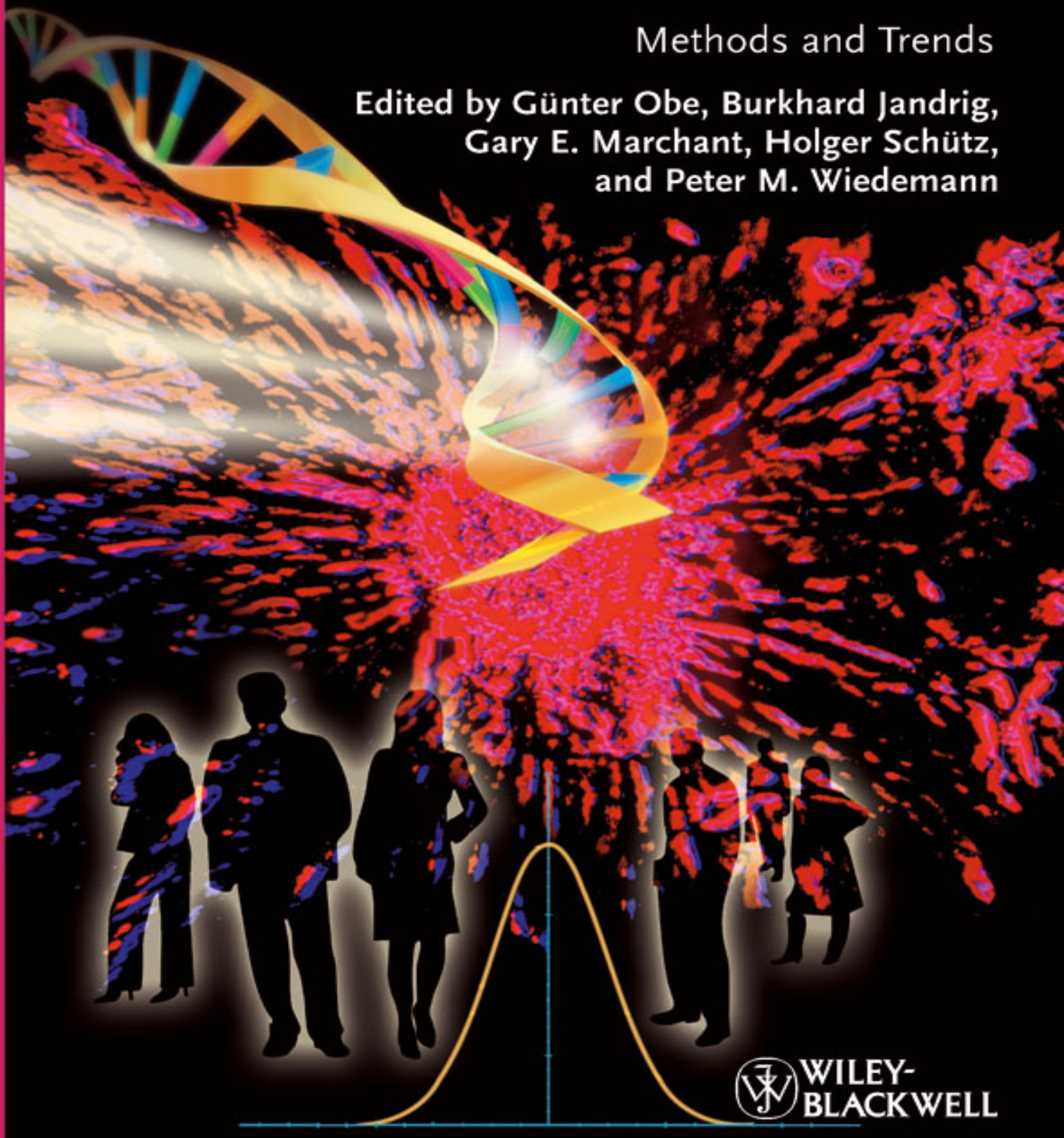
Cancer Risk Evaluation

Methods and Trends

Edited by Günter Obe, Burkhard Jandrig, Gary E. Marchant, Holger Schütz, and Peter M. Wiedemann



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Preface

Both the modern biomedical research such as genomics and proteomics and the rapid advances in high-throughput screening molecular technologies have revolutionized the knowledge about functional and regulatory genomics, which is beginning to make an immense impact on our understanding of human health and disease. These developments have also brought great hope to improve cancer risk assessment, even to solve scientific controversies about cancer risk claims, such as the debate whether electromagnetic fields from mobile telephony cause cancer in humans.

During the past few years, we were able to focus on this question in an integrated multidisciplinary research project on the implications of modern biomedicine on risk assessment (IMBA), sponsored by the Helmholtz Association of German Research Centres. As a health technology assessment project, IMBA analyzed how new developments in biomedicine, which are often summarized under the term “toxicogenomics,” will transform the present risk management framework. IMBA looked into a wide range of scientific and social challenges that deserve careful attention, particularly on issues related to risk assessment, risk perception, and risk communication.

In 2008, we organized an international workshop in Berlin as part of the IMBA project. The aim of the workshop was to compare the potential of genomics and traditional approaches used in cancer risk assessment, particularly genotoxicity studies, with regard to their potential to inform assessment of unclear risks, that is, risks where evidence is insufficient for a conclusive risk assessment. The unclear risks chosen for discussion were radio frequency electromagnetic fields. Topics such as the validity and reliability of genotoxic research for cancer risk assessment, the prospects of toxicity testing and risk assessment, and

the implications for policy making were critically reviewed and evaluated by experts in the fields of ionizing and nonionizing radiation, genotoxicity, molecular medicine, and epidemiology.

The discussions during the workshop motivated us to plan a publication on these topics. Further impetus came from the ongoing societal debate on the health implications of electromagnetic fields, which seems not to be solved but stimulated by new molecular biomarker studies and high-throughput technologies in this field. We think that in a climate of excitement about the promises of molecular medicine, it is crucial to explore the validity of molecular biomarkers and evaluate their added value for risk assessment. We hope that this book will contribute to effective interdisciplinary communication and collaboration in the fields of molecular biology, cancer research, risk assessment, and public health policy.

We are grateful to all authors of the book for investing their valuable time in writing their contributions and participating in the review process in order to make the book valuable for all readers. Last but not least, we appreciative the support of the Helmholtz Association of German Research Centres.

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Chapter 1

Introduction

Cancer is one of the leading causes of human mortality. Over the past 30 years, the global burden of cancer has more than doubled. According to the recent World Cancer Report, published by the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), in 2008 there were 7 million deaths from cancer. Affected by the still growing and aging world population, this figure is expected to increase to 17 million annually by 2030 [1]. While many environmental cancer risk factors, such as exposures to ionizing radiation or tobacco smoke, alcohol consumption, or excessive sun exposure, have been established [2], assessments of cancer hazards and risks are difficult and often highly uncertain. Of the more than 900 agents that have been evaluated by IARC, only 12% have been classified as being clearly carcinogenic to humans [3]. And even if an agent has been identified as a carcinogen, the risk it poses to a given population is often hard to estimate. The reasons for these difficulties are manifold. First of all, there are different types of cancer that differ in their etiology. Another reason – and that is the focus of this book – is that cancer causation is hard to investigate. Experimental studies in humans are for obvious ethical reasons not possible, thus cancer risk assessment has to rely on indirect evidence.

At present, assessments of carcinogenicity are based on three pillars: epidemiological studies in humans, studies in experimental animals, and genotoxicity studies. Epidemiological studies aim at identifying the causes of

cancer by studying the covariation between exposure to an agent and cancer incidence. Although there is a long debate on if and when epidemiology actually can provide causal evidence [4], there is little disagreement that epidemiological studies are the most important source of knowledge for cancer risk assessment [2, 5]. In studying the carcinogenicity of agents, epidemiological studies have to rely on given exposures to the respective agents, for instance, radon emanating from the soil or electromagnetic fields emitted from mobile communication devices. These conditions are usually not under control of the investigators, and although epidemiologists have developed an elaborate methodology to match specific study demands [6], problems such as bias and confounding frequently limit the conclusiveness of their results.

Compared to epidemiology, animal studies have the advantage of permitting experimental designs, where (at least in principle) everything can be controlled. This allows the most stringent test of a causal relationship between the exposure to an agent and an adverse effect. At least for chemical agents, there is a kind of “gold standard” that is used for carcinogenicity testing, which includes 2-year studies with rodents [7]. However, these studies are time consuming and expensive, limiting the number of agents that are tested [2]. Beside ethical considerations regarding the use of animals in research, the appropriateness of animal models for investigating and predicting human diseases has been disputed [8]. It should also be noted that this gold standard is not so well established for some physical agents. For example, many animal studies investigating the potential carcinogenicity of radio frequency electromagnetic fields (RF EMF) use only one type of animals and often for a short period [9]. An important limitation of using animal studies for carcinogenicity testing is that the experimental results always have to be

extrapolated to humans, which is of course acknowledged in evaluations of evidence for cancer risk assessment [2, 5].

Basically, the same holds for genotoxicity studies, where experimental findings also have to be evaluated with regard to their implications for humans. Their value lies in the fact that cancer results primarily from genetic changes in single cells. Therefore, agents that are able to damage cellular DNA lead to mutations and then possibly to cancer. For instance, people exposed to ionizing radiation have both an elevated cancer risk and elevated frequencies of chromosomal aberrations in their peripheral lymphocytes, showing the mutagenic activity of ionizing radiation. Mutations are initiating events for the development of cancer and therefore testing of various agents for their possible mutagenicity is an important part of cancer risk assessment [10].

Over the past years, new technologies have been developed that promise new insight into cancer risk assessment by focusing on the role of the genome for understanding cancer initiation and development [11, 12]. These so-called omics technologies include genomics for DNA variations, transcriptomics for messenger RNA, proteomics for peptides and proteins, and metabolomics for intermediate products of metabolism. Technological breakthroughs allow simultaneous examination of thousands of genes, transcripts, proteins, and metabolites with high-throughput techniques and analytical tools to extract information. These new technologies are expected to provide a highly sensitive detection of low-dose effects, more reliable extrapolation of risk estimates across doses, routes, and species, and valuable insight into the mechanism of action of toxicants. Overall, the ability to classify chemicals and other stressors based on their effects at omics level would permit the development of new testing strategies in cancer risk assessment. At present, genomics-

and transcriptomics-based approaches are most promising, while metabolomics, though in principle quite potent, is quite nascent in its development, as present techniques and the methodology are far away from inspecting the whole metabolome. High-throughput screening technologies have their own technical limitations and uncertainties. The transcriptome and proteome are highly dynamic and change rapidly and dramatically in response to perturbations or even during normal cellular events. The modern screening technologies still have the problem of reproducibility and variability between studies and are prone to produce false positive results [13, 14].

An important aspect here is quality control of scientific investigations. Although in general not limited to the omics field, the huge amount of data produced with microarray experiments and the extensive data processing required for analysis make open data accessibility to allow independent reevaluation of findings an important claim, which is increasingly acknowledged in the scientific community [15, 16]. Another aspect of quality control is how to evaluate the reliability of controversial scientific results. As said before, it is difficult to rule out errors in high-throughput screening research. Even more complicated is the proper dealing with fraud suspicions. Although fraud in science is by no means a new phenomenon, recent scandals in highly prestigious scientific journals have also called the public's attention to this issue [17]. Thus, the highly welcome new approaches to cancer risk assessment also call for the establishment of rules that allow a careful evaluation of study results. Furthermore, better risk communication is required for informing health professionals, the media, and the general public about the meaning of omics findings for risk assessment [18]. A particular problem here is if and when uncertainties in risk assessment should be communicated to a nonexpert audience. On a more general level, the