Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods. Statistical Analysis and Radiotherapy Assessment

Multivariable Cox regression models for primary and secondary outcome groups

We defined four primary outcome groups by a priori interest, based on ● known tissue-sensitivity to radiation carcinogenesis; ● genetic susceptibility; ● as precursor lesions for malignancies, potentially amenable to early detection. Primary outcome groups were breast fibroadenoma (fibroepithelial neoplasms) and uterine leiomyoma (myomatous neoplasms) (female subcohort, N=2,574), nerve sheath tumors, and osseous/chondromatous neoplasms. We assessed the role of radiotherapy treatment (see also below for breast fibroadenoma and uterine leiomyoma), and we tested six main chemotherapeutic groups (alkylating agents, anthracyclines, epipodophyllotoxins, vinca alkaloids, platinum agents, and antimetabolites). For nerve sheath tumors we additionally included an indicator variable for NF1/NF2-associated childhood cancer types (eTable 3), to ascertain the influence of genetic predisposition. Information on individual NF1/NF2 status is not available for our cohort.

For the remaining outcome groups (secondary outcomes), effects of treatment (surgery only, chemotherapy only, radiotherapy only, and chemotherapy plus radiotherapy combined) were assessed.

Radiotherapy assessment

Trunk dose

We assessed the total maximum prescribed radiotherapy doses for the trunk, based on the maximum dose to the smallest radiotherapy field, as approximation of the estimated dose in the breast. To derive cumulative trunk doses, we summed total body irradiation (TBI) dose, chest dose, and 50% of the total abdominopelvic dose. The latter was chosen in accordance with the way breast dose from abdominal radiotherapy is approximated in DCOG LATER breast cancer screening guidelines[1]; The 50% approximation averages out those for (1) women with breast/nipple doses from abdominal fields where the nipple (diaphragm) was close to the upper field edge, for whom the breast received

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50-100% of prescribed dose, and (2) women who had abdominal radiotherapy with upper field edges below the diaphragm, for whom less or far less than 50% of the prescribed dose reached the breast. In case of multiple fields to the chest or to the abdominopelvic area (treatments for primary tumor or recurrences/metastases), we summed the physical/prescribed doses for these areas as follows: when the same location was irradiated we assessed the total maximum dose to smallest field. When two or more non-overlapping fields to the chest or abdominopelvic area were given, the dose to the field with the highest dose was assigned.

- Example 1 (two overlapping fields): for a patient who was irradiated with a total chest field of 15 Gy (primary treatment) and a boost to a smaller chest field of 8 Gy (boost) without any other chest or abdominopelvic field, a trunk dose of 23 Gy was assigned (maximum dose to smallest field).
- Example 2 (chest and abdominopelvic field): for a patient who received an abdominal field of 24 Gy (primary treatment) and a total chest field of 18 Gy (metastasis treatment), we assigned a trunk dose of 30 Gy (maximum chest dose plus 50% of abdominopelvic dose).
- Example 3 (two non-overlapping fields): for a patient who received a field to the left side of the chest of 14 Gy and a field to the right side of the chest (10 Gy), trunk dose was assigned to be 14 Gy (dose of the field with the highest dose).

Abdominopelvic dose

As approximation of the dose estimated in the uterus, doses to the abdominopelvic area from consecutive treatments were summed when the same location was irradiated whereas the highest dose was assigned in case of two or more non-overlapping radiotherapy fields.

- Example 1 (two overlapping fields): full abdominopelvic field 20 Gy and a boost to the hemi-abdominopelvic 10 Gy. The abdominopelvic dose was assigned to be 30 Gy (maximum dose to smallest field).

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- Example 2 (two non-overlapping fields): for a patient who received a field to the left side of the abdominopelvic of 15 Gy and a field to the right side of the abdominopelvic (10 Gy), abdominopelvic dose was assigned to be 15 Gy (dose of the field with the highest dose).

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eTable 1. Patient and Benign Tumor (BT) Characteristics of the DCOG-LATER and Sibling Cohorts

	Childhood cancer survivors				Siblings			
	Cohort		BT cases*		Cohort		BT cases*	
Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**5,843**	**100**	**542**	**9.3**	**883**	**100**	**56**	**6.3**
Sex								
Male	3,269	56.0	247	45.6	363	41.1	14	25.0
Female	2,574	44.0	295	54.4	520	58.9	42	75.0
Attained age, years								
<25	1,844	31.6	198	36.5	247	28.0	16	28.6
25-29	1,079	18.5	105	19.4	139	15.7	10	17.9
30-34	1,047	17.9	88	16.2	153	17.3	8	14.3
35+	1,873	32.1	151	27.9	344	38.7	22	39.3
Time since childhood cancer diagnosis, years								
<15	901	15.4	148	27.3	-	-	-	-
15-24	2,527	43.3	201	37.1	-	-	-	-
25-34	1,672	28.6	144	26.6	-	-	-	-
35+	743	12.7	49	9.0	-	-	-	-
Localization first BT								
Head and neck	-	-	196	36.1	-	-	8	14.3
Thorax	-	-	92	17.0	-	-	18	32.1
Abdomen and pelvis	-	-	157	29.0	-	-	23	41.1
Extremities	-	-	78	14.4	-	-	5	8.9
Location unknown	-	-	19	3.5	-	-	2	3.6
Type of first BT†								
Adenomas 814-838	-	-	75	13.8	-	-	7	12.5
Fibromatous neoplasms 881-883	-	-	28	5.2	-	-	3	5.3
Lipomatous neoplasms 885-888	-	-	97	17.9	-	-	10	17.9
Myomatous neoplasms 889-892	-	-	39	7.2	-	-	7	12.5
Fibroepithelial neoplasms 900-903	-	-	44	8.1	-	-	12	21.4
Blood vessel tumors 912-916	-	-	26	4.8	-	-	1	1.8
Osseous/chondromatous neoplasms 918-924	-	-	23	4.2	-	-	1	1.8
Meningiomas 953	-	-	89	16.4	-	-	1	1.8
Nerve sheath tumors 954-957	-	-	50	9.2	-	-	1	1.8
Other benign tumors‡	-	-	71	13.1	-	-	13	23.2
Sex-specific organs								
No	-	-	429	79.1	-	-	28	50.0
Male	-	-	8	1.5	-	-	0	0
Female	-	-	105	19.4	-	-	28	50.0
Calender period of BT diagnosis								
1990-1999	-	-	87	16.0	-	-	9	16.1
2000-2009	-	-	221	40.8	-	-	22	39.3
2010-2015	-	-	234	43.2	-	-	25	44.6
Vital status								
Deceased	484	8.3	-	-	-	-	-	-
Alive	5,359	91.7	-	-	-	-	-	-

Abbreviations: N, number; BT, benign tumor.

Numbers do not always add up to 100% because of missing data or rounding.

*BT cases defined as DCOG LATER cohort members affected by any first histologically confirmed BT, diagnosed at least five years after initial childhood cancer diagnosis.

†BT outcome categories defined by ICD-O benign tumor groupings denoted by 3-digit codes and only the first BT per survivor is counted; see also eTable 2 for more detail on specific tumor types.

‡Defined as any other M-code not represented in the other pre-defined categories.

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eTable 2. Overview of Benign Tumor Types According to *ICD-O*–Defined Morphology Subgroups*

ICD-O morphology subgroup	N		ICD-O morphology subgroup	N
Adenomas 814-838	93		**Blood vessel tumors 912-916**	26
Gastrointestinal tract	57		Across body	
Thyroid			*Hemangiomas*	20
Follicular adenomas and adenomas	14		Brain	
Parathyroid	10		*Cavernous hemangiomas*	6
Liver	4			
Other organ/body part	8			
Fibromatous neoplasms 881-883	32		**Osseous/chondromatous neoplasms 918-924**	23
Across body			Across body	
Fibromas	32		*Enchondromas and osteochondromas*	21
Lipomatous neoplasms 885-888	102		**Meningiomas 953**	98
Across body			Brain	97
Angiolipomas and lipomas	102		Spinal	1
Myomatous neoplasms 889-892	50		**Nerve sheath tumors 954-957**	55
Uterus			Across body	
Leiomyomas	43		*Neurofibromas*	24
Other organ/body part	7		*Schwannomas*	23
			Acoustic neuromas	6
			Other neuromas	2
Fibroepithelial neoplasms 900-903	49		**Other benign tumors†**	80
Breasts (45 females and 1 male)			Ovaries	
Fibroadenomas	46		*Mucinous cystadenomas*	10
Other organ/body part	4		Other organ/body part	63
			Glandula parotis and glandula submandibularis	
			Pleomorphic adenomas	7

Abbreviations: N, number.

*Numbers per subgroup are larger than those cited in eTable 1 for the first benign tumor per person, because for specific outcome analyses, any first benign tumor of a particular type is counted rather than the number cited in eTable 1.

†Other benign tumors: cystic, mucinous and serous neoplasms 884-849 (N=16); squamous cell neoplasms 805-808 (N=15); germ cell neoplasms 906-909 (N=11); complex mixed and stromal neoplasms 893-899 (N=7); odontogenic tumors 927-934 (N=5); neuroepitheliomatous neoplasms 949-952 (N=4); granular cell tumors and alveolar soft tissue sarcomas 958 (N=3); lymphatic vessel tumors 917 (N=3); paragangliomas and glomus tumors 868-871 (N=3); giant cell tumors 925 (N=3); miscellaneous bone tumors 926 (N=3); soft tissue tumors and sarcomas, not otherwise specified 880 (N=2); specialized gonadal neoplasms 859-867 (N=2); gliomas 938-948 (N=2); and myxomatous neoplasms 884 (N=1).

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eTable 3. Childhood Cancer Types Associated With NF1 and NF2, Based on Literature[¶^]

Cancer/tumor site*	NF1	NF2	ICCC-3 group
Juvenile myelomonocytic leukemia	yes	-	only morphology code 9946/3
Ependymoma	yes	yes	03a01
Glioma	yes	yes	03a02; 03b01; 03b02; 03d01; 03d02; 03d03
Medulloblastoma/PNET	yes	-	03c01; 03c02
Meningioma	yes	yes	03e05
Neuroblastoma	yes	-	04a; 04b
Wilms' tumor (see chapter for site specific syndrome)	yes	-	06a01
Rhabdomyosarcoma	yes	-	09a
Neurofibrosarcoma/MPNST	yes	-	09b02
Schwannoma/MPNST	yes	yes#	09b02
Gastrointestinal stromal tumor	yes	-	12a01

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third edition; MPNST: malignant peripheral nerve sheath tumor, preferred name for neurofibrosarcoma or malignant schwannoma; NF1/NF2, neurofibromatosis type 1/2; PNET, primitive neuroectodermal tumor.

*Lists only childhood cancer groups.

#Spinal cord schwannoma.

¶Lindor NM, McMaster ML, Lindor CJ, et al. Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr. 2008; 38:1-93.

^Based on Table 1 in Steliarova-Foucher E, Stiller C, Lacour B, et al. International Classification of Childhood Cancer, Third Edition. Cancer. 2005; Apr 1;103(7):1457-67.

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eTable 4. Multivariable Cox Regression Analyses for Risk of Adenoma, Lipomatous and Fibromatous Neoplasm, and Blood Vessel Tumor in 5-Year Survivors of Childhood Cancer in the DCOG-LATER Cohort*

		Adenomas (N=93)†			Lipomatous neoplasms (N=102)			Fibromatous neoplasms (N=32)			Blood vessel tumors (N=26)		
	N total	N cases	HR	95% CI	N cases	HR	95% CI	N cases	HR	95% CI	N cases	HR	95% CI
Sex													
Male	3,269	49	1.0 (Ref)		55	1.0 (Ref)		18	1.0 (Ref)		15	1.0 (Ref)	
Female	2,574	44	1.1	0.7-1.6	47	1.0	0.7-1.6	14	0.9	0.5-1.9	11	0.9	0.4-2.0
Age childhood cancer diagnosis, years													
0-4	2,641	31	2.1	1.2-3.7	39	1.2	0.8-2.1	15	3.1	1.0-9.7	9	0.6	0.2-1.9
5-9	1,583	27	1.8	1.1-3.1	25	0.9	0.6-1.6	12	2.9	1.0-8.6	8	1.0	0.4-2.7
10-17	1,619	35	1.0 (Ref)		38	1.0 (Ref)		5	1.0 (Ref)		9	1.0 (Ref)	
Year childhood cancer diagnosis													
1963-1984	1,791	58	1.0 (Ref)		54	1.0 (Ref)		17	1.0 (Ref)		10	1.0 (Ref)	
1985-1994	2,113	23	1.8	1.0-3.4	38	1.2	0.8-2.0	12	1.5	0.6-3.6	13	1.5	0.6-4.0
1995-2001	1,939	12	4.1	1.7-9.7	10	1.0	0.5-2.2	3	0.9	0.2-3.6	3	0.7	0.2-3.0
Treatment‡													
Surgery only or no recorded treatment	603	5	1.0 (Ref)		9	1.0 (Ref)		0	1.0 (Ref)§		0	1.0 (Ref)§	
Chemotherapy, no radiotherapy	2,898	26	1.6	0.6-4.2	40	1.0	0.5-2.2	7			10		
Radiotherapy, no chemotherapy	445	12	1.7	0.6-4.9	13	1.4	0.6-3.2	7	7.7	2.6-23.3	4	2.9	0.9-9.8
Radiotherapy and chemotherapy	1,854	49	2.8	1.1-7.1	40	1.1	0.5-2.2	18	4.4	1.7-11.0	12	2.2	0.9-5.3

Abbreviations: CI, confidence interval; Gy, Gray; HR, hazard ratio; N, number.

*Numbers per subgroup are larger than those cited in eTable 1 for the first benign tumor per person, because for specific outcome analyses any first benign tumor of a particular type is counted rather than the any first benign tumor number cited in eTable 1.

†Model includes N=92 adenoma cases due to missing values.

‡Treatment data includes primary treatment and all recurrences; radiotherapy (yes/no), chemotherapy (yes/no), and hematopoietic cell transplantation (yes/no) data were missing for 30, 34, and 68 survivors, respectively.

§Treatment groups were collapsed.

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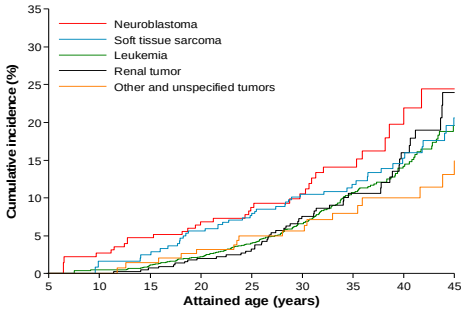
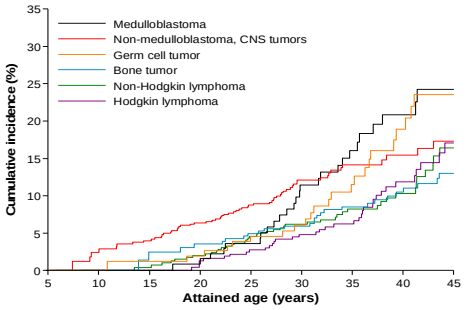
eFigure 1. Cumulative Incidence of Benign Tumors for 5-Year Survivors of Childhood Cancer (CCSs) by Attained Age and Time Since Childhood Cancer Diagnosis According to Childhood Cancer Type, Accounting for Death as Competing Risk

Panel A



No. at risk									
Neuroblastoma	5	195	231	205	174	127	80	34	14
Soft tissue sarcoma	2	125	222	280	266	216	145	98	57
Leukemia	0	810	1,325	1,482	1,220	874	518	267	82
Renal tumor	0	298	445	439	365	267	159	90	32
Other and unspecified tumors	1	107	157	171	152	123	86	61	39

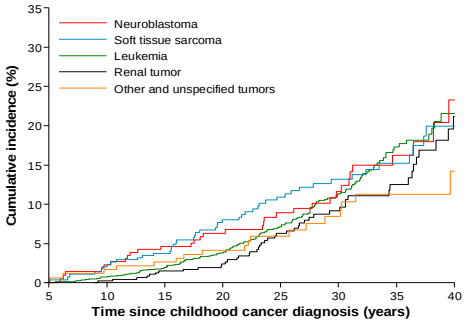
Panel B



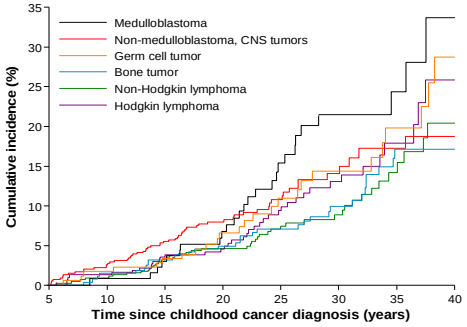
No. at risk									
Medulloblastoma	0	24	71	111	100	75	53	35	9
Non-medulloblastoma, CNS tumors	0	176	368	430	363	228	132	70	39
Germ cell tumor	2	78	95	132	136	104	74	47	31
Bone tumor	0	22	86	190	236	211	162	121	82
Non-Hodgkin lymphoma	0	95	289	431	417	321	219	131	55
Hodgkin lymphoma	0	13	83	252	333	284	209	112	50

Panel C

Panel D



No. at risk								
Neuroblastoma	192	230	235	190	157	106	57	23
Soft tissue sarcoma	254	306	309	250	196	133	78	41
Leukemia	1,425	1,643	1,593	1,141	751	444	197	52
Renal tumor	358	440	456	391	294	183	104	44
Other and unspecified tumors	163	197	210	170	120	93	54	19



No. at risk								
Medulloblastoma	98	112	115	94	57	38	16	4
Non-medulloblastoma, CNS tumors	523	515	455	297	161	74	47	24
Germ cell tumor	158	173	173	122	81	56	32	13
Bone tumor	210	248	252	202	167	104	57	23
Non-Hodgkin lymphoma	389	461	468	373	243	152	64	19
Hodgkin lymphoma	282	332	315	247	168	97	37	10

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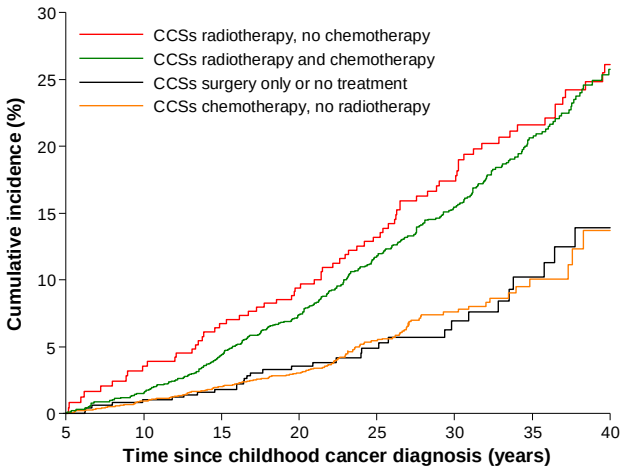
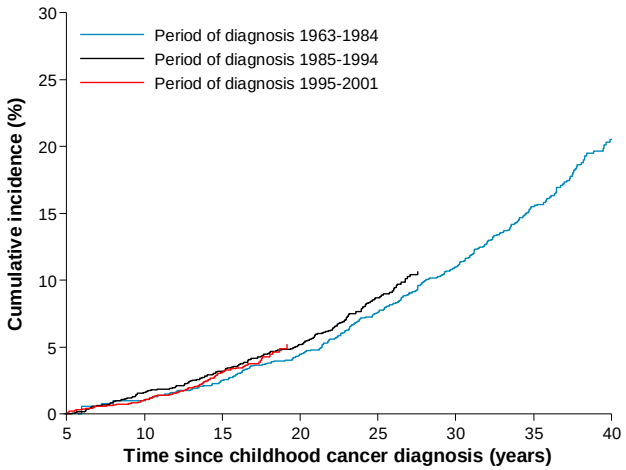
eFigure 2. Cumulative Incidence of Benign Tumors for 5-Year Survivors of Childhood Cancer (CCSs) by Time Since Childhood Cancer Diagnosis, Accounting for Death as Competing Risk

Panel A



No at risk								
CCSs radiotherapy, no chemotherapy	230	257	263	271	222	171	121	76
CCSs radiotherapy and chemotherapy	934	1,209	1,379	1,218	952	725	395	117
CCSs surgery only or no treatment	457	494	491	335	228	134	88	36
CCSs chemotherapy, no radiotherapy	2,401	2,675	2,430	1,643	984	444	135	40

Panel B



No at risk								
Period of diagnosis 1963-1984	0	834	1,352	1,550	1,525	1,441	743	272
Period of diagnosis 1985-1994	2,113	1,988	1,917	1,833	870	39	0	0
Period of diagnosis 1995-2001	1,939	1,835	1,312	94	0	0	0	0

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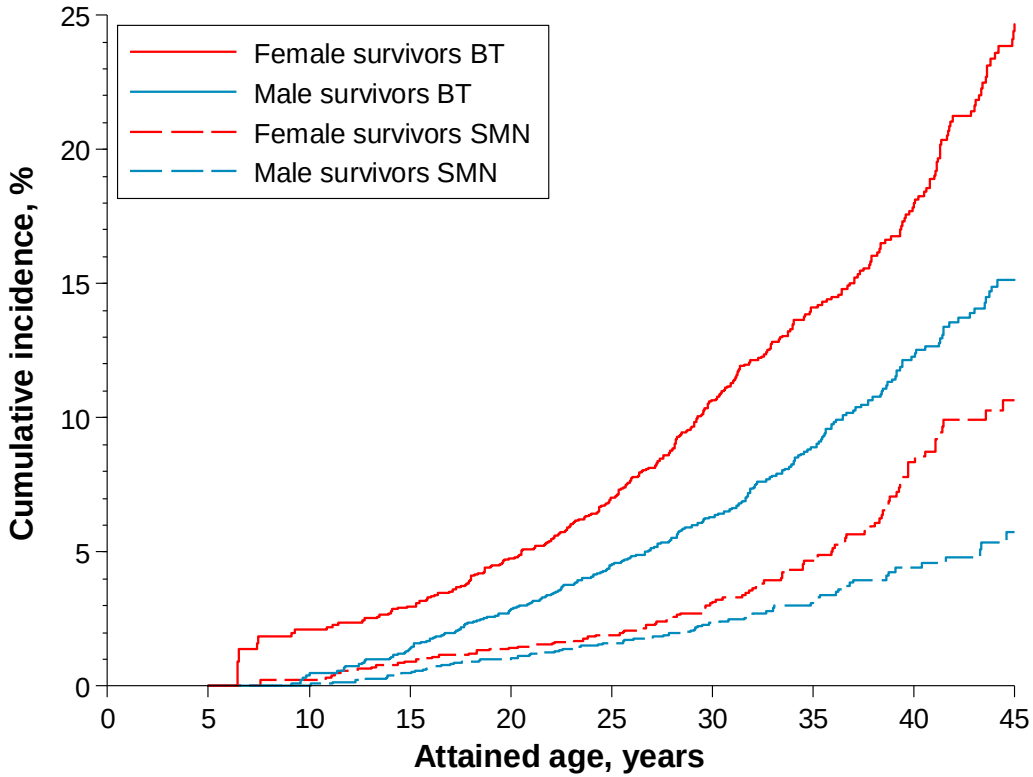
eFigure 3. Cumulative Incidence of Benign Tumors (BTs) and Subsequent Malignant Neoplasms (SMNs) for Female and Male 5-Year Survivors of Childhood Cancer (CCSs) by Attained Age, Accounting for Death as a Competing Risk



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Reference

1. Dutch Childhood Oncology Group: Richtlijn follow-up na kinderkanker meer dan 5 jaar na diagnose. SKION, Den Haag/Amsterdam; 2010. https://www.skion.nl/voor-professionals/behandelrichtlijnen/210/behandelrichtlijnen/838/richtlijn-follow-up-na-kinderkanker/ Accessed: July 25, 2018.

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