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Table of Contents

Abbreviations 2
List of figures 2
List of tables 2
1. The aim 3
2. Genetic susceptibility to spontaneous and radiation-induced cancers 3
3. Non-genetic factors predisposing to spontaneous and radiation-induced cancers 5
3.1. Smoking 5
3.2. Reproductive factors 5
3.3. Age and sex 5
3.4. Race and/or ethnicity 6
3.5. Body mass index 7
3.6. Chemotherapy 7
4. Cancer risk models and transfer of risk between patient cohorts 8
References 10

Abbreviations

SMN second malignant neoplasm

SPC Second Primary Cancer

List of figures

Figure 1. Schematic overview of the relationship between the relative susceptibility and age at exposure. Concept based on a presentation by Kotaro Ozasa given at the 5th International Symposium on the System of Radiological Protection, Adelaide, 18-21 November 2019.

List of tables

Table 1. Effects of heritable and environmental factors in cancers at various sites, according to data from the Swedish, Danish and Finnish twin registries.

Table2. Number of deaths and excess relative risk (ERR) estimates per Gy for specific causes of death by sex among members of the Life Span Study cohort.

1. The aim

The aim of this deliverable is to review and determine the contribution of genetic and environmental factors that influence the organ-specific risk of second malignant neoplasm (SMN) and to develop models of risk transfer between patient populations. A review analysis was carried out of factors influencing the individual risk of developing SMN. How high is the contribution of the genetic and environmental factors to the individual risk of SMN? What is the nature of the interaction of ionising radiation with co-exposures to other agents (e.g. multiplicative, additive) for various cancers and how the information should be considered for risk transfer between different patient populations?

The deliverable is partly based on literature and documents prepared by the UNSCEAR task group working on second primary cancer after radiotherapy. The author of this deliverable is a member of the group.

2. Genetic susceptibility to spontaneous and radiation-induced cancers

Genetic susceptibility to cancer is based on gene changes, or mutations, that can be inherited and increase the individual risk of developing the disease. Most cases of susceptibility are based on genes inherited in an autosomal dominant manner with incomplete penetrance, increasing the risk of specific cancer types. Most common examples are (Garber and Offit 2005):

- Hereditary breast and ovarian cancer syndrome (HBOC), caused by mutations in the BRCA1 and BRCA2 genes that increase the risk of breast and ovarian cancer in women and breast and prostate cancer in men.
- Cowden syndrome (CS), caused by mutations in the PTEN gen that increase the risk of developing benign and malignant tumors of the breast, uterus and thyroid.
- Lynch syndrome (HNPCC) caused by mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6 or PMS2) that increase the risk of colorectal cancer and uterine (endometrial) cancer as well as other extracolonic tumors.
- Familial adenomatous polyposis (FAP) caused by mutations in the APC gene that increase the risk of colon cancer.
- Hereditary Leukemia and Hematologic Malignancies Syndromes caused by mutations in several genes such as FANCA, RAD51 (leukemias) and CEBPA or DDX41 (myeloid neoplasms).

Two rare genetic disorders increase the risk of multiple types of cancer that usually occur early in life. One is the Li-Fraumeni Syndrome (LFS) that is based on mutations in the TP53 gene. It is inherited in an autosomal dominant pattern where one copy of the altered gene is sufficient to increase the risk of developing cancer. The other is Ataxia telangiectasia that is based on mutations in the ATM gene. It is inherited in the autosomal recessive disease were both copies of the gene must be mutated for the disease to occur. Heterozygotes of the gene are normal but have an increased risk of developing breast cancer. Finally, mutations in the RB gene increase the risk of retinoblastoma during childhood and, to a lower extent, of multiple cancer later in life.

Although the risk of cancer is high in persons with cancer susceptibility mutations/syndromes, the carrier frequency is rather low. This translates into a relatively low impact of genetic factors to overall cancer etiology. Indeed, studies on monozygotic and dizygotic pairs of twins suggest that inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms (table 1) (Lichtenstein et al. 2000).

Table 1. Effects of heritable and environmental factors in cancers at various sites, according to data from the Swedish, Danish and Finnish twin registries. Source: (Lichtenstein et al. 2000).

Site or Type	Proportion of Variance (95% CI)*			Fit of Model	
	Heritable factors	Shared environmental factors	Nonshared environmental factors	χ^2 (df)	P value
Stomach	0.28 (0–0.51)	0.10 (0–0.34)	0.62 (0.49–0.76)	8.9 (38)	1.0
Colorectum	0.35 (0.10–0.48)	0.05 (0–0.23)	0.60 (0.52–0.70)	25.8 (38)	0.93
Pancreas†	0.36 (0–0.53)	0 (0–0.35)	0.64 (0.47–0.86)	0.5 (3)	0.92
Lung	0.26 (0–0.49)	0.12 (0–0.34)	0.62 (0.51–0.73)	28.1 (38)	0.88
Breast‡	0.27 (0.04–0.41)	0.06 (0–0.22)	0.67 (0.59–0.76)	10.1 (18)	0.93
Cervix uteri†‡	0 (0–0.42)	0.20 (0–0.35)	0.80 (0.57–0.97)	0.3 (3)	0.96
Corpus uteri‡	0 (0–0.35)	0.17 (0–0.31)	0.82 (0.64–0.98)	6.6 (18)	0.99
Ovary‡	0.22 (0–0.41)	0 (0–0.24)	0.78 (0.59–0.99)	6.0 (18)	1.0
Prostate§	0.42 (0.29–0.50)	0 (0–0.09)	0.58 (0.50–0.67)	26.5 (18)	0.09
Bladder†	0.31 (0–0.45)	0 (0–0.28)	0.69 (0.53–0.86)	1.7 (3)	0.64
Leukemia†	0.21 (0–0.54)	0.12 (0–0.41)	0.66 (0.45–0.88)	0.0 (3)	0.99

*CI denotes confidence interval.
†Data for all countries and both sexes are pooled because of small numbers.
‡Data are for women only.
§Data are for men only.

The interesting question is how far susceptibility to spontaneous cancers influences susceptibility to radiation-induced cancers. Major source of knowledge comes from studying patients treated by radiotherapy who developed SMN. There is no doubt that heterozygous carriers of ATM mutations are susceptible to radiogenic cancer (AGIR 2013). Also, enhanced risk of radiogenic cancer is observed among retinoblastoma patients (Schonfeld et al. 2021). Interestingly, radiation has been found not to interact with BRCA1 and BRCA2 carriers (AGIR 2013). Also, despite a strong theoretical rationale, Li-Fraumeni patients do not appear to have an increased risk of radiogenic cancers (Hendrickson et al. 2020).

The development of whole genome sequencing allowed studies to identify common genetic variants that could be associated with cancer risk in the general population as well as variants that could be associated with response to cancer treatment. Those studies generally investigated known variants in candidate genes, such as involved in DNA damage response. However, very few of the results from candidate gene studies cold be consistently replicated in independent study populations (Morton et al. 2018; Rajaraman et al. 2018). More recently, genome wide association studies (GWAS) are carried out to identify, in an hypothesis-free approach, potential single nucleotide polymorphisms (SNP) that correlate with an increased risk SMN also termed second primary cancers (SPC). Potential risk alleles were identified in PRDM1, POX1 and TAGLN genes, but have not been validated (Morton et al. 2018).

A lack of low impact of the genetic background on susceptibility to radiation-induced cancer is also demonstrated by the analysis of the relationships between radiation exposure and risks of first and second primary cancers among Hiroshima and Nagasaki survivors. It was found that radiation exposure confers equally high relative risks of second as first primary cancers, suggesting that patients who developed primary cancers are not characterized by an enhanced susceptibility to radiogenic cancer (Li CI et al. 2010).

3. Non-genetic factors predisposing to spontaneous and radiation-induced cancers

Apart from the genetic factor in causation, cancer is believed to originate from replication errors in the stem cell component of tissues (Tomasetti et al. 2017) and from environmental factors (Golemis et al. 2018). The relative contribution of these factors is difficult to generalize, but currently it is assumed that between 40% and 45% of cancers are associated with preventable risk factors, mainly environmental. These include mainly smoking, natural background radiation (UV and ionising), obesity and diet (Gapstur et al. 2018; Golemis et al. 2018). In addition, the host factors age and sex predispose to cancer.

How far do these factors interact with radiation in inducing cancer?

3.1. Smoking

Smoking is known to interact with radon and gamma radiation in inducing lung cancer (Darby et al. 2005; Cahoon et al. 2017) and the interaction is regarded as sub-multiplicative. In patients treated for Hodgkin´s lymphoma smoking potentiated the risk of SMN, resulting in risk levels stronger than the sum of the individual effects (Gilbert et al. 2003). Smoking also potentiates radiogenic lung cancer in patients treated by radiotherapy for breast cancer (Kaufman et al. 2008). The results were confirmed in a more recent large study where smoking was observed to potentiate not only radiotherapy-related SMN of the lung but all smoking-related cancers that include cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, esophagus (adenocarcinoma/squamous cell carcinoma), stomach, colorectum, liver, pancreas, nasal cavity/paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous), urinary bladder, kidney (body/pelvis) and ureter, and myeloid leukemia (Shiels et al. 2014). Similar results were reported by (DiMarzio et al. 2018).

3.2. Reproductive factors

Age at menarche is known as an important factor potentiating the effect of radiation on breast cancer among Hiroshima and Nagasaki survivors (Brenner et al. 2018). Similar results were observed among cancer patients treated by radiotherapy where the highest risk of SMN was seen in women who were irradiated close to menarche (Cooke et al. 2013). Also menopausal age was shown to impact the risk of second primary breast cancer in survivors of Hodgkin's lymphoma and childhood cancer treated with chest radiotherapy (Cooke et al. 2013). In accordance with this Hodgkin's lymphoma patients with the longest duration of intact ovarian function after treatment experienced a much larger risk of second primary breast cancer compared with those entering premature menopause relatively shortly after treatment (De Bruin et al. 2009). On the other hand, a later study did not show any association between gonadal hormones and the risk of second primary breast cancer in Hodgkin's lymphoma patients (Krul et al. 2017).

3.3. Age and sex

The impact of age on susceptibility to radiation-induced cancer was summarized in detail by UNSCEAR (2013 2013) and more recently by Wojcik and Pei (Wojcik 2020). A schematic summary of the relationship between sensitivity and age at exposure in shown in figure 1. For all cancers pooled, the sensitivity decreases with age at exposure. However, strong differences exist for individual cancer types so pooling of all cancers leads to a strong

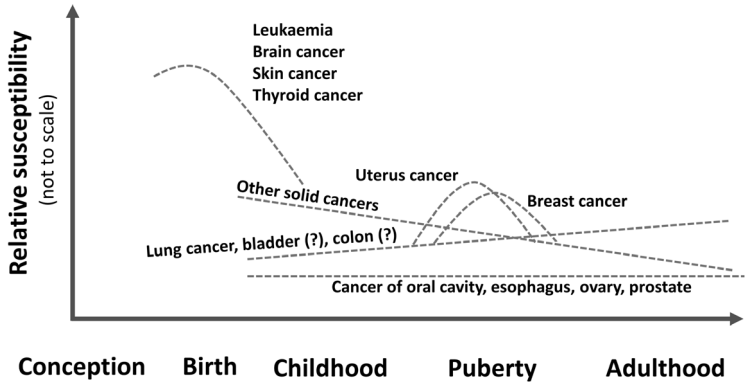

Figure 1. Schematic overview of the relationship between the relative susceptibility and age at exposure. Concept based on a presentation by Kotaro Ozasa given at the 5th International Symposium on the System of Radiological Protection, Adelaide, 18-21 November 2019. Source: (Wojcik 2020).

With respect to sex, women show an approximately two times higher excess relative risk per Gy as compared to men (Ozasa et al. 2012). The reverse is true for leukemias (table 2).

Table 2. Number of deaths and excess relative risk (ERR) estimates per Gy for specific causes of death by sex among members of the Life Span Study cohort. Source: (Ozasa et al. 2012).

Number of Deaths, Excess Relative Risk (ERR) Estimates per Gy for Specific Causes of Death by Sex

Cause of death	Based on radiation dose to:	Males				Females			
		Number of deaths	ERR/Gy[a]	(95% CI[b])	*P*	Number of deaths	ERR/Gy[a]	(95% CI[b])	*P*
All causes	Colon	22302	0.15	(0.10, 0.20)	<0.001	28318	0.30	(0.24, 0.35)	<0.001
Cancer									
All solid cancer	Colon	5235	0.31	(0.21, 0.42)	<0.001	5694	0.66	(0.52, 0.80)	<0.001
Esophagus	Stomach	260	0.39	(−0.006, 0.97)	0.054	79	1.1	(0.04, 3.0)	0.04
Stomach	Stomach	1689	0.13	(−0.02, 0.30)	0.09	1436	0.51	(0.28, 0.78)	<0.001
Colon	Colon	262	0.50	(0.09, 1.09)	0.01	359	0.58	(0.16, 1.1)	0.003
Rectum	Bladder	199	−0.26	(NA[c], 0.19)	0.18	228	0.66	(0.06, 1.5)	0.03
Liver	Liver	879	0.30	(0.08, 0.58)	0.006	640	0.46	(0.15, 0.85)	0.002
Gallbladder	Liver	121	0.85	(0.19, 1.9)	0.005	298	0.23	(−0.12, 0.76)	0.24
Pancreas	Pancreas	210	0.22	(−0.17, 0.83)	0.33	303	−0.06	(NA[c], 0.43)	>0.5
Other digestive system	Colon	33	0.26	(NA[c], 2.33)	>0.5	51	2.6	(0.51, 6.6)	0.005
Lung	Lung	901	0.40	(0.17, 0.67)	<0.001	657	1.1	(0.68, 1.6)	<0.001
Breast	Breast	6	9.1	(0.52, 128)	0.01	324	1.5	(0.93, 2.3)	<0.001
Uterus	Uterus	–				547	0.22	(−0.09, 0.64)	0.19
Ovary	Ovary	–				157	0.79	(0.07, 1.9)	0.03
Prostate	Bladder	130	0.33	(NA[c], 1.2)	0.30	–			
Bladder	Bladder	100	0.88	(0.02, 2.3)	0.04	83	1.5	(0.21, 3.8)	0.02
Kidney parenchyma	Colon	42	0.11	(NA[c], 1.4)	>0.5	38	1.5	(0.01, 4.9)	0.049
Renal pelvis and ureter	Colon	13	3.5	(0.25, 14)	0.02	20	1.9	(NA[c], 8.0)	0.13
Other	Colon	390	0.36	(0.02, 0.83)	0.04	474	0.54	(0.14, 1.0)	0.005
Lymphoid and hematopoietic malignancies									
Leukemia	Bone marrow	163	4.6	(3.0, 6.9)	<0.001	155	3.9	(2.5, 6.1)	<0.001
Malignant lymphoma	Bone marrow	125	0.70	(0.08, 1.7)	0.02	159	−0.18	(−0.21, 0.24)	0.33
Multiple myeloma	Bone marrow	34	0.11	(NA[c], 1.6)	>0.5	59	0.86	(0.02, 2.5)	0.04
Other neoplasms	Colon	224	0.30	(−0.10, 0.88)	0.17	294	1.1	(0.44, 2.0)	<0.001
Non-neoplastic diseases									
Blood diseases	Bone marrow	80	1.8	(0.68, 3.8)	<0.001	158	1.6	(0.76, 2.8)	<0.001
Circulatory disease	Colon	7607	0.07	(−0.001, 0.16)	0.053	11447	0.14	(0.06, 0.23)	<0.001
Respiratory disease	Colon	2401	0.16	(0.02, 0.31)	0.02	2718	0.28	(0.11, 0.47)	<0.001
Digestive disease	Colon	1659	0.05	(−0.09, 0.23)	0.50	1735	0.18	(−0.01, 0.40)	0.07
Genitourinary disease	Colon	449	−0.07	(NA[c], 0.28)	>0.5	860	0.28	(0.01, 0.62)	0.04
Infectious disease	Colon	1043	0.01	(−0.16, 0.22)	>0.5	919	−0.07	(NA[c], 0.18)	>0.5
Other disease	Colon	1830	0.03	(−0.12, 0.21)	>0.5	3017	−0.01	(−0.15, 0.15)	>0.5
External causes	Colon	1372	−0.24	(NA[c], −0.11)	0.001	1060	0.14	(−0.07, 0.41)	0.21

[a] ERR was estimated using the linear dose model, in which city, age at bombing, and attained age were included in the background rates, but not as radiation effect modifiers.
[b] The lower limit was not estimable, but an implicit lower bound (1/d_max) was −0.28 for males and −0.27 for females (see text).

3.4. Race and/or ethnicity

It is well known that the spontaneous incidence of certain types of cancer differ by region (Doll 1967). Being either the effect of life-style factors or race. Several authors analysed the impact of race on radiotherapy-related SMN among prostate and breast cancer patients. In the USA spontaneous prostate cancer incidence

is threefold higher among black men than among Asian/Pacific islanders (Withrow et al. 2020). Following RT, a significantly higher risk of SMN (several cancers combined) was observed among Asian/Pacific islanders as compared to non-Latino white men, black men and Latino men (Withrow et al. 2020). A somewhat different results was reported for bladder cancer as SMN: white men had a significantly higher risk than black men (Zhang et al. 2021). Among breast cancer survivors, the risk of SMN was higher in black women and Asian/Pacific islanders as compared to Hispanic and non-Hispanic white women (Calip et al. 2015). A very similar conclusion was reached by authors of a study that focused on the risk of second primary contralateral breast cancer (Watt et al. 2021).

3.5. Body mass index

Overweight/obesity is a risk factor for many primary cancers, notably colorectal cancer, as well as breast, endometrial, oesophageal, pancreatic, and kidney cancers (Golemis et al. 2018). Not surprisingly, high body mass index is associated with a high risk of SMN in patients treated for breast cancer (Druesne-Pecollo et al. 2012) and colon cancer (Gibson et al. 2014). Interestingly, in the latter study the risks were similar in magnitude to those observed for first cancers in this population suggesting increased prevalence of overweight or obesity, rather than increased susceptibility to treatment.

3.6. Chemotherapy

Radiotherapy (RT) is often combined with chemotherapy (CT) with the aim of improving cancer cure. The enhanced efficacy of combined therapy (radiochemotherapy) is attributed to spatial cooperation and enhancement of radiation effects (Nishimura 2004). Spatial cooperation refers to the action of CT on distant metastases and RT on the primary tumor. Enhancement of radiation effect on the primary tumor is based on: 1) augmentation of radiation damage by incorporating drugs into cancer cell DNA, (2) inhibition of RT-induced DNA damage repair, (3) redistribution of cell cycle phases leading to accumulation of cancer cells in a radiosensitive phase, (4) elimination of hypoxic cells, and (5) inhibition the cell repopulation.

The interaction between RT and CT is not restricted to cancer tissue but also applies to normal tissues. Thus, it is not surprising that CT potentiates RT-induced early and late toxicities (Bentzen et al. 2007; AGIR 2013). However, a higher level of toxicity does not necessarily correlate with a higher risk of SPC. The reason for this is that toxicities, especially late ones, are caused by cell death while SPC can only arise in cells that survive with cancer-related mutations in the DNA.

The impact of various CT modalities on the risk of RT-induced SPC has been published by several authors. Risk is often given for pooled SPC types because of poor statistical power when particular cancer sites are analysed. As one of the first, D´Angio et al. (D'Angio et al. 1976) observed that actinomycin-D reduced the risk of RT-induced SPC in a cohort of patients with various primary cancers. CT consisting of cyclophosphamide, vinca alkaloids and antifolic agents had no effect on the risk of RT-induced SPC (D'Angio et al. 1976). A reduced risk of RT-induced SPC was observed among 20-year or longer survivors of childhood cancers treated by a combination pf CT and RT as compared to RT alone (Turcotte Lucie M et al. 2019). The results of these epidemiological studies received support from an experimental study, where CT in combination with RT induced a lower level of cytogenetic damage in peripheral blood lymphocytes than RT alone (Wegierek-Ciuk et al. 2021). The results negatively correlated with the level of apoptosis, suggesting that the reduced level of cytogenetic damage was caused by a selective elimination of cells damaged by combined CT and RT treatment. However, studies exist where a potentiation of RT-induced SPC risk was potentiated by CT. A study focusing on breast cancer induced by RT of childhood cancers revealed that combination of doxorubicin and RT potentiates the risk of SPC as compared to RT alone (Veiga et al. 2019). Similarly, it was observed that doxorubicin potentiates the risk of RT-induced SMN among Wilm´s tumor

patients (Breslow et al. 1995). Guerin et al. (Guerin et al. 2007) caried out a pooled analysis of risk factors contributing to SPC following treatment of various primary cancers and found that CT generally potentiated the risk of RT-induced SPC, with concomitant treatments having a stronger effect than sequential treatments. A potentiating effect of CT on RT-induced leukaemia was also reported by Haddy et al. (Haddy et al. 2006) who studied survivors of childhood malignancies. The conclusion from all the studies is that there is not a single pattern of how CT modifies the risk of RT-induced SPC.

An interesting question is how far CT alone induces SPC. Here, the results are also controversial, not in the least because many studies are small, lacking statistical power. A recent metanalysis revealed that treatment with cisplatin is not associated with a significantly increased risk of SPC (Liang et al. 2017). However, high doses of cisplatin, alkylating agents and doxorubicin can lead to SPC among childhood cancer survivors (Turcotte L. M. et al. 2019; Veiga et al. 2019). These conclusions are supported by a study of the Dutch Childhood Cancer Oncology Group showing that both doxorubicin and cyclophosphamide increase the risk of SPC (Teepen et al. 2017). However, reports also exist demonstrating that CT of adult breast cancer patients leads to a reduction of SPC risk (Schaapveld et al. 2008; Li Z et al. 2020). So does chemotherapy for Hodgkin disease (Travis et al. 2003; Schaapveld et al. 2008).

Given the multitude of factors that promote cancer formation (Hanahan and Weinberg 2011; Fouad and Aanei 2017) it is not surprising that the sole activity of CT and its interaction with RT can have various effects on normal tissue of patients, depending on the type and dose of therapy, location of the primary cancer and the individual patient response. That CT can induce SPC can be explained by the mutagenic action of the drugs leading to cell transformation (Blagosklonny 2005) and by its inhibitory effect on the immune system leading to loss of cancer immunosurveillance (Zitvogel et al. 2008). That it can reduce the risk of SPC can be explained by the elimination of radiation-damaged cells or – as in the case of breast cancer – by ovarian ablation leading to modified hormonal status of the survivors (Schaapveld et al. 2015).

In conclusion, reports exist showing that chemotherapy can both enhance and reduce the risk of radiotherapy-induced SMN. Thus, a generalised statement regarding its role in SMN is not possible.

4. Cancer risk models and transfer of risk between patient cohorts

The AGIR and BEIR VII reports give excellent summaries of the problem of transferring risk between populations in the situation of uncertainty regarding the mode of interaction of radiation with risk modifiers (BEIR_VII 2006; AGIR 2013). The text below is largely based on these reports.

The summary risk coefficients of radiation induced cancer risk are expressed either as excess relative risk (ERR) or excess absolute risk (EAR) experienced over a lifetime as a result of receiving a unit dose of radiation. The cancer risk models used to predict the incidence or mortality of cancer in an exposed population are expressed either in terms of ERR or EAR. For predicting the risk of cancer in the same population from which data was derived the selection of the model is of little relevance. However, this does become important when a model developed based on a specific population is used to predict the risk of radiogenic cancer in a different population characterized by a different background cancer risk. ERR models imply that radiation interacts with factors responsible for the background cancer level and increases the level proportionally. EAR models assume no interaction, meaning that radiation will increase the cancer level by a certain number that is related to the dose, irrespective of the background. If risk is transferred from a population with a high to a population with a low background cancer level, the use of an ERR model will result in a lower absolute number of predicted cases. If the EAR model is used, a fixed number of cancer cases is transferred implying a reduction of the relative risk. So, the effect of radiation upon the risk of cancer in different populations

(with different background incidence rates) is indicative of the influence of background factors upon the radiogenic risk and therefore of the sensitivity of an individual to radiogenic cancer (since individuals will be exposed to different levels of background factors in any particular population). However, this will only be the case if transfer of radiogenic risk from one population to another is more than additive (ie some interaction with background factors exist) and there is a significant difference between background rates of a particular cancer type.

In the field of radiological protection, the problem of risk transfer applies to situations where cancer risks due to low doses are predicted based on the unit of effective dose derived from the LSS. However, it also applies to the problem of predicting the risk of SMN in a cohort of patients based on data from a different cohort. The doses absorbed by normal tissues of cancer patients are higher than those relevant for radiological protection of the general population. Also, cancer patients are usually exposed to co-therapies such as chemotherapy which can have an impact on the risk of radiogenic cancer. So the mode of risk transfer between patient cohorts may be different from that applied to cohorts of the general population.

There are two approaches based on epidemiologic data that can be used to select the most appropriate risk transfer model. The first approach is based on investigating interactions of various risk factors with radiation. Here, a problem are the numerous confounding factors and the results described in this report demonstrate that, except for smoking, for which the mode of interaction is clearly multiplicative, the nature of interaction between radiation and other environmental factors is poorly understood. Hence, this approach cannot be used to deduce the right risk transfer model for cancer patients undergoing radiotherapy.

The second approach is to compare risk estimates based on one cohort to that in another cohort. If estimates of ERR per Sv/Gy are comparable, this suggests that relative risk transport may be appropriate, whereas if estimates of the EAR per person-year-Sv/Gy are comparable, this suggests that absolute risk may be appropriate. For studies on the general population, some comparative investigations on some of the commoner types of cancer have been carried out: Preston et al. (Preston et al. 2002) examined breast cancer in eight groups, Ron et al. (Ron et al. 1995) studied thyroid cancer in seven groups and Little et al. (Little et al. 1999) studied leukemia in three groups exposed to radiation. Based on these investigations, the ICRP, in its latest recommendations (ICRP_103 2007) inferred the nature of the transfer of risks between populations. It concluded that insufficient information exists for most types of cancer to assume anything other than a 0.5:0.5 mixture of the transfer of the ERR and EAR between populations. The exceptions are breast and leukemia, for which pure EAR models are used, thyroid and skin, for which pure ERR models are used, and lung for which a 0.3 ERR and 0.7 EAR model is used. Interestingly, BEIR VII (BEIR_VII 2006) recommends a similar approach, except that a somewhat higher weight for the ERR is suggested for all cancers except breast, thyroid and leukemia, for which the mode of transfer is similar to that suggested by the ICRP.

Comparative analyses between patient cohorts have not been carried out for the risk of SMN. Consequently, it is currently not clear whether a different approach should be adopted for transferring risk between patient cohorts than that adopted by the ICRP for transferring risk between populations of healthy people. In view of lack of evidence for the contrary, it appears most prudent to rely on the risk transfer approach applied by the ICRP.

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