

Contents

List of chapters:

Detailed contents.....	vi
Terminology and abbreviations	x
1 – Summary overview of the report.....	1
2 – Objectives and format of the report.....	3
3 – Sunlight and skin cancer: recall of essential issues.....	5
4 – Sources of vitamin D.....	10
5 – Toxicity of vitamin D and long term health effects.....	21
6 – Current recommendations for vitamin D intakes	29
7 – Determinants of vitamin D status	33
8 – Biological effects of vitamin D relevant to cancer	52
9 – Ecological studies on sun exposure and cancer	59
10 – Observational studies on individual sun exposure and cancer.....	77
11 – Observational studies on dietary intakes of vitamin D and cancer.....	83
12 – Observational studies on serum 25-hydroxyvitamin D, cancer and all-cause mortality.....	92
13 – Meta-analysis of observational studies on vitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma.....	100
14 – Randomised trials on vitamin D, cancer and mortality.....	113
15 – Vitamin D, cancer prognostic factors and cancer survival.....	119
16 – Special topics: non-Hodgkin lymphoma and VDR genetic variants	122
16 – Special topics: non-Hodgkin lymphoma and VDR genetic variants	122
17 – Vitamin D and cancer in specific populations or conditions	133
18 – Vitamin D: predictor or cause of cancer and of other chronic health conditions?.....	140
19 – Should recommendations for sun protection and vitamin D intakes be changed?	143
20 – Further research: a plea for new randomised trials on vitamin D	145
21 – Overall conclusions of the IARC Working Group on vitamin D and cancer.....	148
References.....	149
Annex Latitude of residence in Europe and serum 25-hydroxyvitamin D levels: a systematic review	201

Detailed contents

1 – Summary overview of the report.....	1
2 – Objectives and format of the report	3
2.1 Background.....	3
2.2 Objectives of the report.....	4
2.3 Format of the report.....	4
2.4 Overview of the methodology used.....	4
3 – Sunlight and skin cancer: recall of essential issues	5
3.1 The skin cancer burden	5
3.2 Wavelengths of solar radiation relevant to skin cancer.....	5
3.3 Action spectra for sunburn, skin cancer and vitamin D synthesis	6
3.4 Malignant melanoma of the skin (“melanoma”).....	6
3.5 Squamous cell carcinoma (SCC).....	7
3.6 Basal cell carcinoma (BCC).....	7
3.7 Exposure to artificial UV light and skin cancer.....	8
3.8 Conclusion.....	8
4 – Sources of vitamin D	10
4.1 Overview of vitamin D physiology	10
4.2 Endogenous skin synthesis of vitamin D ₃	10
4.2.1 Summary of mechanisms.....	10
4.2.2 Constitutive limiting rate for endogenous vitamin D synthesis in the skin	11
4.2.3 Clinical observations on expression of regulation of endogenous vitamin D synthesis	11
4.2.4 UVB in vitamin D skin synthesis and in carcinogenic action	12
4.2.5 Conclusions for endogenous vitamin D synthesis	12
4.3. Exogenous sources of vitamin D	13
4.3.1 Dietary sources of vitamin D	13
4.3.2 Vitamin D ₂ and vitamin D ₃	13
4.3.3 Limiting rate for exogenous vitamin D pathway.....	13
4.3.4 Conclusions on exogenous sources of vitamin D	15
5 – Toxicity of vitamin D and long term health effects	21
5.1 Acute toxicity of vitamin D.....	21
5.2 Long-term use of less than 25 µg vitamin D supplements per day	21
5.3 Use of high doses of vitamin D supplements over several weeks or months	21
5.4 Discussion of the safety of long-term use of high doses of vitamin D	22
5.5 Conclusions	24
6 – Current recommendations for vitamin D intakes	29
6.1 WHO/FAO.....	29
6.2 Europe	29
6.3 United States of America (USA) and Canada.....	30
6.4 Australia, New Zealand.....	30
6.5 Special groups	30
6.5.1 Pregnant and lactating women.....	30
6.5.2 Newborns	31
6.5.3 Elderly people	31
6.6 Conclusions	31
7 – Determinants of vitamin D status.....	33
7.1 Measurement of 25-hydroxyvitamin D level	33
7.2 Skin synthesis.....	33
7.2.1 Exposure to solar ultraviolet B radiation (UVB)	33
7.2.2 Seasonal variations	33
7.2.2.1 Latitudinal variations.....	34
7.2.4 Sunscreen use	34
7.2.5 Decreased sun exposure	35

7.3	Individual characteristics and lifestyle.....	36
7.3.1	Gender	36
7.3.2	Age	36
7.3.3	Obesity	36
7.3.4	Smoking	37
7.3.5	Physical activity	37
7.3.6	Skin pigmentation and ethnicity.....	37
7.4	Interferences with dietary sources	39
7.4.1	Dietary components	40
7.4.2	Dietary or injectable supplements	40
7.4.3	Medications	40
7.4.4	Intestinal absorption disorders	40
7.5	Comparisons between artificial UVB sources and oral supplementation	41
7.6	Relative contribution of multiple determinants on 25-hydroxyvitamin D serum level	41
7.7	Inter individual variations in serum 25-hydroxyvitamin D levels not explained by factors influencing vitamin D bioavailability	42
7.8	Conclusions	43
8 – Biological effects of vitamin D relevant to cancer	52	
8.1	Introduction	52
8.2	Anti-neoplastic properties of the 1 α ,25-dihydroxyvitamin D.....	52
8.3	Extra-renal production of 1 α ,25-dihydroxyvitamin D	52
8.4	Extra-skeletal distribution of VDR	53
8.5	The VDR gene	54
8.6	VDR-mediated and non VDR-mediated anti-neoplastic activities	54
8.7	Effects on the immune system and on inflammatory processes	55
8.8	Cancer resistance to anti-neoplastic effects of 1 α ,25-dihydroxyvitamin D and analogues	55
8.9	Animal models for vitamin D and cancer	55
8.10	Cancer treatment with 1 α ,25-dihydroxyvitamin D ₃ and analogous compounds	56
8.11	Conclusions	56
9 – Ecological studies on sun exposure and cancer	59	
9.1	Background and objective of the chapter.....	59
9.2	Latitude and cancer incidence or mortality	59
9.2.1	Colorectal cancer	59
9.2.2	Prostate cancer	59
9.2.3	Breast cancer	60
9.2.4	Non-Hodgkin lymphomas (NHL)	60
9.2.5	Ovarian cancer	60
9.2.6	Cervical and endometrial/uterine cancer	60
9.2.7	Other tumour types.....	61
9.3	Skin cancer and risk of subsequent cancer	61
9.3.1	Rationale for studying the risk of new primary cancer after skin cancer.....	61
9.3.2	The three major studies.....	61
9.3.3	Other studies on skin cancer and second primary cancer	63
9.3.4	Discussion.....	65
9.4	Issues in interpreting ecological studies	65
9.4.1	Methodological problems	65
9.4.2	Validity of equating latitude to amounts of vitamin D synthesis	66
9.4.3	Discussion of association between latitude and vitamin D status.....	69
9.4.4	Alternatives to vitamin D synthesis.....	69
9.5	Conclusions of the Working Group on ecological studies	71
9.5.1	Studies on latitude and sun irradiance	71
9.5.2	Studies on second primary cancer after non-melanoma skin cancer (NMSC)	71
10 – Observational studies on individual sun exposure and cancer.....	77	
10.1	Background and objective of the chapter.....	77
10.2	Case-control studies	77
10.3	Cohort studies.....	78

10.4	Discussion	79
10.5	Conclusions	80
11 – Observational studies on dietary intakes of vitamin D and cancer		83
11.1	Background and methods	83
11.2	Colonic adenomas and colorectal cancer (CRC)	83
11.3	Other cancers of the digestive tract	84
11.4	Breast cancer.....	84
11.5	Prostate cancer.....	84
11.6	Conclusions	84
12 – Observational studies on serum 25-hydroxyvitamin D, cancer and all-cause mortality		92
12.1	Prospective studies of serum 25-hydroxyvitamin D and cancer risk	92
12.2	Studies of predicted serum 25-hydroxyvitamin D and cancer risk	92
12.3	Specific cancer sites	92
12.3.1	Colorectal cancer	92
12.3.2	Prostate Cancer	94
12.3.3	Breast cancer	95
12.3.4	Pancreatic cancer	96
12.3.5	Ovarian cancer	96
12.3.6	Oesophageal and gastric cancer.....	96
12.4	Total cancer	96
12.5	All-cause mortality	97
12.6	Discussion	98
13 – Meta-analysis of observational studies on vitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma		100
13.1	Objective.....	100
13.2	Background.....	100
13.3	Methodology for literature search	100
13.4	Selection of data and methods of analysis	101
13.5	Description of the main characteristics of studies included in the meta-analysis.....	102
13.6	Information and adjustment on season of blood draw	104
13.7	Results of the meta-analysis.....	104
13.7.1	Pooled estimates.....	104
13.7.2	Heterogeneity analysis	105
13.7.3	Sensitivity analyses and publication bias investigation	105
13.8	Discussion	105
13.9	Conclusions	105
14 – Randomised trials on vitamin D, cancer and mortality		113
14.1	Rationale for randomised trials	113
14.2	Randomised trials on vitamin D supplements and cancer incidence	113
14.2.1	UK trial for the prevention of osteoporotic fractures	113
14.2.2	The Women's Health Initiative Trial.....	113
14.2.3	The Nebraska trial	114
14.2.4	Vitamin D supplements and mortality	114
14.3	Discussion	114
14.3.1	Reasons for the negative result of the WHI trial	114
14.3.2	Critiques of the Nebraska trial	115
14.3.3	Another look at the vitamin D dose issue	116
14.4	Conclusions	116
15 – Vitamin D, cancer prognostic factors and cancer survival		119
15.1	Variation in cancer survival by season of diagnosis	119
15.2	Individual measurement of serum 25-hydroxyvitamin D levels	119
15.3	Skin solar elastosis and survival of patients with cutaneous melanoma	120
15.4	Serum 25-hydroxyvitamin D levels and cancer prognostic factors	120
15.5	Discussion	120
15.6	Conclusions	121
16 – Special topics: non-Hodgkin lymphoma and VDR genetic variants		122
16 – Special topics: non-Hodgkin lymphoma and VDR genetic variants		122
16.1	Sun exposure, vitamin D and risk of haemopoietic cancers	122

Vitamin D and Cancer

16.1.1	Non Hodgkin lymphoma (NHL)	122
16.1.2	Other lympho-hematopoietic cancers.....	125
16.1.3	Conclusions.....	125
16.2	VDR genetic variants and cancer	126
16.2.1	VDR polymorphisms and cancer risk	126
16.2.1.1	Prostate cancer	126
16.2.1.2	Breast cancer	126
16.2.1.3	Colorectal cancer	126
16.2.1.4	Other cancers	127
16.2.2	Vitamin D ₃ receptor and cancer prognosis	127
17 –	Vitamin D and cancer in specific populations or conditions.....	133
17.1	Introduction	133
17.2	Search strategy.....	133
17.3	African, Hispanic and Native Americans.....	133
17.4	Asian and North African migrants in Europe.....	134
17.5	End stage renal disease	134
17.6	Psoriasis	135
17.7	Crohn's and celiac diseases	136
17.8	Obesity.....	136
17.9	Obese patients treated with bariatric surgery	137
17.10	Conclusions	137
18 –	Vitamin D: predictor or cause of cancer and of other chronic health conditions?	140
18.1	Low vitamin D status: marker or cause of poor health status?	140
18.2	Results in favour of vitamin D status being an indicator of poor health or a predictor of chronic disease	140
18.3	Results in favour of vitamin D status being a causal factor for poor health and chronic disease occurrence	141
19 –	Should recommendations for sun protection and vitamin D intakes be changed?	143
19.1	On the concepts of “deficiency”, “insufficiency” and “optimal” vitamin D status	143
19.2	Should recommendations for vitamin D intakes be changed?	143
19.3	Should recommendations for sun protection of light-skinned populations be changed?	143
20 –	Further research: a plea for new randomised trials on vitamin D	145
21 –	Overall conclusions of the IARC Working Group on vitamin D and cancer	148
	References	149
	Annex	201