14 Subsequent Primary Cancer After Childhood, Teenage and Young Adult Cancer

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14.1 Introduction

Survivors of childhood cancer experience substantial premature mortality, for example, from the original British Childhood Cancer Survivor Study (BCCSS) cohort (n = 17,981) by 50 years from diagnosis, 30% of 5-year survivors have died when 6% would be expected to have died from mortality rates in the general population (see Fig. 14.1) [1]. Analysis of the same cohort revealed that among survivors at least 45 years from diagnosis, 51% of excess number of deaths were caused by subsequent primary cancer [1]. The original cohort included survivors of cancer diagnosed before 1992, and the cohort has now been extended to include 5-year survivors diagnosed up to 2006 (n = 34,489), and analysis of this extended cohort revealed that among survivors aged 40–49, 50–59 or 60 and older subsequent primary cancer caused 37%, 41% and 31% of the excess number of deaths [2].

We report recent evidence relating to risks, risk factors, and the international initiative to standardise clinical follow-up guidelines which have been published mostly during the past decade. Given the space limitations, we have had to focus on selected research areas where important new data has emerged or where a specific area of research has been identified which is likely to be important for the future.

14.2 Risks of Subsequent Primary Cancer After Childhood Cancer

The types of subsequent primary cancer observed in excess of expected from the general population vary strongly by both attained age and interval from diagnosis. For example within the BCCSS brain tumours (21%) and sarcomas (41%) accounted for 63% of the excess number of SPNs observed among survivors aged 5–19 years; in contrast 52% of the excess number of SPNs observed among survivors aged over 40 years were carcinomas of digestive, genitourinary, respiratory and breast sites, which account for 18%, 18%, 9% and 7% of overall 52%, respectively [3]. These findings were broadly similar to the large-scale population-based cohort from the Nordic countries which also had sufficient follow-up beyond 40 years of age to satisfactorily assess risk [4].

Recently the German Childhood Cancer Registry (Deutsches Kinderkrebsregister, DKKR)

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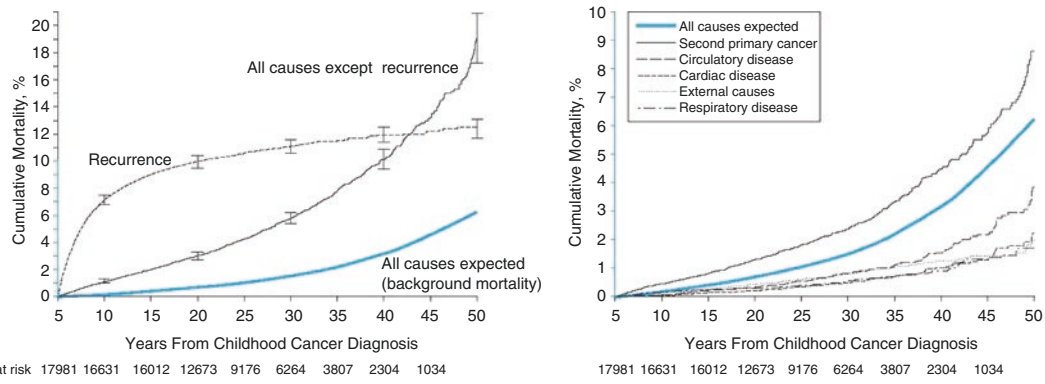

Observed cumulative mortality of all causes of death other than recrrence was 19.0% at 50 years from initial diagnosis, whereas 6.3% was expected based on rates from the general population. Cumulative mortality of death due to recurrence increased rapidly with time from diagnosis to 8.9% by 15 years but then levelled off to 12.4% by 50 years. Cumulative mortality for each cause of death takes into account other causes of death as a competing risk. For second primary cancer, cumulative mortality increased gradually with time to 2.4% by 30 years but then increased rapidly to 8.6% by 50 years. For circulatory disease, the cumulative mortality was low by 30 years (0.8%) but increased to 3.9% by 50 years. Segment of y-axis shown in blue indicates cumulative mortality range of 0% to 10%. Error bars indicate 95& confidence intervals.

Fig. 14.1 Cumulative mortality of causes of death among survivors of childhood cancer. With permissions from [1]

published on subsequent primary neoplasms after a follow-up of up to 35 years in 47,650 survivors a cumulative incidence of 8.27%. Subsequent primary neoplasms were more common in female patients and in those who had a systemic cancer as their initial malignancy. However only patients were included (1980–2014) who were no more than 14 years old at the time of diagnosis and survived at least 6 months thereafter and there are no detailed data on the therapy approaches [5].

In the British Childhood Cancer Survivor Study, the finding that subsequent primary digestive cancer accounted for 18% of the excess number of subsequent primary cancers observed overall among those aged over 40 years is of particular interest because of well-established success of bowel cancer screening in the general population. We therefore compared the risk of bowel cancer among childhood cancer survivors who received direct abdominopelvic radiotherapy with those who have at least one or at least two first-degree relatives previously diagnosed with bowel cancer (see Fig. 14.2) [3]. It is clear that those receiving abdominopelvic radiotherapy experience a risk of subsequent primary bowel cancer which exceeds that observed among the population of individuals with at least two first-degree relatives diagnosed with bowel cancer. In Britain the latter population are currently being considered for screening colonoscopy under the National Health Service bowel cancer screening programme, but currently there are no British survivorship guidelines relating to the directly irradiated abdominopelvic group of survivors of childhood cancer.

Survivors of Wilms' tumour were particularly at risk because 50% of the excess number of deaths observed beyond 30 years from diagnosis was caused by subsequent primary cancer, digestive cancer and most frequently bowel, accounted for 41% of the excess number of cancers observed beyond 30 years from diagnosis [6].

As indicated above brain tumours account for a substantial proportion of the excess number of subsequent primary neoplasms observed in the initial years following diagnosis of childhood cancer. In the BCCSS 9.1% of those irradiated for a childhood brain tumour experienced a sub-

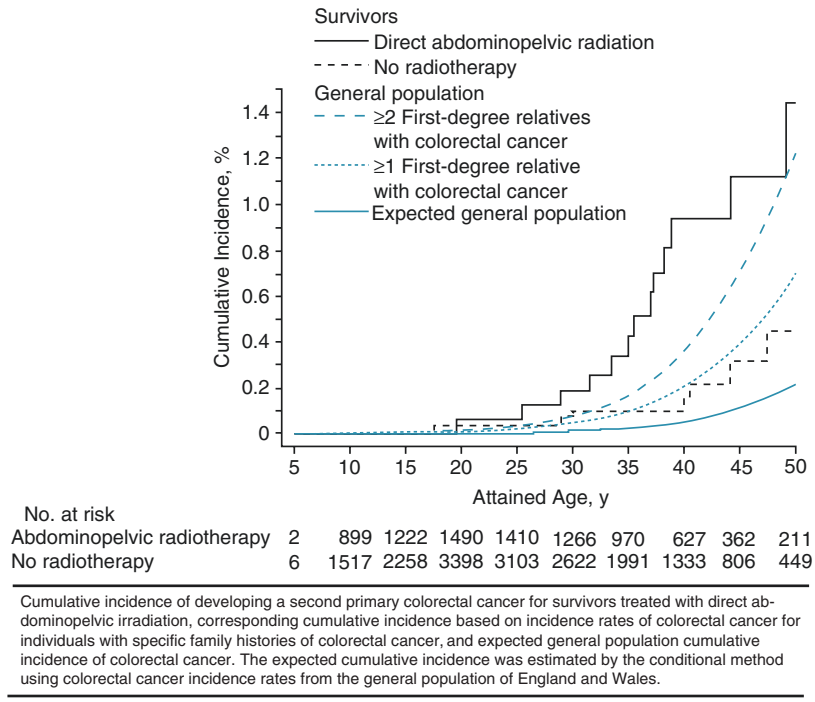

Fig. 14.2 Cumulative incidence of developing subsequent colorectal cancer for survivors treated with direct abdominopelvic irradiation. With permissions from [3]

sequent primary brain tumour by 40 years from diagnosis of original childhood brain tumour [7].

Recently a pan-European collaboration has begun to exploit the advantages which Europe has, one of which relates to the establishment of population-based cancer registration in the Nordic countries and the UK during the 1940s, 1950s and 1960s. The PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup) subsequent primary cancer cohort comprises the largest ever assembled such cohort comprising 69,460 5-year survivors of cancer diagnosed before 20 years in 12 European countries within which there was systematic ascertainment of all subsequent primary cancers diagnosed [8, 9].

Although there was ascertainment of all subsequent primary cancers diagnosed among the PanCareSurFup survivors, there was particular focus relating to subsequent primary bone, soft tissue sarcoma, digestive and genitourinary cancers because these four cancer types account for a substantial proportion of the excess number of subsequent primary cancers in the short and long term. The original aim was to include approximately 300 subsequent primary cancers of each of these four types in a nested case-control study to investigate the extent to which cumulative dose of radiation from radiotherapy, cumulative dose of specific cytotoxics and particular genotypic factors extracted from saliva were related to risk of developing specific types of subsequent primary cancer. So far we have published the cohort studies relating to bone [10] and soft tissue sarcoma [11].

14.3 Risks of Subsequent Primary Cancer After Adolescent and Young Adult (AYA) Cancer

Previous large-scale studies of survivors of AYA cancer have tended to focus on risks of subsequent primary neoplasms after the common cancers such as lymphoma, testicular and breast cancer. Only two studies have investigated the risks of developing any subsequent primary neoplasm after each type of AYA cancer. One study was based on SEER registry data, and the main finding from this study was that AYA cancer survivors had a higher absolute risk of developing a subsequent primary neoplasm compared to childhood or adult cancer survivors [12]. However, this study did not investigate the risks of specific subsequent primary neoplasms after each AYA cancer [12]. Recently published is the largest ever study to investigate the risks of subsequent primary neoplasms after each specific AYA cancer and the first to provide excess risks of specific types of subsequent primary neoplasm after each of 16 types of AYA cancer: breast, cervix, testicular, Hodgkin lymphoma (female), Hodgkin lymphoma (male), melanoma, CNS, colorectal, non-Hodgkin lymphoma, thyroid, soft tissue sarcoma, ovary, bladder, other female genital, leukaemia and head and neck, the Teenage and Young Adult Cancer Survivor Study (TYACSS) [13]. The TYACSS is a population-based cohort of 200,945 5-year survivors of cancer diagnosed when aged 15–39 years in England and Wales from January 1971 to December 2006. During 2,631,326 person-years of follow-up, 12,321 subsequent primary neoplasms were diagnosed in 11,565 survivors [13].

We reproduce, Table 14.1, from a recent publication relating to TYACSS which illustrates two key new findings [13]. Firstly, in individuals who survived at least 30 years from diagnosis of cervical cancer, testicular cancer, Hodgkin lymphoma in women, breast cancer and Hodgkin lymphoma in men, we identified a small number of specific subsequent primary neoplasms that account for 82%, 61%, 58%, 45% and 41% of the total excess number of neoplasms, respectively, and provide an evidence base to inform priorities for clinical long-term follow-up [13]. Secondly, lung cancer accounted for a substantial proportion of the excess number of neoplasms across all AYA groups investigated and indicates a need for further work aimed at preventing and reducing the risk of this cancer among future survivors. This latter finding is in marked contrast to survivors of childhood cancer who do not experience such substantial excess risks of lung cancer, and this likely relates to the evidence that survivors of AYA smoke notably in excess of expected from the general population, whilst in contrast survivors of childhood cancer smoke much less than expected from the general population [13].

14.4 Factors Related to the Risk of Subsequent Primary Neoplasms

14.4.1 Radiation from Radiotherapy

The extent to which tissue is sensitive to the carcinogenic effects of radiation from radiotherapy varies greatly depending on the organ/tissue which is exposed. In Fig. 14.3 this variation on radiation dose–response is illustrated from published reports from the North American Childhood Cancer Survivor Study [14]. The dose–response relationships were all linear with the exception of the thyroid for which there was a reduction in risk beginning between 15 and 20 Gy exposure [14]. The organs/tissue with a linear dose–response comprised two distinct groups: sarcomas, basal cell carcinomas of skin and meningiomas were each characterised by a steep increase in the dose-response; whilst sali-

Table 14.1 AER of all and specific subsequent primary neoplasms after specific first primary neoplasm by time from diagnosis, with percentage of total AER contributed by specific subsequent primary neoplasms

	5–9 years			10–19 years			20–29 years			≥30 years			*p* value[b]
	Obs/exp	AER per 10,000 person-years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person yean (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	
First primary neoplasm: Female breast													
Total subsequent primary neoplasms[c]	371/190.4	11.7 (9.3 to 14.2)	100%	730/391.7	19.6 (16.5 to 22.6)	100%	581/338.5	34.5 (27.8 to 41.2)	100%	195/149.0	25.6 (10.4 to 40.8)	100%	<0.0001
Corpus uteri	46/9.9	2.3 (l.5 to 3.7)	19.7%	100/36.0	3.7 (2.6 to 4.8)	18.9%	51/36.8	2.0 (0.0 to 4.0)	5.8%	7/12.9	−3.3 (−6.2 to −0.4)	..[d]	0.97
Ovary	74/20.6	3.5 (2.4 to 4.6)	29.9%	128/43.0	4.9 (3.6 to 6.2)	25.0%	71/31.2	5.7 (3.3 to 8.0)	16.4%	18/10.1	4.4 (−0.2 to 9.0)	15.7%	0.50
Other female genital	38/30.9	0.5 (−0.3 to l.2)	4.3%	50/33.1	1.0 (0.2 to l.8)	5.1%	18/13.7	0.6 (−0.6 to 1.8)	1.7%	5/4.3	0.4 (−2.1 to 2.8)	1.4%	0.25
Colorectal	24/19.8	0.3 (−03 to 0.9)	2.6%	63/51.6	0.7 (−0.2 to 1.6)	3.6%	65/51.9	1.9 (−0.4 to 4.l)	5.5%	27/26.9	0.1 (−5.6 to 5.7)	0.3%	0.13
Lung	37/14.6	l.5 (0.7 to 2.2)	12.8%	112/48.5	3.7 (2.5 to 4.9)	18.9%	154/58.6	13.6 (10.1 to 17.0)	39.2%	54/30.5	13.1 (5.1 to 21.0)	45.2%	<0.0001
Melanoma	30/23.1	0.4 (−0.3 to 1.1)	3.4%	45/34.0	0.6 (−0.1 to l.4)	3.1%	17/18.1	−0.2 (−1.3 to 1.0)	..[d]	8/5.8	1.2 (−1.9 to 4.3)	4.1%	0.57
Other	122/71.5	3.3 (1.9 to 4.7)	28.2%	232/145.5	5.0 (3.3 to 6.7)	25.5%	205/128.2	10 9 (6.9 to 14.9)	31.4%	76/58.4	9.8 (0.3 to 19.3)	33.8%	0.0001
First primary neoplasm; cervix													
Total subsequent primary neoplasms[e]	241/179.6	5.7 (2.9 to 8.5)	100%	618/509.3	6.9 (3.8 to 10.0)	100%	609/465.2	18.3 (12.2 to 24.5)	100%	207/152.9	32.3 (15.4 to 49.1)	100%	<0.0001

(continued)

Table 14.1 (continued)

	5–9 years			10–19 years			20–29 years			≥30 years			*p* value[b]
	Obs/exp	AER per 10,000 person-years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person yean (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	
Breast	89/104.4	−1.4 (−3.1 to 0.3)	..[d]	251/294.6	−2.8 (−4.7 to −0.8)	..[d]	157/227.0	−8.9 (−12.1 to −5.8)	..[d]	35/58.8	−14.2 (−21.1 to −7.3)	..[d]	[f]
Bladder	11/2.1	0.8 (0.2 to 1.4)	11.3%	40/8.4	2.0 (1.2 to 2.8)	20.6%	52/12.9	5.0 (3.2 to 6.8)	18.3	23/6.1	10.1 (4.5 to 15.7)	21.7%	<0.0001
Colorectal	23/10.4	1.2 (0.3 to 2.0)	16.9%	66/37.9	1.8 (0.8 to 2.8)	18.6%	110/46.7	8.1 (5.4 to 10.7)	29.7%	38/20.0	10.7 (3.5 to 17.9)	23.0%	<0.0001
Lung	45/7.3	3.5 (2.3 to 4.7)	49.3%	101/34.5	4.2 (3.0 to 5.5)	43.3%	137/52.0	10.8 (7.9 to 13.8)	39.6%	52/23.2	17.2 (8.8 to 25.6)	37.0%	<0.0001
Other	73/55.3	1.6 (0.1 to 3.2)	22.5%	160/133.9	1.7 (0.1 to 3.2)	17.5%	153/126.6	3.4 (0.3 to 6.5)	12.5%	59/44.8	8.5 (−0.5 to 17.4)	18.3%	0.24
First primary neoplasm; testicular													
Total subsequent primary neoplasms[g]	124/81.9	3.8 (l.8 to 5.7)	100%	378/246.2	9.0 (6.4 to 11.6)	100%	605/318.3	46.6 (38.8 to 54.4)	100%	328/161.1	127.0 (l00.0 to 154.0)	100%	<0.0001
Prostate	[h]	[h]	[h]	26/20.0	0.4 (−0 3 to 1.1)	4.4%	79/66.3	2.1 (−0.8 to 4.9)	4.5%	79/45.7	25.3 (12.1 to 38.6)	19.9%	<0.0001
Bladder	9/5.0	0.4 (−0.2 to 0.9)	10.5%	30/17.4	0.9 (0.1 to 1.6)	10.0%	84/25.0	9.6 (6.7 to 12.5)	20.6%	41/14.0	22.8 (13.0 to 32.7)	18.0%	<0.0001
Colorectal	16/9.4	0.6 (−0.1 to 1.3)	15.8%	45/33.4	0.8 (−0.1 to 1.7)	8.9%	97/44.1	8.6 (5.5 to 11.7)	18.5%	48/22.3	19.6 (9.2 to 29.9)	15.4%	<0.0001
Lung	7/7.1	−0.0 (−0.5 to 0.5)	0.0%	42/32.0	0.7 (−0.2 to 1.6)	7.8%	83/49.9	5.4 (2.5 to 8.3)	11.6%	39/26.6	9.5 (0.1 to 18.8)	7.5%[a]	<0.0001
Other	91/59.1	2.8 (1.2 to 4.5)	73.7%	235/143.4	6.3 (4.2 to 8.3)	70.0%	262/133.0	21.0 (15.8 to 26.l)	45.1%	118/52.6	49.7 (33.5 to 65.9)	39.1%	<0.0001
First primary neoplasm; female Hodgkin lymphoma													
Total subsequent primary neoplasms[i]	66/38.6	8.0 (3.4 to 12.7)	100%	316/104.2	44.7 (37.4 to 52.1)	100%	374/100.8	119.5 (102.9 to 136.l)	100%	147/44.6	168.6 (129.5 to 207.8)	100%	<0.0001

Breast	20/17.0	0.9 (−l.7 to 3.5)	11.3%	168/52.0	24.5 (19.1 to 29.9)	54.8%	181/48.8	57.8 (46.3 to 69.3)	48.4%	62/18.4	71.8 (46.4 to 97.2)	42.6%	<0.0001
Lung	7/1.0	1.8 (0.2 to 3.3)	22.5%	25/4.8	4.3 (2.2 to 6.3)	9.6%	48/8.0	17.5 (11.6 to 23.5)	14.6%	21/5.2	26.0 (11.2 to 40.8)	15.4%	<0.0001
Other	39/20.6	5.4 (1.8 to 9.0)	67.5%	123/47.4	16.0 (11.4 to 20.6)	35.8%	145/44.0	44.2 (33.9 to 54.5)	37.0%	64/21.0	70.8 (44.9 to 96.6)	42.0%	<0.0001
First primary neoplasm; male Hodgkin lymphoma													
Total subsequent primary neoplasms[j]	51/25.1	5.9 (2.7 to 9.1)	100%	192/72.9	19.5 (15.0 to 23.9)	100%	289/105.1	60.2 (49.3 to 71.1)	100%	171/68.8	121.9 (91.3 to 152.4)	100%	<0.0001
Lung	6/2.1	0.9 (−0.2 to 2.0)	15.3%	56/9.8	7.5 (5.2 to 9.9)	38.8%	82/17.5	21.1 (15.3 to 26.9)	35.0%	54/11.9	50.2 (33.0 to 67.3)	41.2%	<0.0001
Other	45/23.0	5.0 (2.0 to 8.0)	84.7%	136/63.1	11.9 (8.2 to 15.7)	61.3%	207/87.7	39.1 (29.8 to 48.3)	65.0%	117/56.9	71.7 (46.4 to 97.0)	58.8%	<0.0001
First primary neoplasm: Female thyroid													
Total subsequent primary neoplasms[k]	61/47.0	5.0 (−0.5 to 10.5)	100%	155/107.8	13.6 (6.6 to 20.6)	100%	133/95.1	23.9 (9.7 to 38.1)	100%	48/38.9	21.9 (−10.9 to 54.7)	100%	0.03
Breast	27/22.1	1.7 (−1.9 to 5.4)	34.0%	63/53.2	2.8 (−1.7 to 7.3)	20.8%	59/41.2	11.2 (1.7 to 20.7)	46.9%	21/13.7	17.6 (−4.1 to 39.3)	80.4%	0.06
Other	34/24.9	3.3 (−0.8 to 7.3)	66.0%	92/54.6	10.7 (5.3 to 16.1)	79.2%	74/53.9	12.7 (2.1 to 23.3)	53.1%	27/25.2	4.3 (−20.2 to 28.9)	19.6%	0.12

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AER Absolute excess risk, *Obs/exp* Observed number of subsequent primary neoplasms/expected number of subsequent primary neoplasms

[a]The total AER (for the purposes of calculating percentages) after each specific first primary neoplasm is the sum of the positive values for the contributing subsequent primary neoplasms

[b]Multivariable *p* value

[c]All subsequent primary neoplasms in female survivors excluding subsequent primary neoplasms of the breast

[d]Negative numbers for the AER, represented by ··

[e]All subsequent primary neoplasms in female survlvors excluding subsequent primary neoplasms of female genital sites

[f]*p* value not calculated due to negative AERs for all years

[g]All subsequent primary neoplasms In male survivors excluding subsequent primary neoplasms of other male genital sites (prostate sites allowed)

[h]Results not reliable because of small number of subsequent primary neoplasms(<5 observed subsequent primary neoplasms)

[i]All solid subsequent primary neoplasms in female survivors (excluding non-solid tumours)

[j]All solid subsequent primary neoplasms in male survivors (excluding non-solid tumours)

[k]All subsequent primary neoplasms in female survivors excluding subsequent primary neoplasms of the thyroid

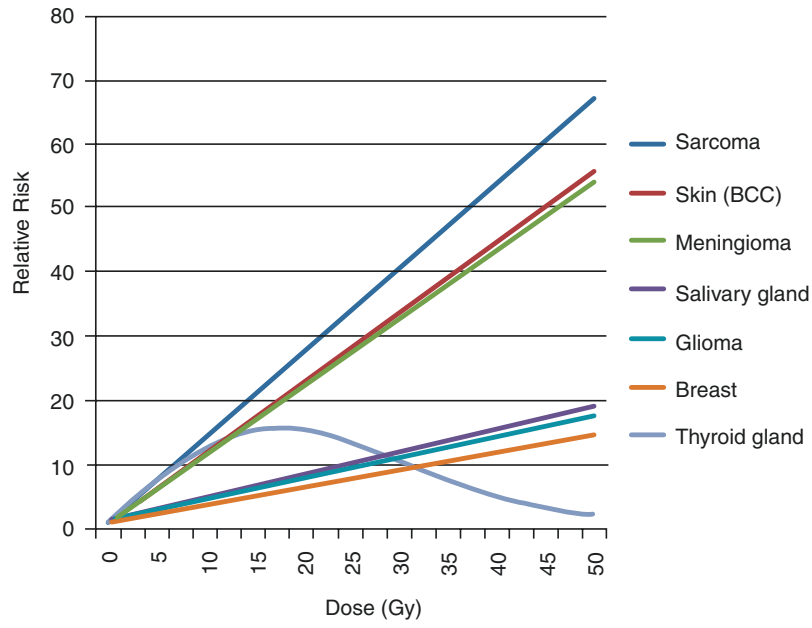

Fig. 14.3 Fitted radiation dose-response by type of second cancer, based on results from published studies. The order of second cancers from top to bottom in the graph is the same as in the key to the right of the panel. BCC-Basal cell carcinoma. With permissions from [14]

vary gland cancer, glioma and breast cancer were associated with a flatter dose–response [14].

There has been a systematic review of the risks of CNS tumours in survivors of childhood cancer [15]. As illustrated by Fig. 14.3, the dose–response for meningioma is much stronger than that for glioma. There has also been a study of the morbidity and mortality associated with meningioma after cranial radiotherapy for mostly leukaemia and brain tumours in childhood, which confirmed significant neurological morbidity [16].

There is on-going debate regarding the benefits/harms of MRI screening for the early detection of meningioma [17–19]. The International Late Effects of Childhood Cancer Guideline Harmonization Group [20] is currently assessing the available evidence and will produce recommendations in due course (see below).

As mentioned above survivors who received abdominopelvic radiotherapy have a risk of bowel cancer which exceeds that experienced by individuals with two first-degree relatives with bowel cancer. There has been a recent systematic review of the risk of gastrointestinal cancers among survivors of childhood cancer which confirmed abdominopelvic radiotherapy as a risk factor and also suggested that exposure to procarbazine and platinum anti-cancer agents may also be risk factors [21]. A very recent study compared the risk of advanced colorectal neoplasia (including advanced adenomas, advanced serrated lesions and colorectal cancer) in survivors of Hodgkin lymphoma treated with abdominopelvic radiotherapy or procarbazine with the risk in the Dutch general population [22]. The prevalence of advanced colorectal neoplasia was higher among Hodgkin lymphoma survivors than controls [25 of 101 (25%) v. 171 of 1426 (12%); $p < 0{\cdot}001$]. The authors suggested that the implementation of a colonoscopy surveillance programme should be considered [22]. The International Late Effects of Childhood Cancer Guideline Harmonization Group [20] is also currently considering evidence relating to survivors of childhood cancer treated with abdominopelvic irradiation and the potential risks/benefits of colonoscopy screening (see below).

14.4.2 Chemotherapy

It has been established for many years that alkylating agents, epipodophyllotoxins and anthracyclines increase the risk of leukaemia in survivors treated with these drugs. Alkylating agent-related leukaemia develops mostly beyond 5 years from exposure and is often characterised with chromosomal anomalies relating to chromosomes 5 and 7. Topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines) related leukaemia tend to develop after a shorter period from exposure and are often characterised with 11q23 anomalies [23–25].

More recently with greater follow-up, there is increasing evidence that specific types of chemotherapy increase the risk of particular subsequent primary solid cancers. Alkylating agent exposure increases the risk of sarcoma, lung, stomach, colorectal, bladder cancer and thyroid cancers [23, 25, 26]. Anthracycline exposure has been reported to increase the risk of breast cancer and sarcoma [26–28].

14.4.3 Genetic Factors

A recent article reviewed the role of genetic variation as a modifier of the association between therapeutic exposure and the risk of subsequent primary neoplasms and reported that almost all studies have focused on candidate gene studies exploring genetic variants in DNA damage detection and repair mechanisms [29]. However most studies were limited by insufficient sample size and absence of replication in independent data. In recent years there have been a small number of genome-wide association studies (GWAS) to identify: loci associated with therapy-related myeloid leukaemia susceptibility [30]; variants associated with therapy-induced subsequent primary neoplasms after Hodgkin lymphoma [31]; and loci modifying the radiation-related risk for breast cancer after childhood cancer [32]. The role of germline genetics in identifying survivors at risk of adverse effects of cancer treatment (including subsequent primary neoplasms) was reviewed recently [33].

14.5 Clinical Follow-Up Guidelines

In recent years there has been a worldwide initiative to establish collaborations to produce (whenever possible evidence-based) internationally standardised guidelines for the long-term follow-up of survivors of childhood and young adult cancer—the "International Late Effects of Childhood Cancer Guideline Harmonization Group". [20]

There have been two guidelines published so far which relate to subsequent primary neoplasms: "Recommendations for breast cancer surveillance for female survivors of childhood, adolescent and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group" [34]; "Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendation from International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup consortium" [35].

There are two guidelines currently being developed in relation to subsequent primary cancers: one concerns subsequent primary brain tumours, including meningiomas and the other concerns colorectal or bowel cancer, as mentioned above.

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