Adult life challenges in survivors of young age cancer

A Norwegian national cohort study focusing on reproduction, economic independence and violent deaths

Maria Winther Gunnes

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Author: Maria Winther Gunnes

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Scientific environment

The work for this thesis was carried out during 2011-2016, at the Department of Global Public Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen, Norway, within the Research Group for Genetic Epidemiology.

My main supervisor is Professor Dag Moster, Department of Pediatrics, Haukeland University Hospital and Department of Global Public Health and Primary Care, University of Bergen, Norway.

Co-supervisor is Professor Tone Bjørge at the Department of Global Public Health and Primary Care, University of Bergen, Norway, and the Norwegian Cancer Registry.

During my time as a PhD student I have been a member of EPINOR, a Norwegian national research school in population based epidemiology.

Acknowledgements

It would be a lie if I did not admit that the transition from having a busy, rewarding and challenging workday at the hospital, to plummet right down to the bottom of the hierarchy again; restlessly wandering through the corridors of IGS, knocking on people's doors to ask for help on very basic statistical and epidemiological problems, suddenly having no known assets with which to contribute, was a very tough one for me. More than once I thought (and talked) about quitting, and returning to my clinical work where I knew I was needed and depended upon. However, since being determined has been a dominant trait of mine since before I could walk or talk (or so I've been told), quitting was no real option, and as time passed, I gradually found peace at where I was and what I was doing. Although still haunted by the Impostor Syndrome (Go on: Google it!), hopefully it has not stopped me from standing here today.

I would like to thank my supervisors and fellow PhD students at the department of Global Public Health and Primary Care, for providing me with a sound environment for conducting epidemiological research. First and foremost, I would like to thank my main supervisor, Dag, for being an excellent mentor during these years. I do not know where I fit into the "great minds think alike" quote, but it was evident from an early stage that we do indeed think alike, and that has been very helpful during the process of planning studies and writing manuscripts. You have led me securely through the different stages of my PhD, but also given me the (sometimes frustrating) freedom to make my own mistakes and learn from them. Thanks also to my co-supervisor professor Tone Bjørge, whose door was always open and replies were fast and thorough, and to my office neighbor and statistical pillar, professor Rolv Terje Lie, for providing me with sound advice on statistical methods (although requiring that I do the work myself). I would like to thank Miriam, my office mate, for bringing a youthful and humorous breath of fresh air into the office, for helping with (in my mind) difficult commands, and for always sharing your chocolate with me.

Thank you to the love of my life, Tore, for entering my life and giving it a whole new dimension, and rewarding me with the ultimate jackpot by virtue of our two boys Jakob and Erlend. The three of you have become the center of my universe, keeping me grounded and filling my days with joy, love, defiance and laughter.

Bergen, December 2016

"We must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become like the radium a benefit for humanity"

Marie Curie, 1921

Contents

Abstract

Background

Cancer in childhood, adolescence and young adulthood now carries a survival rate of above 80%. This leads to an increasing proportion of young age cancer survivors in the adult population. These survivors are at risk of suffering from various late-effects after cancer treatment, which can impact their ability to participate in the society as self-sufficient, independent individuals, holding jobs and establishing families.

Aims/objectives

We wanted to study male reproductive outcomes, economic independence and the risk of suicide or non-suicidal external deaths, in a national cohort of cancer survivors diagnosed before 25 years of age.

Material and methods

Our study cohort consisted of all individuals born alive in Norway during the 20-year period from 1965 to 1985, as identified by the National Registry. By the unique personal identification numbers, we performed linkage with several national registries. The Cancer Registry of Norway, identified all individuals diagnosed with cancer before the age of 25 years. Further data was supplied by the Medical Birth Registry of Norway, the Norwegian Tax Administration, the Norwegian National Education Database, the Causes of Death Registry of Norway, and the Norwegian Labour and Welfare Administration. Our study population was followed prospectively over time, and data was analyzed using various regression models allowing for adjustments for confounders.

Results

Cancer before the age of 25 was associated with a 28% reduction in paternity for male cancer survivors, and more than 3-fold increased risk use of assisted reproduction. The risk of adverse offspring outcomes was not increased. Furthermore, the paternity

deficit was sustained when analyzing the married subcohort for most cancer diagnoses, except for survivors of central nervous system (CNS) tumors, suggesting a "social infertility" in this survivor group. We found the cancer survivors to have slightly less probabilities of marrying compared to the non-cancer references, although this was only significant when cancer was diagnosed during childhood (below age 15 years).

In survivors of both sexes, there was an overall increased risk of receiving governmental financial assistance (27 % for men, 36 % for women) and of not being employed (42 % for men, 36 % for women). However, for those in paid employment, there were only slight differences in the representation in higher-skilled occupations. In general, slightly lower incomes were found for the cancer survivors. Income discrepancies were most pronounced for female survivors and for survivors of tumors of the CNS.

For the analyses on suicide and non-suicidal external deaths, there was a 2.5-fold increased risk of suicide for the cancer survivors, both when diagnosed during childhood and as an adolescent/young adult. There was no increased risk for non-suicidal external deaths. The suicides occurred at a median time of 12 years from cancer diagnosis, and only a small number occurred within the first year. The absolute number of suicides was low.

Conclusions/implications

Our study identifies areas of struggle for cancer survivors diagnosed during childhood, adolescence and young adulthood. With an increasing survivor population, it is important to be aware of these challenges in order to secure optimal transfer of knowledge, development of guidelines, and ultimately securing adequate follow-up to the long-term survivors. Some of our findings need confirmation in further studies, whereas others confirm previous findings.

List of publications

1. Gunnes MW, Lie RT, Bjørge T, Ghaderi S, Ruud E, Syse A, Moster D. Reproduction and marriage among male survivors of cancer in childhood, adolescence and young adulthood: a national cohort study. *British Journal of Cancer* 2016; 114(3):348-56. Doi: 10.1038/bjc.2015.455.

2. Gunnes MW, Lie RT, Bjørge T, Syse A, Ruud E, Wesenberg F, Moster D. Economic independence in survivors of cancer diagnosed at a young age: A Norwegian national cohort study. *Cancer* 2016;122(24):3873-3882. Doi: 10.1002/cncr.30253.

3. Gunnes MW, Lie RT, Bjørge T, Ghaderi S, Syse A, Ruud E, Wesenberg F, Moster D. Suicide and violent deaths in survivors of cancer in childhood, adolescence and young adulthood- a national cohort study. *Int J of cancer* 2016, Oct 26 (Early view). Doi: 10.1002/ijc.30474

Abbreviations

ALL: Acute lymphoblastic leukemia

AML: Acute myeloid leukemia

ART: Assisted reproduction techniques

AYA: Adolescents and young adults

AYAC: Adolescent and young adult cancer

BCCSS: British childhood cancer survivor study

CAYAC: Childhood, adolescent and young adult cancer

CCS: Childhood cancer survivor

CCSS: Childhood cancer survivor study

CI: Confidence interval

CNS: Central nervous system

CRN: Cancer registry of Norway

DAG: Directed acyclic graph

HL: Hodgkin's lymphoma

HR: Hazard ratio

ICSI: Intracytoplasmic sperm injection

IVF: In-vitro fertilization

NHL: Non-Hodgkin lymphoma

RR: Relative risk

WHO: World Health Organization

Definitions (for this thesis)

Adolescent and young adult cancer: Cancer diagnosis aged 15 through 24 years

Childhood cancer: Cancer diagnosis aged 0 through 14 years

Adolescent cancer: Cancer diagnosis aged 15 through 19 years

Young adult cancer: Cancer diagnosis aged 20 through 24 years

Late effects: Conditions that develop after completion of therapy

Long-term effects: Conditions that develop during therapy and persist after completion of therapy

Young age cancer survivor: Everyone receiving a cancer diagnosis before age 25, from the time of diagnosis

1. Introduction

«When we made ward rounds, someone would say «leukemia» and that would be the signal to sort of shake your head-too bad- and move on. I remember one child- a girl. She looked at me. "I'm dying. I'm dying. Can't you save me Dr. Pinkel? Can't you save me?"".

Donald Pinkel, MD, former Director of St. Jude Children's Hospital.

1.1 Incidence

1.1.1 Pediatric cancer

During the last 30 years, on average 134 children below the age of 15 have annually been diagnosed with cancer in Norway[1]. The types of cancer in children are often divided into 1/3 leukemia (predominantly acute lymphoblastic leukemia (ALL)), 1/3 brain tumors, and 1/3 "others" (comprising lymphomas, neuroblastomas, bone/soft tissue sarcomas and kidney tumors among others) (Figure 1). Some cancers are primarily found in children (neuroblastoma, retinoblastoma, rhabdomyosarcoma). There has been no significant increase in the incidence of childhood cancer in Norway over the past three decades[1], whereas a small increase has been detected on a European and northern European level[2, 3]. A slight male predominance exists with regards to the incidence of childhood cancer, with a male-to-female ratio of approximately 1.2[1, 4]. Childhood and adolescent cancer comprise only about 0.5% of the annual cancer cases in Norway[5].

Figure 1. Distribution of childhood cancer diagnoses in Norway

Cancer diagnoses 1985-2014 in children <15 years (%)

- Leukemia — 31 %
- Central Nervous System — 29 %
- Lymphoma — 9 %
- Soft tissue sarcoma — 6%
- Sympathetic nervous system — 5 %
- Kidney — 5 %
- Bone — 4 %
- Germ cell tumor — 3 %
- Other — 8 %
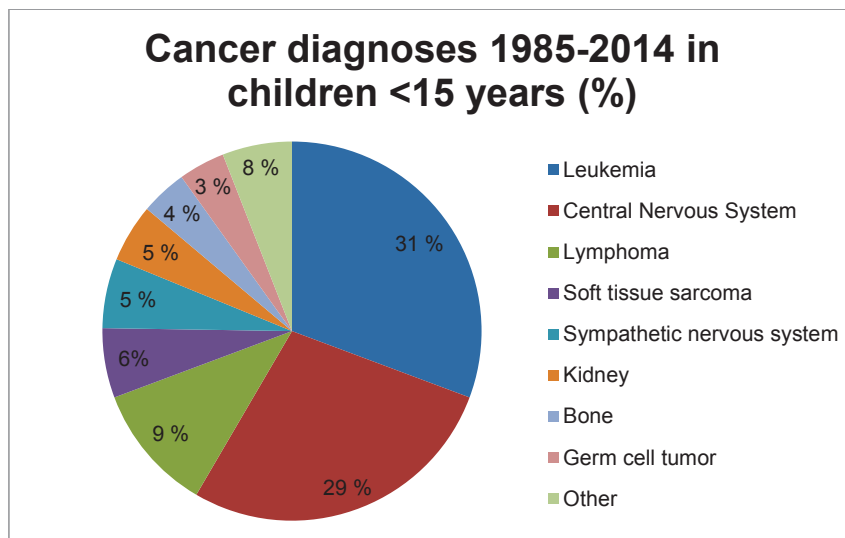
Ref: Annual report 2015, Norwegian Childhood Cancer Registry[1].

1.1.2 Adolescent and young adult cancer

Adolescent and young adult cancer (AYAC) is a term commonly used to cover the age group between 15-24 years diagnosed with cancer (in some cases extending up to 29 or 39 years)[6]. In this age group (15-24 years), there has been on average 234 newly diagnosed cancers annually in Norway (2009-2013), which is 1.7 times the cancer incidence in children[7]. On a European level, there has been a steady increase in incidence rates for adolescents, at a rate of 2% per year, during 1988-1997[8]. The most frequent cancer diagnoses for men in this age group are germ cell tumors (mainly testicular), central nervous system (CNS) tumors and lymphomas. For women, CNS tumors, lymphomas, carcinomas (including thyroid, cervix, ovary and breast) and malignant melanomas are the most common diagnoses (Figure 2)[5, 9, 10]. There are some sex-related differences in incidence in this age group, exemplified by thyroid carcinoma and malignant melanoma being more frequently diagnosed in females, whereas germ cell tumors occur more frequently in males (usually testicular tumors). However, for most cancer sites there is a higher incidence rate in men[4].

Figure 2. Distribution of adolescent and young adult cancer diagnoses in Norway

Cancer diagnoses 2011-15 in 15-24 year olds MEN (%)

- Germ cell tumors — 35 %
- Central nervous system — 15 %
- Lymphoma — 14 %
- Leukemia — 8 %
- Malignant melanoma — 4 %
- Colon — 4 %
- Bone — 3 %
- Remaining sites — 18 %

Cancer diagnoses 2011-15 in 15-24 year olds   WOMEN (%)

- Central nervous system — 14 %
- Lymphoma — 17 %
- Melanoma of the skin — 11 %
- Leukemia — 8 %
- Thyroid gland — 9 %
- Cervix and ovary — 8 %
- Colon — 7 %
- Remaining sites — 27 %
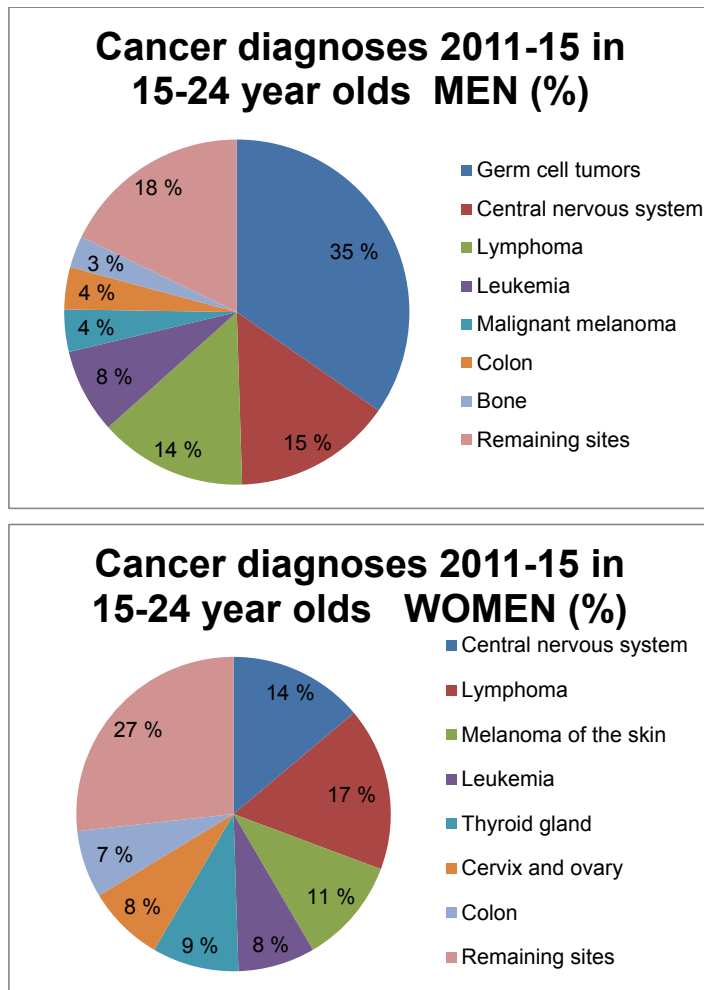
Ref: Cancer in Norway 2015[5]

Recently, a new term has been used to encompass childhood, adolescent and young adult cancers: CAYA, introduced by the International Late Effects of Childhood Cancer Guideline Harmonization Group in 2013[11]. The term has been used for describing survivors of cancer diagnosed before the age of 25 or 30. In this thesis, however, I will mainly refer to childhood cancer and adolescent and young adult cancer as two separate groups, as defined above.

1.2 Treatment

The access to health care and treatment of all life-threatening disease, such as cancer, is a statutory right and essentially free-of-charge for all Norwegian permanent residents, regardless of their employment status or economic situation, according to the Patients' Rights Act[12].

1.2.1 Treatment of childhood cancer

The diagnostic work-up and treatment decisions of all childhood cancer in Norway is undertaken at four (previously five) regional pediatric oncology centers. There is a high level of collaboration and national consensus regarding treatment according to Nordic or European protocols, often involving the possibility to participate in a clinical trial. This ensures equality of treatment regardless of the patient's and family's geographical location and financial situation.

Due to the rapid growth of most childhood cancers, they are markedly responsive to chemotherapy, and the treatment is often multi-modal, including chemotherapy, surgery and radiation, or different combinations of these. More recently, immunotherapy has also been included in childhood cancer trials[13].

Advances in treatment of acute leukemia in children has been one of the major successes of modern medicine[14]. In 1948, Dr Sidney Farber published a landmark paper in the New England Journal of Medicine, describing temporary remission in five children with acute leukemia from the treatment with a folate antagonist[15]. This is the first description of successful treatment of this previously untreatable and uniformly fatal disease with an average survival of three months. However, also in these patients, the cancer inevitably relapsed and led to premature death of the patients. During the 1960-1970's, introduction of different multi-agent chemotherapy regimens proved lasting remissions and ultimately cure for some leukemia patients, also in Norwegian children[14, 16].

In general, the 1960's and 1970's could be regarded as the decades of introduction of multi-agent chemotherapy and the start of (permanently) curing young patients with cancer. The 1980's and early 1990's could be referred to as the "dose intensification" period where more and more treatment (multi-modal) was added together, with increasing toxicity and potential for late effects for the survivors. Since the late 1990's the focus has been on reducing toxicity (while maintaining and still improving the survival rates), and since 2000, the focus has shifted more to individualized therapy based on biologic markers and treatment response[17]. The reduction in therapeutic exposure to certain chemotherapeutic agents and radiotherapy has led to a reduction in the excess late mortality in this group[18]. Norway was one of the first European countries (in the mid-1970s) to replace CNS irradiation with intensified intrathecal chemotherapy and higher dosages of Methotrexate as CNS prophylaxis for the treatment of ALL (now considered standard treatment) [19]. We may therefore see a slightly different late-effect profile in ageing survivors in Norway than other European/Nordic countries.

Figure 3. Development of childhood cancer therapy over time (exemplified by acute leukemia)
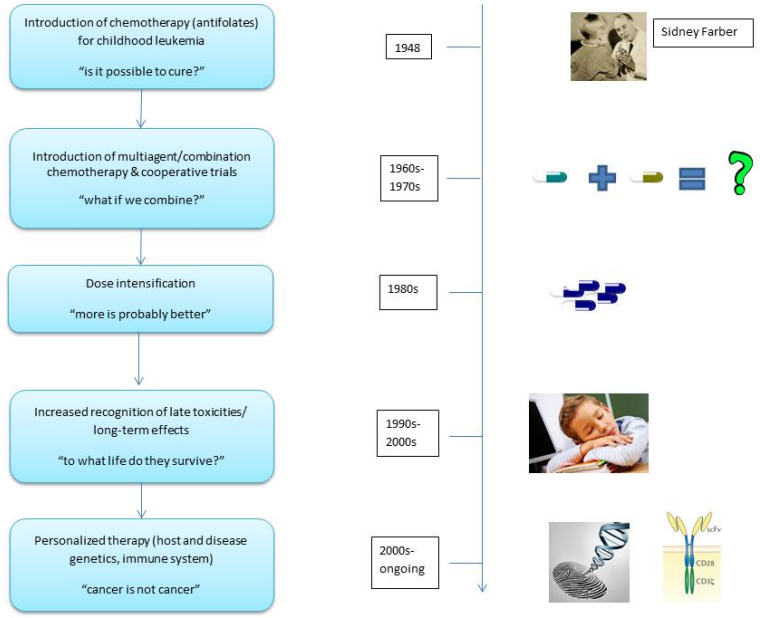
1.2.2 **Treatment of adolescent and young adult cancer**

The treatment of AYAC in Norway has not been as consistent as for childhood cancer. The treatment for AYAC has been dispersed to a much larger number of centers, and to a lesser degree, the same treatment protocols are used at the different centers.

There is some evidence that adolescents and young adults diagnosed with cancer achieve better survival rates when treated with pediatric treatment protocols/at pediatric group institutions as opposed to adult ones, especially when diagnosed with leukemia[20-22]. The question remains unanswered whether this is due to different treatment regimens or owing to different vigilance of complications during treatment, and most probably a combination is the right answer. Within the next few years, all adolescent cancer patients (15-18 years of age) in Norway will be treated at pediatric oncology centers, in close collaboration with adult hemato-oncologists.

1.3 Survival

Long-term survival (often referred to as >5-year) after treatment of cancer in childhood has improved dramatically during the past 40 years, and has reached a 5-year survival rate of around 80% across most of Europe and the US (Figure 4)[3, 14, 23, 24]. Much of this success is due to collaboration within the setting of multicenter- and multinational clinical trials[25]. In the UK, two thirds of children with cancer were offered participation in a clinical trial during the past three decades[26], and there is no reason to believe that this is less in Norway. A recent publication from Denmark reports that 95% of Danish children with cancer are treated according to (and reported to) an international protocol[27]. For other tumor types (e.g. high grade brain tumors and bone tumors), the improvement has not been as dramatic, and survival rates are only slightly improving[3, 14]. Nonetheless, better imaging modalities and improved surgical techniques have led to a more accurate surgical and radiation treatment for this subgroup, hopefully lessening the burden of late effects in survivors.

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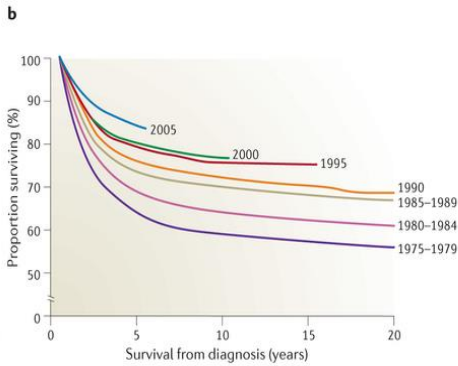
Nature Reviews | Cancer

Figure 4. Improvement in childhood cancer (< age 20) survival rates over time, data from the Surveillance, Epidemiology, and End Results program (US). Ref: Robison & Hudson, Nature reviews/Cancer, 2014[24]. Reprinted with permission from Nature Publishing Group.

Long term survival rates after treatment of cancer in adolescence and young adulthood have also improved to a 5-year survival rate of >80%. However, survival remain significantly worse than for children for some comparable cancers (e.g. acute lymphatic leukemia, Hodgkin's lymphoma and Ewing sarcoma), and the change in the relative survival is considerably poorer for AYAs compared with younger and older cancer patients (Figure 5)[6, 22, 28, 29].
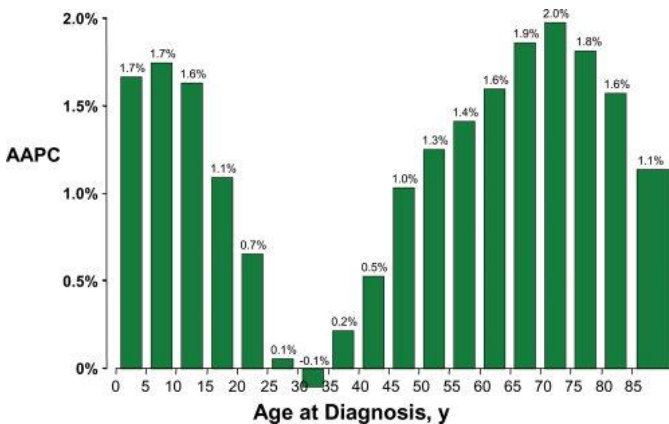
Figure 5. Average annual percentage change (AAPC) in 5-year relative survival (all deaths) of patients diagnosed with invasive cancer (1975-1998). Ref: Zebrack et al, Cancer 2006[28]. Reprinted with permission from John Wiley and Sons.

1.3.1 **Survivor**

The term "cancer survivor" lacks a consistent definition and is used to describe an individual from the time of cancer diagnosis in some contexts (as in this thesis), whereas in others, is not applicable until one has survived a certain time after diagnosis (most commonly 5 years)[30]. Fitzhugh Mullan, a physician diagnosed at age 32 with an extra-gonadal seminoma described one common path for those diagnosed with cancer: The path of survival. He further divided survival into three periods: Acute survival (the period after diagnosis and during treatment), extended survival (after cessation of treatment, during the period of "watchful waiting"), and permanent survival[31]. During this final and (for most) protracted phase, many of the late-effects after cancer treatment manifest.

1.3.2 **Survivor population**

In the US, about 1 in 530 adults between the age of 20 and 39 years is currently a survivor of pediatric cancer, comprising a total of 388,501 individuals by January 2011[32, 33]. The estimates for Europe range from 300,000-500,000 long-term childhood cancer survivors, expecting to exceed 500,000 by 2020[34]. This "survivor population" will continue to increase as cure rates now surpass 80% in total for cancer in childhood and adolescence. It is therefore extremely important to follow this survivor population, for medical as well as social and economic outcomes. This will facilitate the development of adequate guidelines for follow-up, customized to the unique framework of health care, public welfare system and social structure within the different countries.

During the past two decades, several large study cohorts for long term follow-up after cancer in childhood and adolescence have been established (Table 1)[35-39]. There are (to my knowledge) no comparable, large cohorts of AYA cancer survivors, but a few are in the making (Table 2).

1.3.3 Unique challenges for the AYAC group

Challenges AYAs with cancer face during diagnosis and treatment are unique and pervasive[40]. Firstly, cancer awareness and awareness of bodily symptoms is low in this age group, which may lead to a delay in diagnosis. Secondly, when diagnosed with cancer, they are offered entry into a clinical trial at a much lower rate than their childhood cancer comparisons (Figure 6), and the care provided is split between pediatric and adult oncology departments[6, 41]. Thirdly, the biology of their malignancies is distinct from that of children and other adults, and therefore, the results from studies on children or adults cannot necessarily be extrapolated to the AYA survivors[42].
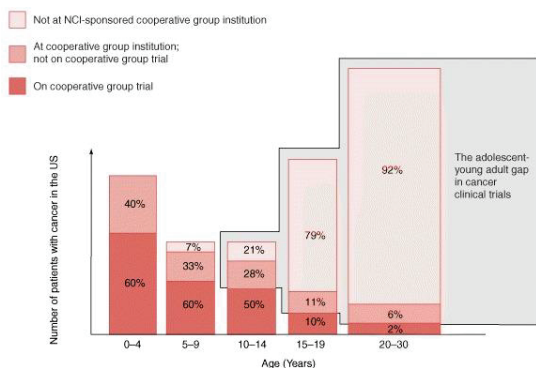
Figure 6. The AYA gap in cancer trials
Ref: Bleyer/Albritton; Cancer Medicine, 6th ed, 2003[6]. Reprinted with permission.

The developmental phase during adolescence and young adulthood is unique[41, 43, 44]. It is a critical time for establishing one's autonomy, gaining independence from caretakers and making important decisions regarding education and future career, decisions which have long-lasting (often life-long) implications. This vulnerable process can be disrupted when faced with a diagnosis of a life-threatening illness such as cancer. In addition, changes in physical health and physical appearance during treatment (hair loss, weight gain or loss, amputation) may have adverse effects on the development of peer relationships and on self-esteem. These are critical issues that must be addressed when treating AYAs with cancer. The access to participation in

AYA peer groups (virtual or in person) is identified by AYAs as one of the most important needs (ranked higher than the support from family and friends) when diagnosed with cancer[29].

Furthermore, the long-term follow-up in this age group poses a major challenge. A great number of survivors might want to "leave their cancer behind" and will opt out of follow-up programs. AYA cancer survivors are a mobile group (they move because of studies, work, etc.), they often do not see the need for continued follow-up and care, and parents are to a lesser extent involved in their decision-making[41]. In the US, a large proportion of AYA cancer survivors are uninsured, and do not engage in the traditional primary health care system[44], making long-term follow-up difficult. At the same time, this group of survivors has been identified as a group that is particularly vulnerable to various adverse psychosocial outcomes[24], making it an important task to ensure the provision and utilization of adequate follow-up in this survivor group.

1.3.4 Table 1. Overview of large childhood cancer survivorship study cohorts

Name	CCSS[45]	BCCSS[46]	SCCSS[37]	AliCCS[39]	DCOG Later[35,36]	FCCSS/LEA[47] (Not completed)
Country	US + Canada	UK	Switzerland	Denmark, Norway, Sweden, Finland, Iceland	Netherlands	France
Coordinating center/website	St Jude's Children's Research hospital/ ccss.stjude.org	Centre of Childhood Cancer Survivor Studies/ www.bccss.bham.ac.uk	Swiss childhood cancer registry/ www.childhoodcancerregistry.ch	Danish Cancer Society/ www.aliccs.org	Academic medical centre-Emmas Children's hospital/ www.skionlaterstudie.nl/english/	Institut National de la Santé et de la Recherché Médicale (FCCSS) No website https://clinicaltrials.gov/ct2/show/NCT01620372) (Info: Assistance Publique Hopitaux De Marseille (LEA)
Cohort size	35,923 eligible (24,368 included December 2015)	34,489 (extended cohort)	4,116 (0-15 years) contacted (2014 update)	33,160	6,168	18,000 (estimated)/2,385 (ongoing)
Study design	Hospital based (31 centers)	Population based	Population based	Population based	Hospital based (nationwide)	Multicentric, hospital-based
Age at diagnosis (years)	<21	<15	<21 (complete coverage for 0-15 year olds only)	<20	<18	<19/<18
Years from diagnosis	>=5	>=5	>=5	>=1	>=5	>=5/>2-4 years
Years of diagnosis	1970-1999	1940-2006 (extended cohort)	1976-2005	1943-2008	1963-2002	1942-1999/ 1980-ongoing
Cancer diagnoses	Leukemia, CNS, lymphoma, Wilms, neuroblastoma, soft tissue sarcoma, bone tumors	All	All + LCH	All	All	Solid Tumor/ Leukemia

Method of data collection	Periodic surveys, self-report	One-time survey (self-report), national registry linkage	Questionnaire, linkage with national registries, clinical follow-up for nested studies	National registry linkage	Clinic visits, self-report, linkage with national registries	Medical records, National registries, questionnaire
Comparison population	Siblings mainly, general population	General population	Siblings, general population	Matched population controls	General population and matched controls	National statistics
Detailed treatment data	Yes, >90%	Limited for all, extensive for nested case-control studies	Limited for >90%, extensive for nested case-control studies	Limited for all, extensive for nested case-control studies	Yes, 100%	Yes/Yes (>80%)

Abbreviations: ALiCCS: Adult Life after Childhood Cancer in Scandinavia, BCCSS: British Childhood Cancer Survivor Study, CCSS: Childhood Cancer Survivor Study, DCOG: Dutch Childhood Oncology Group, FCCSS: French Childhood Cancer Survivor Study; LEA: Leucémies de L'Enfant et l'Adolescent, SCCSS: Swiss Childhood Cancer Survivor Study

Table adapted from Bhatia et al, J of Clin Onc, 2015[35] and Winther et al, Acta Oncol, 2015[36] , and updated with more recent details where applicable.

1.3.5 Table 2. Overview of large adolescent and young adult cancer survivorship study cohorts

Name	TYACSS[48]	CAYACS[49]	AYAs Late Effects[50]	AYA HOPE[51]
Country	UK	Canada (British Columbia)	Denmark	USA
Coordinating center/website	University of Birmingham www.bccss.bham.ac.uk	BC Cancer Agency www.bccrc.ca/dept/cc	Danish cancer society www.cancer.dk	National Cancer institute https://healthcaredelivery.cancer.gov/aya/overview.html
Cohort size	200,945 (goal ~300,000)	3,841 (expansion pending)	>40,000	524
Study design	Population-based	Population-based (regional, British Columbia only)	Population-based	Population-based (not nationwide), feasibility study
Age at diagnosis (years)	15-39	0-24	15-39	15-39
Years from diagnosis	>=5	>=5	>=1	2-3 years
Years of diagnosis	1971-2006	1970-1995 (update pending)	1943-2009	July 1st 2007- Oct 31st 2008
Cancer diagnoses	All	All	All	Germ cell, Hodgkin's lymphoma, NHL, ALL, sarcoma
End of follow-up	2014	2000	2010 (?)	2010
Method of data collection	Linkage of national registries	Regional registry linkage	National registry linkage	Survey questionnaire
Comparison population	General population	General population, and matched case-control	Matched population controls	None
Detailed treatment data	No	Yes, approx. 80%	No (?)	N/A

Abbreviations: ALL: Acute lymphoblastic leukemia; AYA: Adolescents and young adults; CAYACS: The Childhood/Adolescent/Young Adult Cancer Survivors program; NHL: Non-Hodgkin's lymphoma; TYACSS: The Teenage and Young Adult Cancer Survivor Study.

1.4 Late-effects

Long-term survivors after treatment for childhood and AYA cancer have increased risks of suffering from one or more adverse chronic health condition as a result of their treatment. Most large studies, both from Europe and the US, conclude that approximately 2 out of 3 childhood cancer survivors (CCS) have at least one chronic medical condition, and 1 out of 3 have at least one severe or life-threatening adverse event, by young adulthood[52-54]. Some cancer diagnoses carry larger risks of late-effects, such as bone tumors, CNS tumors, and Hodgkin's disease, mainly due to the treatment received, although this might change as the effects of more recent treatment strategies emerge[52]. The dominant late-effects include secondary malignancies, cardiovascular disease, neurocognitive impairment, musculoskeletal morbidity and endocrine dysfunction (including fertility impairment). Late-mortality is found to be increased in this survivor group compared to their non-cancer peers, but the full knowledge of the degree of excess lifetime morbidity is still unknown (Figure 7)[24, 55, 56].
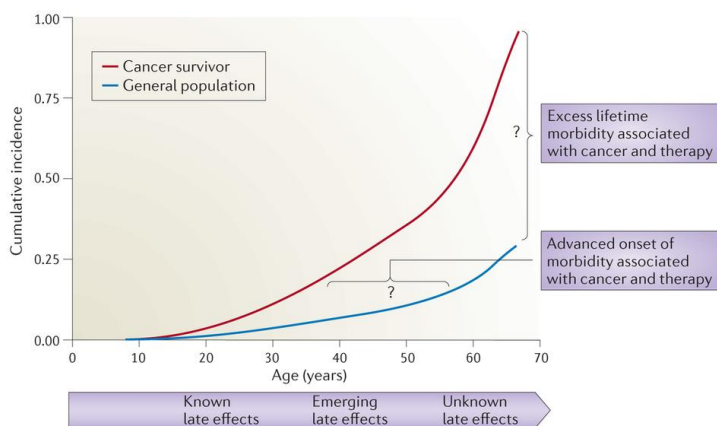
Figure 7. Gaps in knowledge regarding very long-term outcomes of childhood cancer survivors. Ref: Robison & Hudson, Nature reviews: Cancer, 2014[24]. Reprinted with permission from Nature Publishing Group.

However, a relative reduction in late mortality within this survivor population (comparing those treated during earlier vs more recent years) has been found recently, probably as a result of lowering therapeutic exposures, which may continue to improve as survivors of more modern treatment eras reach older age[18, 46, 55]. There are also a variety of psychosocial challenges that many survivors of cancer in young age have to live with. An overview of the major health-related and psychosocial challenges is depicted in Figure 8.
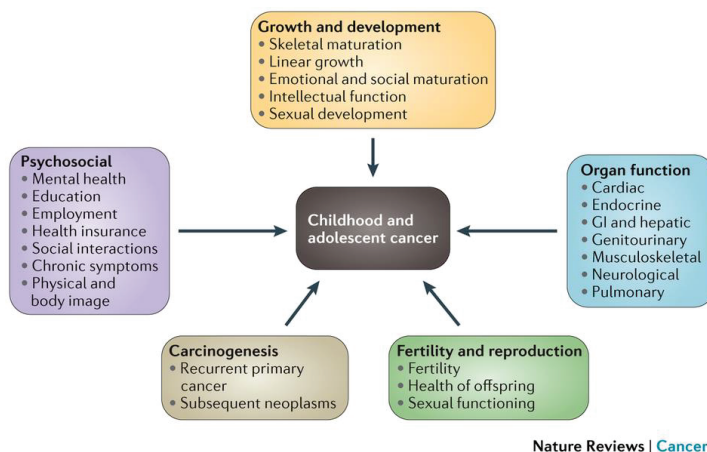
Figure 8. Health-related and psychological challenges among survivors of cancer in young age. Ref: Robison & Hudson, Nature Reviews Cancer, 2014[24]. Reprinted with permission from Nature Publishing Group.

1.4.1 Cancer treatment and the potential impact on fertility

Many publications exploring the impact of cancer and cancer treatment on subsequent reproduction exist, both in the young adult[57-60] and pediatric[59-63] population. There is an indisputable connection between cancer (some cancer types in particular) and its treatment, and subsequent reproductive challenges [64, 65].

Cancer and cancer treatment in boys and young men may impair fertility by damage to the testicles (gonadotoxic chemotherapy and irradiation), to the gonado-hypothalamic-pituitary axis (irradiation), or to the genitourinary organs (surgery and irradiation)(Figure 9)[66]. The Childhood Cancer Survivor Study (CCSS) finds that

radiation therapy of >4 gray (Gy) to the testis, a high cumulative alkylating agent dose score or the treatment with cyclophosphamide, ifosfamide, procarbazine or cisplatin (dose-response relationship) alone significantly reduce the risk of siring a pregnancy [64 65]. Furthermore, semen analyses from the St Jude lifetime cohort study revealed impaired spermatogenesis with increasing alkylating agent exposure[67]. Some studies also find a reduction in semen quality already present at the time of cancer diagnosis (i.e. before treatment), especially for testicular cancer and Hodgkin's lymphoma. Results are, however, conflicting[68-70].

The seminiferous tubules in the testicles (where the Sertoli cells and spermatogenic cells are situated) are sensitive to even low dose radiation, as well as to high doses of chemotherapy. Alkylating agents and cisplatin (drugs often used in high dose in the treatment of bone sarcomas, Hodgkin's lymphoma and testicular cancer) are particularly damaging, resulting in decreased or absent spermatogenesis. The interstitial tissue (where the Leydig cells are situated) is less sensitive to the insults of radiochemotherapy, allowing secondary sexual characteristics to develop normally. However, it is unknown whether or not mild Leydig cell dysfunction leads to premature androgen deficiency as this population ages. There are reports of androgen deficiency requiring testosterone replacement after total body irradiation in the conditioning for hematopoietic stem cell transplantation in CCS, as well as persistently low testosterone levels in long-term survivors of testicular cancer (all ages)[71, 72].

Figure 9. Cancer treatment and the potential impact on male fertility and hormone production.
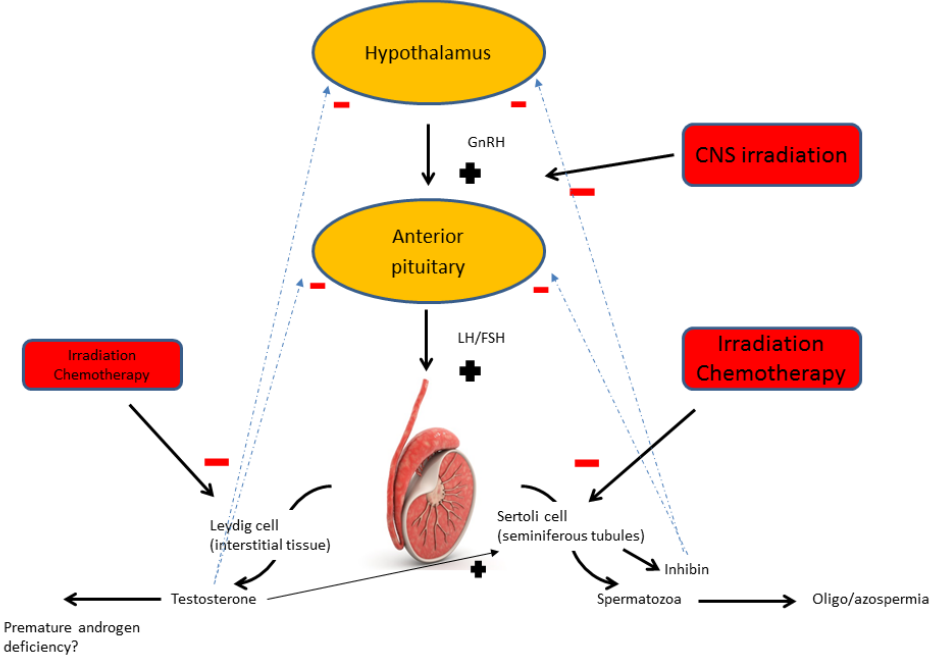
Abbreviations: CNS= Central nervous system, FSH= Follicle stimulating hormone, GnRH= Gonadotropin releasing hormones, LH= Luteinizing hormone.

For female cancer survivors, preservation of fertility after treatment includes an undamaged hypothalamic-pituitary-ovarian axis, a sufficient reserve of ovarian follicles, a uterus that is able to contain and accommodate a developing fetus, and well-functioning organs such as heart and kidneys. Cancer and its treatment can disrupt one or several of these components and consequently impair fertility, cause premature ovarian insufficiency and undesirable pregnancy outcomes[57, 73, 74]. In contrast to male germ cells, the current (dominant) belief is that the ovary already contains all of its ovarian follicles at birth, and is therefore particularly sensitive to the toxic effects of cancer therapy[65, 75]. Human oocytes are extremely sensitive to irradiation, with median lethal dosages as low as 2 Gy, although effective sterilizing

doses varies with age and natural follicle decline[65]. Acute ovarian failure is reported in the majority after total body irradiation (10-15 Gy) and after total abdominal irradiation of 20-30 Gy, especially when including pelvic irradiation >10 Gy[76, 77]. There is no clear evidence that the prepubertal ovary is protected from the damaging effects of cancer treatment, although the threshold of radiosensitivity depends on the ovarian follicle reserve, which declines naturally with age[65].

However, the ovary seems less susceptible than the testicle to chemotherapy-induced damage. A recent CCSS study found only the chemotherapeutic agents busulfan and lomustine to be individually associated with impaired fertility in non-irradiated female patients, and to a lesser degree than previously thought, alkylating agents (cyclophosphamide only at very high cumulative doses), although these drugs are often administered in combination[63]. This was supported in a recent study of female long-term Hodgkin's lymphoma survivors, where most individual chemotherapy exposures were not associated with a strong independent effect on female fertility[78]. However, premature ovarian insufficiency is an issue for women previously treated with chemotherapy (especially alkylating agents), even in the absence of menopausal symptoms[63, 78, 79]. This should lead to an assessment of future fertility potential and the advice that delaying childbearing until the late 30s might be unwise.

Reduced parenthood in cancer survivors may result from an interplay of several factors, including medical (direct cytotoxic effects of chemotherapy and radiotherapy), social (severe cognitive and medical disabilities resulting in a reduced ability to find a partner and sustain a long-term relationship) and psychological (fear that the cancer or its treatment will have an effect on the next generation, and fear of relapse).

Fertility preservation

For males, sperm cryopreservation is an effective method of fertility preservation, in addition to gonadal shielding from irradiation. Cryopreservation of sperm is limited to males above a certain age, requiring spermarche to have occured[65]. So far, methods to preserve fertility in younger boys (e.g. testicular tissue cryopreservation followed by

auto-transplantation, and in-vitro spermatogenesis) are experimental and currently not in clinical use[80]. In young females however, ovarian tissue cryopreservation and re-transplantation has led to multiple reports of successful pregnancies and healthy babies being born, also in the Nordic countries[81]. Still, only one live birth is so far reported in the literature for ovarian tissue preserved from a premenarchal girl.[82]

Oophoropexy (surgically relocating the ovaries from the field of irradiation) increases the likelihood of preserving ovarian function (if not exposed to concomitant fertility-impairing chemotherapy), although this approach might still render the uterus vulnerable for radiation-induced damage. For young adult women, oocyte cryopreservation, or emergency in vitro fertilization (IVF) and embryo banking (given that the woman has a partner) are successful methods of fertility preservation. However, these latter methods require some time, leading to a sometimes unacceptable delay in treatment initiation.

Reproductive outcomes

For female CCS, there is compelling evidence that pelvic/flank irradiation is associated with increased risks of prematurity, low birth weight, fetal malposition and spontaneous abortions, as a result of radiation-induced uterine dysfunction and vascular insufficiency[73, 83, 85]. There is no evidence that treatment with chemotherapy (without concomitant irradiation) is associated with abnormal fetal growth/development or uterine function during pregnancy[63].

Treatment of male childhood and AYA cancer has, in some publications, been associated with an increased risk of congenital malformations in the offspring, whereas other studies have found no association.[57, 77, 85-89]

1.4.2 Socioeconomic outcomes

Marriage

Several publications have demonstrated a reduction in marriage rates for survivors of cancer in childhood when compared to general population or sibling marriage rates[90-

[94]. This is particularly the case for males, those receiving CNS radiation, having CNS or bone tumors. AYAC survivors also seem to be less likely to marry, but this is an understudied group, and not many publications address this[95, 96]. A large, Norwegian population-based study on cancer (all ages) and marital status showed generally unaffected marriage rates in both men and women with a previous history of cancer[97].

Employment

Several studies have found that survivors of cancer in childhood, adolescence and young adult age, have an increased risk of unemployment[98-100], although there seems to be important differences for survivors in Europe and the US. In the US, health insurance is often associated with employment, and cancer survivors might suffer from discrimination in the labor force to a larger degree than what has become apparent in Europe. Receiving a cancer diagnosis at a young age may contribute to a delay in the completion of education, and consequently a delay in employment.

Occupation and income

A study from the U.S found that childhood cancer survivors were underrepresented in higher-skilled occupations, compared to their siblings[100], as well as in some survivor subgroups (black, diagnosed at a young age and high-dose cranial irradiation). There are few other publications analyzing differences in type of occupation and within-occupation income differences.

There are studies indicating a lower income in general for adult survivors of cancer in young age[100, 101], although in some studies, this is only apparent for certain cancer sites, and especially for survivors of CNS tumors[99, 102].

Governmental financial assistance

In Norway, financial assistance is intended to ensure the coverage of basic subsistence costs on a temporary basis, and aims to aid financial independence[103] when all other options for self-support are exhausted. In order to qualify for financial assistance, one must be a permanent and legal resident of Norway, unable to support oneself through

gainful employment, own savings or with the aid of other financial rights. The monetary amount of financial assistance is determined by the local Labor and Welfare Administration (NAV) on an individual basis, and often provided together with information and advice. During the years 2010-2014, on average 31 per 1000 inhabitants received financial assistance in Norway, with the highest rate of recipients being in the age group 18-24 years, the largest group being single males (39%), and the rate among the immigrant population (37% of all recipients) is high[104].

1.4.3 External deaths and high-risk behavior

Survivors of childhood and adolescent cancer have increased mortality rates, both in terms of death from cancer directly and death from late-effects after cancer cure[18, 105]. Suicide and non-suicidal violent deaths are among the leading causes of death in young people in Norway (Figure 10) as well as worldwide[106-109]. Suicide rates in Norway are similar to other Nordic countries (except Finland, where the suicide rate is approximately doubled)[110]. Negative life-events, adverse childhood experiences and physical illness are some of the risk factors associated with suicide and suicidal behaviour in young individuals[106, 108, 111].
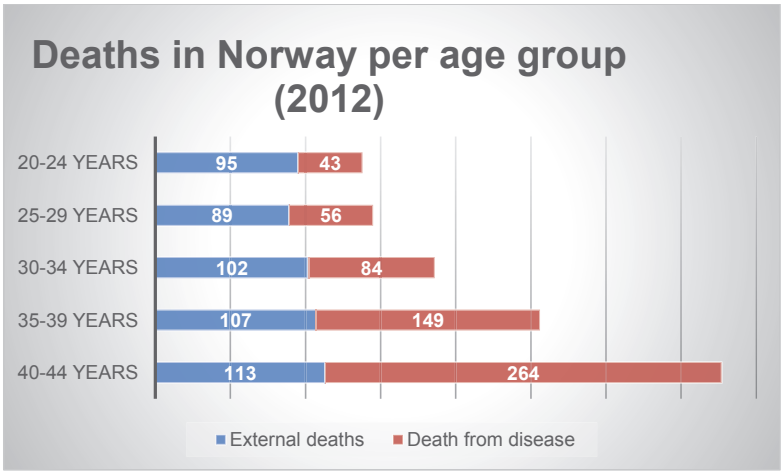
Figure 10. External deaths and death from disease in Norway (2012) in individuals aged 20-44 years. Source: Norwegian Institute of Public Health[112].

There are large cohort studies showing an approximately two-fold increased risk of suicide after a cancer diagnosis, especially during the first year after diagnosis. Most studies are conducted in an adult population or in a mixed population where CAYAC survivors constitute a very small percentage[113-116]. Suicide rates are briefly described in two publications on late mortality of 5-year survivors from the Childhood Cancer Survivor Study (CCSS)[56, 117], but details regarding suicide deaths are not presented. In these publications the risk of death by suicide or other external causes is not increased. The most recent paper on CCS long term mortality in 5-year survivors from the British Childhood Cancer Survivor Study (BCCSS) finds an increased standardized mortality ratio (SMR) of 1.2 (95% CI 1.1-1.4) for external causes of death, but this is not explored further or separated into suicide and non-suicidal external deaths[46]. The only pan-Nordic study on late cause-specific mortality found a SMR for suicide of 0.77 (95% CI 0.47-1.2)[118]. The latter study was published in 2001 and was based on 5-year cancer survivors diagnosed before the age of 20 from 1960 to 1989. Another Nordic publication studied late and very late mortality in 5-year CCS, but did not in detail study the risk of suicide[55]. Some publications present increased suicide ideation in childhood cancer survivors[119-121], but no large, population based study fully exploring suicide in CCS and AYA cancer survivors is available.

Some reports indicate an increased engagement in risk-taking behaviors like excessive drinking and smoking in survivors of childhood cancer[122, 123]. This could possibly lead to an increased risk of non-suicidal external deaths, either from a direct causal effect (such as drunkenness), or as indicators of risk taking and health compromising behaviors (such as smoking or driving too fast). A study from Finland found health compromising behavior during adolescence to be strong risk factors for accidental death in adulthood, whereas poor health was not found to be associated with a risk of injury death[124]. There are publications from adult cancer populations which demonstrate an increased risk of non-iatrogenic injuries and death from these causes following a cancer diagnosis[125, 126] Studies on AYAC survivors are largely lacking.

1.5 Long-term follow-up and survivor care

It was pointed out already in the mid-70s that the follow-up after cure must be life-long in order to detect late-effects early[127]. However, large, multinational efforts towards this goal have only accelerated during the past two decades.

European initiatives

In 2007, an international group of pediatric cancer experts issued the "Erice statement", with ten points considered essential for childhood cancer survivors' cure and care[128]. One of the points stated the need for a continuing systematic follow-up after cure for the identification of long-term effects after cancer treatment. In 2008, PanCare was initiated, which is a European network of professionals, survivors and their families, receiving funding for different late-effect projects from the European Union, with the long-term aim of securing every European childhood and adolescent cancer survivor optimal long-term care[129]. One of the projects within PanCare is PanCareSurFup, where one of the work packages focus on developing harmonized pan-European guidelines for the follow-up of childhood and adolescent cancer survivors. This has been identified as a need in a survey of pediatric oncology experts from 31 European countries, which demonstrated that a current national implementation of long-term follow-up guidelines was only present in 55% of the countries[130]. Thus far (December 2016), three recommendations have been published from the international late-effects of childhood cancer guideline harmonization group; for breast cancer surveillance, cardiomyopathy surveillance and for premature ovarian insufficiency surveillance[11, 79, 131]. Efforts are also underway within the PanCareSurFup consortium (in collaboration with ENCCA: European Network for Cancer Research on Children and Adolescents) to develop a "Survivorship Passport", a system where a document is individualized (by a computer) for each survivor based on the input of different treatment variables and patient characteristics[132].

Current situation in Norway

Survivors of pediatric and adolescent cancer (<18 years at diagnosis) in Norway are currently followed on an out-patient basis at their nearest geographical pediatric oncology center from the end of therapy, and for a duration of 10 years for most cancers, or at least through puberty. There is no standard routine or guidelines for transfer of care to the general practitioner or another hospital specialist after this. This results in an inadequate long-term follow-up for most pediatric cancer survivors. Since 2001, all residents of Norway are entitled to be registered as a patient with a specific general practitioner of choice[133]. This was introduced in order to ensure continuity of care in the primary care setting. However, at the time point of discharge from pediatric oncology specialized-care follow-up, the cancer survivors are at an age where they often move for reasons of studies or work, and this frequently leads to an inadequate transfer of information to the new general practitioner unless the adolescent/young adult (or his/her parents) is well informed and assumes a certain responsibility for own health. This might be problematic, as this is also an age where most young individuals are seeking independence from their caretakers, and strive towards living life like their peers, without having to think about the possible future consequences of their life-saving, but nonetheless possibly damaging, cancer therapy. This might lead to the cancer survivors making uninformed and ill-considered choices in terms of risky health behaviors, or not pursuing recommended follow-up care (e.g. regular breast cancer screening for female Hodgkin's lymphoma survivors).

There is no late-effect program in Norway that systematically recalls previous patients or ensures continued care within the specialized care system. Once the survivors have passed a certain age (this varies across the health regions, but usually 18-20 years of age), they can no longer address the department previously in charge of their treatment and care with emerging problems. This might act as another barrier for adequate care. A "survivorship passport" does not exist on a national level, but different (and mostly incomplete) local variants exist at some centers.

There are no comprehensive national guidelines for complete follow-up care for survivors of childhood and adolescent cancer in Norway. The information given at the end of follow-up at the pediatric oncology department varies accordingly. Some doctors have more knowledge about late-effects than others, and in some cases, very junior doctors with minimal experience in pediatric oncology see the patients at their last visit. This is in contrast to Sweden, where national guidelines on long-term follow-up of childhood cancer survivors recently are completed and published[134]. In 2005, the *National Competence Center for studies on late-effects after cancer therapy* was established at Oslo University Hospital, but since survivors of cancer at all ages are covered, the focus on CCS/AYAC survivors is very limited[135]. Neither is follow-up care offered in a non-study setting, and only selected populations (e.g. on the basis of certain cancer diagnoses) are invited to participate and avail of the services offered.

Literature review completed Dec 12, 2016.

2. **Aim of the thesis**

The overall aim of this thesis was to study some of the challenges survivors of cancer in childhood, adolescence and young adulthood face as adults, and specifically:

- To examine reproductive outcomes and marriage in male young age cancer survivors, focusing on first offspring rates, adverse offspring outcomes, assisted reproduction and marriage (paper 1)

- To investigate economic independence in young age cancer survivors, by studying employment, occupation, income and financial assistance (paper 2)

- To examine the risk of suicide and non-suicidal external deaths in survivors of cancer <25 years (paper 3)

3. **Material and methods**

3.1 Data sources

National Registry

The National Registry is the central population registry in Norway, and contains demographic information on all residents in Norway from 1960 onwards, including date of birth, place of residence, and date of emigration or death[136]. Also dates of birth of children and marital status are registered consecutively[137]. The registry is maintained by the Norwegian Tax Administration.

Cancer Registry of Norway (CRN)

Since 1953, the Cancer Registry of Norway (CRN) has received information on all patients with a cancer diagnosis. Information from clinical notifications, pathological notifications and death certificates are the main reporting sources. Information about site, histological type and stage of disease at the time of diagnosis is provided. It also contains limited information on treatment planned. Through 1992, registration of topography was based on a modified version of International Classification of Diseases (ICD-7)[138]. Since 1993, ICD-O (ICD for oncology), versions 2 and 3, have been the basis for coding for both site and morphology[139]. Until 1992, tumor morphology was coded according to the Manual of Tumor Nomenclature and Coding (MOTNAC). Since 1986, non-solid tumors have been coded according to separate coding systems. Reporting of newly diagnosed cancers is mandatory for all clinicians and pathologists in Norway. The completeness of the CRN has been assessed in several studies, and has consistently been found to be >95%, which makes it among the most complete in comparison with other European cancer registries[139].

The CRN includes all confirmed cases of malignancy within the Norwegian population. It also includes some benign tumors mainly within the CNS (such as meningeomas and craniopharyngeomas).

Records of social services, income, occupation and education were delivered from Statistics Norway (SSB). SSB is in charge of the transfer of data obtained from various national registries. Information on education was provided by the Norwegian National Education Database, whereas the Norwegian Tax Administration is responsible for the information on work-related income and details of occupation and employment.[140-142]. Records of the uptake of different welfare benefits (including disability pension and financial assistance) through membership of the National Insurance Scheme (NIS) was provided by the Norwegian Labour and Welfare Administration (NAV)[143, 144]. In order to qualify for disability benefit in Norway, one has to be member of the NIS (compulsory membership for all Norwegian residents) during the last three years preceding the disability, and have a permanently reduced earning capacity by at least 50% due to illness and/or injury.

The Medical Birth Registry of Norway (MBRN)

MBRN is a population based registry containing information on all births in Norway since 1967 (more than 2.8 million births)[145, 146]. MBRN is based on compulsory notification of every birth or late abortion from 16 weeks of gestation onwards, and includes identification of the parents in terms of their personal identification numbers, demographic information of the parents, the mother's diagnoses before and during pregnancy, complications during pregnancy and delivery, length of pregnancy as well as information on the infant, including birth defects and other perinatal problems. Since 1998, data obtained in neonatal wards on congenital conditions for infants transferred to such units after birth have been included as well. The registry contains information on the use of assisted reproductive technologies (ART) from 1984 and close to complete data on the uptake of ART is available from 1988 onwards, including the method used (in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)[147]. The registry contains only the proportion of attempts resulting in a successful pregnancy/conception and is therefore not to be considered a complete

registry of all attempts of assisted fertilization. ICSI has been available in Norway since 1995[148].

Causes of Death Registry of Norway (CDR):

The CDR contains digitized information on the causes of death in Norway dating back to 1951, and has been administered by the Norwegian Institute of Public Health since 2001[149].The statistics on causes of death are prepared on the basis of death certificates. The degree of coverage in this registry is high, and encompass >98% of all deaths in Norway[149]. In three different assessments of the quality of worldwide death registries, the Norwegian Death Registry was ranked in the second-best[150, 151] and best[152] group.

Every resident in Norway (from1960 onwards) has a unique 11-digit personal identification number that is used by all the registries[136]. This identification number makes this precise record linkage possible.

3.2 Study population

All individuals born alive in Norway during 1965-1985 were included in our initial cohort (n=1,218,013). All the study data from SSB were transferred with personal identification numbers replaced by unique study numbers, securing a de-identified research database for further analyses. The study cohort was followed into adulthood by linkage of the national registries mentioned in the previous section.

In the study population, 5,842 were registered in the CRN as receiving a cancer diagnosis before the age of 25. After exclusion of those with an uncertain cancer diagnosis (n=10), cancer diagnosed at autopsy only (n=355, mostly diagnosed before 1980 and below 8 years of age), cancer stated on the death certificate only (n=13), and those not born in Norway (n=24), the cohort included 5,440 individuals diagnosed with cancer before the age of 25. These constitute the "cancer survivor" group within the study cohort.

An overview of the cancer cohort is presented in tables 3 and 4.

Table 3. Classification of the cancer cohort according to International Classification of Childhood Tumors, 2nd edition (with some adaptations):

| | Age at cancer diagnosis | | | | | | Calendar period of cancer diagnosis | | | | | | Total |
| | 0-14 years | | 15-19 years | | 20-24 years | | 1965-79 | | 1980-94 | | 1995-2007 | | |
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	
I Leukemia	343	290	74	33	54	51	121	107	270	210	80	57	845
ALL	235	218	51	18	19	14	65	65	194	160	46	25	
AML	45	38	16	12	23	22	11	14	49	37	24	21	
Unspecified	63	34	7	3	12	15	45	28	27	13	10	11	
II Lymphoma	122	57	131	105	182	124	29	10	226	140	180	136	721
HL	42	31	76	75	127	91	8	5	116	90	121	102	
NHL	67	23	55	28	53	31	11	3	106	46	58	33	
Unspecified	13	3	0	2	2	2	10	2	4	4	1	1	
III Central nervous system	321	222	122	117	150	142	111	75	315	231	167	175	1074
IV Sympathetic nervous system	77	66	4	7	5	1	35	31	48	38	3	5	160
V Eye	42	25	0	2	0	0	19	11	23	14	0	2	69
VI Kidney	67	61	1	2	4	4	39	31	29	32	4	4	139
VII Hepatic	19	11	3	3	3	6	10	2	14	13	1	5	45
VIII Malignant bone	64	50	61	29	30	18	18	6	93	63	44	28	252
IX Soft tissue sarcoma	46	61	41	30	37	28	11	24	74	67	39	28	243
X Germ cell													
Ovary		25		31		44		4		57		39	100
Testis	43		179		516		18		286		434		738
XI Carcinomas													
Thyroid/endocr glands	7	18	11	52	21	69	1	1	22	74	16	64	178
Malignant melanoma	14	25	40	103	77	220	4	7	69	186	58	155	479
Breast	0	1	0	2	1	20	0	0	0	8	1	15	24
Cervix/uterus		0		1		67		0		31		37	68
Colon	0	3	6	5	19	15	0	0	6	6	19	17	48
Bladder	4	1	5	3	9	5	2	0	9	6	7	3	27
Salivary	3	4	3	10	7	7	2	0	7	10	4	11	34
XII other/unspecified (incl skin, non-melanoma)	21	26	31	27	41	50	9	9	40	49	44	45	196
Total	1193	946	712	562	1156	871	429	318	1531	1235	1101	826	5440

Abbreviations: ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, HL: Hodgkin's lymphoma, NHL: Non-Hodgkin's lymphoma

Table 4. Classification of the cancer cohort (based on ICD-7, ICD-O-2 and MOTNAC codes) used for papers 2 and 3:

| Cancer site | Age at cancer diagnosis | | | | Calendar period of cancer diagnosis | | | | | | Total |
| | 0-14 years | | 15-24 years | | 1965-1979 | | 1980-1994 | | 1995-2007 | | |
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	
Leukemia	343	290	128	84	121	107	270	210	80	57	845
Lymphoma	122	57	313	229	29	10	226	140	180	136	721
CNS	321	222	272	259	111	75	315	231	167	175	1074
Testis	43		695		18		286		434		738
Malign. melanoma	14	25	117	323	4	7	69	186	58	155	479
Bone and soft tissue	110	111	169	105	29	30	167	130	83	56	495
Cervix/ uterus/ovary		25		143		4		88		76	168
Other	240	216	174	290	117	85	198	250	99	171	920
Total	1193	946	1868	1433	429	318	1531	1235	1101	826	5440

Abbreviations: CNS: Central nervous system; ICD: International Classification of Diseases; ICD-O-2: International Classification of Diseases for Oncology, second version; MOTNAC: Manual of Tumor Nomenclature and Coding.

Footnote: There are discrepancies between Table 3 in this thesis and Table 1 of paper 1. In paper 1, we excluded those who emigrated or died before age 15, as well as those diagnosed with a secondary malignancy, before describing the cohort.

3.3 Statistical analyses

Paper I: For the analyses of male reproduction and marriage, an extended Cox proportional hazards regression model was employed, with age at cancer diagnosis as a time-varying covariate, yielding Hazard Ratios (HRs) with 95% Confidence Intervals (CIs). For dichotomous offspring outcomes, a log binomial regression model was applied to calculate relative risks (RRs) with 95% CIs.

Paper II: For the analysis of governmental financial assistance (FA), an extended Cox proportional hazards regression model with a time-varying covariate for cancer was used to calculate HRs with 95% CIs. When analyzing income and employment, RRs with 95% CIs were calculated using binomial logistic regression, and regression coefficients with p-values (two-sided alpha of 0.05) for various percentiles were estimated using quantile regression models. Occupation was explored using multinomial regression models resulting in relative risk ratios (RRRs) with 95% CIs, and differences in income within occupational categories were analyzed by both linear and quantile regression.

Paper III: When analyzing violent deaths, HRs with 96% CIs were estimated, using an extended Cox proportional hazard regression model with age at cancer diagnosis as a time varying covariate. Basic cohort characteristic differences were assessed using independent t-test, chi-squared test or Fishers exact test, as appropriate.

Table 5. Overview of materials and methods for the three papers in the thesis:

Paper	Paper I- reproduction and marriage	Paper II- economic independence	Paper III- external deaths
Main aim	To examine reproductive outcomes and marriage in men diagnosed with cancer <25 years (first offspring rates and adverse outcomes, assisted reproduction and marriage rates)	To investigate economic independence with respect to employment, occupation, income and financial assistance in men and women diagnosed with cancer <25 years	To investigate the risk of suicide and non-suicidal external deaths in men and women diagnosed with cancer < 25 years
Study design	Population-based cohort of male cancer survivors	Population-based cohort	Population-based cohort
Study population	All males born alive in Norway from 1965-1985	All individuals born alive in Norway from 1965-1985	All individuals born alive in Norway from 1965-1985
Observation period/follow-up period	From reproductive age (15 years) to the date of birth of first offspring, death, emigration or 31.12.2011 (31.12.2007 for analysis on marriage), whichever occurred first	From the age of 18 years to the date of first receipt of financial assistance, death, emigration or 31.12.2007, whichever occurred first. For analyses of income and employment: cross sectional analyses for the tax year of 2007	From birth (for suicide analysis) or the age of 15 years (for non-suicidal external deaths) until death (from suicide, non-suicidal external death, or other cause), emigration or 31.12.2008
Statistical methods	Extended Cox-regression model (for paternity and marriage), log-binomial regression model (for offspring outcomes and assisted reproduction)	Extended Cox-regression model (for financial assistance), log-binomial regression model (for employment and income), quantile and linear regression (for income), multinomial regression (occupation)	Extended Cox-regression model, independent t-test, chi-squared test, Fishers exact test
Adjustments	Year of birth, parental education, age at marriage, age of offspring's mother	Year of birth and parental education	Year of birth and parental education
Stratifications	Cancer site, age at cancer diagnosis, time period of cancer diagnosis	Sex, cancer site, age at cancer diagnosis	Cancer site, age at cancer diagnosis

SPSS versions 21-23 (IBM Corp, Armonk, NY, USA), Stata versions 12-14 (StataCorpLP, College Station, TX, USA), and R version 3.2.2 (R Foundation for statistical Computing, Vienna, Austria) were applied for statistical analyses.

3.4 Ethical considerations:

All data were kept in de-identified form, with the personal identification numbers removed and never accessible to the investigators. The study protocol was approved by the Norwegian Data Inspectorate as well as the Regional Committee for Research Ethics (permission number 2009/1196/REK vest), including a waiver of individual consent.

For the third paper, studying suicide and non-suicidal external deaths, because of small case numbers and a sensitive topic, we discussed this explicitly with the head of the Regional Committee for Research Ethics. The reason for this was that the bereaved might be able to identify their relative as one out of a few with the same cancer diagnosis committing suicide and that this might be a burden. For this reason, we excluded some information from the paper, e.g. a detailed breakdown of the suicide methods applied, as we believe this would not add much scientific value to the paper but might cause distress for the bereaved. On the other hand, we considered the topic of suicide, however sensitive, an important one to study in this context, and that the published information was ethically acceptable. This view was supported by the head of the Regional Committee for Research Ethics.

4. **Results**

4.1 Paper I Reprodutive outcomes and marriage in young male cancer survivors

Among 626,495 males born in Norway during 1965-1985, after excluding emigrants and deceased before age 15 (defined as fertile age), 2,687 were diagnosed with cancer before age 25. Of these cancer survivors, 30% were diagnosed during childhood (0-14 years of age), 26% during adolescence (15-19 years), and 43% during young adulthood (20-24 years). The largest tumor groups were gonadal and germ cell (testicular) tumors, CNS tumors, lymphomas and leukemias. We registered 1,087 first offspring among the cancer survivors and 368,469 first offspring among the cancer-free references. There was a significant reduction in paternity in the male cancer survivors (HR=0.72; 95% CI 0.68-0.76), and this estimate varied across the different cancer sites. The most pronounced reduction in paternity was for those who had received a cancer diagnosis before 1995 and among those diagnosed below 15 years.

There was no increased risk of adverse offspring outcomes in the firstborn of the male cancer survivors, including preterm birth, low birthweight, small for gestational age, perinatal death or congenital malformations. There was an increased risk of the use of assisted reproductive technology (and especially ICSI) to impregnate their partner for the male cancer group (RR=3.3; 95% CI 2.7-4.1), in particular for survivors of testicular cancer, (low grade) brain tumors, Hodgkin lymphoma, leukemias, malignant bone tumors, sympathetic nervous system tumors and thyroid cancer.

When analyzing marriage, we found a slightly decreased likelihood of getting married for the male cancer survivors (HR=0.9; 95% CI 0.9-1.0), and this was significantly reduced for the survivors of low-grade brain tumors. Analyzing the sub-cohort of married individuals only for the outcome of first offspring, the reduction in

paternity remained (HR=0.7; 95% CI 0.7-0.8) for most tumor groups, but the reduction was no longer as marked for the survivors of CNS tumors.

4.2 Paper II Economic independence

We identified a total of 1,212,013 individuals born in Norway during the period 1965-1985, and of these a total of 5,440 received a cancer diagnosis before the age of 25. Forty percent of the survivors were diagnosed in childhood (0-14 years), the rest during adolescence and young adulthood. The largest tumor groups were brain tumors, leukemia, testicular cancer and lymphoma. There was an increased risk of receiving governmental financial assistance for the cancer survivors (RR=1.3; 95% CI 1.1-1.4 (males), and RR=1.4; 95% CI 1.2-1.5 (females), disability pension recipients excluded). After exclusion of emigrants, deceased and lost to follow-up, 1,146,444 individuals remained alive and living in Norway in 2007, and were included in the analysis on employment, occupation and income. Of these, 3,945 had received a cancer diagnosis before the age of 25. We found a 34% increased risk of not undertaking paid employment in 2007 among the cancer survivors compared to the non-cancer reference group (RR=1.4; 95% CI 1.2-1.7 (males), RR=1.4; 95% CI 1.2-1.6 (females)). A significantly increased risk of unemployment was found for survivors of lymphoma (females), CNS tumors (both sexes), testicular cancer, bone/soft tissue tumors (males), regardless of age at diagnosis (childhood vs AYA). There were in general only slight income reductions in the cancer survivors compared to the non-cancer references, and these were most pronounced for survivors of CNS tumors. The representation in higher-skilled occupations did not differ significantly, and income differences within each occupational category were largely non-significant.

4.3 Paper III External deaths

Among the 1,218,013 individuals in the study cohort, 5,440 received a cancer diagnosis before the age of 25 years. There were 24 suicides and 15 accidental deaths among the cancer survivors, compared to 3,375 suicides and 6,690 accidental deaths

in the cancer-free reference group. This resulted in a 2.5-fold increased risk for suicide in the cancer survivors (95% CI 1.7-3.8), but no increased risk of accidental deaths (HR=1.0; 95% CI 0.6-1.7). The mean age at suicide differed significantly for cancer survivors (28.0 years) and the non-cancer comparisons (25.1 years), whereas there was no difference in sex distribution, marital status, disability pension status or suicide methods. Stratified by cancer site, the risk was significantly increased for survivors of CNS tumors (low grade and unclassified only), testicular cancer, bone/soft tissue sarcoma, leukemia and lymphoma, although based on small numbers. The risk estimates were similar regardless of being diagnosed in childhood or during adolescence or young adulthood. The time between cancer diagnosis and suicide ranged from 6 to 497 months, with a median time of 146 months (12.1 years) (10th percentile 18 months, 90th percentile 387 months).

5. **Discussion**

5.1 Methodological considerations:

5.1.1 **Internal and external validity**

Internal validity

Biased effect estimates result from inadequacies in the study design, conduct or analysis, also referred to as reduced internal validity or systematic errors[153]. Examples of such errors, or biases, are selection bias (i.e. the study cohort's representativeness in relation to the source population), information bias (exposure and/or outcome are systematically erroneously measured or classified), and (uncontrolled) confounding.

We consider the risk of selection bias in our study to be negligible, due to the fact that the entire Norwegian population born during a 20-year period is studied, and that the registration of both births and cancer is mandatory. The possibility of misclassification bias (a type of information bias) is considered minimal due to the fact that the registries used are validated and of high quality (CRN and MBRN)[139, 146]. However, the possibility for this bias to be present due to typing errors or data processing errors still exists. There are two types of misclassification bias: Differential (which will lead to an over- or underestimation of the effect estimate) and non-differential (which will bias the effect estimate towards null). Differential misclassification occurs when the classification of outcome is dependent upon the value of the exposure (and vice versa). A possible example from our study would be if there is a heightened awareness (and as such a higher detection rate at birth) of congenital anomalies in the survivors of childhood cancer. An example of non-differential misclassification is the fact that the registration of fathers in the MBRN is based on information from the mother. This might lead to a misclassification of biological fathers. We have no reason to believe that this potential misclassification is unevenly distributed between the cancer group and the comparisons.

A confounder is a variable that is associated with both the exposure and the outcome (but not an effect of any of them)[153]. If a confounder is not considered in the statistical model, the estimated association between exposure and outcome might be biased. In order for a variable to cause confounding, it must, by definition, be a common cause of (i.e. exist prior to) both the independent (exposure) and the dependent (the outcome) variable, and can be drawn in a simplistic way in a directed acyclic graph (DAG) (Figure 11).
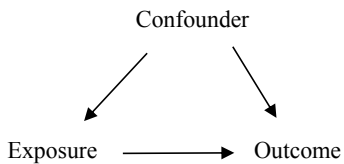
Figure 11. A simple directed acyclic graph.

In the case of our study, there are very few known factors that influence the occurrence of cancer in young age (our exposure) or the treatment received (a proxy of the exposure). As such there are not many possible confounders, by the strict definition of confounding. If not careful, one might overadjust and introduce bias into the analysis rather than remove it. An example is adjustment for marital status in an analysis of the outcome of income (Figure 12).
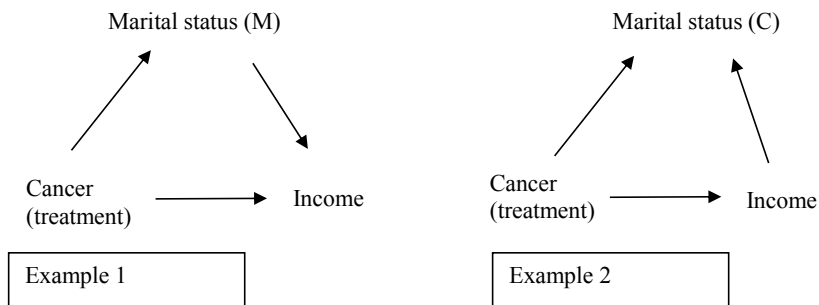
Figure 12. Simple directed acyclic graph depicting a collider and a mediator.

Marital status is, in this example, not a confounder, since it is not a common cause for the exposure (cancer) and outcome (income). However, marital status can act as a mediator ("M", an intermediary variable) of the effect of cancer on income. In this model, having had cancer may affect the probability of getting married (positively or negatively), and through this have an effect on personal income (single household vs dual-earning household). It can also act as a collider (C) on the path between cancer and outcome; cancer might affect the chances of finding a partner, and income might in itself influence the probability of getting married. Adjusting for a collider (Figure 12, example 2) will introduce bias (collider-stratification bias) into the analysis and distort the estimated association between the exposure and the outcome[154].

Adjusting for a mediator (Figure 12, example 1) may lead to overadjustment, and will at best serve to disentangle the direct effect (via marital status) of the exposure on the outcome from the total effect, which might not be the most interesting in this example. Controlling for an intermediary variable (or a descendant of such a variable) in a regression analysis might introduce overadjustment bias[155]. If one is interested in the total causal effect of an exposure on an outcome of interest, adjusting for intermediate variables will usually bias the results towards null, and this can either obscure a true effect or create an effect where in reality there is none. However, if one is interested in a controlled direct effect through intermediary variables, adjustment for intermediary variables might be correct (given that the no-interaction assumption holds)[156]. One might also consider applying various mediation analysis techniques, if the main interest is to decompose the total effect of an exposure on an outcome into direct and indirect effects[157]. We have not applied mediation analysis in our research papers. For this thesis, we were interested in the total causal effect of the exposure (cancer before age 25) through treatment as a proxy, on the different study outcomes, and carefully had to consider which variables to include in the models.

There is an ongoing discussion regarding a possible relationship between childhood cancer and parental socioeconomic status (SES). Some publications show a correlation between poor socioeconomic status and both the incidence of and the survival from childhood cancer, although results from studies deviate from showing a

correlation to no correlation, to even an inverse correlation (high SES associated with worse survival) [158-161]. In our analyses, we adjusted for parental education, in order to take this into account, but this provided, in general, very small changes in our estimates.

External validity

Internal validity is a prerequisite for external validity, which is the generalizability of the study to other populations than the source population. A common cause of low external validity in observational research studies is when the study sample is not representative. An example of this is when the source population is obtained from a single facility or geographic location, where the findings, due to elemental differences between the study population and the general population, cannot be generalized. The findings of our study, based on the entire Norwegian population born over a 20-year period, should therefore be generalizable to other populations with similar cancer treatment programs and social structures, and to cancer survivors born and treated during the same time period as ours. It cannot automatically infer generalizability to the outcomes of young cancer patients treated in more recent time (i.e. today), due to the fact that many treatment regimens have changed dramatically during the past decades. Only future studies can determine whether the effect of the development of less toxic treatment regimes, will change the risk of occurrence of the unfavorable outcomes.

5.1.2 **Tumor classification**

For classification of tumors in the AYA age group no standardized classification system exists, and tumors of this age group do not readily fit into the classification system usually used for childhood cancers (International classification of childhood cancer; ICCC[162]), or the adult cancer classifications system (International Classification of diseases in oncology; ICD-O[138]). There is no agreed standard for classification of cancer in a mixed cohort (such as ours) of childhood and AYA cancer. For the first paper in this thesis, we used the ICCC, second edition, with some

modifications, in order to encompass the AYA cancer diagnoses within the framework of the ICCC. For the second and third paper, we classified the tumors into large tumor groups, based on a combination of histology and topography, in order to be able to assume, to some degree, treatment type and intensity received. CNS tumors are subclassified into categories based on morphology reflecting their biologic behavior and aggressiveness. This is a well-known way of subcategorizing brain tumors (World Health Organization (WHO) grade I-IV)[163]. Handling large datasets like the ones in this thesis will always carry the possibility of misclassification bias.

5.1.3 **Study population and design**

Study design

There are several ways to follow a cohort over time, resulting in different study designs, each with their own strength and limitations[164]. In an ideal scientific world, one could say the best study design would be to randomize individuals of the cohort into exposed and unexposed groups and follow-up prospectively (a randomized control design), but this is not feasible in an epidemiological population-based observational study. The closest one can get to a randomized controlled study in this setting, is a prospective cohort study, where exposure is recorded at study start (or during follow-up), and the cohort is followed forward in time for the incidence of the disease. This is the design used for most of the analyses in this thesis, where the exposure is cancer before age 25, and the "disease" is the various study outcomes.

This differs from a case-control design, where the cases and controls are defined by outcome status (i.e. disease vs no disease), and then (usually) retrospectively studied with regards to whether exposures differed in the two groups.

Study cohort and variables of time

The Lexis diagram (Figure 13) represents the interconnected time-variables involved within our study cohort; date of birth, age at diagnosis, time period of diagnosis, date and age at end of follow-up. This makes the choice of statistical methods difficult, as does the choice of which time-variables to adjust for or stratify by. For cross-

sectional analyses, this is less of a problem, but for survival analyses/Cox regression models, where time is a factor already included in the analysis, adjusting for or stratifying by more time-variables might lead to errors in the model and consequently estimates that are imprecise or fail to converge due to collinearity. Thus, in most of the analyses in this thesis, adjustment was made for year of birth, and in some cases stratification was made by age at cancer diagnosis, but only one time-variable at a time was taken into any given model.
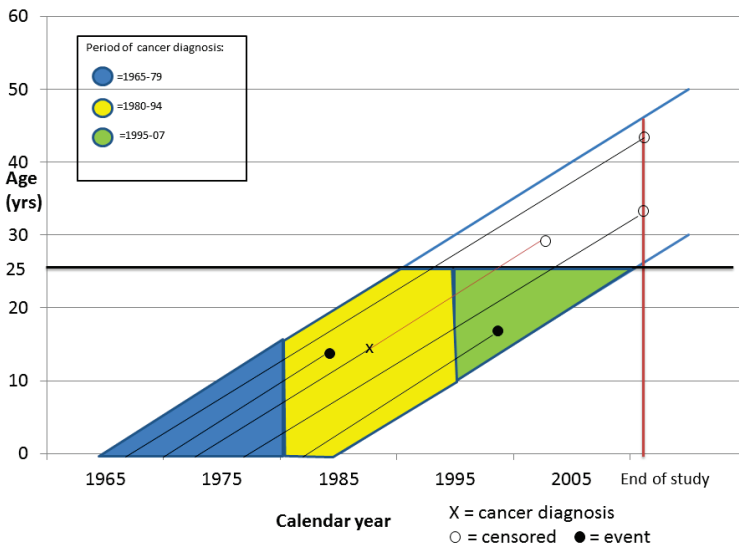
Figure 13. Lexis diagram illustrating the study cohort with various time variables and the Cox model with regards to time.

5.1.4 Choice of statistical methods

Cox proportional hazards regression

The Cox proportional hazards regression model was originally developed for survival analysis, and has been extended to fit various "time-to-event" analyses, including an estimation of the influence of several covariates (including the exposure and various confounders) on the risk of the outcome/event of interest[153]. The model is based on the assumption of proportional hazard functions, that is the ratios of hazards which

are estimated in the model are constant during the follow-up time. In the case of non-proportionality, a stratified Cox model can be applied.

Extended Cox model with time-varying covariate

In order to fully make use of the prospective nature of our data as well as take into account the possibility of changing membership of the classifying event (cancer diagnosis <25 years) during follow-up, we used an extended Cox proportional hazards regression model for most of our analyses, with age at cancer diagnosis as a time-dependent covariate. Using this method, the variable is equal to 0 as long as no cancer diagnosis (<25 years) is made, and changes to 1 when a cancer diagnosis is made before the age of 25. Thus, as an example, in our analysis on paternity, those fathering their first child before being diagnosed with cancer (experiencing the outcome before the classifying event) will contribute all their observation-time to the "non-cancer" person-time in the analysis. In similar analyses with mortality as the study outcome, the bias that occurs when the exposure is not modeled as a time-dependent covariate is called "immortal time bias" or "guarantee-time bias"[165]. "Guarantee time" refers to a span of time in the observation period when the outcome under study could not have occurred because the classifying event has not yet occurred (Figure 14). Not allowing for a change in the status of the classifying event (the exposure), may lead to inaccurate and wrongful/erroneous results. Other possible strategies to remove this bias are by conditional landmark analysis or inverse probability weighting.
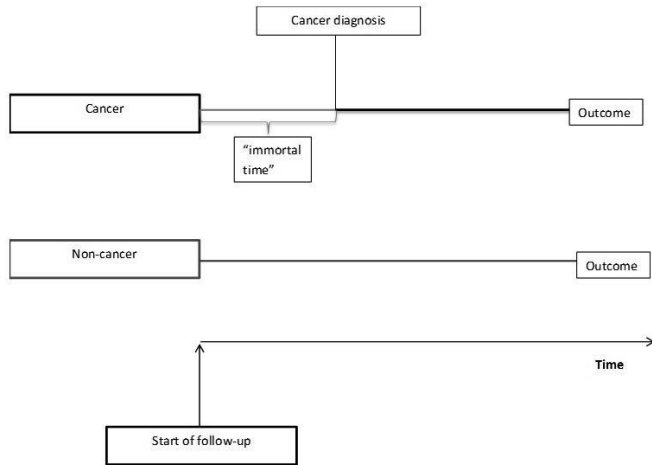
Figure 14. Illustration of "immortal/guarantee time".

Competing risk

An alternative method for some of our analyses (e.g. for the outcome of suicide and external deaths), could be a competing risk model, since death from other causes (disease-related) might be a competing risk. A competing risk is an event of equal (or more significant) clinical importance that alters the probability of the event of interest occuring[166]. Regression on the cause-specific hazard function can be performed with a fitted Cox proportional hazard regression model, while the subdistribution hazards model (by Fine and Gray) is a competing risk approach which calculates the subdistribution hazard and is a regression on the cumulative incidence function (CIF)[167]. When time-to-event is the main research question, a depiction of this will not be valid with the Kaplan-Meier approach in the presence of competing risks, and for this reason, a competing risk approach (on the CIF) would be preferred.

However, for a regression on risks or hazards, it remains possible to fit a proportional hazards regression model and to treat the competing event as censored, although an

assumption of independence between competing events needs to be performed to allow correct interpretation of this cause-specific hazard[168].

If the association of the exposure with the event of interest is in direct opposition with the contributing effect of the competing event, the cause-specific hazard (by Cox regression) and the subdistribution hazard (by the competing risk model) might be quite different[168]. We chose the extended Cox proportional hazard regression model for our papers, but for the analysis in paper III, we also ran a competing risk model, which gave very similar results.

Log binomial model

For estimating relative risks in cohort studies of rare outcomes (often referred to as an incidence of <10%), the adjusted odds ratio (OR) from logistic regression can be used as an approximation of relative risk[169]. However, when analyzing the risk of common outcomes (incidence or absolute risk >10%), this approximation no longer holds true, and the OR will overestimate the RR if it is >1, and underestimate the RR if it is <1 (Figure 15). A different approach for estimating the adjusted relative risk in cohort studies, is the use of the log binomial model[170], for the analysis of a dichotomous outcome. We used this model for analyzing the offspring outcomes in paper I, and for analysis of employment and high/low income in paper II.
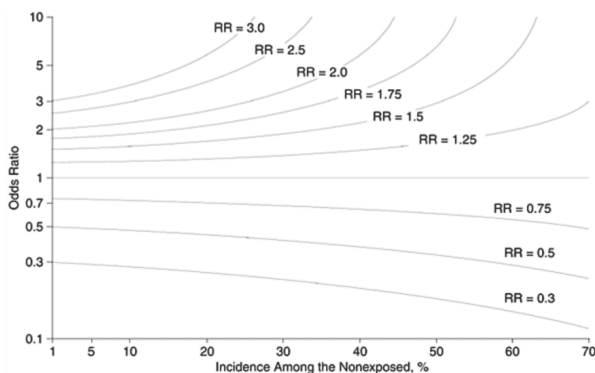
Figure 15. The relationship between risk ratio (RR) and odds ratio by incidence of the outcome. Ref: Zhang et al, JAMA, 1998[169]. Reprinted with permission from the American Medical Association.

Quantile regression:

For our second paper, we wanted to study the association of a cancer diagnosis and subsequent income. This could be done by ordinary least square regression, but this method might not give a comprehensive representation of the total effect of cancer on salaries, especially if the impact of cancer differs across the different income percentiles. To better be able to study this association, we performed quantile regression (not only for the median income, but for several other percentiles) for males and females separately, and for the different cancer groups. The results presented in paper 2 are regression on differences in the median income (50 p), which is less vulnerable to outliers and heavy-tailed distributions than ordinary least squares regression (on the mean). This allows us to acknowledge income heterogeneity and consider that the relationship between cancer and income might change depending on which quantile we look at (Figure 16).
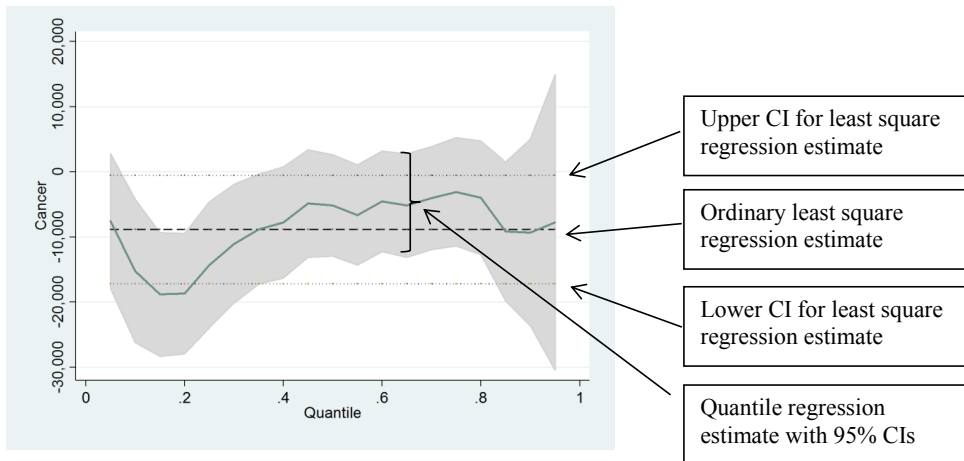
Figure 16. Quantile plot for income (females), comparing 1,479 cancer survivors with 508,288 cancer-free references.

This plot for females show that the unfavorable effect of cancer on income is more pronounced in the lower income quantiles (10-30th percentiles), where it is significant. Although the ordinary least square regression in this plot shows a

reduction in income (overall) for the cancer survivors, the detailed picture is only demonstrable with quantile regression.

5.1.5 Interaction effect/effect modification

Statistical interaction (or effect modification) is the study of how the effect of one independent variable (on the dependent variable) changes when the value of another independent variable changes[153]. An example of this for the current study is whether the effect of cancer on suicide risk is affected by marital status (i.e. differs between married and unmarried individuals). Statistical interaction is detected by adding a term to a model that is the product of the two variables (but only when the regression coefficient is statistically significant). If the interaction analysis comes out as non-significant (usually with a significance level of 5%), there is no need for the interaction term in question to be included in the model. This was the case when we ran these analyses for paper III. One can also visualize interactions graphically in regression plots. Another way to study this is by performing stratified analyses, stratified on the variable of interest (e.g. marital status), which we have done for some of our analyses (stratification by cancer site, sex, age at diagnosis or time period of diagnosis).

5.1.6 Other methodological considerations

An important limitation of our study, is that the information regarding treatment (received from the CRN) is scarce and to some extent unreliable. We have for this reason not included this information as a variable in the study. For pediatric cancer, which has been treated uniformly across the country since the early 1970s, we can to some degree assume broad categories of treatment received for different forms of cancer. The treatment for some cancer groups have undergone major changes during the study period. For adolescents and young adults in Norway, the treatment diversity is much greater. Therefore, we were unable to assess a dose-response relationship with the outcomes concerned.

We did not have any information regarding mental or physical illness in the survivors, only on the diagnoses qualifying for disability pension. It would have been an asset to our study if we had more national registries available to us, such as the Norwegian Prescription Database or the Norwegian Patient Registry, although these registries would not have been possible to link with our data prior to 2004 and 2008 respectively. Regarding our definition of "cancer survivor", we could have defined a cut-off of e.g. 1- or 5-year survival to be able to be included in the cancer survivor group, in order to conform to other groups' definitions. However, we felt that some important information might be lost doing this, and our Cox regression model accounts for this variation in observation time. For some of the rarer outcomes studied, the statistical power was limited despite having a large study cohort. Another limitation was that we only have follow-up until 2007/2008 (2011 for reproductive outcomes), and more recent years were not available within the allocated time frame of this PhD study.

5.2 Discussion of results

5.2.1 Reproductive outcomes

For the reproductive outcomes in this study, we decided to only focus on the male survivors. One of the reasons for this decision was the relative abundance of papers reporting reproductive outcomes in female survivors in comparison to male survivors. Another aspect was the fact that we did not have information regarding treatment received. This might be even more critical to have when studying associations between cancer and subsequent pregnancy outcomes in females. In addition to the fertilization process, women have to nurture and carry the developing fetus, and deliver the baby, and all stages of this process might be affected by cancer treatment.

In line with most other studies on reproduction after a cancer diagnosis in childhood or during adolescence/young adulthood in males, we found a significant reduction in paternity for the cancer survivors, and this was most pronounced in survivors of testicular cancer, brain tumors, lymphoma, leukemia, retinoblastoma, malignant bone

tumors and sympathetic nervous system tumors[58-60, 62, 171-173]. Studying the risks during the different time periods of treatment, the paternity deficit was particularly pronounced for those being diagnosed with cancer before 1995, and among those diagnosed during childhood (<15 years). Our results align well with other studies examining the relationship of cancer treatment and fertility. In particular, large tumor groups like lymphomas, with both pre- and post-pubertal exposure to gonadotoxic radiation (Hodgkin lymphoma (HL)) and chemotherapy (both HL and non-Hodgkin lymphoma (NHL)) show an association with impaired fertility. Efforts to reduce irradiation and gonadotoxic chemotherapy in particular for HL patients has been (and still is) ongoing[174, 175]. The treatment of testicular cancer is also one that has undergone major treatment changes that have changed the effect on future fertility potential, including the reduction in the use of radiation therapy and the introduction of retroperitoneal lymph node dissection around 1980[58, 171].

The reduced paternity found in survivors of brain tumors has also been demonstrated in many previous studies[58, 59, 62]. We wanted to study whether this was predominantly associated with medical or social factors. Therefore, we did an analysis examining the paternity in the married sub-cohort only, and this lead to a smaller, and non-significant, paternity deficit in the survivors of CNS tumors. This may suggest that the reduced fertility in this tumor group has a dominant social component, i.e. not being able to find a partner or sustain a long-term relationship. This was applicable to both high grade and low grade tumors. For most other (large) tumor groups, the paternity deficit persisted when analyzing the married individuals only, suggesting a predominantly biological factor.

The possible damage to germ cell DNA caused by mutagenic cancer therapies has led to an interest in whether this could lead to a permanent DNA damage transferable to the next generation and giving rise to congenital malformations. The paternal contribution to the recurrence of birth defects in the next generation has been found to be significantly higher than the maternal contribution, suggesting a greater contribution of paternal genes through genomic imprinting[176]. The association between paternal cancer and congenital malformations in the offspring has been

studied previously, and the results are for the most part reassuring in finding no association, although some discordance exist in the literature (Table 6).

We found no increased risk of congenital malformation in the first offspring of male cancer survivors, neither when analyzing major birth defects separately, nor when the analyses were stratified according to cancer type. Our results were reassuring and confirms the (by now) well-documented absence of an association between a paternal history of cancer and subsequent congenital abnormalities in the offspring.

Table 6. Overview of recent (2008 to present) papers studying the association between paternal cancer and the risk of congenital offspring malformations.

Publication	Age at cancer diagnosis	Offspring to male CS (n)	Offspring to male CS with congenital malformations (n)	Result of risk estimation	Design, controls (country)
Magelssen et al, Hum Reprod, 2008[57]	15-35 years	487	27	OR_{adj}:1.5 (95% CI 1.1-2.3)	Hospital registry (Norway)
Chow et al, Arch Pediatr Adolesc Med, 2009[177]	0-19 years	470	9	RR: 0.83 (95% CI 0.41-1.69)	Population based, population control (USA)
Winther et al, Clin Genet, 2009[87]	0-19 years	819	18 (9 fathers irradiated, 9 non-irradiated)	PPR_{adj}: 0.9 (95% CI 0.6-1.5)	National cohort, sibling controls (Denmark)
Ståhl et al, J of the NCI, 2011[88]	All	8,670	322 (major congenital abnormality, incl ART conceptions)	RR:1.117 (95% CI 1.05-1.31) (major)	National cohort, general population control (Denmark and Sweden)
Signorello et al, J of Clin Oncol, 2012[86]	0-20 years	1,906 (+ some >4 offspring, details missing)	30	$p > 0.05$ for association of radiation or alkylating agent exposure	Multicenter cohort (CCSS), cancer controls (different treatment exposures) (USA)
Winther et al, J of Clin Oncol, 2012[178]	0-19 years	722	65	RR (irradiated vs non-irrad): 1.02 (95% CI 0.59-1.44) (both sexes)	Population based, cancer controls (different treatment exposures) (Denmark)
Gunnes et al, Br J of Cancer, 2016[179]	0-24 years	1,087	42	RR_{adj}: 0.92 (95% CI 0.69-1.24)	National cohort, population control (Norway)
Seppänen et al, Int J of cancer, 2016[89]	0-34 years	6,862 (male and female CS) (offspring to male CS not specified)	220 (male and female CS) (number of offspring to male CS not specified)	PR_{adj}: 1.07 (95% CI 0.91-1.25) (male and female CS) PR_{adj}: 1.12 (95% CI 0.90-1.39) (offspring of male CS only)	Population based, sibling control (Finland)

Abbreviations: Adj=Adjusted; ART= Assisted reproductive technologies; CI= Confidence interval, CS= Cancer survivor, OR= Odds ratio, PR= Prevalence ratio; PPR=Prevalence proportion ratio, RR= Risk ratio.

The actual uptake of assisted reproduction in male survivors of young age cancer on a population level and across cancer diagnoses is underexplored. We found a threefold increased probability of the first offspring of male cancer survivors being conceived as a result of assisted reproductive technology (and ICSI in particular). These results are concordant with publications of male survivors of cancer in older age, and of smaller studies on ART in male survivors of certain cancer types (like Hodgkin's lymphoma and testicular cancer)[57, 58, 180, 181]. Unfortunately, we did not have information on ART attempts not leading to a successful pregnancy, which could have given a better picture of the total reproductive burden.

5.2.2 Socioeconomic outcomes

Marriage

We found a slightly reduced probability of subsequent marriage among male survivors (paper I) of cancer in the whole group combined, and the lowest estimates were found for survivors of CNS tumors (39% reduction in marriage) and survivors of retinoblastoma (46% reduction). When stratifying the analyses on age at diagnosis, our results were in line with previous publications on CCS[90-93]. We found a significantly reduced probability of marriage in the survivors of cancer <15 years (HR: 0.81; 95% CI 0.70-0.95). Many children with cancer undergo treatment which have devastating effects on the developing body and (often) brain, leaving many survivors neuro-cognitively impaired in addition to having various physical handicaps (e.g. amputation for bone sarcomas), which might drastically affect their ability to find a partner and sustain a long-term relationship. For the AYAC survivors in our cohort, there was no reduction in marriage probability (HR: 0.96; 95% CI 0.88-1.06). This could be explained by the treatment not affecting mental capacities as much when received during or after adolescence, when the brain is still developing, but nevertheless is much more developed than in a child. Our results contrast the only other available study reporting marriage rates in AYACS separately, which found the survivors less likely to be currently married, as well as having an increased risk of divorce[95].

One shortcoming regarding most of the studies of cancer's effect on social outcomes (including ours) is that very few have information on cohabitation rates in addition to marriage. Many young people today chose to cohabitate rather than marry, and information on this would be a more correct measure of social support than marital status alone. However, we have no reason to expect this distribution between cohabitation and marriage to differ between the cancer survivors and their comparisons, leaving the relative probabilities unaffected. Marriage (or cohabitation) is an aspiration for most young adults in society, and is in many settings used as a measure of "social success". Again, available research on AYAC survivors is scarce regarding social outcomes, and needs to be addressed in future studies[96].

Employment and income:

The possible effect of cancer on subsequent employment and earnings is important to study, and especially in young survivors, as the majority now become long-term survivors and have most of their life ahead upon finishing cancer treatment. The degree of financial independence achieved has important societal implications. Areas of deficit can be identified from large national studies, allowing adequate support programs to be developed. We know from a previous Norwegian study that CCS and AYAC survivors have a more than four-fold increased risk of receiving disability pension[182]. We were therefore interested in studying the economic impact of cancer on the cancer survivors that are capable of working, i.e. those that are not receiving disability pension. Most studies on employment and income in young age cancer survivors have not differentiated on this matter, and may therefore not be directly comparable to ours.

There is a shortage of studies regarding occupational outcomes of AYAC survivors, as they tend to be included in large studies of adult cancer survivors, in which case they will frequently constitute only a small proportion. AYAs face challenges that are unique and different from both survivors of cancer in childhood and adulthood. It is therefore important to study the occupational and financial outcomes of these survivors in particular, in order to introduce measures that can increase work

participation and economic independence in this group. We found 30-50% increased risk of unemployment both in CCS and AYAC survivors, and in particular for survivors of lymphoma (females), brain tumors, testicular cancer, and bone/soft tissue tumors. Our results are comparable to the overall conclusions from a large meta-analysis on CCS and unemployment published in 2006, but when separating studies from the US from the ones conducted in Europe, the odds ratio for the latter studies combined was 1.0[98]. However, the studies included in this meta-analysis from Europe were quite small, with the largest study including 500 survivors.

More recent studies of cancer survivors (all ages) have shown an increased risk of unemployment following cancer, but there is still a shortage of comparable studies for these outcomes in survivors of cancer in young age[101, 183]. A Swedish study of CCS find survivors of CNS tumors at increased risk of unemployment and reduced incomes, but no such differences are found for the survivors of non-CNS tumors[99]. A recent Finnish study (published after our paper 2) of CCS did not find any difference in unemployment risk[184]. However, in that study the recipients of early retirement were included in the analysis, and assuming that a significant majority of these were receiving early retirement in the form of disability pension, this cannot therefore directly compare with our study. Studies from the US show an overall 3-fold increased risk of unemployment for CCS, and in particular associations are found between unemployment and neurocognitive deficits, cranial irradiation, and poor physical health[98, 185, 186]. US studies also demonstrate a high proportion of AYA cancer survivors reporting problems with returning to work/studies after a cancer diagnosis[187].

We did not find any significant difference in the representation in high-skilled occupations for employed survivors of cancer in young age, but a reduced representation in manual labor occupations. These findings correspond well with a recent study on French CCS[188].

Overall, we found slightly decreased incomes for the cancer survivors, however this was not significant for the survivor group as a whole (recipients of disability pension

excluded). We did find significant income reductions for certain tumor groups, and in particular for CNS tumor survivors, both males and females. There were some differences in the effect of cancer across the different income percentiles (as described in chapter 5.1.4).

Previous European studies show a modest income decline in CCS and AYAC survivors, although survivors of certain cancers (e.g. CNS tumors) seem more vulnerable than others[99, 102, 184, 189]. One study of income in CCS survivors from the US found lower personal incomes within different occupational categories for survivors compared with siblings[100]. In our study, unfortunately, we did not have information on hours worked per week, which could give us a possible explanation of the income discrepancies found. Although, in the only European study published where information on working hours was available, adjusting for this did not change the result of lower incomes (compared to siblings) in the cancer survivors[102].

There is no doubt that a cancer diagnosis in childhood, adolescence and young adulthood puts an added financial strain on the survivors and their families, the magnitude seems to partly depend on the social structure where they live, and whether health care is public and free of charge, linked to employment and previous earnings, or something in between[96, 190]. A study from the US found a substantial economic burden after a cancer diagnosis during adolescence and young adulthood, both in form of excess annual medical expenditures and as excess annual productivity losses, in the order of >5,000 USD annually per survivor[191]. In our study, we found an increased risk of requiring governmental financial assistance after a cancer diagnosis in young age, in particular when diagnosed as an adolescent or young adult, suggesting insufficient economic flexibility in this survivor group.

The compensatory mechanisms for unfavorable occupational and financial outcomes after a cancer diagnosis seem to be superior in Western European countries compared to the US. In the US, health insurance is traditionally linked to one's employment, in contrast to the free public health care present in most Western European countries. The ultimate goal for the majority of young age cancer survivors is to be able to lead

high-quality, independent lives (both financially and socially), contributing to society on an equal basis to their non-cancer peers[96]. The health care and social services should facilitate this through adequate work-rehabilitation and social support programs, reliable income compensation mechanisms and empowerment of the cancer survivors.

5.2.3 **External deaths**

We found a more than two-fold increased risk of suicide for survivors of cancer, regardless of being diagnosed during childhood or as an adolescent/young adult. These results are novel and carry important implications. The absolute suicide risk, however, was low for the cancer survivors as well as for the non-cancer comparisons.

Previous research (mostly from the US) show an increased risk of suicide ideation and attempts among CCS, but this has previously not been fully explored in terms of completed suicides on a population level[120, 121, 192]. The only Nordic study exploring this in a national cohort including survivors of cancer diagnosed between the age of 15 and 30, found a risk ratio of 1.6 for suicidal behaviour (defined as suicide attempts and completed suicides together), and the highest risk was found during the first year after diagnosis[193]. This is also studied in large population-based studies of survivors of cancer in all ages, where a 2-3 fold increased risk for suicide is found during the first year after diagnosis[113-115]. The late-mortality (>5-year survivors) studies have for the most part not shown an increased risk of external deaths or suicide, but further details regarding this have not been further explored in these studies[46, 55, 56, 194, 195]. The most recent (and largest to-date) late-mortality study, from the BCCSS, found a 20% increased risk of death by external causes[46]. When stratified into cancer site, the increased risk was significant for the survivors of CNS neoplasms and neuroblastoma, and the excess mortality ratios for external causes of death were only increased for those treated before 1990.

In our study, we have also included survivors of AYA cancer, which leaves us with a different cancer cohort than most others, focusing on CCS only. In addition, we

follow the survivors from a cancer diagnosis is made (not restricting to >5 year survivors only), and this might partially explain the differences in the results between our study and the late-mortality studies previously mentioned.

Of interest, when stratifying our suicide analysis by reception of disability pension, the estimate for suicide risk was lower for the recipients of disability pension than for those not receiving this. In addition, for those diagnosed with brain tumors in our study, only survivors of low-grade and unspecified tumors committed suicide. This could illustrate that it might not be the survivors most heavily treated, or those in regular contact with the health care system or the social security system that are most at risk of suicide in this population.

Furthermore, of the suicides committed in the cancer group in our study, none were receiving disability pension on the background of a mental disorder. Depression and other mental disorders are well-known risk factors for suicide in young people[106, 196]. Danish population-based studies have found an increased risk of antidepressant use in childhood cancer survivors, as well as an increased risk of hospital contact for mental disorders[197, 198]. A recent Norwegian study of survivors of cancer diagnosed before age 25 also confirmed an increase in the prescription of antidepressants[199]. Findings from the BCCSS present a higher prevalence of mental health dysfunction in CCS, especially in survivors of CNS and bone sarcomas[200]. Finally, according to a recent CCSS publication, there is an association between chronic health conditions and symptoms of emotional distress in adult survivors of childhood cancer [201]. Unfortunately, we did not have information regarding hospitalizations (neither somatic nor psychiatric) or medication prescribed, which perhaps could have shed a light on the burden of chronic health conditions in relation to suicide risk in our study.

We did not find an increased risk of dying from non-suicidal external causes (like traffic accidents and accidental poisoning). This is in contrast to large studies on adult cancer patients, finding an increased risk of death by external causes (also non-suicidal) and non-fatal injuries [125, 126]. This might suggest different self-support

mechanisms in younger vs older cancer patients, as well as support previous findings of CCS largely not undertaking high-risk behaviors[202, 203].

The ultimate goal for identifying increased suicide risks in subgroups within a population, is to be able to introduce preventative measures. However, prevention begins with awareness. Some known risk factors for suicide in young individuals are mental health problems, family history of suicide, non-intact parental units, alcohol use/abuse, stressful life events and social isolation[108, 196]. Norway was among the first countries to establish a national program for suicide prevention in 1994[196]. There are diverging reports on the effectiveness of different suicide prevention methods. Asking for and identifying individuals at risk and providing them with supportive contacts either from their family or from the health care providers, as well as restricting access to lethal means (firearms, medication), are identified as the main strategies proven to be effective[111, 204]. As a preliminary measure, based on our results, this awareness of a heightened suicide risk among survivors of cancer in young age needs to be raised for both health care workers involved in the follow-up care of these survivors, as well as for the survivors and their families themselves. However, our results need confirmation in more studies, and preferably in even larger study populations.

6. **Conclusions and future perspectives**

In this study, we have explored some of the adult life challenges after cancer in childhood, adolescence and young adulthood.

We studied reproductive outcomes of male cancer survivors, and found a paternity deficit, which seemed to have a social component, at least for the survivors of CNS tumors. The risk of unfavorable offspring outcomes was not increased, including congenital malformations. We found the risk of assisted reproduction to be increased more than 3-fold for the partners of male cancer survivors' first offspring, which was evident for most larger tumor groups. Efforts to decrease gonadotoxicity of the current treatment regimens as well as to develop new and improved methods for fertility preservation, in particular for pre-pubertal boys, must be continued.

Furthermore, we found the cancer survivors to be at increased risk of financial dependency, illustrated by an increased risk of unemployment and the need for governmental financial assistance. Unfavorable income discrepancies were most pronounced for female survivors and for survivors of brain tumors. For the employed survivors, the representation in higher-skilled occupations was for the most part not significantly different between the cancer survivors and their non-cancer comparisons. These findings indicate that occupational rehabilitation and (re)integration programs for young cancer survivors should be strengthened, in order to empower them to make use of their full potential, and facilitate their contributions to society and in the work force.

We found a more than two-fold increased risk of suicides in the cancer survivors, both when diagnosed in childhood and as AYAs, and this risk persisted for a long time after cancer diagnosis. We found no difference in the risk of non-suicidal external deaths (like road accidents, accidental poisonings). A potential increased suicide risk should be considered when developing long-term follow-up guidelines for CCS and AYACs, but our findings need confirmation in subsequent, and preferably even larger, studies.

The Norwegian Directorate of Health commissioned a working group in 2010 with the mandate of determining which groups of cancer patients should systematically be followed after completion of therapy and suggest models of care, with regards to late effects. The report issued included a small section on survivors of childhood cancer. Establishing multi-disciplinary regional late-effect clinics to coordinate follow-up for this growing at-risk adult population was recommended[205]. Despite this, in 2016, there are still no governmental initiatives towards the systematic establishment of such follow-up clinics. Late-effects clinics are already established in the other Nordic countries, but Norway is lagging behind in this initiative. I hope my findings in this thesis can be used to identifying some of the areas where follow-up care is needed, and that I will be able to continue working towards adequate long-term follow-up care for this growing proportion of our adult population.

7. Reference list

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

M W Gunnes*,[1,2], R T Lie[1,3], T Bjørge[1,4], S Ghaderi[3], E Ruud[5], A Syse[6] and D Moster[1,2,3]

[1]Department of Global Public Health and Primary Care, University of Bergen, Postboks 7804, Bergen 5018, Norway; [2]Department of Pediatrics, Haukeland University Hospital, Bergen 5021, Norway; [3]Norwegian Institute of Public Health, Bergen 5018, Norway; [4]Cancer Registry of Norway, Oslo 0304, Norway; [5]Department of Pediatric Medicine, Oslo University Hospital, Oslo 0424, Norway and [6]Department of Research, Statistics Norway, Oslo 0033, Norway

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).

*Correspondence: Dr MW Gunnes; E-mail: maria.gunnes@uib.no

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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
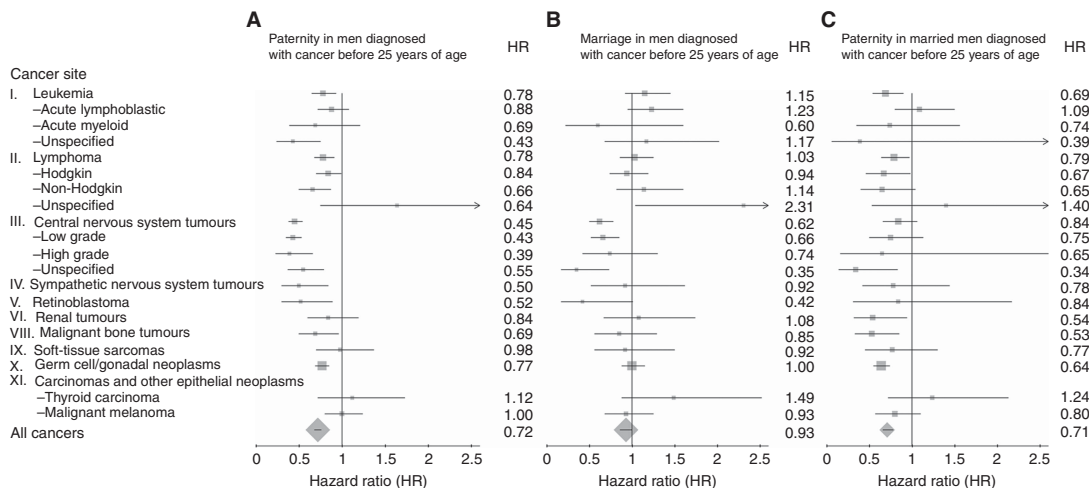

Figure 1. Forest plot of hazard ratios for paternity and marriage. (A) Hazard ratios (HRs) with 95% CIs of fathering a first offspring after cancer diagnosis, for all cancer survivors ($n = 2605$, secondary malignancies excluded), subdivided into different cancer diagnoses, with the non-cancer male population 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

Diagnostic group[a]	Age at diagnosis			Calendar year of diagnosis			
	Number (% of total number in age category)			Number (% of total number in diagnostic period)			
	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 off-spring 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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)

	Cancer	Non-cancer	Pearson Chi-Square (2-sided)
Supplementary Table . Pregnancies derived from assisted reproductive technology (ART) in partners of 1,087 male cancer survivors and partners of 368,469 male non-cancer references, and relative risk of intracytoplasmic sperm injection in relation to other methods			
Total number of first pregnancies from ART (total number of first offspring)	80 (1,087)	8,278 (368,469)	
Offspring outcomes Number (% of ART offspring):			
▪ Perinatal death	0 (0)	162 (2)	p=0.21
▪ Congenital malformations	3 (4)	488 (6)	p=0.42
▪ Prematurity (22-36 weeks of gestation)	9 (11)	1,278 (15)	p=0.32
▪ Low birth weight (500-2499 grams)	9 (11)	1,213 (15)	p=0.39
▪ Birth plurality			
○ Single births	66 (83)	6,794 (82)	
○ Twin births	14 (18)	1,453 (18)	
○ Triplet births	0 (0)	30 (0.4)	
			Relative Risk[b] (95% Confidence Interval)
Method of ART Number (% of ART offspring):			
▪ In vitro fertilization (IVF)	24 (30)	3,217 (39)	1.51(1.25-1.81)
▪ Intracytoplasmic sperm injection (ICSI)[a]	47 (59)	4,612 (56)	
▪ Combination	2 (3)	86 (1)	
▪ Unspecified	7 (9)	363 (4)	

[a]Of the 47 first offspring of cancer survivors conceived by ICSI, the fathers' cancer diagnoses were lymphoma (8), central nervous system tumors (8), gonadal/germ cell tumors (21), as well as leukemia, neuroblastoma, renal tumor, malignant bone tumor, soft tissue sarcoma, thyroid carcinoma and malignant melanoma (all <5 cases).
[b]Relative risk with 95% confidence interval for ICSI as method of ART versus IVF/combination/unspecified.

II

Original Article

Economic Independence in Survivors of Cancer Diagnosed at a Young Age: A Norwegian National Cohort Study

Maria W. Gunnes, MD[1,2]; Rolv Terje Lie, PhD[1,3]; Tone Bjørge, PhD, MD[1,4]; Astri Syse, PhD[5]; Ellen Ruud, PhD, MD[6,7]; Finn Wesenberg, PhD, MD[4,6,7]; and Dag Moster, PhD, MD[1,2,3]

BACKGROUND: The impact of cancer on socioeconomic outcomes is attracting attention as the number of survivors of cancer in young age continues to rise. This study examines economic independence in a national cohort of survivors of cancer at a young age in Norway. **METHODS:** Through the linkage of several national registries, the study cohort comprised 1,212,013 individuals born in Norway during 1965 through 1985, of which 5440 had received a cancer diagnosis before age 25 years. Follow-up was through 2007, and the main outcomes were receipt of governmental financial assistance, employment, income, and occupation. Analytic methods included Cox proportional hazard regression, log-binomial regression, and quantile regression models. **RESULTS:** Individuals in the cancer survivor group had an increased probability of receiving governmental financial assistance (men: hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.3-1.5; women: HR, 1.5; 95% CI, 1.3-1.6) and of not being employed (men: HR, 1.4; 95% CI, 1.2-1.7; women: HR, 1.4; 95% CI, 1.2-1.6) compared with those in the noncancer group. Income discrepancies were particularly pronounced for survivors of central nervous system tumors. There was no difference in representation in higher skilled occupations. **CONCLUSIONS:** Survivors of cancer at a young age in Norway had an increased risk of being economically dependent and unemployed. This was evident in several tumor groups and was most pronounced in female survivors. There were only small differences in income or representation in higher skilled occupations for most employed survivors compared with the noncancer group. The current results are important for understanding the impact of a cancer diagnosis at a young age on subsequent job market outcomes. *Cancer* 2016;122:3873-82. © 2016 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: adolescent, cancer, childhood, cohort studies, employment, income, occupations, socioeconomic factors, survivors, young adult.

INTRODUCTION

During the last 4 decades, the treatment of cancer in young individuals has improved substantially and has led to an expanding number of survivors in the adult population.[1] As many as two-thirds of these cancer survivors suffer from a variety of late effects and chronic conditions, possibly affecting their ability to fully participate in the job market.[1,2]

Previous studies have demonstrated that subgroups of childhood cancer survivors (CCS) (typically ages birth to 14 years, and sometimes up to age 20 years, at diagnosis) have an increased risk of being unemployed, earning low incomes, and receiving social security benefits compared with their siblings or the general population.[3-5] However, there are important discrepancies regarding the vocational and financial outcomes of cancer survivors who are diagnosed at a young age in Europe and the United States. In a meta-analysis, the unemployment risk among CCS in the United States is found to be tripled, but the results from European studies diverged.[3,4,6,7] Reports from the Childhood Cancer Survivor Study in the United States indicate that CCS have reduced personal incomes and a higher representation in lower skilled jobs compared with their siblings as well as an increased risk of unemployment, particularly for survivors of brain and bone tumors and in those diagnosed before age 4 years.[7,8] Previous Nordic studies of cancer survivors revealed only modest reductions in income compared with siblings or the cancer-free general population, but those studies are limited because they included only selected cancer diagnoses, or cancers diagnosed at all ages, or childhood cancers only.[4,6,9] A recent Swiss study indicated that CCS have lower monthly incomes compared with their siblings, but it did not assess occupation or

compensatory financial assistance (FA) measures and was questionnaire based; therefore, it may have been subject to response bias.[10] The enrollment in governmental supplemental security income and disability insurance programs is increased for CCS in both Norway and the United States.[5,11] The total impact of a cancer diagnosis during the vulnerable developmental period of childhood, adolescence, and young adulthood on later economic independence largely has been unexplored.

Survivors of cancers diagnosed in adolescence and young adulthood (typically ages 15-29 years, and sometimes up to age 39 years, at cancer diagnosis) are faced with particular survivorship challenges, because their diagnoses and treatments occur in a different psychosocial and biologic context from those in survivors who are diagnosed at younger or older ages.[12] However, most research in this population originates from publications in which adolescents and young adults (AYAs) are only a small percentage of the much larger adult survivor group, and comparison groups often are limited.

The developmental period of adolescence and young adulthood poses unique challenges, and important information regarding economic and work-related matters in AYA cancer survivors is currently lacking.[12-14] This is a time when individuals seek independence from their parents and develop autonomy through relationship building with peers and through making important, often permanent decisions regarding higher education and pursuits of a prospective career. It is also a time of continuous physiologic development, including maturation of the prefrontal cortex, which is important for executive functions and the implementation of goal-oriented behaviors.[14,15] Disruptions to this brittle process may lead to unfavorable decision making that could have long-lasting implications. Having to cope with a life-threatening cancer diagnosis during adolescence and young adulthood is a potent intrusion during this already challenging phase of life, and AYAs with cancer report financial difficulties, disruptions in social relationships, and employment challenges, especially when they are diagnosed during early adolescence and young adulthood.[15,16] Therefore, it is of utmost importance to study the work-related outcomes in this group and to develop targeted interventions, including vocational rehabilitation programs, for future AYA cancer survivors.

AYA cancer survivors are difficult to track in a clinic-based setting because of a combination of high mobility (relocating to study/work), treatment and follow-up at both pediatric and adult cancer departments, and often a reduced interest and/or lack of opportunity to participate in follow-up care programs.[13] Thus there is a need for large, population-based studies with national coverage, including noncancer comparisons, to address the full impact of economic late effects in CCS and AYA cancer survivor populations. Such studies may aid in the development of risk-based follow-up strategies (including interventions) during the transition into and passage through adulthood. The objective of the current study was investigate economic independence by studying employment, occupation, income, and the need of governmental FA in a large, population-based Norwegian cohort of cancer survivors who were diagnosed before age 25 years.

MATERIALS AND METHODS

The study cohort included all individuals born alive in Norway during 1965 through 1985 identified through the national registry. Patients with cancer were identified through the Cancer Registry of Norway (CRN) (exclusions were made if a cancer diagnosis was made by autopsy only or if the basis for the cancer diagnosis was uncertain). Follow-up was through 2007, at which time the cohort members had reached ages 22 to 42 years. The term "cancer survivor" in our study comprises all individuals who had a cancer diagnosis before age 25 years.

Data Sources

We linked several national registries in Norway using the unique 11-digit personal identification number assigned to every resident. The national registry contains updated demographic information on all residents in Norway.[17] Reporting newly diagnosed cancer cases to the CRN has been compulsory for all clinicians and pathologists since 1951. The quality and completeness of CRN data have been identified as high, in line with other Western European cancer registries.[18,19] The CRN provides information on cancer cases, including date of diagnosis, cancer site, and tumor morphology.[19] Information on demographics, FA, income, employment, and disability pensions (DPs) was provided by Statistics Norway.[20,21] Data on education were provided by the Norwegian National Education Database.[22]

Study Outcomes

Governmental FA is a benefit available to all legal residents of Norway. It is intended as a temporary measure when all other means of self-support have been exhausted and is independent of prior work history and other social security benefits.[23] The local Labor and Welfare Service (NAV) office makes a monthly individual assessment on the amount needed for necessary subsistence costs.

For information on income and employment in 2007, only "work-related income" was used, which includes income from work only (employed or self-employed), and not income from social security benefits (including DPs). This includes any degree of work-related income. Thus all individuals with some form of employment are included in the income analyses, and those with no income are excluded. For the analysis on employment, we defined unemployment as not having registered a work-related income in 2007. To qualify for a DP in Norway, an individual's earning capacity has to be permanently reduced by at least 50% because of illness and/or injury, and vocational rehabilitation measures have to be completed.

To analyze fields of occupation, we used the occupational codes according to the International Standard Classification of Occupations (ISCO-88), which reflect the skill level required for the occupation category.[24] Occupation was classified into 4 categories; "unskilled" (ISCO group 9), "semiskilled blue collar" (ISCO groups 6-8; agriculture, craft, machine operators), "semiskilled white collar" (ISCO groups 4 and 5; clerks, service, and sales), and "skilled" (ISCO groups 1-3; managers, professionals, and technicians), in accordance with recent European Union classification standards.[25]

Statistical Analyses

For the outcome of governmental FA, an extended Cox regression model was applied to the whole cohort, with age at cancer diagnosis as the time-dependent variable, yielding hazard ratios (HRs) with 95% confidence intervals (CIs). This method was chosen to fully take advantage of the prospective nature of the data and to account for the changes in hazard rates during the course of follow-up. The follow-up for this analysis started at age 18 years (parents are obliged by law to sustain their children until that age) and ended at the date of the first occasion an individual received FA, censoring at the date of death, emigration, or December 31, 2007, whichever occurred first.

To analyze income and employment, a cross-sectional analysis for those who were alive and living in Norway in 2007 was performed using binomial logistic regression and quantile regression models, yielding relative risks (RRs) with 95% CIs and regression coefficients with P values, respectively, comparing the cancer survivors with the cancer-free group. High income was defined as income >80th percentile of that for all individuals born in the same year and with the same sex, and low income was defined correspondingly as income <20th percentile. After testing for interaction, separate analyses of male and female survivors were con-

ducted, conforming to recommendations for studies on labor market outcomes in cancer survivors.[26]

To study occupational fields, multinomial logistic regression was applied using "skilled" as the reference category, yielding RR ratios (RRR) with 95% CIs. Linear regression analysis of differences in income within the occupational categories was performed (after the exclusion of outliers).

Cancer survivors were further categorized into major cancer groups (leukemia, lymphoma, central nervous system [CNS] tumors, testicular tumors, malignant melanoma, bone and soft tissue sarcomas, cancers of the female genital tract [cervix/uterus/ovarian], and "other"). Survivors also were classified into CCS (those aged < 15 years at cancer diagnosis) and AYAs (ages 15-24 years at cancer diagnosis). Analyses were adjusted for year of birth and for parental education (the highest education achieved by both parents) divided into 3 categories—lower education (<11 years), intermediate education (11-14 years), and tertiary education (>14 years)—to account for differences in household socioeconomic status as a possible confounder.[27] Marital status was included as a mediator in early analyses but was not included in the final model, because the estimates produced were similar, and adjusting for this variable could have introduced collider-stratification bias.

We wanted to determine the impact of a cancer diagnosis on survivors who were healthy enough to work; thus, we excluded DP recipients from all analyses except for the analysis on FA, for which the results with and without DP recipients are presented.

SPSS version 21 (IBM SPSS, Armonk, NY) and STATA version 14 (StataCorp LP, College Station, Tex) were used for statistical analyses. The study was approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics of Western Norway.

RESULTS

In total, 1,218,013 individuals were born in Norway during 1965 through 1985. Of these individuals, 5440 were diagnosed with cancer before age 25 years and were included in the FA analysis. After the exclusion of those who emigrated (n = 34,840; 1.3% of the cancer survivor group, 2.9% of the noncancer control group), died (n = 34,774), were lost to follow-up (n = 719; all in the noncancer group), and were missing residential code (n = 1226; all in the noncancer group), 1146,444 individuals were alive and still living in Norway in 2007, including 3945 cancer survivors (2170 men and 1775 women). Approximately 40% of those survivors were diagnosed as children, and the

TABLE 1. Characteristics of Cancer Survivors by Cancer Site Stratified by Sex, Age, and Period of Cancer Diagnosis

	No. (%)				
	Age at Cancer Diagnosis				
	0-14 Years		15-24 Years		
Cancer Site[a]	Men	Women	Men	Women	Total
Leukemia	343 (28.8)	290 (30.7)	128 (6.8)	84 (5.9)	845 (15.5)
Lymphoma	122 (10.2)	57 (6)	313 (16.8)	229 (16)	721 (13.3)
CNS tumors	321 (26.9)	222 (23.5)	272 (14.6)	259 (18.1)	1074 (19.7)
Testicular cancer	43 (3.6)		695 (37.2)		738 (13.6)
Malignant melanoma	14 (1.2)	25 (2.6)	117 (6.2)	323 (22.5)	479 (8.8)
Bone and soft tissue tumors	110 (9.2)	111 (11.7)	169 (9.1)	105 (7.3)	495 (9.1)
Female genital tract tumors		25 (2.6)		143 (10)	168 (3.1)
Other	240 (20.1)	216 (22.8)	174 (9.3)	290 (20.2)	920 (16.9)
All cancer	1193 (100)	946 (100)	1868 (100)	1433 (100)	5440 (100)

Abbreviation: CNS, central nervous system.
[a] Cancer sites are based on *International Classification of Diseases* (7th edition) site codes and on *Manual of Tumor Nomenclature and Coding* and *International Classification of Diseases for Oncology* (2nd edition) morphology codes.

TABLE 2. Hazard Ratios and 95% Confidence Intervals for Receipt of Governmental Financial Assistance in Cancer Survivors, by Cancer Site and Age at Diagnosis, Compared With Cancer-Free Individuals

		Men			Women		
		HR (95% CI)			HR (95% CI)		
Cancer Site[a]	No. of FA Recipients	Model 1[b]	Model 2[c]	Mean Age at FA, y	Model 1[b]	Model 2[c]	Mean age at FA, y
Noncancer	239,996	Reference	Reference	23.1	Reference	Reference	23.1
Leukemia	134	1.24 (0.95-1.60)	1.15 (0.86-1.53)	22.6	1.72 (1.34-2.21)	1.62 (1.23-2.12)	21.1
Lymphoma	181	1.43 (1.13-1.80)	1.37 (1.07-1.75)	22.4	2.12 (1.68-2.70)	2.02 (1.57-2.62)	21.9
CNS tumors	245	1.74 (1.20-1.80)	1.13 (0.85-1.49)	22.8	1.71 (1.40-2.08)	1.48 (1.15-1.91)	22.4
Testicular cancer	156	1.27 (1.05-1.54)	1.27 (1.04-1.56)	22.3			
Malignant melanoma	73	1.14 (0.71-1.83)	1.20 (0.73-1.95)	24.2	0.63 (0.44-0.90)	0.65 (0.45-0.95)	23.1
Bone/soft tissue tumors	99	1.79 (1.36-2.36)	1.62 (1.18-2.22)	22.7	1.63 (1.20-2.20)	1.52 (1.08-1.24)	23.1
Female genital tract tumors	44				1.45 (0.99-2.11)	1.29 (0.84-1.98)	23.4
Other	168	1.36 (1.05-1.75)	1.24 (0.94-1.65)	23.5	1.28 (1.03-1.60)	1.28 (1.01-1.63)	22.6
All cancer	1100	1.38 (1.26-1.51)	1.27 (1.14-1.41)	22.7	1.45 (1.32-1.60)	1.36 (1.22-1.52)	22.4
Age at cancer diagnosis, y							
<15	310	1.16 (1.00-1.36)	0.98 (0.81-1.18)	22.8	1.23 (1.05-1.45)	1.09 (0.90-1.32)	22.1
15-24	790	1.53 (1.36-1.72)	1.46 (1.29-1.66)	22.7	1.61 (1.43-1.82)	1.54 (1.35-1.76)	22.5

Abbreviations: CI, confidence interval; HR, hazard ratio; CNS, central nervous system; FA, financial assistance.
[a] Cancer sites are based on *International Classification of Diseases* (7th edition) site codes and on *Manual of Tumor Nomenclature and Coding* and *International Classification of Diseases for Oncology* (2nd edition) morphology codes.
[b] Those who were receiving disability pensions were included (adjusted for year of birth and parental education).
[c] Those who were receiving disability pensions were excluded (adjusted for year of birth and parental education).

remaining were diagnosed as AYAs (Table 1). The largest cancer site groups were CNS tumors (20%), leukemia (16%), testicular cancer (14%), and lymphoma (13%).

FA

For all cancers combined, there was an increased risk of receiving governmental FA for both male and female survi-

vors (men: HR, 1.4; 95% CI, 1.3-1.5; women: HR, 1.5; 95% CI, 1.3-1.6) (Table 2). Excluding individuals who were receiving a DP (n = 33,408) yielded smaller but nonetheless significantly increased risks (Table 2). In particular, survivors of leukemia (women), lymphoma, CNS tumors, testicular cancer (men), and bone and soft tissue sarcomas were at increased risk of receiving FA, whereas

TABLE 3. Relative Risks and 95% Confidence Intervals for Unemployment in Cancer Survivors, by Cancer Site and Age at Diagnosis, Compared With Cancer-Free Individuals

	Men		Women	
Cancer Site[a]	No. Unemployed/Total No. (% Not Employed)[b]	RR (95% CI)	No. Unemployed/Total No. (% Not Employed)[b]	RR (95% CI)
Noncancer	25,009/570,080 (4.4)	1.00 (Ref)	33,982/543,580 (6.3)	1.00 (Ref)
Leukemia	6/221 (2.7)	0.63 (0.29-1.39)	17/204 (8.3)	1.42 (0.90-2.23)
Lymphoma	17/334 (5.1)	1.19 (0.76-1.90)	23/222 (10.4)	1.72 (1.18-2.51)
CNS tumors	20/286 (7)	1.60 (1.06-2.44)	36/281 (12.8)	2.11 (1.56-2.86)
Testicular cancer	43/644 (6.7)	1.59 (1.19-2.12)		
Malignant melanoma	5/106 (4.7)	1.19 (0.50-2.80)	13/303 (4.3)	0.75 (0.44-1.27)
Bone/soft tissue tumors	12/152 (7.9)	1.84 (1.07-3.16)	10/122 (8.2)	1.33 (0.73-2.41)
Female genital tract tumors			12/130 (9.2)	1.49 (0.87-2.53)
Other	18/270 (6.7)	1.64 (1.05-2.55)	23/356 (6.5)	0.97 (0.64-1.49)
All cancers	121/2013 (6)	1.42 (1.20-1.69)	134/1618 (8.3)	1.36 (1.16-1.61)
Age at cancer diagnosis, y				
<15	40/621 (6.4)	1.38 (1.12-1.71)	47/517 (9.1)	1.53 (1.16-2.01)
15-24	81/1392 (5.8)	1.51 (1.12-2.04)	87/1101 (7.9)	1.30 (1.06-1.59)

Abbreviations: CI, confidence interval; CNS, central nervous system; Ref, reference category; RR, relative risk.
[a] Cancer sites are based on *International Classification of Diseases* (7th edition) site codes and on *Manual of Tumor Nomenclature and Coding* and *International Classification of Diseases for Oncology* (2nd edition) morphology codes.
[b] Those who were receiving disability pensions were excluded (adjusted for year of birth and parental education).

female survivors of malignant melanoma had a reduced risk (Table 2). The mean age at the first receipt of FA was 23.1 years for the noncancer controls and 22.6 years for the cancer survivors ($P < .001$). The mean age was similar when survivors were stratified by sex, age at diagnosis, and cancer type (Table 2). When we reran the models censoring the individuals who had received a cancer diagnosis after age 25 years, the results were similar.

Employment

Cancer survivors had a 34% increased risk of not being employed (HR, 1.3; 95% CI, 1.2-1.5) compared with cancer-free individuals, and the results were similar separately for men and women (Table 3). There was a significantly increased risk of unemployment among survivors of lymphoma (women), CNS tumors (both sexes), testicular cancer, and bone and soft tissue cancer (men), regardless of age at diagnosis.

Income

The median income for the male CCS in the cohort was 366,369 Norwegian kroner (NOK) (equivalent to $62,283 US dollars [USD], according to the annual conversion rate of 0.17 in 2007[28]). For men in the noncancer comparison group, the median income was 379,794 NOK ($64,565 USD). For female cancer survivors, the median income was 259,088 NOK ($44,045 USD) compared with 272,077 NOK ($46,253 USD) in the cancer-free female comparison group (Table 4). In general, the cancer survivors had lower median incomes

than individuals in the noncancer comparison group (Fig. 1), although the difference was not statistically significant (men, $P = .07$; women, $P = .28$). Survivors of CNS tumors had significantly reduced incomes across all quantiles (data not shown) and an increased risk of being in the low-income category versus cancer-free controls with the same birth year and sex (men: RR, 1.3; 95% CI, 1.1-1.6; women: RR, 1.4; 95% CI, 1.1-1.7) (Table 4). In the female survivor group, there was also an increased risk of low income for survivors of lymphoma (HR, 1.4; 95% CI, 1.1-1.7) and an increased probability of high income (and higher annual salaries across all quantiles) for survivors of malignant melanoma (HR, 1.3; 95% CI, 1.1-1.6). The median income was significantly reduced for male survivors who were diagnosed in childhood (<15 years of age) and, to a lesser degree, for AYA cancer survivors (Table 4). Adjustment for parental education did not change the estimates significantly.

Occupation

The largest occupational category for both cancer survivors and cancer-free controls was "skilled" (legislators, managers, professionals, technicians, and associate professionals), amounting to 49% and 48% in the 2 groups, respectively. By using this occupational category as reference, the cancer survivors were less likely to be in the employment category "semiskilled blue collar" (both sexes) (Table 5). An analysis by cancer site revealed a particularly low probability for this occupational category in the survivors of bone and soft tissue cancer (men) and

TABLE 4. Work-Related Income in Cancer Survivors, by Cancer Site and Age at Diagnosis, Compared With Cancer-Free Individuals

Variable	No. of Individuals[a]	Median Income, NOK[b]	P[c]	RR (95% CI)	
				Low Income[d]	High Income[e]
Men					
Noncancer	543,788	379,794	Ref	1.00 (Ref)	1.00 (Ref)
All cancer	1884	366,369	.07	1.06 (0.98-1.16)	0.92 (0.84-1.01)
Cancer site[f]					
Leukemia	215	350,265	.72	1.11 (0.86-1.43)	0.83 (0.62-1.12)
Lymphoma	317	368,100	.34	1.08 (0.88-1.34)	1.00 (0.80-1.25)
CNS tumors	263	326,066	.01	1.33 (1.09-1.63)	0.71 (0.53-0.96)
Testicular cancer	598	378,767	.92	0.92 (0.77-1.09)	0.95 (0.80-1.12)
Malignant melanoma	99	397,139	.38	0.83 (0.53-1.30)	1.08 (0.75-1.56)
Bone/soft tissue tumors	140	372,795	.40	1.18 (0.88-1.59)	0.94 (0.67-1.32)
Other	252	362,391	.35	1.07 (0.84-1.36)	1.02 (0.80-1.31)
Age at cancer diagnosis. y					
<15	580	339,523	<.01	1.19 (1.03-1.38)	0.85 (0.71-1.02)
15-24	1304	378,934	.64	1.01 (0.90-1.13)	0.95 (0.85-1.06)
Women					
Noncancer	508,288	272,077	Ref	1.00 (Ref)	1.00 (Ref)
All cancer	1479	259,088	.28	1.20 (1.09-1.31)	0.94 (0.85-1.05)
Cancer site[f]					
Leukemia	186	242,797	.96	1.07 (0.81-1.41)	0.75 (0.53-1·05)
Lymphoma	197	249,060	.47	1.38 (1.10-1.74)	0.74 (0.53-1,03)
CNS tumors	244	222,414	.03	1.38 (1.12-1.69)	0.81 (0.61-1.08)
Malignant melanoma	290	300,786	.03	0.93 (0.73-1.19)	1.34 (1.12-1.61)
Bone/soft tissue tumors	112	261,811	.90	1.35 (0.99-1.83)	0.85 (0.56-1.28)
Female genital tract tumors	118	276,719	.86	1.27 (0.94-1.73)	0.95 (0.66-1.39)
Other	332	254,212	.05	1.18 (0.96-1.45)	0.95 (0.75-1.20)
Age at cancer diagnosis, y					
<15	469	243,655	.17	1.18 (1.00-1.39)	0.76 (0.62-0.94)
15-24	1010	268,911	.80	1.21 (1.08-1.35)	1.03 (0.91-1.16)

Abbreviations: CI, confidence interval; CNS, central nervous system; NOK = Norwegian kroner; Ref, reference category; RR, relative risk.

[a] Those who were receiving disability pensions were excluded.

[b] The conversion rate in 2007 was 1 NOK = $0.17 US dollar.

[c] P values are for differences in median income with cancer-free individuals as the reference group (adjusted for year of birth and parental education).

[d] Low income was defined as less than the 20th percentile of work-related income in 2007 by year of birth and sex (adjusted for parental education).

[e] High income was defined as greater than the 80th percentile of work-related income in 2007 by year of birth and sex (adjusted for parental education).

[f] Cancer sites are based on *International Classification of Diseases* (7th edition) site codes and on *Manual of Tumor Nomenclature and Coding* and *International Classification of Diseases for Oncology* (2nd edition) morphology codes.

malignant melanoma (men). There was no significant difference in occupational categories for survivors of CNS tumors (data not shown) compared with the cancer-free reference group. Analyzing within-group differences in income for the 4 occupational categories, the median annual salary was significantly reduced for male cancer survivors in the "skilled" occupational category (a reduction of 16,447 NOK [$2796 USD]), but no differences were observed for women or for either sex in the other 3 categories (Table 5).

DISCUSSION

We observed that CCS and AYA cancer survivors were at an increased risk of being financially dependent, as demonstrated by a 4-fold to 5-fold increased risk of receiving FA from the government as well as an increased risk of not being employed. Unfavorable outcomes were particularly prevalent in survivors of CNS tumors, lymphoma, and bone/soft tissue sarcomas; whereas survivors of malignant melanoma in general fared better. For the cancer survivors holding jobs, incomes were only slightly reduced compared with those in the cancer-free reference group. The occupational fields were similar in the cancer survivors and the cancer-free group, although cancer survivors were represented less in manual labor occupations. Furthermore, the median incomes within the occupational categories were largely comparable.

The increased risk of receiving FA was more pronounced in female cancer survivors and in survivors of certain cancer sites. The threshold to apply for governmental financial support may be lower for cancer survivors, and applications may be more easily approved for individuals who have a history of a cancer diagnosis. Receipt of FA also could be because of a desire not to

work full-time, or the inability to work full-time, thus requiring supplemental income sources.[29,30] However, it is important to keep in mind that FA is a temporary measure and does not suggest long-term financial dependency. Nonetheless, the increased use of financial assistance suggests that the economic flexibility of young cancer survivors is not optimal in Norway. Because FA is an uncertain and temporary compensatory measure, other measures probably would be more appropriate for this group if their long-term health and welfare is to be secured.
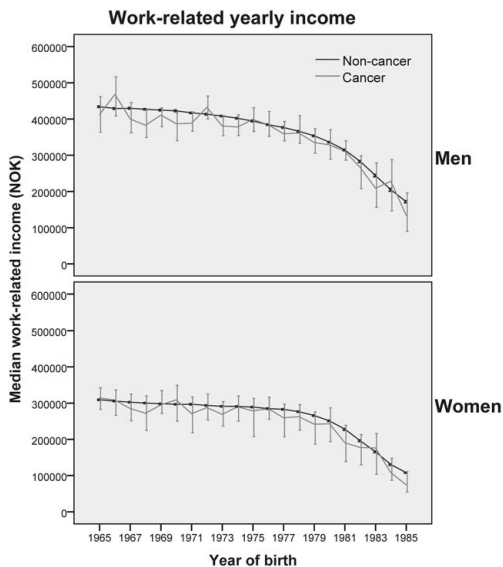
Figure 1. The median annual work-related income in 2007 (in Norwegian kroner [NOK]; conversion rate, 1 NOK = $0.17 US dollars), with 95% confidence intervals, is illustrated according to birth year stratified by sex and cancer.

Our finding of increased unemployment for CCS and AYA cancer survivors correlates well with some previous publications on this topic.[3,6,7,9,31] Studies from the United States have indicated that poor physical health, and particularly neurocognitive deficits, is strongly associated with unemployment, and US studies have demonstrated an overall 3-fold increased risk of unemployment in CCS.[3,29] Certain important differences were observed when we compared our results with those from a Swedish study in which there was no significant association between a previous cancer diagnosis (at age < 16 years) and not being employed.[4] The different results may be because we also included AYA cancer survivors in our study. In addition, we had no information regarding students, and the Swedish study excluded individuals who were aged <25 years at follow-up, leaving out a group particularly vulnerable to unemployment.[32]

Only a few studies have investigated income inequalities and occupational differences between survivors of cancer diagnosed at a young age and the general population.[4,6,9] In our study, we examined differences not only in the median income but the whole range of income quantiles. For the most part, our results were reassuring, although cancer survivors did have slightly lower earnings compared with individuals in the noncancer group. This may be a matter of survivors choosing to work reduced hours, but it may also reflect reduced working capacity because of chronic medical conditions in the survivor group. Unfortunately, data were not available on hours worked per week; however, because of strict work discrimination laws in Norway, the most likely explanation for the reduced income among the cancer survivors is reduced working hours. We observed reduced representation in manual labor occupations in the cancer group and only slight within-group differences in income. This is in contrast to US studies, in which CCS (ages 0-19 years at

TABLE 5. Relative Risk Ratios for Occupational Category and Income Differences in Cancer Survivors Compared With Cancer-Free Individuals

Employment Category/ ISCO Group	No. (% Employed in Occupational Category)		RRR for Occupational Category (95% CI)[a]		P for Income Differences[b]	
	Noncancer Controls	Cancer Survivors	Men	Women	Men	Women
Unskilled/ISCO 9	35,508 (3.9)	109 (3.7)	0.73 (0.54-0.97)	0.84 (0.60-1.18)	.68	.92
Semiskilled blue collar/ISCO 6-8	167,814 (18.3)	531 (18)	0.88 (0.78-0.99)	0.59 (0.40-0.87)	.65	.25
Semiskilled white collar/ISCO 4 and 5	276,584 (30.2)	879 (29.7)	0.94 (0.82-1.08)	0.95 (0.84-1.08)	.86	.50
Skilled/ISCO 1-3	437,331 (47.7)	1438 (49)	1.00 (Ref)	1.00 (Ref)	.02	.08

Abbreviations: CI, confidence interval; ISCO, International Standard Classification of Occupation; Ref, reference category; RRR, relative risk ratio.
[a] Analyses were adjusted for year of birth and parental education.
[b] P values are for income differences within occupational categories for cancer survivors compared with noncancer controls (adjusted for year of birth and parental education).

diagnosis) were more often employed in lower skilled jobs than their siblings and had lower personal incomes within the different occupational categories.[8,29] Those studies also indicated that neurocognitive limitations, mainly as a result of cranial irradiation, are associated with employment in lower skilled jobs. This discrepancy between previous US studies and the current analysis from Norway may reflect the separation of health insurance and employment within the Norwegian system and that education is available free of charge in Norway, therefore a history of cancer does not restrict access to higher education or higher skilled occupations.

In this study, we particularly observed indications of economic dependency in survivors of lymphoma (especially women), CNS tumors, and bone and soft tissue sarcomas. Multiple publications have reported that survivors of CNS tumors suffer from adverse medical late effects, especially those who received CNS irradiation during childhood, and fall behind during education and in job market participation.[2,4,33-36] Lymphoma survivors (especially Hodgkin lymphoma) reportedly also are at increased risk of adverse long-term outcomes, particularly heart failure (because of the widespread use of irradiation until the mid-1990s) as well as secondary malignancies.[37] These late effects are likely to influence the outcomes measured in the current study. Regarding survivors of bone cancer, although surgical techniques have improved dramatically since the 1970s, musculoskeletal morbidity is still increased, which may explain the poor work-related outcomes in this group.[2,38] The fortunate economic outcomes of melanoma survivors in our study are probably linked to pre-existing socioeconomic status before cancer diagnosis, because previous research has demonstrated that increased incidence is associated with higher socioeconomic class.[39] In addition, melanomas in children and AYAs most frequently present as localized lesions, are treated only by surgery, and have an excellent prognosis.[40]

An altered association to working life may negatively affect an individual's integrity, life satisfaction, and social relationships. For individuals who are diagnosed with cancer during adolescence and young adulthood, when primary developmental tasks such as identity development, seeking independence from parents, and exploring educational and occupational paths, this may be particularly pronounced. The return to (or maintenance of) school or work for CCS and AYAs is vital if a cancer survivor is to become independent and self-sustained as an adult.[31] It has been demonstrated that vocational training and job assistance measures are associated with an increased odds of employment after cancer in AYAs.[41] Therefore, identifying subgroups of CCS and AYA cancer survivors who are at risk of low job market participation is important to implement vocational rehabilitation services early for individuals in the more vulnerable survivor groups (lymphoma, CNS tumors, and bone/soft tissue sarcomas). Accounting for future education and employment within the treatment setting has also been identified as a key issue by AYA survivors along with the availability of counseling and FA.[12]

Strengths of this national cohort study include coverage of an entire population, without selection or recall bias, as well as minimal loss to follow-up. Our inclusion of AYA cancer survivors provides important information on the socioeconomic outcomes in this survivor group, which is currently lacking. Challenges unique to AYA cancer survivors include increased mobility (and, consequently, increased loss to follow-up), not wanting to partake in follow-up care or studies, and failure to take responsibility for their own health care.[13] Limitations of the study include the lack of individual treatment data, which could allow for more precise correlation of different treatment exposures with economic outcomes, as well as the lack of information on the study participants' work preferences or hours worked per week. Information on student status also was not available, and this may have an effect on our outcomes, particularly for the youngest members of our cohort. Previous research has indicated that CCS have a delay in educational accomplishments, although the final educational achievements (at least in Europe) seem to be comparable to those in controls.[35,36] In our cohort, 18% did not have an occupational code. Within the Norwegian registry system, this means that they could be students, self-employed, or unemployed.

Knowledge of the possible disadvantageous effects after cancer in childhood, adolescence, or young adulthood on labor market outcomes and subsequent income is vital if authorities are to appropriately target subgroups in need of counseling and interventions. Norway is an egalitarian society with public health care and strongly enforced antidiscrimination laws. Public welfare interventions, such as work reintegration programs and more permanent compensation for reductions in earnings directed specifically toward CCS, may be warranted.

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CONFLICT OF INTEREST DISCLOSURES

AUTHOR CONTRIBUTIONS

Maria W. Gunnes: Responsible for the overall article content; contributed to the conception, design, analysis, and interpretation of the data; and drafted and revised previous and final versions of the article. **Rolv Terje Lie**: Contributed to the design, analysis, and interpretation of the data; revised the article, including final approval; and was accountable for all aspects of the work. **Tone Bjørge**: Contributed to the study conception and design; revised the article, including final approval, and was accountable for all aspects of the work. **Astri Syse**: Contributed to analysis and interpretation of the data; revised the article, including final approval; and was accountable for all aspects of the work. **Ellen Ruud**: Contributed to the study conception and design; revised the article, including final approval; and was accountable for all aspects of the work. **Finn Wesenberg**: Contributed to the study conception and design; revised the article, including final approval; and was accountable for all aspects of the work. **Dag Moster**: Contributed to the design, analysis, and interpretation of the data; revised the article, including, final approval; and was accountable for all aspects of the work.

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Suicide and violent deaths in survivors of cancer in childhood, adolescence and young adulthood—A national cohort study

Maria W. Gunnes[1,2], Rolv T. Lie[1,3], Tone Bjørge[1,4], Sara Ghaderi[3], Astri Syse[5], Ellen Ruud[6,7], Finn Wesenberg[4,6,7] and Dag Moster[1,2]

[1] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[2] Department of Pediatrics, Haukeland University Hospital, Bergen, Norway
[3] Norwegian Institute of Public Health, Bergen, Norway
[4] Cancer Registry of Norway, Oslo, Norway
[5] Department of Research, Statistics Norway, Oslo, Norway
[6] Department of Pediatric Medicine, Oslo University Hospital, Norway
[7] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway

Suicide risk in adult cancer patients is found to be elevated, but limited information exists regarding risks of suicide and non-suicidal violent deaths when diagnosed with cancer in young age. We investigate suicide and violent deaths in a national cohort including individuals diagnosed with cancer before age 25. Through the linkage of different national registries (Cancer Registry of Norway, Norwegian Causes of Death Registry and the National Registry) a cohort of all live births in Norway during 1965–1985 was defined and followed up through 2008. Individuals diagnosed with cancer before age 25 and the cancer-free references were compared using an extended Cox proportional hazard regression model. The cohort comprised 1,218,013 individuals, including 5,440 diagnosed with cancer before age 25. We identified 24 suicides and 14 non-suicidal violent deaths in the cancer group. The hazard ratio (HR) of suicide in the cancer group was 2.5 (95% confidence interval (CI) 1.7–3.8), and was increased both when diagnosed with cancer in childhood (0–14 years of age); HR = 2.3 (95% CI: 1.2–4.6), and during adolescence/young adulthood (15–24 years); HR = 2.6 (95% CI: 1.5–4.2). Survivors of bone/soft tissue sarcomas, CNS tumors and testicular cancer were at particular risk. The risk of non-suicidal violent death was not increased in the cancer survivors (HR = 1.0; 95% CI: 0.6–1.7). Although based on small numbers and the absolute risk of suicide being low, these are novel findings with important implications for establishing adequate follow-up including suicide prevention strategies for young cancer survivors.

Improved survival after cancer in young age has led to an increased attention towards the long-term medical and psychological well-being of these survivors. In developed countries, suicide and violent deaths are the most common causes of death in the 15–30 age group.[1–3] Hence, it is important to

define at-risk individuals or groups, in order to develop appropriate prevention strategies.

The risk of suicide in cancer patients (regardless of age at diagnosis), is found to be increased, and especially during the first year after diagnosis.[4–7] However, large prospective studies of suicide risk in childhood and adolescent/young adult (AYA) cancer survivors are lacking, and risk estimates are not necessarily transferable to this age group. One Swedish study of cancer survivors diagnosed between 15 and 30 years of age found a 1.6-fold increase in risk of suicidal behavior (completed suicide and suicide attempts combined).[8] Previous studies of late mortality (all causes) in childhood cancer survivor (CCS) populations (surviving >5 years from diagnosis) have not found an increase in the risk of death from external causes or suicide, except for a recent publication from the British Childhood Cancer Survivor Study, where a standardized mortality ratio (SMR) of 1.2 [95% confidence interval (CI) 1.1–1.4] for (all) external causes of death was found.[9–13] Suicidal ideation, however, appear to be increased in CCS, at least in a selected, US population.[14,15]

Since both cancer in young age and suicide are infrequent events, large population-based studies are needed for investigating a possible association. Suicide is a definite event, and

What's new?
The onset of cancer at a young age profoundly affects psychological health and potentially increases the risk of death by suicide. Little is known, however, about the extent of suicidal behavior exhibited by childhood, adolescent and young adult cancer survivors. Using national registry data, the authors of the present study examined suicides and violent deaths in cancer patients diagnosed before age 25, finding that suicide risk is increased more than two-fold for cancer survivors diagnosed before age 15 and for those diagnosed during adolescence/young adulthood (15–24 years). Suicide screening and prevention efforts may be necessary components of follow-up care in these patient populations.

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may serve as the ultimate surrogate marker of the burden of late- and long-term effects after cancer in young age. The aim of the current study was to investigate, through a prospective design, the risk of suicide and violent deaths in a population-based cohort including survivors diagnosed with cancer before the age of 25 in Norway.

Material and Methods
Our cohort consisted of all individuals born in Norway from 1965 to 1985, identified by the National Registry and followed through 2008 (age 23–43 years at end of follow-up).[16] Information on cancer diagnoses before the age of 25 (including date of diagnosis, primary site and morphology) was supplied by the Cancer Registry of Norway (CRN), and information on cause of death was provided by the Norwegian Cause of Death Registry.[17] Quality assessments have found the data from both the CRN and the Norwegian Causes of Death registry to be of high quality.[17,18] Cancer was categorized into major cancer sites according to International Classification of Diseases (ICD)-7, ICD for oncology (ICD-O-2), and Manual of Tumor Nomenclature and Coding (MOTNAC).[18] External causes of death were identified by diagnostic codes in the ICD 8–10, as registered on the death certificate (Supporting Information Table S1).[19,20] Information on emigration and marital status was provided by the National Registry, on disability pension by the Norwegian Labour and Welfare Service and on parental education by the Norwegian National Education Database. Precise record linkage was made possible by a unique personal identification number, assigned to all residents in Norway since 1960.

Statistical Analyses
An extended Cox proportional hazards method was applied, with age at cancer diagnosis as the time-varying covariate, yielding hazard ratios (HRs) with 95% confidence intervals (CIs). This method was chosen in order to fully take advantage of the prospective nature of our data, to allow change in status of the classifying event (cancer) during follow-up, avoiding immortal-time bias,[21] and thus maintaining full statistical power. The cohort member changed follow-up strata from non-cancer to cancer at the time of cancer diagnosis, and thereby contributed their observation time to the non-cancer (non-exposed) group prior to their cancer diagnosis. Analyses were adjusted for year of birth and parental education (highest educational level achieved by either the mother or father of each cohort member) in order to control for preexisting differences in socioeconomic status. We did not include intermediary variables such as marital status or disability pension in the final Cox regression model, since these variables are down-stream in the causal pathway, and adjustment might lead to overadjustment bias.[22] Stratified analyses for these variables are precluded by small numbers, and interaction analyses revealed nonsignificant results. For basic characteristic differences, we used independent t test, chi-squared test or Fishers exact test, as appropriate.

Follow-up started at birth for suicide as the outcome (due to some suicides occurring in the age group 8–14 years), and at age 15 years for the outcome of non-suicidal violent (external) causes of death. Follow-up ended at death by suicide or other external causes, death by other causes, emigration or December 31st 2008, whichever occurred first. The term cancer survivor in this study comprises all individuals in the cohort diagnosed with cancer before 25 years of age.[23] SPSS version 23 (IBM Corp, Armonk, NY, USA) and STATA version 14 (StataCorp 2015, College Station, TX, USA) were used for statistical analyses. The study was approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics of Western Norway.

Results
Of the 1,218,013 individuals in our cohort, 5,440 were diagnosed with cancer before the age of 25. Among the individuals diagnosed with cancer, there were 24 suicides, compared with 3,375 in the cancer-free reference population (Table 1). There was no significant difference regarding disability pension status ($p = 0.06$), marital status ($p = 0.74$), suicide methods ($p = 0.60$), or sex ($p = 1.00$) between cancer survivors committing suicide and the non-cancer comparisons (Table 2). The cancer survivors were slightly older at suicide (mean age 28.0 years) compared to the non-cancer references (mean age 25.1 years, $p = 0.03$). Death by external causes (other than suicide) was recorded in 14 individuals in the cancer group and 6,690 in the non-cancer comparisons (Table 1). Six of the cancer patients who completed suicide were diagnosed during 1965–1979, 16 during 1980–1994 and two during 1995–2007. The suicides in the cancer group were completed at a range of 6–497 months from cancer diagnosis

Table 1. Suicide and non-suicidal external deaths in 5,440 cancer individuals compared with 1,212,573 individuals in the cancer-free reference group

External cause of death[1]:	Non-cancer Number of deaths	Cancer Number of deaths	HR[2] (95% CI)
Suicide	3,375	24	2.5 (1.7–3.8)
Accidental deaths (all):	6,690	15	
Transport accidents	3,635	6	0.7 (0.3–1.7)
Fire	238	0	
Accidental drowning	969	2	2.0 (0.5–7.9)
Accidental falls	346	1	1.3 (0.2–9.1)
Accidental poisoning	1,502	6	1.7 (0.8–3.8)
Homicide	280	0	
Events of undetermined intent	49	0	
All external causes of death (suicide included)	10,394	39	1.6 (1.2–2.2)
All external causes of death (suicide excluded)	7,019	15	1.0 (0.6–1.7)

Abbreviations: HR = Hazard ratio; CI = Confidence interval.
[1]Classified according to Supporting Information Table.
[2]Risk of specified external cause of death in cancer survivors compared to the non-cancer references.

Table 2. Basic characteristics of individuals committing suicide in the cancer group and non-cancer comparisons

	Non-cancer	Cancer	p values for difference between cancer and non-cancer[1]
No of suicides (total number of deaths)	3,375 (29,008)	24 (1,403)	0.03
Age at death (years, mean +/- SD)	25.1 (6.7)	28.0 (7.6)	0.03
Sex			1.00
Male (total) (%)	2,637 (78)	19 (79)	
Female (total) (%)	738 (22)	5 (21)	
Marital status (total) (%)			0.74
Married	348 (10)	3 (13)	
Unmarried	2,375 (70)	18 (75)	
Missing	652 (20)	3 (13)	
Disability pension (total) (%)			0.06
Yes	215 (6)	4 (17)	
No	3,160 (94)	20 (83)	
Suicide mechanism (total)	3,375	24	0.60

[1]By independent *t* test, chi-squared, or Fishers exact test, as appropriate.

(median 146 months; 10th percentile 18 months, 90th percentile 387 months), and 2/24 (8.3%) within the first year of diagnosis (Fig. 1). None of the cancer survivors committing suicide were receiving disability pension on the background of a diagnosis of depression or anxiety at the time of suicide.

There was more than twofold increased risk of death by suicide in the cancer survivors compared to the cancer-free references (HR = 2.5; 95% CI: 1.7–3.8) (Table 1). The risk of death by all external causes was significantly increased in the cancer survivor population when including suicide (HR = 1.6; 95% CI: 1.2–2.2) but not when analyzing external causes excluding suicide (HR = 1.0; 95% CI: 0.6–1.7). Assessing specific external causes of death, we found no significant

difference in the risk for any of these (except suicide) between the cancer group and the non-cancer references (Table 1). When analyzing the risk of suicide stratified by sex, the estimates were similar, although reaching statistical significance for men only (HR = 2.4; 95% CI: 1.6–3.8). The risk of suicide was increased both when diagnosed with cancer before age 15 years (childhood cancer survivors (CCS)), HR = 2.3; 95% CI: 1.2–4.6, and between age 15 and 24 years (adolescent and young adult (AYA) cancer survivors), HR = 2.6; 95% CI: 1.5–4.1 (Table 3). The suicide risk was increased particularly for survivors of central nervous system (CNS) tumors (HR = 3.9; 95% CI: 1.9–8.3), testicular cancer (HR = 2.9; 95% CI: 1.3–6.4), leukemia (HR = 3.3; 95% CI:
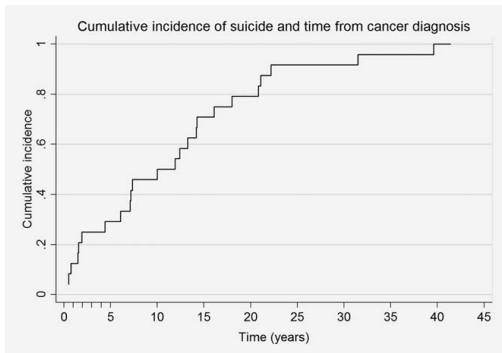
Cumulative incidence of suicide and time from cancer diagnosis

Figure 1. Cumulative incidence of suicide in the cancer group, and time (in years) from cancer diagnosis to suicide.

Table 3. Hazard ratio (HR) with 95% confidence interval (CI) for suicide stratified by cancer site and age at diagnosis compared to the cancer-free references

Cancer site	No. of suicides (total no of individuals)	HR (95% CI)
Non-cancer	3,375 (1,212,573)	Ref
All cancer	24 (5,440)	2.5 (1.7–3.8)
Leukemia	4 (845)	3.3 (1.3–8.9)
Lymphoma	2 (721)	1.5 (0.4–5.9)
Central nervous system tumors	7 (1,074)	3.9 (1.9–8.3)
Testicular cancer	6 (738)	2.9 (1.3–6.4)
Malignant melanoma	0 (479)	
Bone and soft tissue sarcomas	3 (495)	8.2 (2.6–25.5)
Female genital tract tumors	0 (167)	
Other	2 (921)	3.7 (0.5–26.5)
Age at diagnosis		
0–14 years	9 (2,139)	2.30 (1.15–4.60)
15–24 years	15 (3,301)	2.55 (1.54–4.14)

1.3–8.9) and bone/soft tissue sarcomas (HR = 8.2; 95% CI: 2.6–25.5), although each category was based on small numbers (Table 3).

Discussion

In this population-based study of all residents born in Norway over a 20-year period, we found a more than twofold increased risk of suicide in persons diagnosed with cancer before age 25, when compared to cancer-free references. The risk of violent death (suicide excluded) was not increased.

We propose alternative explanations for the deviating results on suicide risk found in the current study compared to previous late-mortality studies.[9–12] First, our data are of high quality as we utilize national registries with a uniform recording of all completed suicides within the whole source population, while the aforementioned studies compared suicide rates among cancer survivors with expected rates based on official statistics. Second, our cohort study included also AYA cancer survivors), and third, our analyses were not restricted to 5-year survivors. By using a Cox model (with a time-varying covariate) we take full advantage of the prospective nature of our data, and are able to estimate unrestricted and unbiased suicide risks among the cancer survivors.

We also wanted to study external causes of death other than suicide, since there are some publications stating disadvantageous behavior related to alcohol and drug use in CCS, which we hypothesized could lead to an increased risk of violent (external) deaths (accidental poisoning, road traffic accident, drowning).[24,25] Our results do not provide any support for this, based on the risk estimates of non-suicidal violent deaths, although death naturally measures the most extreme outcome possibly resulting from this behavior. We also wanted to study non-suicidal external deaths since there is a possibility that a small number of suicides might be misclassified as accidental deaths.[26,27]

In our material, survivors of bone/soft tissue sarcomas, brain tumors, leukemia and testicular cancer were particularly vulnerable to suicide. Seven individuals with a brain tumor committed suicide, none of whom had a high grade tumor (according to the WHO classification of tumors of the central nervous system[28]). This is consistent with studies from the US reporting increased suicidal ideation in survivors of brain tumors, and in particular low-grade tumors followed by observation or treated by surgery alone.[14,29] In a large Norwegian study, Hem et al also found significantly increased risk of suicide in individuals with brain tumors (all ages).[5] Our results suggest that increased vigilance should be applied not primarily to survivors of high grade brain tumors and those most heavily treated, but also to survivors with low-grade tumors, treated by one modality or observation only. However, these results need confirmation in further studies.

An increased suicide risk in patients with testicular cancer was found in a recent publication, especially when diagnosed at a young age (<30 years), which corresponds well with our study.[30] In contrast, the previously mentioned Norwegian study did not find increased risk of suicide in testicular cancer patients.[5] This discrepancy is probably due to the different age distribution in the previous Norwegian study and ours. Neither did the Swedish study by Lu et al find an increased risk of suicide behavior in testicular cancer patients, but a direct comparison to our study is difficult as the Swedish study did not differentiate between suicide attempts and completed suicides.[8] There are recent reports of increased psychological distress, impaired health-related quality of life and increased prevalence of chronic fatigue in survivors of testicular cancer, which are factors that might be associated with suicide risk.[31,32]

Previous studies have demonstrated a particularly high suicide risk within the first year following a cancer diagnosis.[5,7,8] In our material, the time between diagnosis and suicide varied from 6 to 497 months, and the median time from cancer diagnosis to suicide was 250 and 86 months for childhood and AYA survivors respectively. Only two suicides occurred within the first year after diagnosis, both in the AYA group. This might be explained by different (and largely unknown) underlying factors leading to suicide in young compared to older cancer patients.

Weaknesses of our study include a lack of information on suicide attempts or suicide ideation, and information on comorbidity was only available for somatic or psychiatric disease severe enough to qualify for disability pension. Access to Supporting Information could have given a more complete understanding of the underlying mechanisms of the increased suicide risk and how better to identify survivors at risk. Another weakness is the lack of treatment data, which could have provided a clearer insight into the possible association between specific treatment exposures and suicide. Further studies are therefore needed to confirm the findings of this study, both through large, population-based studies, and also through other study designs with access to complete treatment data.

Strengths of our study include the prospective cohort and national registry design, virtually eliminating inclusion- and selection bias, and ensuring complete follow-up. In addition, all cancer diagnoses are represented in the current study, analyses were not restricted to 5-year survivors and we also studied non-suicidal violent deaths. Despite studying very rare outcomes, and thereby analyzing small numbers, there are, to our knowledge, no population-based cohort studies on suicide and violent deaths in larger populations of CCS and AYA cancer survivors currently available.

This study present novel information on a heightened suicide risk in individuals diagnosed with cancer in childhood, adolescence and young adulthood in Norway, which might be generalizable to other countries with similar social structures and cancer treatment programs. Survivors of low grade brain tumors and testicular cancer seem particularly vulnerable. The absolute risk of suicide, however, was low both for the cancer survivors and for the cancer-free references. The risk factors for suicide in young age are complex and involve a spectrum of different underlying mechanisms and vulnerabilities, including adverse childhood experiences, chronic medical conditions and certain personality factors. In epidemiological studies of suicide risks, such as the current one, information on many of these risk factors is not available. Once a heightened suicide risk is demonstrated, the ultimate goal is to implement suicide prevention strategies tailored for the group at risk. Our findings complement existing knowledge on the long-term well-being of survivors of cancer in young age. Until further studies have confirmed specific at-risk groups within the increasing number of survivors of cancer in young age, the perspective of suicide prevention should be considered in developing long term follow-up guidelines for this survivor group as a whole.

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Supplementary table. Classification of external causes of death in the Norwegian Cause of Death Registry.

Cause of death	ICD-10 (1996-)	ICD-9 (1986-95)	ICD-8 (1969-85)
External causes of injury and poisoning (overall)	V01- Y89	E800-E999	E800-E999
Suicide	**X60-X84, Y87.0**	**E950-E959**	
i. Hanging/strangulation/suffocation	X70	E953	
ii. Submersion (drowning)	X71	E954	
iii. Poisoning (by solids/liquids/gases)	X60-X69	E950-E952	
iv. Firearms/guns/explosives	X70-X75	E955	
v. Jumping from a high place	X80	E957	
vi. Sharp object (cutting/piercing)	X77	E956	
vii. Other/unspecific	X84	E958	
Accidents	**V01-X59, Y85**	**E800-E929**	
i. Transport accidents (including road traffic accidents)	V01-V99, Y85	E800-E848	E800-E845
ii. Fire accidents	X00-X09	E890-E899	E890-E899
iii. Accidental drowning	V90, V92, W65-74	E830, E832, E910	E830, E832, E910
iv. Accidental falls	W00-W19	E880-E888	E880-E887
v. Accidental poisoning	X40-X49	E850-E869	E850-E877
Homicide	**X85-Y09**	**E960-E969**	**E960-E969**
Events of undetermined intent	**Y10-Y34**	**E980-E989**	**E980-E989**

Abbreviations: ICD=International Classification of Diseases; 8th-10th revisions.