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Reproduction and marriage among male survivors of cancer in childhood, adolescence and young adulthood: a national cohort study

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Background: Increased survival after cancer in young age has made long-term follow-up studies of high external validity important. In this national cohort study, we explored the impact of cancer in young age on reproduction and marital status in male survivors.

Methods: Hazard ratios (HRs) and relative risks (RRs) of reproductive and marital outcomes were studied for male survivors of cancer in young age (<25 years) and cancer-free male comparisons, born during 1965–1985, by linking compulsory national registries in Norway.

Results: Male cancer survivors ($n=2687$) had reduced paternity (HR: 0.72, 95% confidence interval (CI): 0.68–0.76). This was most apparent in survivors of testicular cancer, brain tumours, lymphoma, leukemia and bone tumours, and when diagnosed with cancer before 15 years of age. Male cancer survivors were more likely to avail of assisted reproduction (RR: 3.32, 95% CI: 2.68–4.11). There was no increased risk of perinatal death, congenital malformations, being small for gestational age, of low birth weight or preterm birth in their first offspring. Male cancer survivors were less likely to marry (HR: 0.93, 95% CI: 0.86–1.00), in particular brain tumour survivors.

Conclusions: In this national cohort study, we demonstrated reduced paternity and increased use of assisted reproduction among male cancer survivors, but no adverse outcome for their first offspring at birth.

The number of survivors after treatment of cancer in childhood, adolescence and young adulthood has steadily increased over the past decades (Steliarova-Foucher *et al*, 2004), due to improvements in treatment regimens and supportive care. It is now expected that close to 80% of those diagnosed with cancer during childhood or adolescence will survive their cancer and subsequent treatment (Steliarova-Foucher *et al*, 2004; Gatta *et al*, 2014). This leads to a growing number of adults in need of specialised care and counselling during specific life events, such as attempts to establish a family and reproductive health issues. In the United States, ~1 out of 530 adults between the age of 20 and 39 years is currently a survivor of paediatric cancer (Ward *et al*, 2014) and this number is expected to rise as the survivors of the recent decades with improved cancer treatment reach adult age.

However, as treatment for these cancers has become more successful, the concern regarding severe late effects has also increased. Adult survivors of childhood cancer have a high prevalence of adverse health outcomes, especially pulmonary, cardiac and endocrine (Hudson *et al*, 2013; de Fine Licht *et al*, 2014; Gudmundsdottir *et al*, 2015), as well as risk of secondary malignancies (Oeffinger *et al*, 2006; Geenen *et al*, 2007; Olsen *et al*, 2009).

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The effects of previous cancer treatment on pregnancy and reproductive outcomes among female survivors diagnosed with cancer in young age are relatively well explored (Green *et al*, 2009; Reulen *et al*, 2009; Signorello *et al*, 2012). Less detailed and comprehensive information is, however, available regarding male survivors and studies are often hampered by a limited number of participants, selection bias and low power (Green *et al*, 2010; Tromp *et al*, 2011; Van Dorp *et al*, 2012; Wasilewski-Masker *et al*, 2014). The objective of this study was to examine detailed reproductive outcomes of men diagnosed with cancer before the age of 25 years in a complete, national cohort. By linking several compulsory national databases in Norway holding medical, social and demographic data, we assessed medical aspects of reproduction at a population level (paternity, the use of assisted reproductive technology (ART) and offspring outcomes) and also whether a potential difference in paternity rates could be explained by a difference in the ability to find a partner (social aspect of reproduction). Our registry design rewarded us a large population-based cohort of high scientific validity available for analysis.

MATERIALS AND METHODS

Data sources. The Cancer Registry of Norway (CRN) has received information on all patients with a cancer diagnosis since 1953. Reporting is mandatory for all clinicians and pathologists in Norway (Cancer Registry of Norway, 2013), and information about site, histological type and stage of disease at the time of diagnosis is recorded. The completeness of the CRN has been found to be >95% (Larsen *et al*, 2009), consistent with other Northern European cancer registries (Gatta *et al*, 2014). Cancer Registry of Norway provided information on the cancer cases including date of diagnosis, site (International Classification of Disease, Seventh Edition (ICD-7; World Health Organization, 1957) and, for some diagnoses (leukemia, lymphoma and central nervous system (CNS) tumours), tumour morphology (Manual of Tumor Nomenclature and Coding (MOTNAC; American Cancer Society, 1968) for cancers diagnosed until 1992 and International Classification of Diseases for Oncology, Second Edition (ICD-O-2) morphology codes from 1993 onwards (World Health Organization, 1990; Larsen *et al*, 2009)).

The Medical Birth Registry of Norway (MBRN) holds information on all births in Norway since 1967 (Irgens, 2000; Medical Birth Registry of Norway, 2013). The Medical Birth Registry of Norway is based on compulsory notification of every birth or late abortion from 16 weeks of gestation onwards and includes identification of the parents, complications during pregnancy and delivery, length of pregnancy, as well as information on the infant. The registry contains information on the use of ART from 1984 and close to complete data on the uptake of ART services in Norway, including method of treatment (*in-vitro* fertilisation, intracytoplasmic sperm injection (ICSI), combination or non-specified), is available from 1988 onwards (Romundstad *et al*, 2008). We identified members of the study cohort registered in MBRN as fathers. For their first offspring, MBRN provided information on stillbirths and neonatal deaths, gestational age, birth weight, congenital anomalies and whether the birth was a result of ART (including method).

The Central Population Registry contains demographic information on all residents in Norway from 1960 onwards (Norwegian Tax Administration, 2015). The registry provided date of birth, emigration or death and information on marital status. Data on education were provided by the Norwegian National Education Database, where all education statistics on an individual level has been registered since 1970 (National Education Database, 2013).

Every resident in Norway has since 1960 been assigned a unique 11-digit personal identification number, which enables precise record linkage between registries.

Study cohort. Our study cohort consisted of all males born alive in Norway during the 20-year period from 1965 through 1985. Those who lacked an identification number, emigrated or died before the start of reproductive age (defined here as 15 years) were excluded ($n=16\,140$). The cancer cases were identified through the CRN and information was available for cancers diagnosed through 31 December 2007. We excluded those who had an uncertain basis for their cancer diagnosis or a cancer diagnosis at autopsy only ($n=217$). The cancer site grouping used for this study was based on a modified version of the International Classification of Childhood Cancer, Second Edition (Kramarova and Stiller, 1996), based on ICD-O-2 and MOTNAC morphology codes, as well as ICD-7 topography codes. For the tumours of the CNS, we divided the cancer diagnoses into low- and high-grade tumours according to the WHO classification (Louis *et al*, 2007). The term cancer survivor was used to encompass all individuals diagnosed with cancer before age 25 years and surviving beyond reproductive age (15 years of age).

The male cancer survivors who were diagnosed with a second cancer ($n=82$) during follow-up were excluded from the analyses. There were missing data on marital status for 4539 individuals including 143 of the cancer survivors.

Statistical analyses. We estimated the hazard ratio (HR) with a 95% confidence interval (CI) of fathering a first offspring in the male cancer survivors compared with the non-cancer male group, using Cox regression. We started follow-up at 15 years of age, ended at the date of birth of the first offspring and censored at death, emigration or 31 December 2011, whichever occurred first. We then categorised the cancer cohort into diagnostic groups (as described), age at diagnosis (0–14 years, 15–19 years and 20–24 years) and diagnostic time periods (1965–79, 1980–94 and 1995–2007), and repeated the analyses on these subgroups. In order to fully make use of the prospective nature of our data and account for changes in the hazard rates over time, we formed a time-dependent Cox regression model. For this model studying paternity (defined as the date of birth of the first offspring) as outcome, we defined age at cancer diagnosis as a time-dependent covariate. This covariate was equal to 0 as long as the cohort member had not been diagnosed with cancer before the age of 25 years and changed value to 1 when cancer (<25 years of age) was diagnosed. For the cohort member diagnosed with cancer before 15 years of age, this covariate was equal to 1 at the start of the follow-up. By using this model, the cancer survivors fathering their first child before their cancer was diagnosed ($n=72$) were included in the non-cancer comparison group for this analysis. We decided to study the first offspring only, as this is the most unambiguous measure of parenthood in the absence of both treatment data and data on reproductive desire.

Adjustments were made by including year of birth of the cohort members as a continuous variable, as well as parental education (highest educational level achieved by the parents of the cohort) as a categorical variable, divided into three categories: lower education (<11 years), intermediate (11–14 years) and tertiary education (>14 years).

For the analysis on marriage, this was similarly modelled as described above, with an extended Cox model including age at cancer diagnosis as a time-dependent covariate. The follow-up ended at the date of first marriage and cases were censored at death, emigration or 31 December 2007, whichever occurred first. Thus, the male cancer survivors who married before receiving their cancer diagnosis were included in the non-cancer reference group

for the analysis on marriage. This was done to make correct use of the prospective nature of the data and to avoid conditioning on a future cancer diagnosis. We then analysed paternity in the married men only, for the cancer survivors compared with the cancer-free male reference group. In this analysis, we started follow-up of the childless males at the age of 15 years and ended at the date of birth of the cohort member's first offspring, censoring at death, emigration or 31 December 2011, whichever occurred first. Here, a standard Cox proportional hazard regression model was employed and only the married men ($n = 204\,652$) were part of this sub-analysis. In addition to adjustments described for the previous analyses, this analysis was also adjusted for the cohort member's age at marriage.

We estimated the relative risk (RR) of perinatal death (comprising stillbirth >22 weeks gestation and neonatal death <28 days), congenital anomalies, preterm birth (subdivided into gestational age of 22–28 weeks and 29–36 weeks), low birth weight (subdivided into birth weight of 500–1499 g and 1500–2499 g), small for gestational age (SGA) and the risk of the pregnancy being conceived using assisted reproduction, in the male cancer survivors first offspring compared with the first offspring of the cancer-free reference group. A log binomial regression model was employed and the results are presented as RRs with 95% CIs. For the analysis on prematurity, low birth weight and SGA, we included only singleton pregnancies. Small for gestational age was defined as birthweight below -2 s.d. from the mean, sex-specific for each gestational age in weeks (Skjærven *et al*, 2000). Adjustments were made for birth year of the offspring's father (the cohort member) and age of the offspring's mother (the partner of the cohort member).

SPSS version 21 (IBM SPSS, Armonk, NY, USA) and STATA version 12 (StataCorp LP, College Station, TX, USA) were used for statistical analyses. Figure 1 was made in R statistical software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics for Western Norway.

RESULTS

A total of 626 495 males were born in Norway from 1965 through 1985. After excluding those who emigrated or died before fertile age, the study cohort comprised 2687 cancer survivors diagnosed with cancer before the age of 25 years and 607 668 cancer-free male comparisons (Table 1). There were 1087 first offspring among the male cancer survivors, the corresponding number being 368 469 in the male non-cancer reference group. Thirty per cent of the cancer cases were diagnosed in childhood (0–14 years of age), 26% in adolescence (15–19 years) and 43% in young adulthood (20–24 years). There were relatively few survivors being diagnosed in the first time period of 1965–1979 (9%) and thus the majority was diagnosed after 1980 (Table 1).

The most prevalent cancer type overall was gonadal and germ cell tumours (27% of which the majority were diagnosed as young adults), hereafter referred to as 'testicular cancer', followed by CNS tumours (18%), lymphoma (15%) and leukemia (13%; Table 1).

We observed a significant reduction in paternity in the male cancer survivors (HR: 0.72, 95% CI: 0.68–0.76) compared with the non-cancer males (Figure 1A). Divided into cancer site, we found

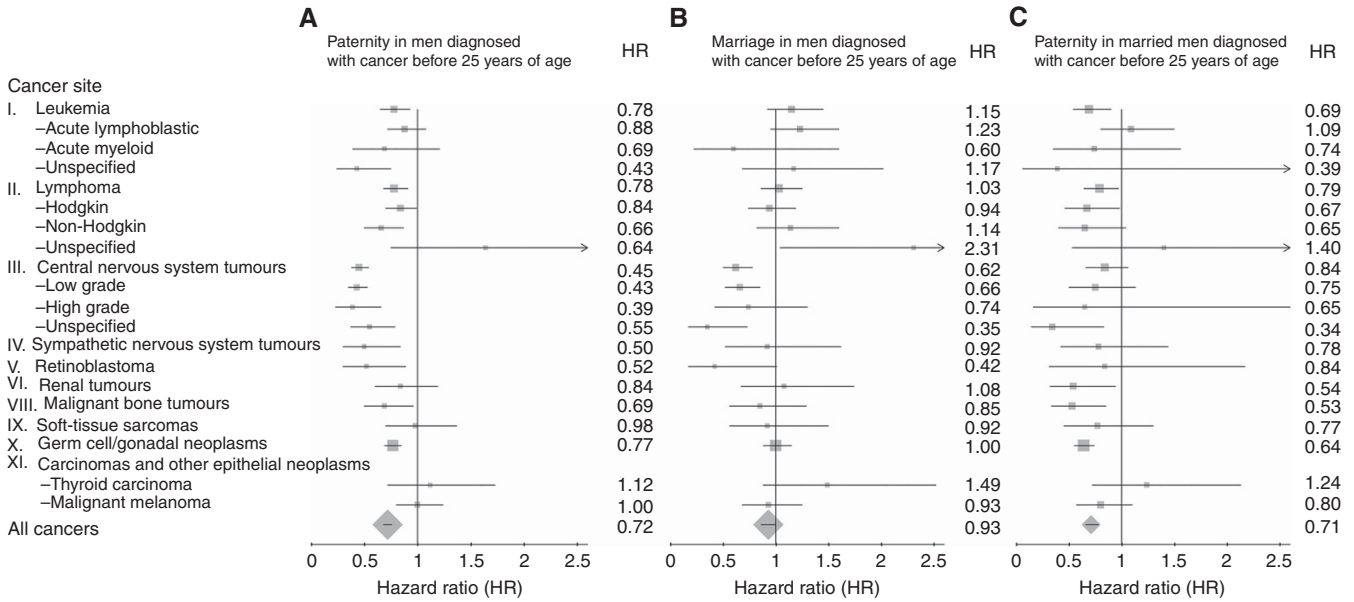

Figure 1. Forest plot of hazard ratios for paternity and marriage. (**A**) Hazard ratios (HRs) with 95% CIs of fathering a first offspring after cancer diagnosis, for all cancer survivors ($n = 2605$, secondary malignancies excluded), subdivided into different cancer diagnoses, with the non-cancer male population as reference ($n = 607\,668$). (**B**) Hazard ratios with 95% CIs of marriage in the cancer survivors ($n = 2462$), with the cancer-free male population as reference ($n = 603\,272$). (**C**) Hazard ratios with 95% CIs of fathering a first offspring in the married population only, in the cancer survivors ($n = 667$) *versus* the male non-cancer reference population ($n = 203\,985$). The horizontal lines through the squares represent 95% CI, arrows indicate upper CI above 2.5. Solid boxes indicate HR in each cancer group with dimensions proportional to weights (inverse of s.d.). The diamonds represent the pooled HR for all cancers, with 95% CI. All analyses are adjusted for birth year of the cohort members (father) and education of parents; and for the analysis presented in **C**, adjustment was also made for age (of cohort member) at marriage. Age at cancer diagnosis was entered as a time-varying covariate in the extended Cox regression analysis for **A** and **B**. Only results from cancer groups containing >30 survivors are depicted. The cancer site grouping used is a modified version of the International Classification of Childhood Cancer (Kramarova and Stiller, 1996), based on ICD-O-2 and MOTNAC morphology codes and ICD-7 topography codes. The grading of CNS tumours is based on the 2007 WHO classification of tumours of the CNS (Louis *et al*, 2007).

Table 1. Characteristics of the male cancer survivors

	Age at diagnosis			Calendar year of diagnosis			
	Number (% of total number in age category)			Number (% of total number in diagnostic period)			
Diagnostic group[a]	**0–14 Years**	**15–19 Years**	**20–24 Years**	**1965–79**	**1980–94**	**1995–07**	**Total (%)**
I. Leukemia	214 (26.1)	74 (10.4)	54 (4.7)	59 (23.9)	207 (15.4)	76 (6.9)	342 (12.7)
Lymphoblastic leukemia	169	51	19	45	149	45	239
Myeloid leukemia	18	16	23	3	33	21	57
Leukemia, unspecified	27	7	12	11	25	10	46
II. Lymphoma	97 (11.8)	131 (4.5)	182 (15.7)	20 (8.1)	211 (15.7)	179 (16.4)	410 (15.3)
Hodgkin lymphoma	41	76	127	7	116	121	244
Non-Hodgkin lymphoma[b]	50	55	53	8	93	57	158
Lymphoma,unspecified	6	0	2	5	2	1	8
III. CNS neoplasms[c]	214 (26.1)	122 (17.1)	150 (13.0)	60 (24.3)	260 (19.3)	166 (15.2)	486 (18.1)
Low grade	148	76	96	44	170	106	320
High grade	34	25	27	8	54	24	86
Unspecified	32	21	27	8	36	36	80
IV. Sympathetic nervous system tumours	40 (4.9)	4 (0.6)	5 (0.4)	19 (7.6)	27 (2.0)	3 (0.3)	49 (1.8)
V.Retinoblastoma	39 (4.8)	0 (0)	0 (0)	17 (6.9)	22 (1.6)	0 (0)	39 (1.5)
VI. Renal tumours	56 (6.8)	1 (0.1)	4 (0.3)	30 (12.1)	27 (2.0)	4 (0.4)	61 (2.3)
VII. Hepatic tumours	8 (1.0)	3 (0.4)	3 (0.3)	5 (2.0)	8 (0.6)	1 (0.1)	14 (0.5)
VIII. Malignant bone tumours	38 (4.6)	61 (8.6)	29 (2.5)	7 (2.8)	77 (5.7)	44 (4.0)	128 (4.8)
IX. Soft tissue sarcomas	28 (3.4)	30 (4.2)	15 (1.3)	4 (1.6)	50 (3.7)	19 (1.7)	73 (2.7)
X. Germ cell and other gonadal neoplasms	39 (4.8)	179 (25.1)	516 (44.6)	16 (6.4)	284 (21.1)	434 (39.7)	734 (27.3)
XI. Carcinomas and other malignant epithelial neoplasms							
Thyroid carcinoma[d]	5 (0.6)	11 (1.5)	21 (1.8)	0 (0)	21 (1.6)	16 (1.5)	37 (1.4)
Malignant melanoma	13 (1.6)	40 (5.6)	77 (6.7)	3 (1.2)	69 (5.1)	58 (5.3)	130 (4.8)
Skin, non-melanoma[e]	9 (1.1)	10 (1.4)	24 (2.1)	2 (0.8)	18 (1.3)	23 (2.1)	43 (1.6)
Colon	0 (0)	6 (0.8)	19 (1.6)	0 (0)	6 (0.4)	19 (1.7)	25 (0.9)
Urinary/bladder	4 (0.5)	5 (0.7)	9 (0.8)	2 (0.8)	9 (0.7)	7 (0.6)	18 (0.7)
XII. Other and unspecified malignant neoplasms	15 (1.8)	35 (4.9)	48 (4.2)	3 (1.2)	50 (3.7)	45 (4.1)	98 (3.6)
Total	819 (100)	712 (100)	1156 (100)	247 (100)	1346 (100)	1094 (100)	2687[f] (100)

Abbreviations: CNS = central nervous system; ICD-7 = International Classification of Disease, seventh edition; ICD-O-2 = International Classification of diseases for oncology, second edition; MOTNAC = Manual of Tumor Nomenclature and Coding. Characteristics of the male cancer survivors (including overall and specific cancer sites), stratified according to age and time period of cancer diagnosis.

[a]The cancer site grouping used is a modified version of the International Classification of Childhood Cancer (Kramarova and Stiller, 1996), based on ICD-O-2 and MOTNAC morphology codes and ICD-7 topography codes.

[b]Including Burkitt lymphoma.

[c]The grading of CNS tumours is based on the 2007 WHO classification of tumours of the CNS (Louis *et al*, 2007).

[d]Including adrenal (endocrine) carcinoma ($n = 3$).

[e]Excluding basal cell carcinoma, site grouping based on ICD-7 site code 190.

[f]Including 82 individuals with a secondary malignancy.

significantly reduced paternity in survivors of testicular cancer, CNS tumours (both low grade, high grade and unspecified), lymphoma (both Hodgkin lymphoma (HL) and non-HL), leukemia, malignant bone and sympathetic nervous system tumours, as well as retinoblastoma.

When studying the impact of time period of cancer diagnosis and age at cancer diagnosis, we found the reduction in paternity in our material most pronounced in the patients receiving a cancer diagnosis before 1995 (HR: 0.61, 95% CI: 0.51–0.72 (diagnosed 1965–79); HR: 0.66, 95% CI: 0.61–0.72 (1980–94)) and among those diagnosed below age 15 years (HR: 0.59, 95% CI: 0.52–0.66). Adjustment for parental education and birth year did not change our estimates.

The first offspring of the male cancer survivors did not have an increased risk of perinatal death or congenital anomalies (Table 2), neither when analysing only major birth defects (according to the EUROCAT classification (EUROCAT, 2012)), nor when the subgroups of cancer diagnoses were analysed separately (results not shown). There were a total of 42 first offspring of the male cancer survivors registered with a congenital malformation in the MBRN (4%). Similarly, we could not demonstrate any increased risk for preterm birth (22–36 completed weeks of gestation), low birth weight (500–2499 g) or being SGA, in the offspring of male cancer survivors (Table 2). All estimates for adverse offspring outcomes of the male cancer survivors in comparison with the non-cancer male reference group were below 0, suggesting no increased risk for adverse outcomes, although not reaching statistical significance. Although including multiple pregnancies for analysis provided similar results, the results presented include singleton births only.

There was a threefold increased likelihood of pregnancies resulting from ART (RR: 3.32, 95% CI: 2.69–4.10) for the male cancer survivors' first offspring (Table 3). For sub-analyses on the associations between assisted reproduction and age at cancer diagnosis as well as treatment period, this was only significant for fathers diagnosed with cancer after 14 years of age and after 1980 (results not shown), although based on small numbers. The use of ART to impregnate their partner was significantly increased for survivors of testicular cancer, CNS tumours, lymphoma, leukemia, malignant bone tumours, sympathetic nervous system tumours and thyroid cancer, although there were small numbers in the three latter cancer groups (Table 3). With regards to method of ART,

Table 2. RR with 95% CI for selected first offspring outcomes

Offspring outcome	Male cancer survivors[a] (% of total first offspring)	Non-cancer male reference population (% of total first offspring)	RR[b]	95% CI
Perinatal death[c]	6 (0.6)	2424 (0.7)	0.72	0.33–1.61
Congenital malformation[d]	42 (3.9)	15 395 (4.2)	0.92	0.69–1.24
Premature delivery[e]	52 (4.9)	21 490 (5.9)	0.83	0.63–1.08
22–28 Weeks	1 (0.1)	1625 (0.4)	0.21	0.03–1.50
29–36 Weeks	51 (4.8)	19 955 (5.5)	0.87	0.67–1.14
Low birth weight[e]	30 (3.0)	15 865 (4.4)	0.69	0.49–0.97
500–1499 g	5 (0.5)	2927 (0.8)	0.59	0.25–1.41
1500–2499 g	25 (2.4)	12 165 (3.4)	0.70	0.48–1.04
SGA[e,f]	17 (1.6)	7.979 (2.2)	0.75	0.46–1.19

Abbreviations: CI = confidence interval; RR = relative risk; SGA = small for gestational age. RR with 95% CI for selected first offspring outcomes in 1087 first singleton offspring of 2687 male cancer survivors compared with 368 469 first singleton offspring of 607 668 individuals in the non-cancer male comparisons.
[a]Cancer survivors with secondary malignancies ($N = 82$) are excluded from the analysis.
[b]All analyses are adjusted for birth year of cohort members (fathers), mothers' age and education of parents of cohort.
[c]Perinatal death = stillbirths >22 weeks gestational age and deaths <28 days of age. Of the six deceased offspring of cancer survivors, five were stillbirths and one was neonatal death (<28 days of age).
[d]The congenital malformations in the cancer survivors' offspring included hip deformity/dislocation (seven), foot deformities (four), patent ductus arteriosus (four), ventricular septal defects (four), atrial septal defects (three), obstructive nephropathy (three), malformations of the gastrointestinal tract (two), cleft lip/palate, pulmonary stenosis, diaphragmatic hernia, hypoplasia of the lung, agenesis of corpus callosum, neural tube defect, malformations in the skin and eye (all one). Some offspring were registered with more than one congenital malformation.
[e]Multiple pregnancies ($N = 6245$) are excluded from the analysis on prematurity, low birth weight and SGA.
[f]SGA is defined according to Skjærven *et al* (2000).

there was a significantly increased usage of ICSI compared with *in vitro* fertilisation and unspecified methods in the partners of male cancer survivors compared with the partners of the male non-cancer reference group (RR: 1.51, 95% CI: 1.25–1.81; Supplementary Table). Male cancer survivors had a slightly lower likelihood of getting married compared with the non-cancer group (HR: 0.93, 95% CI: 0.86–1.00; Figure 1B). In the CNS tumour group, there was a significantly decreased likelihood of marriage in the low-grade and nonspecific tumour groups, but in the high-grade group this reduction was not significant. For survivors of testicular cancer, lymphoma and leukemia, we found similar marriage rates to the non-cancer male group (Figure 1B). When analysing the married sub-cohort only, the paternity deficit for the male cancer survivors remained (HR: 0.71, 95% CI: 0.66–0.78; Figure 1C), and especially in the subgroups of testicular cancer, lymphoma and leukemia. The reduced paternity in the CNS tumour group, however, was less pronounced when restricting analyses to the married individuals only.

DISCUSSION

In this national cohort study of Norwegian males born over a 20-year period, we found significantly reduced paternity in men diagnosed with cancer before the age of 25 years when compared with the non-cancer reference group, especially when diagnosed with cancer before age 15 years. Pregnancies conceived by ART were significantly increased, but we could not demonstrate any increased risk for adverse outcomes among the first offspring of the survivors. Male cancer survivors had a slightly lower probability to marry and the paternity deficit persisted when analysing the married individuals only, except for the CNS tumour group.

One strength of the study is the use of compulsory national registries not prone to selection bias and with minimal loss to follow-up. Thus, our sample size is large and fully complete on a population level. Furthermore, health care in Norway is free of charge and provided independent of geographical location and patient age (Molven and Ferkis, 2011).

A weakness of the study is the lack of detailed information on individual cancer treatment. However, treatment for childhood cancer in Norway has for the past 30 years been standardised by common Nordic or European treatment protocols, and given at a small number of centres, ensuring identical treatment regimens for all children with cancer (Gustafsson *et al*, 2000; Pritchard-Jones *et al*, 2013) and making assumptions as to which treatments have been given in this group possible (Gustafsson *et al*, 1998; Moe *et al*, 1997).

The great majority of male cancer survivors in our study were diagnosed after 1980 (>90%, Table 1) and for some cancer sites there have been major changes in treatment regimens with regards to gonadotoxicity since then. For testicular cancer, with the introduction of retroperitoneal lymph node dissection and cisplatin-based chemotherapy from 1980 onwards, this is regarded as a major paradigm shift in the treatment (Fosså and Kravdal, 2000). For CNS tumours, there has been no major change in treatment given over the past decades (Stensheim *et al*, 2011). For HL in paediatric and adolescent patients, there has been an ongoing process of reducing (and in selected cases omitting) radiation since 1995 (Dörffel *et al*, 2013) as well as a shift towards less gonadotoxic chemotherapy regimens (GPOH, 2015). For (young) adult HL patients this has been a slower but nonetheless ongoing process (Kiserud *et al*, 2007). In the case of non-HL, there are no major changes in treatment strategies since 1980 (Stensheim *et al*, 2011). For paediatric leukemia, omitting cranial irradiation and replacing it with intermediate- and high-dose methotrexate intravenously and intrathecally, has been the standard therapy in Norway since 1975 (Moe *et al*, 1981). The agents in use for the treatment of paediatric leukemia have not been subject to major changes over the past few decades, although treatment combinations and dosages have changed. There has been a significant reduction in the use of irradiation for most paediatric cancers over the past four decades (Jairam *et al*, 2013).

Our information regarding ART does not take into account those who have attempted ART not leading to a successful pregnancy. Our ART rates therefore serve as a surrogate marker for ART attempts. There is no evidence to support that cancer survivors would have a higher success rate from ART than cancer-free individuals, thereby leading to an overestimation of the uptake (García *et al*, 2014). There is no information in the MBRN on the use of sperm donors, which would have been useful for our study. ART has been associated with adverse pregnancy outcomes (Romundstad *et al*, 2008); however, despite an increased use of

Table 3. RR with 95% CI for pregnancies resulting from ART

Diagnostic groups[a]	Offspring from ART (total offspring)	RR[b]	95% CI
No cancer	8278 (368 469)	1.00	(Ref)
All cancer[c]	80 (1087)	3.32	2.69–4.10
I. Leukemia	6 (121)	2.29	1.05–5.00
Lymphoblastic leukemia	3 (95)	1.463	0.48–4.44
Myeloid leukemia	1 (12)	3.76	0.57–24.84
Leukemia, unspecified	2 (14)	6.45	1.81–22.94
II. Lymphoma	15 (178)	3.79	2.34–6.15
Hodgkin lymphoma	12 (121)	4.45	2.60–7.60
Non-Hodgkin lymphoma[d]	3 (50)	2.70	0.90–8.67
Lymphoma, unspecified	0 (7)	*	*
III. CNS neoplasms[e]	7 (132)	2.41	1.17–4.95
Low grade	6 (91)	2.94	1.36–6.38
High grade	0 (15)	*	*
Unspecified	1 (26)	1.84	0.27–12.541
IV. Sympathetic nervous system tumours	2 (15)	5.71	1.58–20.65
V. Retinoblastoma	0 (13)	*	*
VI. Renal tumours	2 (32)	2.20	0.55–8.79
VIII. Malignant bone tumours	4 (37)	4.77	1.89–12.06
IX. Soft tissue sarcomas	1 (34)	1.32	0.19–9.14
X. Germ cell and other gonadal neoplasms	38 (349)	3.70	2.69–5.09
XI. Carcinomas and other malignant epithelial neoplasms			
Thyroid carcinoma[f]	2 (20)	4.36	1.17–16.31
Malignant melanoma	1 (80)	0.45	0.06–3.21

Abbreviations: ART = assisted reproductive technology; CNS = central nervous system; ICD-7 = International Classification of Disease, seventh edition; ICD-O-2 = International Classification of diseases for oncology, second edition; MOTNAC = Manual of Tumor Nomenclature and Coding. Relative risk (RR) with 95% Confidence interval (CI) for pregnancies resulting from ART in 80 partners of male cancer survivors (first offspring) when compared to 8,278 partners of the cancer-free male comparisons.

[a]The cancer diagnostic groups defined are based on a modified version of the International Classification of Childhood Cancer (Kramarova and Stiller, 1996), based on ICD-O-2 and MOTNAC morphology codes and ICD-7 topography codes. Only results for cancer groups with >30 cases are presented.

[b]All analyses are adjusted for birth year of the cohort members (fathers) and age of the mother of the offspring. Owing to small numbers in some of our cancer diagnostic groups, the analysis is run only in diagnostic groups containing >35 survivors.

[c]Cohort members with secondary malignancies ($N = 82$) are excluded.

[d]Including Burkitt's lymphoma.

[e]The grading of CNS tumours is based on the 2007 WHO classification of tumours of the CNS (Louis *et al*, 2007).

[f]Including adrenal (extracranial endocrine gland) carcinoma.

ART among the male cancer survivors in our study, we could not demonstrate an increased risk of negative outcomes among their offspring. This applied also when studying the offspring of ART only, in a separate analysis, although the numbers were too small to firmly conclude (Supplementary Table). Several published studies have explored the relationship between a cancer diagnosis and the probability of having children (Madanat *et al*, 2008; Magelssen *et al*, 2008; Green *et al*, 2010; Hudson, 2010). Most, although not all, show reduced reproduction after surviving a cancer diagnosis, in childhood, adolescence and in young adult age (Syse *et al*, 2007), also depending on the site and stage of the cancer. There is, to our knowledge, no population-based study to date looking at the interplay of paternity, assisted reproduction, marriage and offspring outcomes in a national cohort of male survivors of cancer diagnosed in childhood, adolescence and young adulthood. The current study therefore adds important information regarding these complex and interconnected issues, by studying them in a population perspective.

We did not have complete information in our registries on cohabitation rates and therefore used marriage as a marker for the ability to sustain long-term relationships and establishing a family unit. There is no evidence to support that childless cancer survivors would marry more or less frequently (compared with cohabitating without marrying) than the childless non-cancer males (Syse, 2008), nor did we find that the age at first marriage differed (data not shown). In order to take into account socioeconomic status as a possible factor influencing marriage and paternity, we adjusted all analyses for educational achievement (highest education achieved) of the parents of the cohort (as many of the cohort members might not have completed their education at the time of analysis), which did not change our estimates.

Studies have looked at cohabitation/marriage rates in cancer survivors compared with siblings or with the cancer-free general population, with somewhat conflicting results (Frobisher *et al*, 2007; Gurney *et al*, 2009; Koch *et al*, 2011; Kirchhoff *et al*, 2012; Wengenroth *et al*, 2013). Syse (2008) did not find reduced marriage rates in male survivors of any types of cancer (before age 44 years) in Norway, compared with the male population as a whole, and only a nonsignificant slightly lower probability for brain tumour survivors to marry, as well as an increased marriage rate for survivors of testicular cancer. This is, despite a partial overlap in study populations, contrary to our findings and probably reflects the crucial timing of the treatment insult for young male brain cancer patients in our study, as well as the fact that childhood cancer survivors only contribute marginally to the overall estimates for male survivors in the publication by Syse. A Danish registry-based study (Koch *et al*, 2011) found a reduced rate of cohabitation for childhood cancer survivors in general and the largest deficit was found for survivors of CNS tumours, which correspond well with our results.

We did not find an increased risk for detrimental effects of a history of cancer in male survivors on pre- and perinatal outcomes of their firstborn offspring. This has also been demonstrated in two previous Norwegian studies (Magelssen *et al*, 2008; Stensheim *et al*, 2013),

which have partly overlapping data with ours, although only studying cancer diagnosed at 15 and 16 years and above, respectively. However, there have been conflicting results published with regards to the risk of congenital malformations in the offspring of male cancer patients (Magelssen *et al*, 2008; Winther *et al*, 2009; Ståhl *et al*, 2011; Signorello *et al*, 2012; Stensheim *et al*, 2013). A Norwegian (Magelssen *et al*, 2008) and a Swedish (Ståhl *et al*, 2011) study found an increased risk of congenital abnormalities in the offspring of male cancer survivors. However, in the Norwegian study the data were from one hospital only, cancers were diagnosed at age 15–35 years and the numbers studied were relatively small. In the latter study, cancer was diagnosed at all ages and there was no treatment data available. The publications that were able to explore directly the link between treatment exposure (especially radiation therapy to the gonads and alkylating chemotherapy) and genetic disease in the offspring (Signorello *et al*, 2012; Winther *et al*, 2012) could not provide evidence for a causal relationship, which is in concordance with our results (although we were not able to study treatment exposures directly).

We briefly studied the impact of the diagnostic time period and age at cancer diagnosis. As there are various co-dependent time factors associated with a prospective study of a cancer cohort such as ours, this could not be thoroughly studied within our design. Some studies on adult survivors of cancer in young age have described a reduction in late effects in survivors being treated with more modern, and presumably less intense, treatment regimens (Cvancarova *et al*, 2009; Stensheim *et al*, 2011), which is in concordance with our results. Conflicting evidence exist with regard to whether the prepubertal testis is protected from cytotoxic insults or not (Rivkees, 1988; Green *et al*, 2014), although the most recent publication cannot find any protective effect of being treated pre-pubertally with alkylating agent chemotherapy on subsequent adult sperm concentration. Our results suggest vulnerability in children younger than 15 years at diagnosis. This may be attributable to the fact that childhood cancers more often require intensive, multi-modal therapy when compared with young adult cancer, more so than a biological inherent vulnerability to the toxicity of cancer treatment in pre-pubertal children. As we have no access to treatment exposures in our study, we are not able to explore this in detail. Owing to the selection of our cohort, the male cancer survivors in the oldest age group at diagnosis will have been treated with more modern treatment regimens and also at a time when fertility preservation was becoming more available in Norway (Stensvold *et al*, 2011).

As we use the national registry data, our data overlap in part with earlier Norwegian studies published (Syse *et al*, 2007; Magelssen *et al*, 2008; Syse, 2008; Stensheim *et al*, 2011, 2013). Our findings, when comparable, line up well with existing, overall conclusions and do not provide evidence that male childhood cancer survivors (not included in all previous publications) in general fare worse than survivors diagnosed with cancer at an older age. This is an important information for the growing population of childhood cancer survivors. Unfortunately, it is not possible to disentangle the possible influences of data overlap *versus* non-overlap and actual changes that have taken place in more recent times, based on the published information. By jointly considering birth outcomes, parenthood and marriage in a recent time period in a complete national cohort, we contribute novel, updated information on important aspects of adult living for Norwegian male survivors of cancer diagnosed before 25 years of age. This might be transferable to male cancer survivors not only in the Nordic countries but also in non-Nordic countries, which share some of the Nordic welfare traits, and hopefully will contribute to developing adequate counselling and follow-up strategies for male survivors of cancer in young age, during their transition into and passage through adulthood.

Although a large proportion of male survivors of cancer in young age will be able to establish a family and father children, there is still room for improvement, especially with regards to decreasing the toxicity burden of current treatment regimens, as well as improving fertility preservation methods and access to these for young male cancer patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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