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LETTER TO THE EDITOR

Pregnancy outcomes in female survivors of neuroblastoma: a short report from the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study

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Introduction

Although rare, neuroblastoma is the most common extracranial solid tumor in childhood. It is diagnosed mainly in infants and children under five years of age [1], with approximately two thirds of primary tumors in the abdomen and one third in the pelvis, neck, or chest [2]. Modern treatment of neuroblastoma has increased survival, with wide variation by both age and stage of disease at diagnosis [3]. Due to the intense cancer treatment, many survivors are at increased risk for complications later in life [4], including gonadal dysfunction and fertility problems [5,6]. Previous studies have shown a lower probability of becoming pregnant and having a liveborn child in female survivors of childhood cancer [7,8]. However, only a limited number of the studies reported estimates in survivors of neuroblastoma separately. The few studies observed an overall decreased relative risk (RR) of a livebirth compared with women in the background population (0.81, 95% confidence interval (CI) 0.74–0.92) [7] and sisters (0.62, 95% CI 0.42–0.92), which in both studies was similar to the RR in survivors of leukemia, but higher than the RR of survivors of CNS tumors [9]. Another study reported a decreased hazard ratio (HR) of a livebirth in neuroblastoma survivors not exposed to pelvic or cranial radiation, but only among survivors treated with alkylating agents [10]. Finally, two studies assessing miscarriages did not find any significantly higher risk in the neuroblastoma survivors than in the comparison groups [9,11]. As limited studies are available on outcomes of pregnancy, including live births, stillbirths, and abortions, in female survivors of neuroblastoma, the aim of this study was to investigate pregnancy outcomes of 230 female survivors of neuroblastoma in childhood in a Nordic register-based cohort study.

Material and methods

Female survivors of neuroblastoma and population comparisons

The neuroblastoma survivor cohort used in this study is a sub-cohort of the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study of late complications after diagnosis and treatment of childhood cancer in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). The ALiCCS study has been described previously [12]. In brief, the study includes 43,909 children with cancer diagnosed between 1943 and 2008 when they were $<$ 20 years of age and a comparison cohort randomly sampled from the five national population registries and matched to the children with cancer on country, sex, and in a 1:5 ratio. For the current study, we only included female five-year survivors of neuroblastoma diagnosed in the period 1951–2003 who were alive and living in their respective Nordic country between the age of 20 and $<$50 years as well as their matched population comparisons. The exclusion criteria for the final neuroblastoma survivor ($n = 230$) and comparison cohort ($n = 1090$) are seen in Figure 1. Information on classification of disease was available for 79 (34%) survivors who were classified into low-, intermediate-, and high-risk groups, correlating to treatment intensity as described by Norsker et al. [4,13].

Information on live births, stillbirths, and abortions

All cohort members were linked to the medical birth registries of the Nordic countries to ascertain information on live births and stillbirths (Denmark: 1973–2010; Finland: 1987–2012; Norway: 1967–2010; Sweden: 1972–2008). The nationwide birth registries hold information on pregnancies and births from hospital registries [14]. Information on ectopic and spontaneous abortions was available from Denmark

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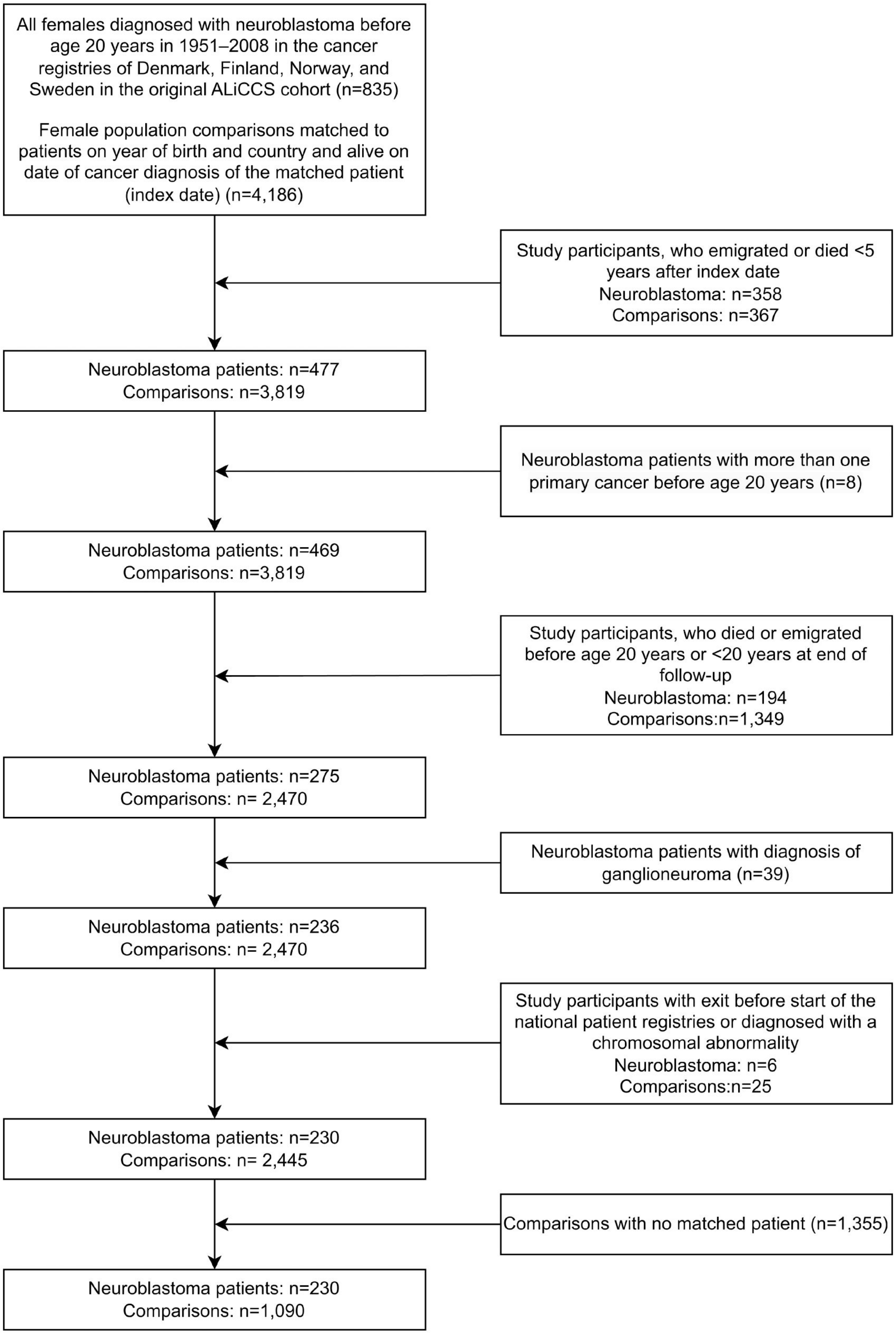

Figure 1. Flow chart of female survivors of neuroblastoma and population comparisons.

(1973–2010) [15,16], Finland (1983–2012) [17], and Sweden (1985–2008) [18]. Using the same registries, we also included information on legally induced abortions for study participants in Denmark and Finland, while information on hydatidiform moles was available only for the Danish cohort.

Statistical analysis

The survivors were followed for a first live birth, abortion, or stillbirth from the age of 20 years or the start of the national birth and abortion registries, whichever came latest. Follow-up ended on the date the survivor or their population comparison turned 50 years or emigrated, or at the end of the study (Sweden: 2008, Finland: 2012, Denmark and Norway: 2010), whichever came first. In all the analyses, age was the underlying time scale. The cumulative incidence of a first live birth or abortion was calculated with the nonparametric Aalen-Johansen estimator. As the mortality rate among survivors of neuroblastoma is higher than in the general population, death was considered a competing risk. We used a Cox proportional hazard model to compare the likelihood of a live birth or an abortion in the neuroblastoma survivors and in the comparisons. The analyses were adjusted for country. R version 4.1.0 with packages 'etmCIF', 'survival', and 'survminer' were used for the statistical analyses.

Results

Descriptive characteristics of the female neuroblastoma survivors and population comparisons are shown in Table 1. Most of the 230 neuroblastoma survivors received their diagnosis at a young age, with 45% ($n = 103$) at <1 year. Of the 79 survivors (34%) for whom treatment information was available, 4 (5%), 50 (63%), and 25 (32%) were in the high-, intermediate-, and low-risk groups, respectively. All four survivors in the high-risk group were diagnosed after 1990 (data not shown). As too few survivors had had a stillbirth, ectopic abortion, or hydatidiform mole, we are unable to report results on these outcomes due to reporting restrictions.

The cumulative incidence of a first live birth or abortion, with death as a competing event, is shown in Figure 2. The cumulative incidence of a first live birth was similar for

Table 1. Descriptive characteristics of the neuroblastoma and comparisons cohort.

Characteristic	Neuroblastoma survivors ($N = 230$)	Population comparisons ($N = 1090$)
Country (%)		
Denmark	54 (23)	242 (22)
Finland	46 (20)	226 (21)
Sweden	93 (40)	452 (41)
Norway	37 (16)	170 (16)
Vital status at end of follow-up (%)		
Alive	208 (90)	1058 (97)
Emigrated	10 (4)	26 (2)
Dead	12 (5)	6 (1)
Age at end of follow-up, years (%)		
20–29	106 (46)	493 (45)
30–39	75 (33)	339 (31)
≥40	49 (21)	258 (24)
Age at cancer diagnosis, months (%)		
	23 (10)	NA
2–11	80 (35)	NA
12–17	15 (7)	NA
18–23	17 (7)	NA
24–59	45 (20)	NA
≥60	50 (22)	NA
Calendar period at cancer diagnosis (%)		
1951–1959	10 (4)	NA
1960–1969	35 (15)	NA
1970–1979	55 (24)	NA
1980–1989	87 (38)	NA
1990–2004	43 (19)	NA
Risk group[a] (%)	$n = 79$	
High[b]	4 (5)	NA
Intermediate[c]	50 (63)	NA
Low[d]	25 (32)	NA
Livebirths (%)		
0	134 (58)	557 (51)
1	35 (15)	174 (16)
2	45 (20)	239 (22)
≥3	16 (7)	120 (11)
Abortions (%)[e]	$n = 193$	$n = 920$
0	159 (82)	802 (87)
1	23 (12)	74 (8)
≥2	11 (6)	44 (5)
Type of abortion		
Spontaneous abortions (%)[e]	$n = 193$	$n = 920$
0	177 (92)	879 (96)
≥1	16 (8)	41 (4)
Induced abortions (%)[f]	$n = 100$	$n = 468$
0	89 (89)	410 (88)
≥1	11 (11)	58 (12)

[a]Information on cancer treatment was available for 79 survivors.
[b]High-risk group: High-dose chemotherapy with ASCT ± irradiation ± surgery.
[c]Intermediate-risk group: Chemotherapy ± irradiation ± surgery, but not ASCT.
[d]Low-risk group: Treated with surgery only.
[e]Information was available for survivors and population comparisons from Denmark, Sweden, and Finland.
[f]Information on induced abortions was available for survivors and population comparisons from Denmark and Finland.

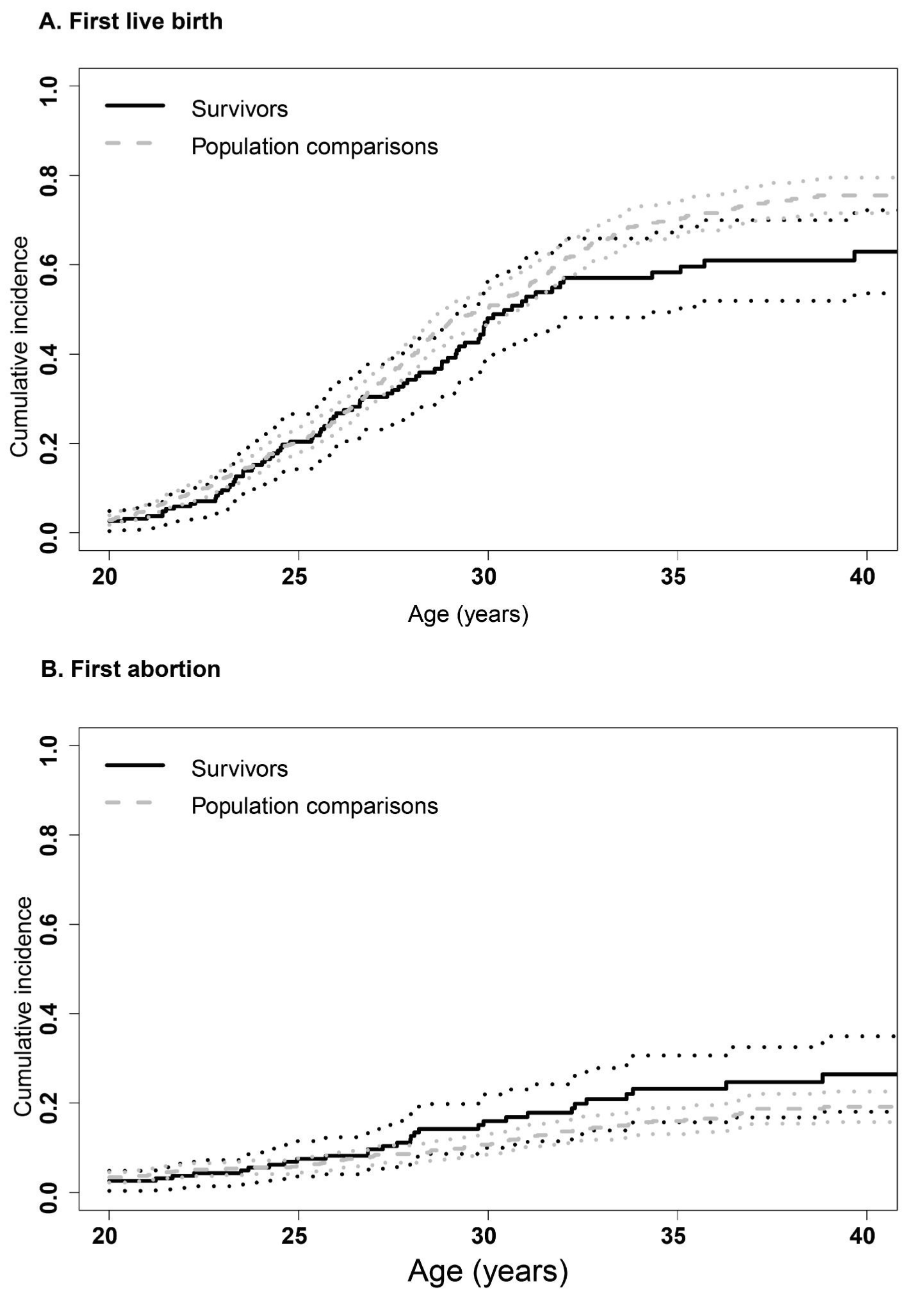

Figure 2. Cumulative incidence with 95% confidence intervals of a first live birth (A) and abortion (B) among female neuroblastoma survivors and population comparisons.

neuroblastoma survivors (48%, 95% CI 41–57) and population comparisons up to the age of 30 years (51%, 95% CI 47–54) but was lower in survivors (61%, 95% CI 53–70) than in comparisons (75%, 95% CI 72–79) by the age of 50 years. The cumulative incidence of having had at least one abortion was higher for survivors (29%, 95% CI 21–40) than for comparisons (20%, 95% CI 16–24) by the age of 50 years; however, the CIs overlapped. Among the 79 survivors in a known risk group at diagnosis, 8/25 (32%) in the low-risk and 14/50 (28%) in the intermediate-risk group had had at least one live birth (data not shown). Too few live births were observed in the high-risk group to be reported as well as for abortions in survivors in each of the three risk groups. Finally, the estimated HRs showed no difference in live births between the survivors and the comparisons, but the HR for having had at least one abortion was increased for survivors (1.86, 95% CI 1.38–2.52).

Discussion

In this Nordic population-based cohort study of 230 survivors of neuroblastoma in childhood, no difference was found in the cumulative incidence of at least one live birth at age 30 years among survivors and population comparisons, while fewer survivors than comparisons had experienced a live birth by the age of 50 years. An increased HR was found among survivors for having had at least one abortion.

Neuroblastoma was diagnosed in most of the survivors (187/230, 81%) before 1990, when the survival rate was poor, especially for high-risk patients with disseminated neuroblastoma [4,19]. In 45% (103/230) of the children who became long-term survivors, neuroblastoma was diagnosed when they were infants. None of the included survivors in the high-risk group were diagnosed before 1990. Since the survival rate for neuroblastoma was low before 1990, one might conjecture that the long-term neuroblastoma survivors in our study had localized disease, treatment included surgery and less gonadotoxic chemotherapy and/or radiotherapy, or had had spontaneous tumor regression with no treatment [4]. Thus, it is conceivable that the long-term survivors diagnosed before 1990 potentially received less toxic treatment modalities than the high-risk patients surviving today. In our data, only 5% of the survivors for whom clinical information was available were in the high-risk group, as compared to 51% diagnosed in 1981−2000 in Denmark [20]. Children with high-risk neuroblastoma, which often metastasizes to bones and/or bone marrow, are treated with intensive multimodality therapy, including chemotherapy and radiotherapy followed by autologous stem cell transplantation (ASCT) [21]. The gonadotoxic damage caused by such treatment was confirmed in a study of the long-term health status of 145 high-risk neuroblastoma survivors treated with high-dose chemotherapy, including busulfan/melphalan as part of the conditioning regimen for ASCT, with 45/58 (78%) of the female survivors having ovarian failure [5]. A large proportion of the long-term survivors in our study probably had low or intermediate risk of disease, which may explain the absence of differences in the HRs for live births between the survivors and the comparisons.

The gonadotoxic effect of alkylating agents was also observed in the Childhood Cancer Survivor Study (CCSS), in which busulfan was linked to fewer pregnancies among female survivors [10]. In that study, the HRs of a first pregnancy and of a live birth among neuroblastoma survivors who were not exposed to pelvic or cranial radiotherapy but were treated with alkylating or similar agents were 0.81 (0.63−1.05) and 0.70 (0.52−0.94), respectively. No difference in pregnancy or live birth was found for neuroblastoma survivors not treated with alkylating or similar agents as compared with their siblings. Radiotherapy to the abdomen or pelvis and total body irradiation (TBI) have also been associated with infertility and gonadal failure, including accelerated oocyte depletion and premature menopause [22–24]. A study from the CCSS on nonsurgical premature menopause (NSPM) in childhood cancer survivors found that pregnancy and live birth rates before the age of 30 years were not significantly different between survivors who developed NSPM and those without NSPM [23]. Our finding of a similar cumulative incidence of live births among survivors and female comparisons at age 30 years, but a lower incidence in survivors at age 50 years, may partly be explained by premature menopause in some survivors.

We found an elevated HR among survivors for having had at least one abortion. Both abdominal or pelvic radiotherapy and TBI have been associated with damage to the uterus, including reduced adult uterine volume [25], less muscular elasticity, and impaired blood flow, as well as endometrial atrophy and insufficiency [26]. These late complications might explain the increased risk for spontaneous abortions observed in female survivors of childhood cancer who had been treated with radiotherapy in childhood or adolescence in other studies [27], and, partly, the increased risk observed in our study.

Strengths and limitations

The strengths of the present study include the population-based design, inclusion of neuroblastoma survivors from the four Nordic countries, a randomly sampled comparison cohort, and information on pregnancy outcomes from nationwide registries, irrespective of cancer status. Our study also has some limitations. We had information only on spontaneous abortions that required a hospital contact. Although we included survivors of neuroblastoma in four countries, the rarity of neuroblastoma limits detailed analyses. In addition, information on risk group was only available for 34% of the survivors, which did not allow for further analyses including risk group. These analyses are important, given the different treatments received by survivors in different risk groups. Thus, the discussion is based on speculative causes of the observed associations as we were not able to make any conclusions about exposure to chemotherapeutic agents, ASCT or radiotherapy and pregnancy outcomes. Finally, because of changes and improvements in treatment regimens for neuroblastoma, the results of the study, which is based on survivors of neuroblastoma diagnosed in 1951–2003 may not fully reflect the fertility of women with neuroblastoma in childhood diagnosed and treated today.

Conclusion

The number of women who gave birth to at least one liveborn child before age 30 years was similar for survivors of neuroblastoma and the general female population, but fewer survivors had given birth to a liveborn child by the age of 50 years. We also observed an increased risk of survivors for having had at least one abortion. As most of the long-term survivors in the study were treated before 1990, further studies are necessary to assess pregnancy outcomes in survivors of neuroblastoma diagnosed more recently.

Acknowledgments

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Ethical approval

The design of the ALiCCS study was originally approved by national bioethics committees, data protection authorities, or the national institutes for health and welfare in each country (Denmark: 2010-41-4334, Finland: THL/520/5.05.00/2016, Norway: REC 2011/884 and Sweden: Ö 10-2010, 2011/19). With reference to the EU General Data Protection Regulation, the research project is listed in a local database at the Danish Cancer Society (2019-DCRC-0053), where all active research projects using personal data must be archived.

Disclosure statement

The authors report there are competing interests to declare.

Authors' contributions

AA: Conceptualization, Methodology, Writing-Original draft preparation, Writing-Reviewing, and Editing. FNN: Funding, Conceptualization, Methodology, Acquisition of data, Writing-Reviewing, and Editing. MK: Methodology, Formal analysis, Writing-Reviewing, and Editing. TTN: Data management, Interpretation of data, Writing-Reviewing, and Editing. ASH: Acquisition of data, Interpretation of data, Writing-Reviewing, and Editing. IØ: Acquisition of Data, Interpretation of data, Writing-Reviewing, and Editing. KV: Acquisition of Data, Interpretation of data, Writing-Reviewing, and Editing. HØ: Acquisition of Data, Writing-Reviewing, and Editing. HH: Acquisition of Data, Writing-Reviewing, and Editing. CR: Conceptualization, Interpretation of data, Writing-Reviewing, and Editing. JFW: Conceptualization, Interpretation of data, Writing-Reviewing, and Editing. LK: Conceptualization, Methodology, Formal analysis, Interpretation of data, Supervision, Writing-Reviewing, and Editing. All authors have approved the final version.

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Data availability statement

The data that support the findings of this study are available from different national services (Denmark: Sundhedsdatastyrelsen, Finland: TLH National Institute for Health and Welfare in Finland, Norway: The Cancer Registry of Norway, with an application through the Norwegian Health Data service; Sweden: The National Board of Health and Welfare) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, the study group welcomes collaboration with other researchers using our registry data. For further information regarding collaboration, please contact Line Kenborg (kenborg@cancer.dk)

References

[1] Cohen LE, Gordon JH, Popovsky EY, et al. Late effects in children treated with intensive multimodal therapy for high-risk neuroblastoma: high incidence of endocrine and growth problems. Bone Marrow Transplant. 2014;49(4):502–508. doi: 10.1038/bmt.2013.218.

[2] Maris JM, Hogarty MD, Bagatell R, et al. Neuroblastoma. Lancet. 2007;369(9579):2106–2120. doi: 10.1016/S0140-6736(07)60983-0.

[3] Coughlan D, Gianferante M, Lynch CF, et al. Treatment and survival of childhood neuroblastoma: evidence from a population-based study in the United States. Pediatr Hematol Oncol. 2017;34(5):320–330. doi: 10.1080/08880018.2017.1373315.

[4] Norsker FN, Rechnitzer C, Cederkvist L, et al. Somatic late effects in 5-year survivors of neuroblastoma: a population-based cohort study within the adult life after childhood cancer in scandinavia study. Int J Cancer. 2018;143(12):3083–3096. doi: 10.1002/ijc.31631.

[5] Haghiri S, Fayech C, Mansouri I, et al. Long-term follow-up of high-risk neuroblastoma survivors treated with high-dose chemotherapy and stem cell transplantation rescue. Bone Marrow Transplant. 2021;56(8):1984–1997. doi: 10.1038/s41409-021-01258-1.

[6] Armenian SH, Kremer LC, Sklar C. Approaches to reduce the long-term burden of treatment-related complications in survivors of childhood cancer. Am Soc Clin Oncol Educ Book. 2015;196–204. doi: 10.14694/EdBook_AM.2015.35.196.

[7] Licht SF, Rugbjerg K, Andersen EW, et al. Temporal changes in the probability of live birth among female survivors of childhood cancer: a population-based adult life after childhood cancer in scandinavia (ALiCCS) study in five nordic countries. Cancer. 2021;127(20):3881–3892. doi: 10.1002/cncr.33791.

[8] van Dorp W, Haupt R, Anderson RA, et al. Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult cancer: a review. J Clin Oncol. 2018;36(21):2169–2180. doi: 10.1200/JCO.2017.76.3441.

[9] Green DM, Whitton JA, Stoval M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the childhood cancer survivor study. Am J Obstet Gynecol. 2002;187(4):1070–1080. doi: 10.1067/mob.2002.126643.

[10] Chow EJ, Stratton KL, Leisenring WM, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the childhood cancer survivor study cohort. Lancet Oncol. 2016;17(5):567–576. doi: 10.1016/S1470-2045(16)00086-3.

[11] van Dijk M, van Leeuwen FE, Overbeek A, et al. Pregnancy, time to pregnancy and obstretic outcomes among female childhood cancer survivors: results of the DCOG LATER-VEVO study. J Cancer Res Clin Oncol. 2020;146(6):1451–1462. doi: 10.1007/s00432-020-03193-y.

[12] Asdahl PH, Winther JF, Bonnesen TG, et al. The adult life After childhood cancer in scandinavia (ALiCCS) study: design and characteristics. Pediatr Blood Cancer. 2015;62(12):2204–2210. doi: 10.1002/pbc.25661.

[13] Norsker FN, Rechnitzer C, Andersen EW, et al. Neurologic disorders in long-term survivors of neuroblastoma - a population-based cohort study within the adult life after childhood cancer in scandinavia (ALiCCS) research program. Acta Oncol. 2020;59(2):134–140. doi: 10.1080/0284186X.2019.1672892.

[14] Gissler M, Louhiala P, Hemminki E. Nordic medical birth registers in epidemiological research. Eur J Epidemiol. 1997;13(2):169–175. doi: 10.1023/a:1007379029182.

[15] Schmidt M, Schmidt SA, Sandegaard JL, et al. The danish national patient registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–490. doi: 10.2147/CLEP.S91125.

[16] Blenstrup LT, Knudsen LB. Danish registers on aspects of reproduction. Scand J Public Health. 2011;39(7 Suppl):79–82. doi: 10.1177/1403494811399957.

[17] Heino A, Niinimaki M, Mentula M, et al. How reliable are health registers? Registration of induced abortions and sterilizations in Finland. Inform Health Soc Care. 2018;43(3):310–319. doi: 10.1080/17538157.2017.1297306.

[18] Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11(1):450. doi: 10.1186/1471-2458-11-450.

[19] de Nully Brown P, Olsen JH, Hertz H, et al. Trends in survival after childhood cancer in Denmark, 1943-87: a population-based study. Acta Paediatr. 1995;84(3):316–324. doi: 10.1111/j.1651-2227.1995.tb13636.x.

[20] Schroeder H, Wacher J, Larsson H, et al. Unchanged incidence and increased survival in children with neuroblastoma in Denmark 1981-2000: a population-based study. Br J Cancer. 2009;100(5):853–857. doi: 10.1038/sj.bjc.6604922.

[21] Smith V, Foster J. High-risk neuroblastoma treatment review. Children (Basel). 2018;5(9):114. doi: 10.3390/children5090114.

[22] Utriainen P, Suominen A, Makitie O, et al. Gonadal failure is common in long-term survivors of childhood high-risk neuroblastoma treated with high-dose chemotherapy and autologous stem cell rescue. Front Endocrinol (Lausanne). 2019;10:555. doi: 10.3389/fendo.2019.00555.

[23] Levine JM, Whitton JA, Ginsberg JP, et al. Nonsurgical premature menopause and reproductive implications in survivors

of childhood cancer: a report from the childhood cancer survivor study. Cancer. 2018;124(5):1044–1052. doi: 10.1002/cncr.31121.

[24] Poorvu PD, Frazier AL, Feraco AM, et al. Cancer treatment-related infertility: a critical review of the evidence. JNCI Cancer Spectr. 2019;3:pkz008.

[25] Larsen EC, Schmiegelow K, Rechnitzer C, et al. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. Acta Obstet Gynecol Scand. 2004;83(1):96–102. doi: 10.1111/j.1600-0412.2004.00332.x.

[26] Marci R, Mallozzi M, Di Benedetto L, et al. Radiations and female fertility. Reprod Biol Endocrinol. 2018;16(1):112. doi: 10.1186/s12958-018-0432-0.

[27] Winther JF, Boice JD, Jr., Svendsen AL, et al. Spontaneous abortion in a danish population-based cohort of childhood cancer survivors. J Clin Oncol. 2008;26(26):4340–4346. doi: 10.1200/JCO.2007.15.2884.