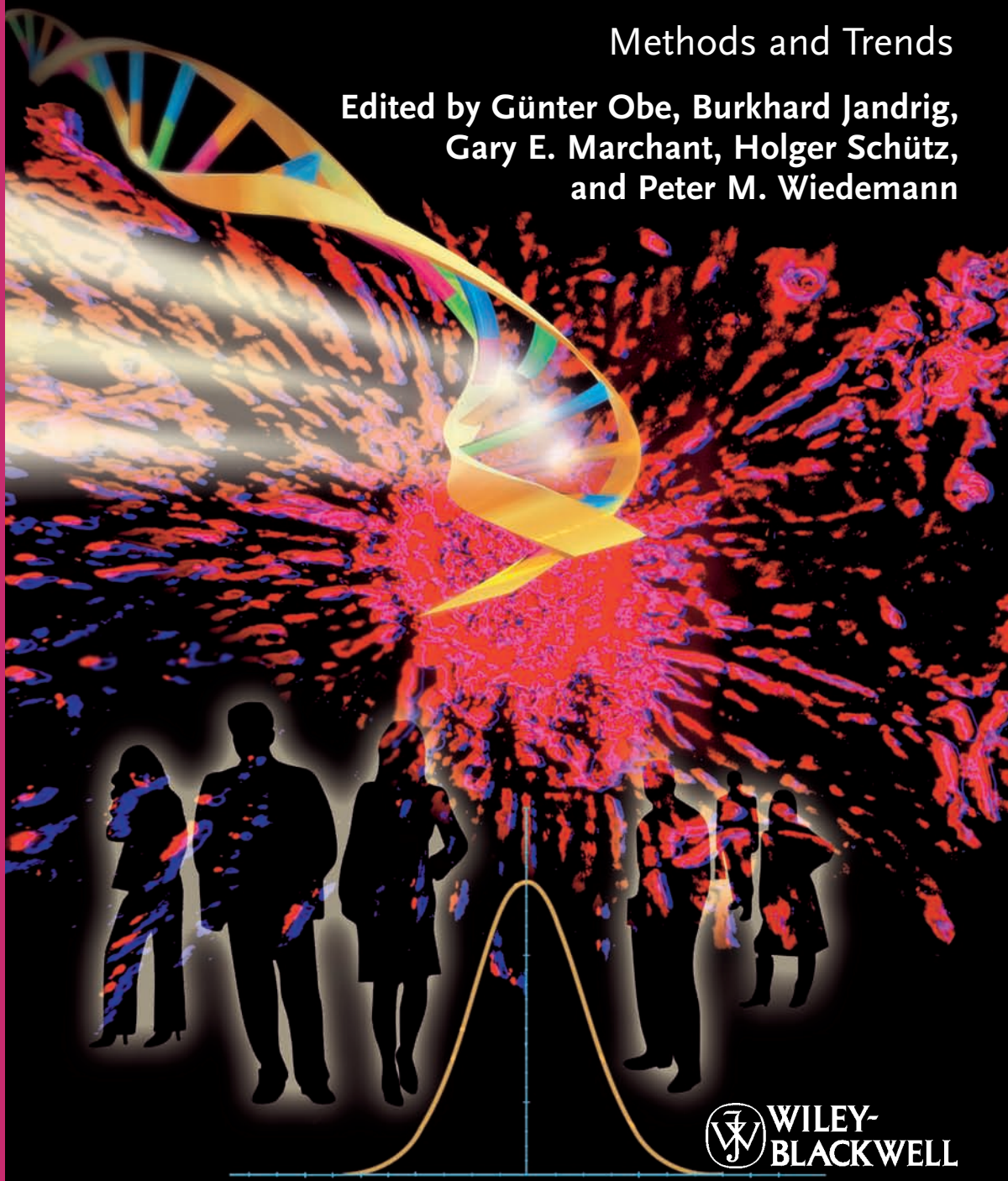
Cancer Risk Evaluation

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.

Berlin, December 2010

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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 question arises how these uncertainties should be addressed in risk management. This is likely to intensify the current debate about the application of the precautionary principle. Of course, these problems are not specific to omics; however, apart from providing new knowledge for risk assessment, omics is also likely to introduce new uncertainties [19–21].

The following chapters of this book provide insight into new developments of cancer risk assessment and their accompanying scientific discussions. While the focus is on cancer and radiation, especially nonionizing radiation, the various chapters provide the reader with a comprehensive view on cancer biology, cancer assessment methods including epidemiology, animal research, and genotoxicity studies as well as omics approaches and applications. Furthermore, it covers the comparative assessment of radiation risks and addresses policy considerations such as risk communication and application of the precautionary principle.

The book is organized in seven parts. Part One gives an overview of the current understanding of cancer development and approaches to cancer risk assessment. Jandrig (Chapter 2) shows that, apart from mutations, other cellular changes have to be taken into account to understand the complex biology of cancer. Epe and Fußer (Chapter 3) describe the various determinants of generation, repair, and steady-state levels of endogenous DNA modifications. Baan and Cogliano (Chapter 4) provide insight into cancer hazard identification as the first step in cancer risk assessment and cancer prevention, as outlined in the IARC Monographs Programme.

The role of epidemiology in cancer risk assessment is addressed in Part Two. Schüz, Berg-Beckhoff, Schlehofer, and Blettner (Chapter 5) consider the particularly challenging possible adverse health effects of exposure to electromagnetic fields (EMF) that have remained a scientific and political controversy until today. Their first example is the relationship between extremely low-frequency (ELF) fields from power lines and the risk of childhood leukemia. Their second example is the relationship

between RF EMF, specifically those emitted from mobile phones, and the risk of brain tumors. Wakeford (Chapter 6) presents data for cancer risk assessment of ionizing radiation. Among others, he provides cancer risk figures based on epidemiology from Hiroshima survivors and children exposed during and after the Chernobyl accident.

Animal studies are indispensable for cancer hazard identification and results of this type of research are presented in Part Three. Buschmann and Dasenbrock (Chapter 7) refer to recent advances in animal studies on RF EMF testing the possible carcinogenic effects related to cell phones and base stations. On the basis of a comprehensive discussion of the PERFORM-A project, they demonstrate how existing data gaps relevant for risk assessment can be closed. Pointing to the strengths and limitations of epidemiological cancer studies of ELF fields, McCormick (Chapter 8) shows how laboratory animal research can fill gaps in EMF cancer risk assessment. The author discusses the findings of various types of experimental animal studies and comes to the conclusion that available animal data do not support an elevated cancer risk.

Part Four highlights the importance of studying chromosomal damage, which is a highly reliable endpoint for cancer hazard and risk assessment. Obe, Lloyd, and Durante (Chapter 9) outline current approaches to investigating chromosomal aberrations. They argue that elevated frequencies of chromosomal aberrations in peripheral lymphocytes of human populations are associated with elevated cancer frequencies and allow calculation of cancer risks in persons exposed to ionizing radiation, such as astronauts. Vijayalaxmi and Prihoda (Chapter 10) show how meta-analysis as a tool for statistical data synthesis can be used to systematically summarize evidence from cytogenetic studies in mammalian somatic cells that have been exposed to radio frequency radiation. They conclude that exposure to radio frequency radiation does not increase frequencies of chromosomal aberrations and micronuclei, which are two endpoints for chromosomal damage.

The potential of omics technologies as new tools for cancer risk assessment are discussed in Part Five. Technological breakthroughs allow simultaneous examination of thousands of genes, transcripts, proteins, and metabolites with high-throughput techniques and analytical tools to extract information. Modern screening technologies speed up the discovery process and give a broader insight into biochemical events that follow the exposure to potentially harmful agents, such as chemical substances, ionizing radiation, or electromagnetic fields. The different methodologies and techniques are discussed in this part with respect to actual applications and future developments. Schweiger and Timmermann (Chapter 11) explain the huge potential that whole genome approaches afford for understanding complex genetic diseases such as cancer. They provide an overview of the advancement of genome analysis technologies and illustrate how these are used for investigating the mechanisms underlying cancer development. The authors close with an outlook on how the genomics approach might ultimately lead to an individualized cancer treatment. Kemmner (Chapter 12) outlines the use of transcriptomics, or gene expression profiling, in cancer risk assessment, for instance, with regard to classification of human cancers and prediction of cancer recurrence

and metastasis. The author discusses technical challenges of gene expression profiling, such as sample preparation and data analysis, and gives examples of microarray applications in cancer research. Proteomics, the analysis of proteins, and its relevance to cancer risk assessment, is discussed by Schramm (Chapter 13). While proteomics comprises a variety of technical disciplines, its application to cancer risk assessment can be described as a multistep process including sample preparation, separation, quantitation, and protein identification. The author discusses particular challenges of these steps and concludes with an outlook on future developments of proteomics for individualized cancer therapy.

Examples of using omics technologies for risk assessment are described in Part Six. Portier and Thomas (Chapter 14) provide a critical discussion of omics and high-throughput screening strategies concerning cancer risk assessment. First, they discuss the difficulties of traditional cancer risk assessment, in particular with animal studies, and then describe how omics might be used to overcome these problems. They conclude that while there is little doubt that omics will be of major importance for future risk assessment, there is still much research needed, before it finds regulatory approval in risk assessment. Morgan and Sowa (Chapter 15) show how omics might be used for risk assessment of exposure to low-level ionizing radiation. So far, risk assessment had to rely mainly on epidemiological data, for instance, from Japanese A-bomb survivors, but here epidemiology clearly reaches its limits. The authors discuss studies that used gene expression profiling, proteomic profiling, and metabolomic profiling to investigate the effects of low-level ionizing radiation. Their conclusion is that while significant progress has been made in using omics for cancer risk assessment, the future challenge is to integrate the various omics technologies to allow a "systems level" approach. The next two chapters then address how transcriptomics and proteomics can be used for cancer risk assessment of RF EMF. Mevissen (Chapter 16) provides an overview of studies investigating the effects of RF EMF exposure on gene expression. She makes it clear that these studies differ strongly in scientific quality and focus, and are insufficient for drawing conclusions regarding effects the RF EMF exposure has on organisms. A similar picture emerges from the review of proteomics studies that is given by Leszczynski (Chapter 17). So far, only few studies have investigated the effects of RF EMF exposure on the proteome, and many of them have methodological shortcomings.

The last part of the book addresses challenges for risk management. Lerchl (Chapter 18) reports recent examples of apparent scientific misconduct and discusses heuristics that can help detect data fabrication. He also offers some advice how to handle such misconduct appropriately. Kiefer (Chapter 19) offers a comparative risk assessment across the electromagnetic spectrum based on the Bradford Hill criteria. He argues that at present only ionizing radiation fulfils all requirements for cancer hazard identification. Wiedemann and Schütz (Chapter 20) discuss the challenges of communicating about uncertainty in cancer risk assessments to nonexperts. They offer ample evidence that, in contrast to common beliefs, informing about uncertainties might create misperceptions and misunderstandings of risk. Furthermore, they discuss how to explain inconclusive scientific evidence, a task particularly important for hazard assessment. Finally, Marchant (Chapter 21) considers the role

of the precautionary principle in risk management. Weighing the pros and cons, he concludes that despite its rhetorical appeal, the precautionary principle remains problematic in its practical application, which in large part is due to the ambiguity and arbitrariness of the principle.

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Part One
Models and Approaches