

# Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study

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## Abstract

**Background:** The 5-year survival rate for individuals with neuroblastoma (NB) is approaching 70%. Few data exist, however, on long-term outcomes of these patients, who are often treated at a very young age.

**Procedures:** Outcome data from 954 5-year NB survivors diagnosed between 1970-86 and enrolled in the Childhood Cancer Survivor Study (CCSS) were obtained. Late mortality, second malignant neoplasms (SMN) and chronic health conditions were analyzed in relation to treatment factors. NB survivors were compared to a cohort of 3899 siblings of CCSS participants for risk of chronic health conditions and selected sociodemographic outcomes.

**Results:** Six percent died more than 5 years after their diagnosis (standardized mortality ratio [SMR]=5.6; 95% confidence interval [CI]:4.4-6.9). The most common causes of death were disease recurrence (n=43) and SMN (n=13). The cumulative incidence of SMN was 4.1% at 25 years and 7.9% at 30 years. Compared to the sibling cohort, survivors had an increased risk of selected chronic health conditions (rate ratio [RR] =8.3; 95% CI:7.1-9.7). The most prevalent outcomes involved the musculoskeletal, endocrine, sensory and neurological systems. NB survivors who were treated with multimodality therapy were more likely to develop a chronic health condition compared to survivors treated with surgery alone (RR=2.2; 95% CI:1.6-3.0). NB survivors were less likely to have ever been employed (p=0.04) or to be married (p<0.001), and had a lower personal income compared to siblings (p=0.009).

**Conclusions:** NB survivors are at elevated risk for early mortality, SMN and chronic health conditions, which underscores the need for long-term medical surveillance.

## Introduction

- Increased Overall Survival for NB patients:
  - 54% (1975-1984)
  - 68.5% (1996-2003) (SEER data)
- Therapy for low and intermediate risk NB has become less intensive
- High-risk patients continue to fare poorly despite the use of multimodal intensive therapy
- NB survivors population has not been well studied even though they are among the youngest treated and potentially most vulnerable patients

## Objectives

- To investigate the occurrence of, and risk factors for, selected long-term outcomes
- To analyze late mortality, second malignant neoplasms (SMN) and chronic health conditions in relation to treatment factors.
- Compare the risk for NB survivors of developing selected chronic health conditions and sociodemographic outcomes relative to siblings

## Methods

- CCSS cohort of 5-year NB survivors diagnosed between 1970-1986 (n = 954)
- Baseline questionnaire and follow-up surveys (2000 and 2002)
- Medical information abstracted from medical record: chemotherapeutic agents and cumulative doses, surgical procedures, quantitative radiation therapy data
- Comparison group of siblings of cancer survivors (n = 3899)

## Results

Characteristics	Survivors (n=954) (%)	Siblings (n=3899) (%)	P-value
<b>Gender</b>			
Male	455 (48)	1875 (48)	0.83
Female	499 (52)	2024 (52)	
<b>Vital status at baseline questionnaire</b>			
Alive	919 (96)		
Dead	35 (4)		
<b>Age at interview (y) at baseline</b>			
<10	33 (3)	76 (2)	<0.001
10-19	616 (65)	1010 (26)	
20-29	280 (29)	1381 (35)	
30-39	23 (2)	1116 (29)	
40-49	2 (0)	316 (8)	
<b>Age at interview (y) at latest follow-up</b>			
<10	10 (1)	12 (<1)	<0.001
10-19	263 (28)	379 (10)	
20-29	519 (54)	1353 (35)	
30-39	155 (16)	1332 (34)	
40-49	7 (1)	823 (21)	
<b>Age at diagnosis (y)</b>			
<1	525 (55)	NA	
1-4	340 (36)	NA	
5-9	66 (7)	NA	
10-14	15 (2)	NA	
15-21	8 (1)	NA	
<b>Year of diagnosis</b>			
1970-1975	228 (24)	NA	
1976-1980	291 (31)	NA	
1981-1986	435 (46)	NA	
<b>Survival time (y) time at baseline</b>			
5-9	103 (11)	NA	
10-14	344 (36)	NA	
15-19	283 (30)	NA	
20-24	187 (20)	NA	
>25	37 (4)	NA	
<b>Survival time (y) at latest follow-up</b>			
5-9	32 (3)	NA	
10-14	62 (6)	NA	
15-19	272 (29)	NA	
20-24	298 (31)	NA	
>25	290 (30)	NA	
<b>Treatment groups<sup>a</sup></b>			
Surgery only	200 (24)	NA	
Surgery +Chemotherapy (CT)	216 (26)	NA	
Surgery+ RT	132 (16)	NA	
Surgery+CT+RT	268 (32)	NA	
Others <sup>b</sup>	16 (2)	NA	

<sup>a</sup>Based on the 832 patients with medical records abstracted.  
<sup>b</sup>20 patients had bone marrow transplantation, including 16 who received total body irradiation (TBI)  
<sup>c</sup>Among 16 patients who did not have surgery, 4 had CT only, 3 had RT only, 6 had both CT and RT and 3 had no treatment

Demographics and health status of study subjects (age adjusted)

Characteristics	Survivors (n=954) (%)	Siblings (n=3899) (%)	P-value
<b>Highest level of schooling<sup>a</sup></b>			
Not High school Grad	3.2	2.7	0.68
High school Grad	48.3	45.4	
College Grad	48.5	51.9	
<b>Ever employed<sup>a</sup></b>			
No	1.3	0.2	0.04
<b>Total household income<sup>a</sup></b>			
<\$19,999	14.7	10.4	0.003
\$20,000-\$39,999	30.9	24.2	
\$40,000-\$9,999	22.9	23.3	
Over \$60,000	31.5	42.1	
<b>Total personal income<sup>a</sup></b>			
<\$19,999	40.7	31.9	0.009
\$20,000-\$39,999	35.6	36.9	
\$40,000-\$9,999	16.8	18.3	
Over \$60,000	6.9	12.9	
<b>Health insurance<sup>a</sup></b>			
Yes	80.0	79.5	0.51
No	13.1	11.7	
Canadian	6.9	8.8	
Ever Married <sup>a</sup>			
Yes	54.9	67.9	<0.001
<b>General health status<sup>a</sup></b>			
No adverse	91.5	95.4	0.006
Adverse	8.5	4.6	
<b>Mental health status<sup>a</sup></b>			
No adverse	93.9	95.6	0.33
Adverse	6.1	4.4	

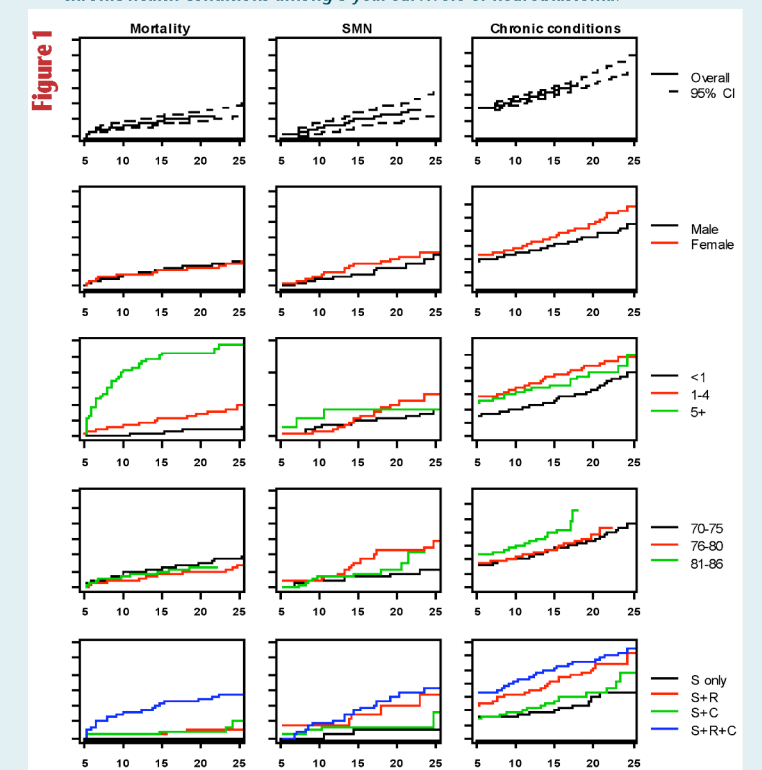
<sup>a</sup> NB survivors and siblings, aged 25+ at last follow-up  
<sup>b</sup> Health status applies only to those who were age >=18 at baseline.

Age-Adjusted rate ratios of selected chronic health conditions first occurring five or more years following diagnosis in NB survivors compared to siblings.

Condition	Cumulative incidence at 20 yrs since dx of survivors (%)	Survivors	Siblings	RR	95% CI	P-value
<b>Musculoskeletal complications</b>	<b>7.8</b>	53.2	2.6	<b>20.1</b>	12.1-35.3	<0.001
Scoliosis surgery	5.8	42.9	1.6	27.0	13.6-53.4	<0.001
Osteoporosis	2.3	12.5	0.9	13.2	5.5-32.1	<0.001
<b>Neurological complications</b>	<b>29.8</b>	152.9	20.0	<b>7.6</b>	6.4-9.1	<0.001
Weakness in arms or legs	13.7	35.3	1.6	22.7	16.4-31.6	<0.001
Decreased sense of touch, feelings in hands, fingers, arms or legs	10.7	45.5	4.4	10.2	7.6-13.7	<0.001
Prolonged pain or abnormal sensations in arms, legs or back	8.1	36.4	3.8	9.6	6.8-13.5	<0.001
Problems with balance	6.6	24.4	4.1	6.0	4.2-8.7	<0.001
Tremor or movement problems	5.4	13.7	1.2	11.2	7.0-18.0	<0.001
Paralysis	5.5	14.5	1.3	11.3	7.3-17.5	<0.001
<b>Endocrine complications</b>	<b>8.3</b>	67.9	5.21	<b>13.0</b>	8.9-19.1	<0.001
Medication needed to initiate puberty	3.1	41.7	0.8	55.4	16.1-191.1	<0.001
Growth hormone deficiency	4.2	24.6	0.6	38.5	15.2-97.3	<0.001
Growth hormone injections	2.8	14.3	0.4	37.0	12.7-107.6	<0.001
Hypothyroidism	4.1	33.7	4.0	8.4	5.1-13.6	<0.001
<b>Sensory complications</b>	<b>8.6</b>	22.6	2.8	<b>8.0</b>	5.6-11.3	<0.001
Cataract	3.1	10.8	0.7	16.2	7.3-35.8	<0.001
Hearing loss/deafness	3.8	6.8	0.8	8.7	5.2-14.6	<0.001
Blindness	3.1	11.0	1.6	6.9	4.0-11.8	0.004

<sup>a</sup>Adjusted rate at age 15.

Cumulative incidence of mortality, second malignant neoplasm, and selected chronic health conditions among 5 year survivors of neuroblastoma.



## Conclusions

- NB survivors are at elevated risk for early mortality, SMN and chronic health conditions (musculo-skeletal, neurological, endocrine complications and hearing loss)
- NB survivors have less favorable sociodemographic outcomes compared to siblings
- Long-term medical surveillance is required for early detection of medical complications in NB survivors