

Contents

Preface	iii
1. Executive Summary	1
2. Introduction	8
2.1 Role of Risk Estimates in Setting Radiation Protection Guidance	10
2.2 Methods Used for the Assessment of Risk at Low Doses and Low Dose Rates	11
3. Epidemiology, Biosamples and Biomarkers: Cancer and Circulatory Disease	17
3.1 Radiation Epidemiology and Biosamples	17
3.1.1 Epidemiologic Cohorts with Biosamples and Low-to-Moderate Doses	17
3.1.1.1 Japanese Atomic-Bomb Survivors	18
3.1.1.2 Mayak Production Association Workers	26
3.1.1.3 Sellafield Nuclear Facility Workers	26
3.1.1.4 U.S. Radiologic Technologists	27
3.1.1.5 U.S. Workers and Veterans	27
3.1.1.6 French Uranium Cycle Workers	27
3.1.1.7 German Wismut Uranium Miners	28
3.1.1.8 Chernobyl Children with ¹³¹ I Exposure	28
3.1.1.9 Kerala, India Residents of High Natural Background Radiation Area	28
3.1.1.10 Women's Environmental Cancer and Radiation Epidemiology Study	28
3.1.1.11 U.S. Childhood Cancer Survivor Study	29
3.1.1.12 Semipalatinsk Nuclear Test Site Area Residents, Kazakhstan	29
3.1.1.13 Biosamples in Offspring of Radiation-Exposed Groups	29
3.1.1.14 Population Databases with a Potential for Radiation Biomarker Studies	30
3.1.2 General Criteria for Identifying Bioindicators and Biomarkers	31
3.1.2.1 Validity of the Bioindicator or Biomarker	32
3.1.2.2 Validity of Study Assays	33

3.1.3	Epidemiologic Biomarker Studies of Radiation and Phenotypic Endpoints or Health Outcomes .	33
3.1.3.1	LSS and AHS Studies of Radiation and Liver Cancer	34
3.1.3.2	AHS Studies of Radiation and Breast Cancer	34
3.1.3.3	WECARE Study of Breast Cancer . . .	34
3.1.3.4	CCSS Genome-Wide Association Study of Radiation and Breast Cancer	36
3.1.3.5	U.S. Radiologic Technologists Study of Breast Cancer	36
3.1.3.6	Residents of High Natural Background Radiation Areas	36
3.1.3.7	Radiation Exposure, Biomarkers and Thyroid Cancer	37
3.1.3.8	Radiation and Inflammation or Immune Markers	38
3.1.3.9	DNA Repair Genes and Radiation-Induced Cancer Risk	40
3.1.3.10	Radiation and Effects on Gene Transcription or Translation	40
3.1.3.11	Epigenetic Radiation Effects	42
3.2	Epidemiology and Available Biomarkers for Studies of Circulatory Disease	42
3.2.1	Circulatory Disease	42
3.2.2	Overview of the Radiation Epidemiology of Circulatory Disease	45
3.2.2.1	Japanese Atomic-Bomb Survivors	45
3.2.2.2	Mayak Production Association Workers	46
4.	Radiation-Induced Biological Effects Related to Cancer and Circulatory Disease	49
4.1	Cancer	49
4.1.1	Genomic Instability and Hallmarks of Cancer . .	54
4.1.2	Pathways, Biomarkers and Bioindicators in Radiation Carcinogenesis	58
4.1.2.1	DNA Damage and Repair	59
4.1.2.2	Cell Survival	61
4.1.2.3	Reactive Species, Inflammatory Response, and Immunity	67
4.1.2.3.1	Reactive Oxygen and Nitrogen Species	68
4.1.2.3.2	Inflammatory Responses . . .	71
4.1.2.3.3	Immunity	72
4.1.2.4	Induction of Gene Mutations	73

	4.1.2.5	Mutation Induction in Irradiated Mice	74
	4.1.2.6	Epigenetic Modifications	77
	4.1.2.7	Induction of Chromosomal Aberrations	77
	4.1.2.8	Mutational Signatures in Cancers	78
4.1.3		More Specific Bioindicators of Radiation Carcinogenesis	80
	4.1.3.1	Radiation-Induced Leukemia in Mouse and Human	80
	4.1.3.2	Tumorigenesis in the <i>Apc</i> ^{min} Mouse	85
	4.1.3.3	Tumorigenesis in <i>Ptch1</i> ^{+/-} Mice	85
	4.1.3.4	Fusion Genes in Papillary Thyroid Carcinoma	86
	4.1.3.5	Thyroid CLIP2 Marker	88
	4.1.3.6	Microsatellite Instability	88
4.2		Circulatory Disease	90
	4.2.1	Pathogenesis of Circulatory Disease	90
	4.2.1.1	Other Atherosclerosis Hypotheses	95
	4.2.1.2	Possible Mechanisms of Low-Dose Radiation Action	96
	4.2.2	Biomarkers of Circulatory Disease	99
	4.2.3	Biomarkers (Potential Bioindicators) that Warrant Further Investigation	107
5.		Biologically Based Dose-Response Models	110
	5.1	General Features of Modeling	111
	5.1.1	Differences Between Mechanistic and Descriptive Mathematical Models	111
	5.1.2	Goals of Mechanistic Mathematical and Purely Descriptive Statistical Modeling	113
	5.1.3	Roles of Model Parameters	117
	5.2	Models of Carcinogenesis	118
	5.2.1	Armitage-Doll Multistage Model (Multistage Models without Clonal Expansion)	119
	5.2.2	Two-Mutation Model (TSCE Model)	123
	5.2.2.1	Human Cohorts (Low-LET)	127
	5.2.2.2	Human Studies (High-LET)	127
	5.2.2.3	Animals	128
	5.2.2.4	Discussion and Conclusion in Relation to MVK/TSCE and Armitage-Doll Models	130
	5.2.3	Generalized MVK and Multistage Models	131
	5.2.3.1	Multiple Pathway Models	131
	5.2.3.2	Models Incorporating Genomic Instability	133

5.2.4	Models Incorporating Molecular or Cellular Data	136
5.2.5	Malignant Cell Growth and Clonal Extinction	137
5.2.6	Initiation, Inactivation and Proliferation Models	139
5.2.7	Evolutionary Cancer Models	140
5.2.8	Summary and Discussion	141
5.3	Models of Circulatory Disease	143
5.3.1	Possible Mechanisms of Low-Dose Radiation Action	143
5.3.2	Mathematical Models of Atherosclerosis	144
5.3.2.1	Model of Cobbold et al. (2002)	144
5.3.2.2	Models of Chemotaxis Inspired by Model of Keller and Segel (1971)	144
5.3.2.3	Model of McKay et al. (2005)	144
5.3.2.4	Model of Little, Gola et al. (2009)	145
5.3.2.5	Model of Ibragimov et al. (2005)	146
5.3.2.6	Model of Ougrinovskaia et al. (2010)	147
5.3.2.7	Mechanical and Fluid Dynamic Modeling of Atherosclerosis	148
5.3.2.8	Fluid Dynamic Modeling of Atherosclerosis	148
5.3.2.9	Multilayer Models	149
5.3.2.10	Models of Cardiac Arrhythmia	149
5.3.2.11	Models of Kidney Function	149
6.	Proposed Generalized Model Framework of Cancer and Circulatory Disease	150
6.1	Potential Role for Adverse Outcome Pathways and Key Events (Bioindicators)	151
6.2	Biologically Detailed Models of Specific Cancers	156
6.3	Parameter Identifiability	158
6.4	Circulatory Disease	160
6.5	Conclusion	161
7.	Research Needs	162
7.1	Studies Using Human Biological Samples	164
7.1.1	Human Biosample Repositories	164
7.1.2	Transcriptomics	165
7.1.3	Proteomics and Metabolomics	165
7.1.4	Epigenomics	166
7.1.5	Circulating Biomarkers of Cancer	166
7.2	Experimental Biological Systems	167
7.2.1	Identification of Key Steps	167
7.2.2	Identification of Target Cells	168
7.2.3	Dose-Response Assays for Biomarkers and Bioindicators	169

7.2.4	Isolating Individual Events in a Chain of Events	172
7.2.5	Biological Platforms for Model Development . . .	173
7.2.6	Individual Susceptibility	174
7.3	Future Developments in Mechanistic Modeling	175
7.3.1	Integration of Epidemiologic Data with Other Data Types	176
7.3.2	Designing Experiments to Target Differences Between Models	176
7.3.3	Using State-of-the-Art Techniques for Model Selection and Multimodel Inference	177
7.3.4	Developing and Testing Models	179
7.4	Summary	182
7.4.1	Additional Data Needs: Cancer and Noncancer Disease	183
7.4.2	Additional Model Development and Testing Needs: Cancer and Noncancer Disease	185
	Abbreviations, Acronyms and Symbols	187
	Glossary	190
	References	198
	Scientific Committee	266
	The NCRP	271
	NCRP Publications	282