovery, and personalized medicine for cancers and various complex diseases. He works with nearly 400 esteemed researchers from around 35–40 countries and has more than 125 high-impact international publications and several book chapters and conference presentations. He is a globally branded editor

for cutting-edge *omics*-related reference books published by top-ranked international publishers. His cancer related books include *Cancer Biomarkers: Minimal and Noninvasive Early Diagnosis and Prognosis* by Taylor & Francis Group/CRC Press, *Omics Approaches in Breast Cancer: Towards Next-Generation Diagnosis, Prognosis and Therapy* and *Omics for Personalized Medicine* by Springer, among others. Due to his dedicated contribution to the field of applied biomedical and biological sciences and unique research strategies, he was recognized by *Who's Who in the World* in 2010 and was listed in the *Limca Book of Records*, the Indian equivalent to the *Guinness Book of World Records*, in 2014.



Mehmet Gunduz, MD, PhD, is the professor and head of the Department of Medical Genetics and Otolaryngology, Faculty of Medicine, Turgut Özal University, Ankara, Turkey. Dr. Gunduz graduated from the Medical School Hacettepe University, Ankara, Turkey, with the fourth highest rank in 1990. He completed his residency in otolaryngology, head and neck surgery, at the same university. He earned his PhD in medical genetics from Okayama University and Wakayama Medical University, Japan, and is a medical practitioner board-certified by both the Turkish and Japanese certification authorities. From 2003 to 2004, he

worked as a visiting scientist at MD Anderson Cancer Center, Houston, Texas. Dr. Gunduz was one of the pioneers in identifying ING family tumor suppressors and has several publications on various cancer-related molecular markers, including breast cancer. He has more than 170 international publications and 3500 citations, several book chapters, and over 200 presentations in national and international conferences.

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The *Noninvasive Molecular Markers for Gynecologic Cancers* book by Dr. Esra and Dr. Gunduz is a timely and valuable contribution to the field of gynecologic oncology. Chapters in this book cover all gynecological cancer types: ovarian, cervical, endometrial, fallopian tube, and vulvar cancers, from different perspectives. For readers from the book, this book includes breast cancer, which gives general information about the disease, identified biomarkers are presented in each chapter. The general information in each chapter about disease epidemiology, clinical features, diagnosis, treatment and prognosis will be helpful for clinical research. The biomarker part of each chapter compares the results of available clinical studies of research studies along with used, upcoming, and novel non-invasive molecular markers from various classes. Therefore, this book is a useful guide for clinical researchers and basic scientists to know the overall idea of the non-invasive markers in various gynecologic cancers to be used clinically and also help us to find new and novel ones.

I certainly find this book fascinating and intellectually stimulating and I believe that there are a lot of scientists and clinicians who will have the similar feelings about the book. I would like to thank all authors of all chapters for their all efforts to develop this highly useful book.

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