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LATE EFFECTS OF CANCER AT A YOUNG AGE

**Registry-Based Studies of the Health of Cancer Patients
and Their Offspring**

by

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To my family

Cure is not enough.

Cover: watercolour painting by Hanna Yritys, 2002.

ABSTRACT

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Late effects of cancer at a young age: Registry-based studies of the health of cancer patients and their offspring

The Department of Paediatrics, Turku University Hospital, University of Turku, Turku, Finland and the Finnish Cancer Registry, Helsinki, Finland.
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Modern cancer therapy has resulted in increased survival among patients diagnosed with cancer at a young age. These improvements have led to the investigation of late morbidity and mortality associated with cancer and its treatments. The aim of this study was to evaluate late effects of cancer treated at a young age on the health of patients and their offspring.

Utilising the nationwide population-based registries in Finland, we evaluated the risk of hypothyroidism and the probability of parenthood in cancer survivors as well as preterm birth, neonatal outcomes, and the risk of cancer among offspring of patients. The survivor cohort, identified from the Finnish Cancer Registry, consisted of 25,784 cancer patients diagnosed between ages 0 and 34 in 1953–2004. By linkage to the population register, siblings of these patients were identified for comparison.

The prevalence of hypothyroidism was higher among former paediatric cancer patients (aged 0–16) than in the general population. The probability of parenthood following early onset cancer was overall significantly reduced compared to siblings.

Offspring of female cancer survivors were at an increased risk of preterm birth, this risk being highest among patients diagnosed in childhood (aged 0–14 years) and early adulthood (aged 20–34 years). The offspring were not, however, at a significantly increased risk of neonatal death or stillbirth, though they were more likely to need monitoring or intensive care in the neonatal period. The risk of sporadic cancer among offspring of male and female cancer survivors was not elevated in comparison to the general population.

The study showed that former cancer patients are at risk of certain adverse endocrine and reproductive health outcomes and should be followed for timely intervention. The offspring of cancer survivors do not; however, appear to be at an increase risk of cancer or early mortality compared to the offspring of siblings.

Keywords: cancer, health, hypothyroidism, late effects, offspring, parenthood, preterm delivery, registry-based.

TIIVISTELMÄ

Laura-Maria Madanat-Harjuoja

Nuoruusiässä sairastetun syövän myöhäisvaikutuksia potilailla ja heidän jälkeläisillään

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Annales Universitatis Turkuensis, Medica-Odontologica, 2011, Turku

Nykyaikaisten hoitojen ansiosta suuri osa nuorena syöpään sairastuneista paranee ja sen takia hoitojen pitkäaikaisvaikutuksiin on alettu kiinnittää yhä enemmän huomiota. Tämän tutkimuksen tarkoituksena oli arvioida nuoruusiässä hoidetun syövän myöhäisvaikutuksia ja lisäksi näiden potilaiden lasten terveyttä.

Hyödyntäen Suomen kattavia väestöpohjaisia rekistereitä, tutkimme kilpirauhasen vajaatoiminnan esiintyvyyttä ja lastensaannin todennäköisyyttä syöpähoitojen jälkeen sekä potilaiden lasten ennenaikaisuuden vaaraa, vastasyntyneisyyskauden terveyttä ja myöhempää syöpävaaraa. Tutkimuskohorttimme muodostui 25 784:stä vuosina 1953–2004 alle 35 vuotiaana syöpään sairastuneesta potilaasta. Potilaiden sisarukset saatiin vertailua varten väestörekisteristä.

Kilpirauhasen vajaatoiminnan esiintyvyys oli suurentunut alle 16 vuotiaana syöpään sairastuneilla väestöön verrattuna. Kaiken kaikkiaan, nuoruusiän syövästä toipuneet saivat lapsia merkitsevästi harvemmin kuin heidän sisaruksensa.

Naispotilaiden lapsilla todettiin suurentunut ennenaikaisuuden vaara. Vaara oli korkein lapsuudessa (0–14 vuotiaana) ja nuorella aikuisiällä (20–34 vuotiaana) syöpään sairastuneiden lapsilla. Lasten varhaiskuolleisuus tai kuolleena syntymisen vaara eivät poikenneet tilastollisesti merkitsevästi sisarusten lasten vaarasta. Vastasyntyneisyyskauden tehostetun valvonnan tarve oli kuitenkin suurentunut verrattuna sisarusten lapsiin. Syöpäpotilaiden lasten syöpävaara oli satunnaisten syöpien osalta samaa luokkaa kuin väestöllä yleensä.

Nuoruusiän syövästä selviytyneillä esiintyy umpieritysjärjestelmään ja lisääntymisterveyteen liittyviä myöhäisvaikutuksia, joiden vuoksi heitä tulisi seurata. Potilaiden lapsilla ei kuintakaan ole kohonnutta syöpävaaraa eikä imeväisiän kuolleisuus ole koholla sisarusten lapsiin verrattuna.

Avainsanat: Ennenaikaisuus, jälkeläiset, kilpirauhasen vajaatoiminta, lisääntymisterveys, myöhäisvaikutukset, rekisteritutkimus, syöpä, terveys, vastasyntynyt.

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ABBREVIATIONS

ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
AC	Adriamycin, cyclophosphamide
ACTH	Adrenocorticotropic hormone
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ASR	Age-standardised rate
CCSS	Childhood Cancer Survivor Study
CDR	Cause-of-Death Register
ChIVPP	Chlorambucil, vinblastine, procarbazine, prednisolone
CI	Confidence interval
CMF	Cyclophosphamide, methotrexate, fluorouracil
CNS	Central nervous system
COPP	Cyclophosphamide, vincristine, procarbazine, prednisolone
CPR	Central Population Register
DRR	Drug Reimbursement Register
FCR	Finnish Cancer Registry
FEC	Fluorouracil, epirubicin, cyclophosphamide
FSH	Follicle-stimulating hormone
FUP	Follow-up
GCCT	Genetic Consequences of Cancer Treatment
GH	Growth hormone
GHD	Growth hormone deficiency
GI	Gastrointestinal
Gy	Gray
HL	Hodgkin's lymphoma
HP	Hypothalamo-pituitary
HR	Hazard ratio
HRT	Hormone replacement therapy
HT	Hypothyroidism

ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
LBW	Low birth weight
LH	Luteinising hormone
MACOP-B	Methotrexate, adriamycin, cyclophosphamide, vincristine, prednisolone, bleomycin
MBR	Medical Birth Register
MOPP	Mechlorethamine, vincristine, procarbazine, prednisolone
MVPP	Mechlorethamine, vinblastine, procarbazine, prednisolone
NHL	Non-Hodgkin lymphoma
OR	Odds ratio
PIC	Personal identity code
PR	Drug Purchase Register
PY	Person-years
SD	Standard deviation
SGA	Small-for-gestational-age
SIDS	Sudden infant death syndrome
SII	Social Insurance Institution
SIR	Standardised incidence ratio
SMN	Second malignant neoplasm
STAKES	National Research and Development Centre for Welfare and Health
TBI	Total-body irradiation
THL	National Institute for Health and Welfare
TSH	Thyroid-stimulating hormone
VACOP-B	Vepesid, adriamycin, cyclophosphamide, vincristine, prednisolone, bleomycin
WT	Wilms' tumour

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their respective Roman numerals:

- I. Madanat LM, Lähteenmäki PM, Hurme S, Dyba T, Salmi TT, Sankila R. Hypothyroidism among pediatric cancer patients: A nationwide, registry-based study. *International Journal of Cancer* 2008; 122(8): 1868–1872.
- II. Madanat LM, Malila N, Dyba T, Hakulinen T, Sankila R, Boice JD Jr, Lähteenmäki PM. Probability of parenthood after early onset cancer: A population-based study. *International Journal of Cancer* 2008; 123(12): 2891–2898.
- III. Madanat-Harjuoja LM, Malila N, Lähteenmäki PM, Boice JD Jr, Gissler M, Dyba T. Preterm delivery among female survivors of childhood, adolescent and young adulthood cancer. *International Journal of Cancer* 2010; 127(7): 1669–1679.
- IV. Madanat-Harjuoja LM, Lähteenmäki PM, Dyba T, Gissler M, Boice JD Jr, Malila N. Early death, stillbirth and neonatal morbidity among offspring of female cancer survivors. Submitted.
- V. Madanat-Harjuoja LM, Malila N, Lähteenmäki PM, Pukkala E, Mulvihill JJ, Boice JD Jr, Sankila R. Risk of cancer among children of cancer patients— a nationwide study in Finland. *International Journal of Cancer* 2010; 126(5): 1196–1205.

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1. INTRODUCTION

Development of cancer treatments, especially chemotherapy, since the 1970s has resulted in increased survival of childhood cancer patients (Pritchard-Jones et al. 2006). Continued advances in strategies of early detection and development of effective treatments have also resulted in improvement in survival among those diagnosed in adolescence and young adulthood, albeit to a lesser extent (Bleyer et al. 2006a; Gatta et al. 2009). According to recent estimates, the five-year survival rate has become as great as 81% in children (0–14 years) and 87% in adolescents and young adults (15–24 years) (Gatta et al. 2009). Each year, approximately 150 children are diagnosed with cancer in Finland (Finnish Cancer Registry 2007). The incidence of childhood cancer in Finland has remained quite stable over the years, with the annual age-standardised incidence rate in 1988–1997 being 173.2 per million (Stiller et al. 2006a). According to data from the Finnish Cancer Registry, approximately 5,000 of the Finnish adult population in 2008 were former childhood and adolescent cancer patients (Finnish Cancer Registry; R. Sankila, personal communication).

As an increasing number of patients survive cancer at an early age, there is heightened recognition of the need for critical evaluation of the consequences of the curative treatments given. Late effects of treatment may manifest as impaired physical, cognitive or psychosocial functioning of a survivor. Approximately two thirds of childhood cancer survivors will experience at least one late effect, and approximately one third will experience a severe or life-threatening late effect (Bhatia et al. 2009).

Because of the young age of these cancer survivors and their potential longevity, any consequences of treatment can be expected to have a significant impact on their lives. Research is necessary to allow for detection of any adverse effects of constantly developing and changing protocols (Leisenring et al. 2009).

Late effects research provides the foundation for risk-based treatments, planning of comprehensive follow-up and creation of appropriate clinical guidelines for follow-up care. Ideally, survivorship research can lead to identification of high-risk populations and, thus, provide the basis for risk-based surveillance (Hudson et al. 2009). Though survival is the primary goal in the treatment of young cancer patients, curative treatments must be weighed against late effects experienced by survivors. Patients may thus benefit from late-effects research in the future as regimens and protocols may be modified to minimise toxicity and maximise efficacy of treatment.

As cancer survival improves, the focus on quality-of-life issues increases (Aaronson et al. 1991; Gotay et al. 1992). Ultimately, the aim of late-effects research is to allow cancer survivors the opportunity for a normal life, decreasing the morbidity related to cancer treatment and improving the overall quality of life such that young cancer survivors can become integrated into society and lead productive lives.

This doctoral thesis was initiated to investigate the long-term effects of cancer and its treatment on the health of survivors of early onset cancer and their offspring. Special focus was placed on thyroid effects and reproductive health after cancer. Reproductive outcomes included parenthood and preterm delivery. Neonatal morbidity and early mortality as well as cancer were explored in the offspring of cancer survivors. The registry-based approach applied in our study is unique in late-effects research.

2. REVIEW OF THE LITERATURE

2.1 Measures of occurrence of disease

Occurrence of disease, in statistical terms the probability of an event, can be expressed in several ways. In cohort studies, where a defined population is followed up for an event over a given period of time, occurrence of disease can be measured through calculation of its prevalence or incidence. Prevalence is defined as the number of cases (old and new) existing at one defined point in time (e.g. the end of follow-up)(dos Santos Silva 1999). Incidence, on the other hand, is a measure of the number of new cases of disease that develop in a population of individuals at risk within a specified time interval.

Three measures of incidence can be calculated: risk, odds of disease and incidence rate (dos Santos Silva 1999). Risk is the probability that an event will occur and is calculated as the proportion of people in a population who are initially free of disease and then develop the disease within a specified time period, while the odds of disease are calculated as the total number of cases divided by the total number of persons who remained disease-free over the study period ie. the ratio of probability of occurrence of an event to that of nonoccurrence. Calculation of both odds and risk assume that the entire population at risk at the beginning of the study period has been followed up during the specified time period. Incidence rate, which expresses the rate at which new cases occur in a population, takes into account the fact that some participants may enter the study some time after it begins and some are lost to follow-up, or die from other causes of death than the disease under study, by calculating the number of new cases per person-years at risk. Incidence rate can also be expressed as an age-standardised rate. Age standardisation is a procedure used for adjusting e.g., incidence rates, designed to minimise the effects of differences in age composition when comparing rates for different populations (Last 2001). Hazard rate is a measure of the likelihood that an event occurs at a certain time-point and can be calculated using e.g., proportional hazard models.

A ratio (odds ratio, risk ratio, hazard ratio, or standardised incidence ratio) is used to express the incidence in one population relative to another (often the exposed population compared to the unexposed or general population). An odds ratio, therefore, is calculated as the odds of an event among the exposed divided by the odds of an event in the unexposed. A standardised incidence ratio is the ratio of the incident number of cases of a specified condition in the study population to the incident number that would be expected if the study population had the same incidence rate as a standard or other population for which the incidence rate is known (Last 2001).

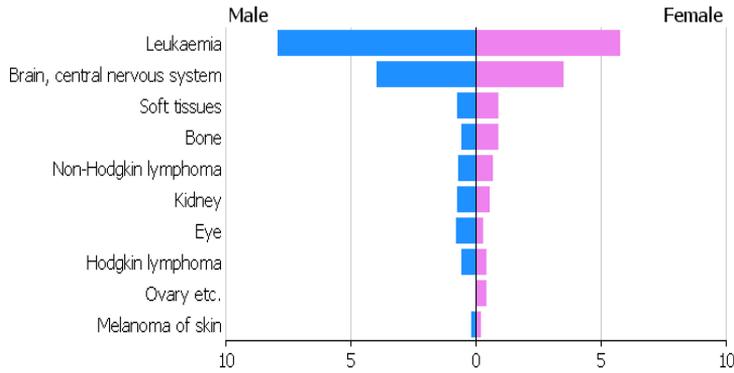
2.2 Malignant disease in childhood: Incidence and survival

In childhood, defined in the context of oncology as birth to 14 years, cancer is rare, accounting for 0.75% of all cancers, with approximately 150 cases diagnosed annually in Finland (**Fig. 1**). There is a male preponderance, boys being 10–25% more likely than girls to be diagnosed with cancer (Bleyer et al. 2006a).

The most common malignant diseases in childhood are acute leukaemia (approximately 30%); central nervous system tumors (approximately 30%); and a group of miscellaneous tumours, consisting most commonly of lymphomas and embryonal solid tumours (nephroblastomas and neuroblastomas).

The prognosis of childhood cancer has improved dramatically over the past 30 years. Today, five-year survival for all cancers combined reaches 81% in this age-group (Gatta et al. 2009). In the Nordic countries, survival rates are among the highest in the world and reached 77% in 1997 (Magnani et al. 2006; Sankila et al. 2006). Survival has increased most among leukaemia and lymphoma patients, at up to 85% in acute lymphoblastic leukaemia (ALL) and 95% in Hodgkin's lymphoma (HL). For acute myeloid leukemia (AML) in the Nordic countries survival is 55% (Magnani et al. 2006) and with most recent protocols reaches even 65% (Lie et al. 2005). In Europe, five-year survival in central nervous system (CNS) cancer is 63%, with small variation by morphology. Survival of retinoblastoma patients is excellent, at 98%, as is the case for nephroblastoma patients (89%). For other solid tumours, survival decreases in the order osteosarcoma (77%), neuroblastoma (72%), rhabdomyosarcoma (69%), and Ewing sarcoma (67%) (Gatta et al. 2009). Finnish survival figures (**Figs. 2A and 2B**) largely follow the prevailing pattern in the Nordic countries. In Europe, the relative mortality for all cancers combined fell significantly among children, by eight per cent from 1995–1999 to 2000–2002. By sub-site, the most significant reductions were seen in mortality from acute lymphoblastic leukaemia and CNS cancers (Gatta et al. 2009).

Finland, Incidence (2008)
ASR (World) age (0-14)



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Figure 1. Incidence of the 10 most common malignancies among girls and boys diagnosed at 0–14 years of age. ASR = Age-standardised rate, using the world population as a standard

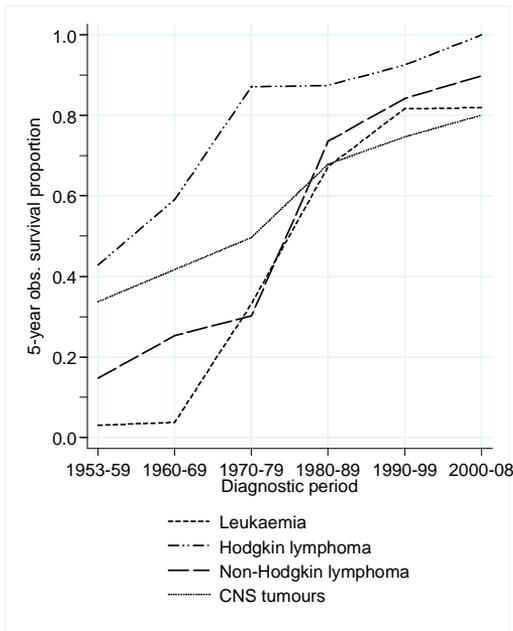


Figure 2A. Five-year observed (obs.) survival proportion by diagnostic era for childhood leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and CNS tumour patients.

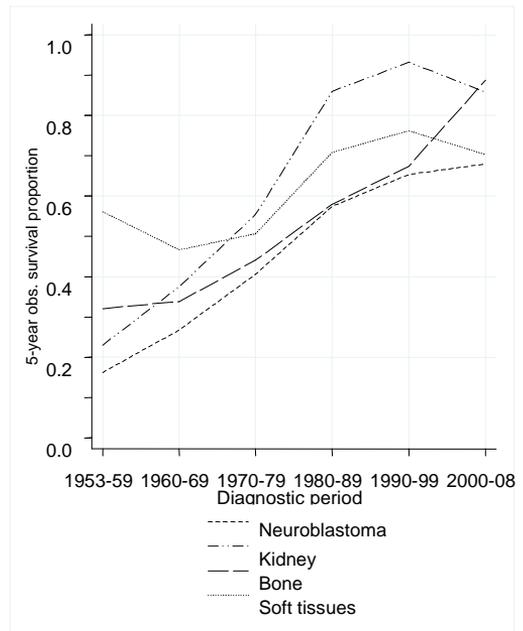


Figure 2B. Five-year observed (obs.) survival proportion by diagnostic era for neuroblastoma, nephroblastoma, and bone and soft tissue tumours in childhood.

Based on data derived from the main database of the Finnish Cancer Registry

2.3 Malignant disease in adolescence and young adulthood: Incidence and survival

Cancer in adolescence, established within the context of oncology as the age range 15–19 years (Barr 1999), accounts for fewer than 0.3% of all cancer cases occurring in Europe (Eucan 1999), with approximately 70 cases diagnosed annually in Finland. Incidence among males is 1.2 times that among females. Cancer incidence among adolescents increased at an annual rate of two per cent in the period 1978–1997 (Stiller et al. 2006b).

The common malignant diseases of childhood are replaced in relative frequency, among adolescents, by sarcomas of the bone and soft tissue and tumours of the male and female genital tract (**Fig. 3A**). Moreover, although in lower frequencies, epithelial tumours, so prevalent in adults, constitute one third of all cancers in adolescents (Barr 2007).

In adolescents and young adults, incidence of Hodgkin's lymphoma increases (Macmahon 1957). The incidence of leukaemia, however, is lower than in children and young adults, with less prognostically favourable biological features (Barr 2007). The relative frequency of ALL and AML also exhibits a transition in adolescents, as the ratio of ALL to AML is less than in childhood. The most common malignancies in this age-group are lymphomas (26%), central nervous system tumours (10%), leukaemias (10%), tumours of the thyroid gland (9%), and malignant melanoma (8%), followed by male (8%) and female (8%) genital system tumours and bone and joint tumours (8%) (Bleyer et al. 2006b). Although thyroid cancer is the second most common malignancy among adolescent female patients, tumours arising in the endocrine system are otherwise rare in this age-group (Franks et al. 1997). Uncommon in childhood, testicular cancer is the most common malignancy in adolescent males and the frequency increases into the young adult years. Cancers of the female genital system consist mainly of carcinoma of the cervix, germ cell tumours of the ovary and ovarian carcinomas. Dysgerminoma is the most common malignant germ cell tumour in adolescent females. Bone tumours peak in incidence in the adolescent years and are twice as common in males as in females. Half of the diagnoses are osteosarcomas, with Ewing sarcoma next in order of frequency. Soft tissue sarcomas in adolescents are fibromatous, with rhabdomyosarcomas being less common than in children (Bleyer et al. 2006a; Barr 2007).

The overall five-year survival rate for all cancers in adolescents in 1988–1997 was 73% in Europe (Sankila et al. 2006). Finnish five-year survival in the adolescent age-group largely matches the European survival time trends (**Figs. 4A and 4B**). Survival of some forms of adolescent cancer is lowered by factors such as higher prevalence of poor prognostic determinants as in ALL, though five-year survival rates of up to 78% have been reached in hospitals using paediatric protocols (Nachman 2003; Barry et al. 2007). The progressive rise in the proportion of astrocytic and glial tumours through adolescence into young adulthood results in 20-year overall survival rates of 65%

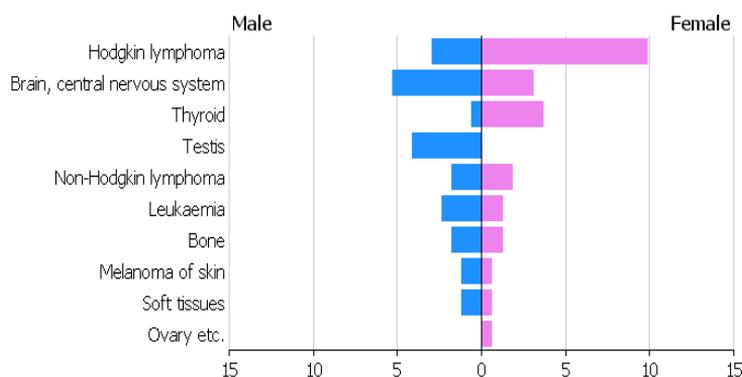
among brain tumour patients in the adolescent age-group, while the equivalent numbers in the next two age quintiles are as low as 40% and 24%, respectively (Bleyer et al. 2006b). Adolescents with thyroid cancer have a survival rate of 90% (Desandes 2007). Although overall survival rates from melanoma exceed 90%, the corresponding figure for metastatic disease is only 15% (Bleyer et al. 2006b; Gatta et al. 2009). Survival in seminoma patients is above 90% in the adolescent age group, while the prognosis for non-seminomatous tumours is less favourable. Overall survival from bone tumours in this age group is 50% (Desandes 2007).

In young adults, commonly defined as the age-group spanning 20–39 years and 20–34 years for purposes of this study, epithelial tumours (carcinomas) account for the majority of malignancies. Malignant disease in this age group contributes two per cent of all cancers, with approximately 500 cases diagnosed annually in Finland. The female to male ratio increases from age 15 to age 40 and is nearly 2:1 between ages 35 and 45. In 2008, according to data obtained from the Finnish Cancer Registry (**Fig. 3B**), breast and thyroid cancer accounted for the largest proportions of cancer in young adult females (15.4% and 16.1%, respectively), with melanoma of the skin (13.8%), cervical cancer (11.0%), and brain and central nervous system malignancies (10.2%) being third, fourth, and fifth most frequent. Common malignancies in males were testicular cancer (29.1%), brain and central nervous system tumours (12%), Hodgkin's lymphoma (9.8%) and non-Hodgkin lymphoma (9.4%).

Among young adult males survival is highest in testicular cancer and Hodgkin's lymphoma, reaching up to 97% with recent protocols (**Fig. 5A**). Survival is nearly as high in melanoma patients at 95%. Five-year survival in brain and CNS tumour and non-Hodgkin lymphoma patients is up to 80% today, while lowest survival rates among males in this age group are seen in leukaemia patients at a little over 60%. Among females in this age group survival is highest following thyroid cancer, with nearly all patients alive five years after diagnosis (**Fig. 5B**). Survival is nearly as high (97%) in female Hodgkin's lymphoma and melanoma survivors. Survival after brain and CNS cancer is slightly higher than that in males diagnosed at the same age at 90%. Of the six largest diagnostic groups, survival is lowest among breast and cervix cancer survivors at 83% and 79%, respectively.

Less attention has been given to the young adult age group than to children and older adults, although there is lack of progress in survival improvement in this age group in comparison to younger and older patients (Bleyer et al. 2009) (**Figs. 5A and 5B**). A possible contributing factor that has been proposed, is the distinct biology of tumours occurring in this age group as compared to that of cancers occurring in younger or older patients (Bleyer et al. 2008). Long-term relative survival is greatest among males and females aged 20 to 29 years, dropping by 10% in both males and females in the 30–39-year age group. Lack of improvement in survival in comparison to older and younger patients is most visible in the 20–29-year age group, with males showing a greater gap than females relative to younger and older patients (Bleyer et al. 2009).

Finland, Incidence (2008)
ASR (World) age (15-19)

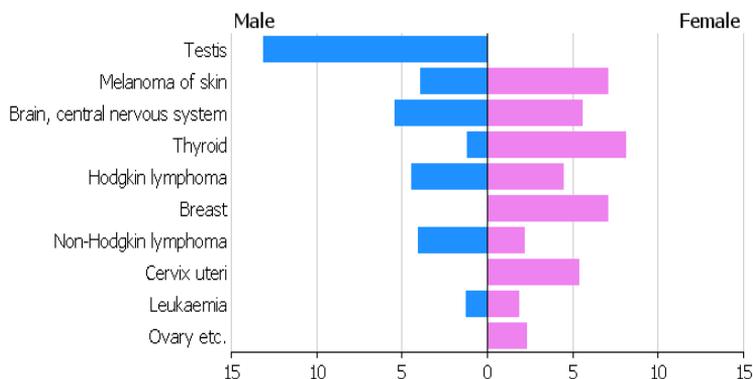


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Figure 3A. Incidence of the 10 most common malignancies among male and female adolescent patients (aged 15–19 years).

ASR = age-standardised rate, using the world population as a standard

Finland, Incidence (2008)
ASR (World) age (20-34)



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Figure 3B. Incidence of the 10 most common malignancies in young adults (aged 20–34 years) by gender.

ASR = age-standardised rate, using the world population as a standard

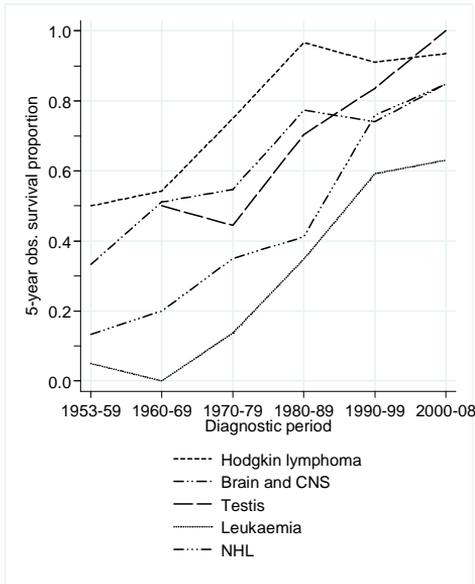


Figure 4A. Five-year observed (obs.) survival proportion by diagnostic era for the five largest primary sites among males aged 15–19 years at diagnosis.

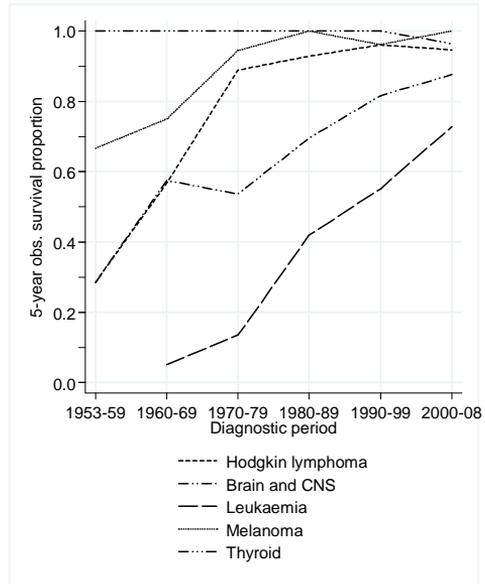


Figure 4B. Five-year observed (obs.) survival proportion by diagnostic era for the five largest primary sites among females aged 15–19 years at diagnosis.

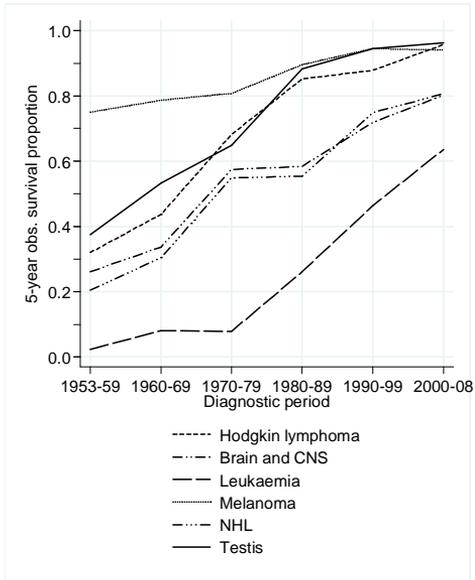


Figure 5A. Five-year observed (obs.) survival proportion by diagnostic era for the six largest primary sites among males aged 20–34 years at diagnosis.

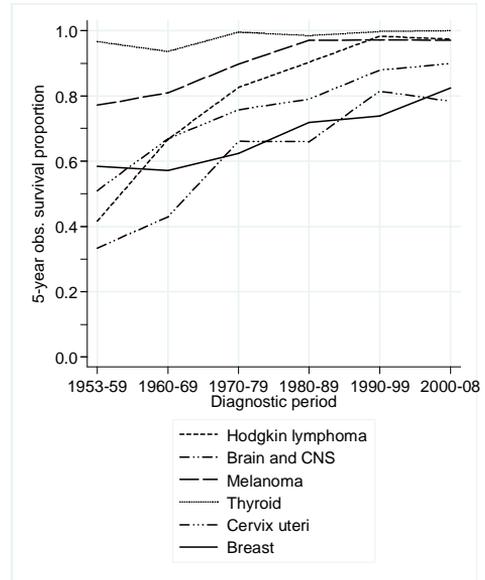


Figure 5B. Five-year observed (obs.) survival proportion by diagnostic era for the six largest primary sites among females aged 20–34 years at diagnosis.

Based on data derived from the main database of the Finnish Cancer Registry

2.4 Sequelae of cancer at a young age

The majority of cancer survivors lead a normal or nearly normal life after treatment. According to one estimate approximately 50% of childhood cancer survivors suffer from an adverse effect in at least one sector of health (Hudson et al. 2003). When a group of patients including some treated in a single institution prior to 1970 were studied, up to roughly 70% presented with some kind of abnormality (Garre et al. 1994). In the context of chronic medical problems, 58% of former childhood cancer survivors had at least one such condition at a median of over 15 years from diagnosis (Stevens et al. 1998).

One recent study found that about 60% of all patients suffer from at least one chronic condition later in life and nearly one third of them have a severe life-threatening condition (Oeffinger et al. 2006). According to the same report, cancer survivors were eight times as likely as their siblings to have a severe or life-threatening chronic health condition and 3.3 times as likely as their siblings to have any chronic health condition (Oeffinger et al. 2006). The groups at the highest risk of having a severe condition were survivors of bone tumours, CNS tumours and Hodgkin's lymphoma. Both female gender and higher age at diagnosis place survivors at an elevated risk of developing a chronic condition. AML survivors receiving only chemotherapy reported excellent to very good health as often as siblings and showed no increased rate of hospitalisations compared to siblings (Molgaard-Hansen et al. 2010). Among the commonly reported severe or life-threatening chronic conditions are second malignant neoplasms, cardiovascular disease (congestive heart failure, coronary artery disease, or cerebrovascular accident), renal failure, endocrinopathies (premature gonadal failure, osteoporosis, or hypothalamic/pituitary dysfunction), major joint replacement, sensory deficits (blindness or hearing loss), and cognitive dysfunction. Overall, the most common late effects reported are endocrinological (Stevens et al. 1998), affecting the growth, reproductive function, and quality of life of the cancer survivor.

2.4.1 *Thyroid effects*

Cancer treatment in childhood, primarily radiotherapy, has been associated with disturbances in thyroid function. Both hypothyroidism and hyperthyroidism have been reported following thoracic, cranial, or neck irradiation. Effects can thus be caused by a central mechanism, resulting from radiation (Rose 2001) or surgery to the hypothalamo-pituitary axis or as a result of scatter to the thyroid gland itself as in total-body irradiation (TBI), or thoracic or cervical radiation. The latter mechanism, known as primary hypothyroidism, is the most common type of treatment-induced thyroid dysfunction and affects 20–30% of patients who have received radiation to the neck region (Koc et al. 2009).

Previously, thyroid effects following childhood cancer treatments have mainly been studied in patients with CNS tumours (Livesey et al. 1989; Ogilvy-Stuart et al. 1991; Schmiegelow et al. 2003a) and Hodgkin's lymphoma patients (Hancock et al. 1991; Bhatia et al. 1996a; Sklar et al. 2000). Identified risk factors for hypothyroidism in

Hodgkin's survivors are high dose of radiation (>4.5 Gy), female gender, higher age at treatment (>15 years), and short time from diagnosis (<5 years) (Sklar et al. 2000). The same study reported a 17.1 relative risk of hypothyroidism and a cumulative risk of hypothyroidism for those treated with 4.5 Gy or more that was 50% at 20 years from diagnosis. The impact of other treatment modalities, such as chemotherapy is unclear (van Santen et al. 2003; Schmiegelow et al. 2003a). Two recent studies reported a risk of thyroid dysfunction after treatment for childhood haematological malignancies, one reporting an increased risk of thyroid dysfunction and thyroid cancer after craniospinal radiotherapy for ALL (Chow et al. 2009), and the other reporting the highest rates of endocrine and metabolic disorders (including hypothyroidism) among ALL and NHL patients treated with a bone marrow transplant after total-body irradiation (Steffens et al. 2008).

2.4.2 Other somatic sequelae

2.4.2.1 Second malignant neoplasms

The risk of second malignancy in childhood cancer survivors and a link to radiotherapy treatment was first suggested in the 1970s (Li et al. 1975). Survivors have been found to be at a 3.6–6.4-fold risk of developing a second cancer when compared to the general healthy population (Olsen et al. 1993; Neglia et al. 2001; Jenkinson et al. 2004). Although absolute excess risk of developing a second primary is low (1.9 per 1,000 patient-years of follow-up) (Neglia et al. 2001), the high mortality and morbidity associated with second malignant neoplasms (SMNs) justifies research efforts to identify risk factors for this complication (Reulen et al. 2010).

Known risk factors for second cancers include female gender (Tarbell et al. 1993; Meadows et al. 2009); younger age at diagnosis (Neglia et al. 1991; Bhatia et al. 1996b; Neglia et al. 2001); and diagnosis with hereditary retinoblastoma, Hodgkin's disease, or soft tissue sarcoma (Strong et al. 1987; Sankila et al. 1996; Wong et al. 1997; Meadows et al. 2009). The childhood cancer survivor study (CCSS) reported risks of SMNs other than those affecting the breast, thyroid, and skin, finding the greatest risks to be following neuroblastoma and soft tissue sarcoma (Bassal et al. 2006). Despite development of modern therapies, a recent study showed that the risk of haematological second malignancies has continued to rise over time (Rihani et al. 2010). Furthermore, another study, evaluating the risk of SMNs after treatment for Hodgkin's lymphoma with low-dose radiation and chemotherapy, demonstrated a similar frequency and latency of sarcomas and of breast and thyroid carcinomas as among patients receiving high-dose radiation (O'Brien et al. 2010). Therefore, modern protocols with low-dose radiation do not appear to reduce second malignancy risk, implicating other culprits in addition to radiotherapy.

Treatment-related factors (e.g., exposure to radiotherapy and certain chemotherapeutic agents and dose) (Nygaard et al. 1991a; Garwicz et al. 2000) as well as certain genetic syndromes are well-established risk factors for second tumours. Long latency and

development within or at the edge of the radiation field are characteristic of radiation-associated cancers (Bhatia et al. 1996b; Metayer et al. 2000). Excess risk for a second primary in childhood cancer survivors has been shown to persist and is elevated at up to 70 years of age (Olsen et al. 2009). Chemotherapy-associated second cancers are characterised by a short latency and a limited period of increased risk (Blayney et al. 1987). A recent study found increased risk of SMNs after leukaemia to be associated with longer duration of 6-mercaptopurine/methotrexate maintenance therapy (Schmiegelow et al. 2009).

Members of families with cancer predisposition syndromes (e.g. Li-Fraumeni, von Hippel-Lindau and Multiple Endocrine Neoplasia Type 2 (MEN 2) syndrome) have been reported to be at risk of multiple subsequent tumours when compared with the general population (Hisada et al. 1998). This risk is highest for childhood cancer survivors and the excess risk mainly for cancers characteristic of these syndromes.

2.4.2.2 Cardiovascular disease

Adverse cardiac effects may result from treatment with chemotherapy, radiotherapy or the combined use of both modalities. Cardiac disease is among the most common chronic health conditions contributing to morbidity and mortality among childhood cancer survivors (Oeffinger et al. 2006; Reulen et al. 2010). Cardiotoxicity of treatments can manifest as cardiomyopathy, subclinical left ventricular dysfunction, valvular disease, pericardial disease, and arrhythmias.

Chemotherapeutic agents that may cause cardiac abnormalities include anthracyclines, alkylating agents, antimetabolites and antimicrotubule agents (Bonadonna et al. 1969; Pai et al. 2000; Simbre et al. 2005). Among these, the cardiac effects of anthracyclines are best characterised. More than 50% of childhood cancer patients are currently treated with anthracyclines (Kremer et al. 2004). Anthracyclines are clinically active against a wide range of malignancies, including Hodgkin's lymphoma, cancers of the breast, non-Hodgkin lymphoma, and leukaemia (Singal et al. 1998). Poor cardiac function was reported in all patients treated with anthracycline doses exceeding 800mg/m² (Steinherz et al. 1991). Long latency of clinical symptoms is a typical characteristic of anthracycline-induced cardiomyopathy (Lipshultz et al. 2005).

Radiotherapy may increase the risk of congestive heart failure, and of pericardial, myocardial, and vascular lesions (Stewart et al. 1995; Byrd et al. 2003; Green 2003). Radiation-induced heart disease has been reported in breast (Cuzick et al. 1994; Darby et al. 2005) and childhood cancer survivors (Mertens et al. 2001), with both groups including a proportion of patients receiving large mediastinal doses. Risk factors for radiotherapy-induced cardiac disease include mediastinal radiotherapy, especially at therapeutic doses exceeding 30 Gy (McGale et al. 2005; Swerdlow et al. 2007). The risk of treatment-induced cardiotoxicity is highest, however, among survivors whose regimens incorporate radiotherapy to the mediastinal region and anthracycline-based chemotherapy, such as those treated for mediastinal Hodgkin's disease and Wilms'

tumour with lung metastases or a left-sided abdominal tumour requiring flank irradiation (Pinkel et al. 1982).

Asymptomatic survivors are at an elevated risk of cardiac abnormality later in life. In subclinical heart conditions, heart failure may develop after an added stress such as pregnancy (Davis et al. 1988; Katz et al. 1997). The physical stress of pregnancy can trigger cardiomyopathy or pulmonary hypertension caused by occult damage from chest irradiation or anthracyclines (Hadar et al. 2004; Lipshultz 2006). One cohort study of 53 paediatric cancer survivors who had received a mean cumulative anthracycline dose of 267 mg/m² demonstrated a low risk of anthracycline-induced clinical heart failure during pregnancy (van Dalen et al. 2006). Larger cohort studies are still needed to confirm this result. Cardiac ultrasonograms in the form of a baseline and a repeat during the third trimester are, therefore, recommended during pregnancy.

2.4.3 Psychosocial consequences

The impact of cancer extends beyond the physical sequelae discussed above. The psychological impact of cancer survivorship was noted as early as the 1970s (Koocher et al. 1980).

As psychosocial difficulties are most prevalent among adolescents in the general population, a childhood cancer survivor is particularly at risk of developing these problems. Although a greater proportion of childhood cancer survivors do as well as their peers, certain subgroups of patients are at risk for various adverse psychosocial outcomes (Schultz et al. 2007). The most vulnerable are former CNS tumour survivors, particularly those diagnosed at an early age (Ilveskoski et al. 1996; Ross et al. 2003; Bhat et al. 2005; Turner et al. 2009) and patients who have received cranial irradiation (Harila et al. 2009). Cognitive (Harila-Saari et al. 2007), physical, and emotional special needs endanger these patients and affect their ability to adjust to society and lead productive lives (Langeveld et al. 2002). Physical sequelae of treatment may also hinder psychosocial well-being, affect employment and ultimately affect the quality of life of a cancer survivor.

Several factors underlie the psychosocial issues faced by cancer survivors. Fear of disease recurrence may cause insecurity (Langeveld et al. 2004). Furthermore, cancer survivors suffer post-traumatic stress (Kazak 1998; Hobbie et al. 2000; Meeske et al. 2001) as a result of the physical stress of cancer treatments and changes in family dynamics. Patients diagnosed during puberty are particularly challenged socially, as normal adolescence may be disturbed and detachment from parents may be postponed (Koch et al. 2006; Johannsdottir et al. 2010). Significantly lower employment rates are observed among patients compared to controls (Pang et al. 2008; Syse et al. 2008a; Johannsdottir et al. 2010), despite similarities in proportions with an academic education between survivors and controls (Koch et al. 2004; Johannsdottir et al. 2010).

2.4.4 Marital status

Studies concerning quality of life of cancer survivors show that cancer survivorship may alter the priorities in one's life. For example, the importance placed on family life has been shown to increase after cancer (Schover et al. 2002; Langeveld et al. 2004).

Marital status has been viewed as an indicator of psychosocial function among cancer survivors. A study of the marriage rates of childhood cancer survivors in the U.K. reported higher marriage rates among females than among males (Frobisher et al. 2007). The largest ever married deficits were among male CNS tumour survivors. Marriage rates were influenced by education, primary site of cancer, age at diagnosis and radiotherapy treatment. A report from the Childhood Cancer Survivor Study (CCSS) found CNS tumour survivorship, cranial irradiation, impaired processing efficiency, and short stature to be correlated with low marriage rates (Janson et al. 2009). Another study found infertility to be an additional factor lowering marriage rates in survivors (Byrne et al. 1989). One study, which examined marriage and fertility in long-term survivors of high-grade osteosarcoma, however, showed lower marriage rates in males than in females, the marriage proportion among females being almost the same as among sisters of patients and treatment having no influence on marriage proportion (Yonemoto et al. 2003). However, in males, marriage proportion was significantly lower than in brothers and was influenced by treatment.

A report from the CCSS study showed a decreased likelihood of marriage among paediatric cancer survivors (Rauck et al. 1999). Overall, female gender and white race were associated with lower marriage rates. Furthermore, fewer survivors with CNS tumours reported having been married in comparison to survivors with other diagnoses, with this marriage deficit in the subgroup of CNS survivors being greater in males. Interestingly, the study also reported lower divorce/separation rates among cancer survivors than in the general population. Several other studies confirmed the latter result (Byrne et al. 1989; Frobisher et al. 2010; Janson et al. 2009). A recent study of the social outcomes of acute myeloid leukaemia, Wilms' tumour, and infratentorial astrocytoma survivors found no differences in marital status between patients and controls (Johannsdottir et al. 2010).

Marriage rates have also been explored in survivors of cancer in adulthood (Syse 2008b; Syse et al. 2009). The former found an increasing trend in marriage rates over time and no deficits were observed overall when comparing cancer patients to the healthy control group (Syse 2008b). In males, no deficits were observed on cancer sub-site level, though in females a former diagnosis of brain or breast cancer was associated with lower marriage rates (Syse 2008b). The latter study explored marriage rates after cancer in older adults (aged 45–80) and found that men with cancer had similar marriage rates as their healthy counterparts while women showed a 25% deficit (Syse et al. 2009). Deficits were most pronounced in breast (odds ratio (OR) 0.69) and ovarian cancer (OR 0.48) survivors (Syse et al. 2009). One study in the literature was found exploring marital stability in survivors of cancer in adulthood (Dorval et al.

1999). This focused on breast cancer patients and found no increased risk of marital breakdown among patients compared to population controls.

2.5 Cancer and reproductive health

2.5.1 Fertility after cancer in childhood

The subject of future reproductive function is of great importance in the child or young adult diagnosed with cancer. Parents of paediatric patients and survivors worry about their reproductive capacity and/or about future health problems their children might experience as a result of their cancer history (Langeveld et al. 2002).

The reproductive system is vulnerable to the deleterious effects of cancer therapy. Nevertheless, more than 50% of paediatric cancer survivors have a good prognosis as regards later fertility. It is, therefore, important to identify subgroups and treatments that pose a threat to later childbearing.

Cancer and its treatment may affect the timing of puberty (Armstrong et al. 2009a; Armstrong et al. 2009b) (precocious/rapid delayed, or gonadal failure) or cause infertility. Adverse effects may be mediated centrally by effects on the hypothalamo-pituitary axis or by direct damage to gonadal tissue. The extent and reversibility of adverse effects of treatment vary by age at treatment and gender of the patient.

The effects of chemotherapy on the gonads depend on agent and dose administered, with large-dose chemotherapy being most deleterious. The known fertility-impairing agents include alkylating agents: cyclophosphamide, chlorambusil, ifosfamide, busulphan, and melphalan. The vinca-alkaloid vinblastine, antimetabolite cytarabine, and platinum agent cis-platin as well as procarbazine are all also identified as gonadotoxic agents (Wallace 2004a).

Treatment regimens used in conditioning for stem cell transplants, solid tumours, osteosarcoma, and traditional protocols for Hodgkin's lymphoma are also associated with a high risk of gonadal damage. Low risk is related to chemotherapy used in ALL, Wilms' tumour, low-grade soft-tissue sarcoma treatments, and germ cell tumours, and in the case of brain tumours that are treated surgically.

Harmful effects of radiotherapy depend on the treatment related factors of site or field of treatment, total dose and fractionation schedule (Speiser et al. 1973; Leiper et al. 1986; Shalet et al. 1989). Cranial irradiation, craniospinal irradiation, total-body irradiation (TBI), and abdomino-pelvic irradiation can all affect reproductive function.

2.5.1.1 Effects on the hypothalamo-pituitary axis

Effects of radiation on the hypothalamo-pituitary (HP) axis are dose-dependent. Lower doses (18–24 Gy) cause isolated growth hormone deficiency while higher doses (>60 Gy) result in panhypopituitarism. Intermediate doses in the range 30–50Gy result in

GHD with or without LH/FSH deficiency, cortisol deficiency, or TSH deficiency. The GH axis is therefore, most radiosensitive, then the gonadotropin axis, followed by the ACTH and TSH axes, indicating selective hypothalamic neuronal and pituitary cell damage by direct radiation (Robinson et al. 2001). Cranial irradiation with doses greater than 35Gy results in testicular and ovarian damage secondary to the radiotherapy-induced gonadotropin deficiency. The threshold doses required to cause such central effects are, accordingly, similar in males and females.

Furthermore, hypothalamo-pituitary dysfunction is time-dependent, as there is an increase in the frequency and incidence of hormonal deficits following radiation damage to the HP-axis with increasing time from radiotherapy. Although primarily attributed to vascular damage, the progressive nature of these neuroendocrine effects was later linked to direct neuronal damage, as studies of regional blood flow did not detect a significant reduction between six months and five years after irradiation (Chieng et al. 1991).

2.5.1.2 Female cancer survivors

2.5.1.2.1 Effects on ovarian function

The exact mechanisms by which cancer treatments disrupt ovarian function are unknown, though treatments have been found to reduce the number of primordial follicles and in this way result in truncated fecundity and premature menopause (Meirow 2000; Thomson et al. 2002a). The amount of gonadal cell depletion is affected by the extent of cytotoxic damage. Intensive treatments may cause infertility and a need for hormone replacement therapy (Byrne 1999; Chiarelli et al. 1999). Though fertile potential may be only slightly affected after treatment, the fertile period may be limited by early menopause.

In a CCSS report, eight per cent of all survivors experienced non-surgical premature menopause, compared with 0.8% of siblings controls (Green et al. 2009a), while the corresponding percentage was 30–40% among those who underwent irradiation to a field that included the pelvis in combination with alkylating-agent chemotherapy (Byrne et al. 1992; Sklar et al. 2006).

Total-body, abdominal, or pelvic irradiation may damage the ovaries (Wallace et al. 1989a; Critchley et al. 1992; Sanders et al. 1996; Wallace et al. 2003). Predicting the onset of ovarian failure following radiotherapy has become possible (Wallace et al. 2003); however, the effects of chemotherapy are difficult to predict, though increasing alkylating agent score is a recognised risk factor for premature menopause (Green et al. 2009a). Methotrexate has been found to be associated with a lower risk of imminent ovarian failure (Lantinga et al. 2006). Around 50% of girls treated for Hodgkin's lymphoma prepubertally with six or more courses of ChIVPP (chlorambucil, vinblastine, procarbazine, and prednisolone) had raised plasma gonadotropin concentrations (Mackie et al. 1996). The use of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) has been shown to be significantly less gonadotoxic than MOPP (mechlorethamine, vincristine, procarbazine, prednisolone) (Viviani et al.

1985). The extent of gonadal damage after radiotherapy depends on dose and fractionation schedule as well as on age at treatment (Lushbaugh et al. 1976; Wallace et al. 1989a; Wallace et al. 1989b; Bath et al. 1999; Wallace et al. 2003). Because of physiological follicular store depletion (Faddy et al. 1976; Gosden et al. 1994), the dose needed to cause acute ovarian failure decreases with age (Wallace et al. 2003).

Although scatter from craniospinal irradiation may directly affect ovarian function, the most common mechanism underlying cranial irradiation is central as both craniospinal and cranial irradiation, typically used in the treatment of some brain tumours (Livesey et al. 1988) and ALL with CNS involvement, cause hypogonadotrophic hypogonadism. It is well established that high-dose cranial irradiation (>30 Gy) causes progressive compromise in hypothalamo-pituitary function (Littley et al. 1989), while effects of low-dose cranial irradiation (18–24 Gy) on the hypothalamo-pituitary axis are merely suggested by subtle disturbances in growth hormone secretion (Crowne et al. 1992; Birkebaek et al. 1998; Brennan et al. 1998), lower first birth rates among irradiated patients in comparison to those who did not receive radiotherapy (Nygaard et al. 1991b), and decreased LH production and short luteal phases in irradiated ALL patients (Bath et al. 2001).

TBI used as conditioning treatment in bone marrow transplants may either act centrally or directly affect the ovaries (Sanders et al. 1996; Thibaud et al. 1998; Bath et al. 1999; Matsumoto et al. 1999) in the same way as abdominal and pelvic radiation, used in the treatment of Wilms' tumour, pelvic rhabdomyosarcoma, and Ewing sarcoma of the pelvis and spine. There are few data available on threshold doses for ovarian dysfunction: 2 Gy has been found to be a sufficient dose to deplete the oocyte pool by half (Wallace et al. 2003). In older women (> 40 years of age), permanent menopause may be induced by gonadal doses as low as 6 Gy (Lushbaugh et al. 1976), while >20 Gy results in ovarian failure in the majority (>97%) of patients treated in childhood and adolescence (Wallace et al. 1989a), reflecting the smaller follicular reserve in older patients and hence increased susceptibility to irradiation (Wallace et al. 2005a). Furthermore, risk of ovarian failure following abdominal radiotherapy increases with dosage (Chiarelli et al. 1999). Pubertal status also influences the effects of radiotherapy, and, therefore, threshold doses (i.e., 10–12 Gy) may cause reversible damage to ovarian function in pre-pubertal girls, while causing permanent damage in post-pubertal girls. Doses of 16–18 Gy are required to cause permanent ovarian damage in girls older than 10 years of age.

2.5.1.2.2 Uterine effects

While radiotherapy has established late effects on uterine function, chemotherapy does not appear to have any significantly lasting adverse effect on uterine function (Nicholson et al. 1993; Salooja et al. 2001). Although the exact mechanisms underlying the deleterious effects of radiotherapy on uterine function are unclear, reduced elasticity of the uterine musculature and uterine vascular damage have been suggested (Critchley et al. 1992; Sanders et al. 1996). As the uterus continues growing for several years after menarche, the pubertal or pre-pubertal uterus is more susceptible

to the deleterious effects of treatment than is the uterus of an adult. Furthermore, at the onset of puberty there is an increase in the dimensions of the uterus and endometrial thickness as well as a change from a tubular to a more pear-shaped organ (Holm et al. 1995; Bridges et al. 1996); therefore, it is expected that radiotherapy carries a significant risk of impaired uterine development if administered in pre-puberty. Thus, in childhood cancer survivors, attained uterine volume correlates with age at radiation.

Clinically, effects of radiotherapy can be seen as reduction in uterine length, blood flow, and endometrial thickness (Critchley et al. 1992). Uterine irradiation in childhood results in an increased incidence of miscarriage, mid-trimester pregnancy loss, and intrauterine growth retardation (Li et al. 1987; Green et al. 1989; Smith et al. 1989; Critchley et al. 1992; Sanders et al. 1996; Green 2001). The extent of damage to the developing uterus depends on site of radiation, dose, and fractionation schedule. Doses between 14 and 30 Gy have been reported to result in uterine dysfunction, with required abdominal doses of 20–30 Gy, while TBI doses of 14.4 Gy are sufficient to cause uterine dysfunction (Critchley et al. 1992; Bath et al. 1999).

2.5.1.3 Male cancer survivors

As both chemotherapy and radiotherapy target cells that divide quickly, the most sensitive cells are those belonging to the spermatogenic epithelium, responsible for sperm production (Howell et al. 1998). Leydig cells, however, are more resistant to the effects of cancer treatment. Therefore, it is common that cancer treatment in males affects not puberty or masculinisation but testis size and sperm production. Another characteristic of male reproductive dysfunction is that although males are at an increased risk of experiencing impaired fertile potential after treatment, the effects are often reversible.

The male gonads are sensitive to the effects of radiotherapy, but also many chemotherapeutic agents are capable of disrupting spermatogenesis (Howell et al. 2001). Cytotoxic agents may damage the testis, resulting in both infertility and hypogonadism (Waring et al. 2000). Also disease processes themselves in the case of testicular cancer and Hodgkin's lymphoma (HL) have been shown to have deleterious effects on spermatogenesis (Skakkebaek et al. 2001; Magelssen et al. 2006), an example being pre-treatment impairment of spermatogenesis in HL as a result possibly of immunological processes (Rueffer et al. 2001).

Site, dose, and fractionation schedule in the administration of radiotherapy and dose and agent in the case of chemotherapy, as well as pubertal status, are key modifiers of risk and reversibility of damage to the male gonads. The pre-pubertal testis is particularly susceptible to the adverse effects of chemotherapy and radiotherapy (Whitehead et al. 1982; Chatterjee et al. 1994; Mackie et al. 1996; Sanders et al. 1996; Papadakis et al. 1999).

Damage induced by chemotherapy in the germinal epithelium is well established in the literature and was first reported in 1948, by Spitz (Spitz 1948), who recognised the

gonadotoxic effect of nitrogen mustard. Since then, several other agents were recognised as harmful to the male reproductive system, among them procarbazine, cisplatin, and alkylating agents (e.g. cyclophosphamide and chlorambucil) (Chapman et al. 1979; Whitehead et al. 1982; Watson et al. 1985; Wallace et al. 1989c; Wallace et al. 1991; Shafford et al. 1993; Mackie et al. 1996). The risk of gonadal dysfunction is highest and independent of age after alkylating agents; intermediate after platinum agents, anthracyclines, and some antimetabolites; and lower after agents such as vinca-alkaloids, methotrexate, dactinomycin, bleomycin and mercaptopurine (Aubier et al. 1989; Siimes et al. 1990; Wallace et al. 2005b). Chemotherapy may have a direct cytotoxic effect on both germ cells and Leydig cells, but may also inflict damage indirectly on Leydig cells by damaging other cell populations and disrupting paracrine regulation.

Most studies of the effect of chemotherapy on testicular function have focused on patients treated with multi-agent regimens for HL (Whitehead et al. 1982; da Cunha et al. 1984; Viviani et al. 1985; Shafford et al. 1993; Hill et al. 1995; Heikens et al. 1996; Mackie et al. 1996). MOPP (mechlorethamine, vincristine, procarbazine, and prednisolone), MVPP (mechlorethamine, vinblastine, procarbazine, and prednisolone), ChIVPP (chlorambucil, vinblastine, procarbazine, and prednisolone) and COPP (cyclophosphamide, vincristine, procarbazine and prednisolone) have been reported to cause azoospermia in 85% of adult males. The gonadotoxic agents being mechlorethamine and procarbazine in MOPP and MVPP, chlorambucil and procarbazine in ChIVPP, and cyclophosphamide and procarbazine in COPP (Whitehead et al. 1982; da Cunha et al. 1984; Viviani et al. 1985; Bramswig et al. 1990; Shafford et al. 1993; Heikens et al. 1996; Mackie et al. 1996).

The deleterious effects of high-dose cyclophosphamide were also noted in a study of childhood ALL patients (Nurmio et al. 2009). ABVD, which excludes procarbazine and alkylating agents, is a far less gonadotoxic regimen for HL, causing azoospermia and oligospermia in 33% and 21% of patients treated, with full recovery by 18 months in all patients re-tested (Viviani et al. 1985). Regimens such as MACOP-B (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisolone, bleomycin) and VACOP-B (vepesid, adriamycin, cyclophosphamide, vincristine, prednisolone, bleomycin) used in the treatment of NHL, despite including cyclophosphamide, result in normal fertility in the majority of men treated, emphasising the role of procarbazine among the known gonadotoxic agents in causing irreversible damage to the germinal epithelium (Muller et al. 1993; Pryzant et al. 1993). Hybrid regimens that alternate combination chemotherapy regimens have been developed to reduce the total dosage of any one particular agent and reduce drug-related side effects. Comparing MOPP to MOPP/ABVD hybrid regimen effects justifies such hybrid regimens, as the percentage of patients developing azoospermia is 76% in the latter compared to 100% in the former (Anselmo et al. 1990).

In patients receiving preconditioning for bone marrow transplant with busulphan (16 mg/kg) and cyclophosphamide (200 mg/kg) or cyclophosphamide (200 mg/kg) only,

combination with busulphan was associated with greater gonadotoxicity (Sanders et al. 1996). Follow-up of patients treated with higher doses (840mg/kg) of cyclophosphamide for nephritic syndrome identified the threshold for impaired spermatogenesis to be at a total dose of 10g (Watson et al. 1985). When cyclophosphamide is used at doses of >7.5 g/m² in combination with dacarbazine, vincristine and doxorubicin, azoospermia was permanent in 90% of patients treated for solid tumours (Bleyer 1990; Meistrich et al. 1992). Germinal epithelial damage has been reported in patients treated for childhood ALL with regimens including cyclophosphamide and cytarabine (Quigley et al. 1989; Mackie et al. 1996). An analogue of cyclophosphamide, ifosfamide as used in the treatment of Ewing's sarcoma and rhabdomyosarcoma (84–126 g/m²), left 33% with normal testicular function (Thomson et al. 2002b).

Although chemotherapy has not been found to cause symptomatic Leydig cell insufficiency, high-dose cyclophosphamide has been shown to cause elevated LH concentrations, which suggests compensated damage to Leydig cell function (Watson et al. 1985).

Total-body, pelvic, and testicular irradiation may cause testicular damage, the degree of impairment being related to radiation dose, fractionation schedule, and age at the time of treatment (Speiser et al. 1973; Leiper et al. 1986; Sklar et al. 1990; Sanders et al. 1996; Socie et al. 2003). TBI may also act centrally, causing hypogonadotrophic hypogonadism – the key mechanism of insult of craniospinal irradiation – though irradiation has also been found to cause primary germ cell damage, indicating that scatter irradiation exposure may also impair testicular function (Castillo et al. 1990). Radiotherapy is thought to damage the testis via effects on the vasculature, while Leydig cell effects may be mediated at high doses by direct cytotoxicity or at lower doses by an indirect effect through damage to the blood supply. While doses higher than 1.2 Gy are required to cause azoospermia (Gurgan et al. 2008) and as low as 0.1 Gy are enough to cause oligoospermia, Leydig cell damage occurs at doses exceeding 20 Gy in pre-pubertal males and at doses higher than 30 Gy in post-pubertal males (Martin et al. 1986; Relander et al. 2000).

2.5.2 Parenthood after cancer

The wish to have a biological child is deeply rooted in human evolution (Fisher et al. 2002). It is not surprising, therefore, that young adult cancer survivors want children, especially if they are childless at diagnosis. In fact, a cancer patient may have more appreciation of being able to have a child after the disease is treated. Children born after cancer, like those born after infertility treatment (Golombok et al. 1995), may be more valued by parents. Confronting the stress of a life-threatening disease can also teach parents resilience in coping with the hassles of daily family life.

Although cancer survivors experience anxiety and distress related to reduced fertility (Oosterhuis et al. 2008) and the health of any future offspring (Schover 2005), two surveys showed that cancer diagnosis increases the value placed on family life and the

importance of parenthood for survivors, thus contributing to the quality of life of former patients (Langeveld et al. 2002; Schover et al. 2002).

The trend in the Western countries of delaying initiation of childbearing to later in life will result in more young adult female cancer survivors who are childless at diagnosis. Therefore, parenthood after cancer is an issue that equally concerns survivors of paediatric, adolescent, and young adulthood cancer.

Most earlier studies have reported reduced post-diagnosis parenthood rates among survivors of cancer in adolescence and adulthood (Syse et al. 2007; Magelssen et al. 2008; Cvancarova et al. 2009) (**Table 1**). Two smaller studies focused on Hodgkin's lymphoma survivors (Kiserud et al. 2007) and testicular cancer survivors (Brydoy et al. 2005). A recent report investigated the risk of siring a pregnancy (Green et al. 2010a) and another the risk of mothering a child (Green et al. 2009b) among former childhood cancer patients.

Syse et al reported 25% reductions in first-birth rates among patients diagnosed between 17 and 44 years, with males (OR 0.76; 95% CI 0.72–0.79) and females (OR 0.73; 95% CI 0.69–0.77) showing similar reductions (Syse et al. 2007). Higher order births were similarly reduced among male patients (OR 0.78; 95% CI 0.75–0.81), while among females the likelihood of having a second- or third-order birth was even lower (OR 0.64; 95% CI 0.61–0.67). Women with breast and gynaecological cancer had the lowest first-birth rates (50% reduced as compared to controls). Female survivors of leukaemia, non-Hodgkin lymphoma; or brain, breast, colon, or skeletal cancer had significantly reduced first-order birth rates. Among males, significant reductions in first-order birth rates were visible after testicular, brain, skeletal, and colon cancer. In both sexes, calendar time of treatment, time elapsed from diagnosis and stage of disease was found to influence the likelihood of parenthood. The decline in fertility disadvantage by treatment decade was most visible in male HL, leukaemia, and testicular cancer survivors.

Table 1. Summary on results of large epidemiological studies of parenthood following cancer.

Reference	Age	Treatment period	Comparison group	N	Data source	Results	
						Males	Females
Green et al. 2009,2010a	0–20	1970–1986	Siblings	11,373	Questionnaire	HR 0.56	RR 0.81
Cvancarova et al. 2009	15–45	1971–1997	Population	6,071	Hospital registry	HR 0.71	HR 0.45
Magelssen et al. 2008	15–35	1980–1997	Population	747	Hospital registry	PP 63%	PP 66%
Syse et al. 2007	17–44	1965–2001	Population	13,452	Population registry	OR 0.76	OR 0.73

Another group reported on the cumulative first-time parenthood probability among survivors aged 15–35 years at diagnosis in a hospital based setting (Magelssen et al. 2008). Female cancer survivors had significantly reduced parenthood rates when compared to the general population (66% vs. 79%) ($p = 0.007$), while male cancer survivors did not display significant reductions in parenthood probability (63% vs. 64%) ($p = 0.41$). There were no significant differences between the most frequent cancer types in males and females. Ten-year parenthood probabilities in the most frequent diagnostic groups were, in men, 41% in malignant lymphoma and 42% in testicular cancer survivors and, in women, 44% in malignant lymphoma and 33% in gynaecological cancer survivors. The extent of the disease significantly influenced 10-year post-diagnosis parenthood probability, which was 44% in localised or regional disease and 34% in those with distant metastases ($p = 0.047$).

Another study, by the same group, reported on 10-year first post-diagnosis cumulative reproduction rates and hazard ratios among survivors of cancer diagnosed at 15 to 45 years of age (Cvancarova et al. 2009). Age at diagnosis, pre-diagnosis parity, and diagnostic era (<1988 versus 1988+) had a significant influence on post-diagnosis parenthood. The highest 10-year post-diagnosis reproduction rates were among childless patients. Males had more favourable hazard ratios than females did. Hazard ratios improved significantly in the era after 1988 among testicular and localised cervical cancer patients with at least one child at diagnosis and marginally for localised ovarian cancer. Post-diagnosis reproduction in pre-diagnosis childless males with a haematological malignancy and childless females with breast cancer did not differ significantly from reproduction in controls.

The above-mentioned registry-based studies all used the general population as the comparison group (Syse et al. 2007; Magelssen et al. 2008; Cvancarova et al. 2009) and focused on survivors of adolescent and young adulthood cancer. Only one population-based study exists (Syse et al. 2007) and the other two reflect parenthood rates among patients treated in a single hospital (Magelssen et al. 2008; Cvancarova et al. 2009).

Few epidemiological studies of parenthood among former childhood cancer patients exist. An older study by Byrne et al. reported adjusted relative fertility of 0.93 (95% CI 0.83–1.04) in female cancer survivors diagnosed between 1945 and 1975 (Byrne et al. 1987). The effects of childhood cancer and its treatment on parenthood rates are explored in two recent reports from the childhood cancer survivor study (Green et al. 2010a; Green et al. 2009b). Survivors aged 15–44 and not rendered surgically sterile were studied by means of self-administered questionnaires. Data on cancer treatments were obtained from medical records. Fertility risks among males and females, compared to a non-randomly-selected group of siblings, were HR 0.56 (95% CI 0.49–0.63) and RR 0.81 (95% CI 0.73–0.90), respectively. For males, testicular radiation doses of more than 7.5 Gy, a higher cumulative alkylating agent dose score, or treatment with cyclophosphamide or procarbazine decreased the HR of siring a pregnancy. Male HL patients were least likely to parent a child, while neuroblastoma

and Wilms' tumour survivors were as likely as siblings to do so. For females, pregnancy rates were lower among patients exposed to hypothalamic/pituitary doses of at least 30 Gy or ovarian/uterine doses greater than 5 Gy. Higher alkylating agent dose scores (3 or 4) and treatment with lomustine or cyclophosphamide lowered pregnancy rates.

2.6 Health of offspring of cancer survivors

2.6.1 Adverse birth outcomes among offspring of cancer survivors

Cancer and cancer therapies, including radiotherapy and certain chemotherapeutic agents, can affect pregnancy outcomes and impact the offspring via direct effects on the female reproductive tract or on neuroendocrine pathways. Pregnancy outcomes of cancer survivors that have been studied include low birth weight and preterm birth (Green et al. 2002a; Signorello et al. 2006; Clark et al. 2007; Reulen et al. 2009), stillbirths (Clark et al. 2007; Winther et al. 2008; Signorello et al. 2010), and spontaneous (Winther et al. 2008) and induced abortions (Winther et al. 2009).

2.6.1.1 Preterm birth and low birth weight

No accurate recent global data exist regarding preterm birth rates, but estimates vary from as low as five per cent in developed countries to 25% in developing countries. In all of the Nordic countries preterm birth rates are very low by international comparison, reflecting high standards of living and good prenatal care. In Finland, preterm birth (<37 weeks) rates have dropped from 9.1% to 4.8% from 1966 to the mid-1980s (Olsen et al. 1995). According to Nordic perinatal statistics, the preterm birth rate has been relatively stable in Finland in recent years (Gissler et al. 2007).

Preterm delivery in female cancer survivors and low birth weight of their offspring have been hypothesised to be linked to direct damage to the vasculature and elastic properties of the uterus (scoliosis or fibrosis) incurred through abdomino-pelvic radiation (Critchley et al. 1992; Sanders et al. 1996). Female childhood cancer survivors studied in a multi-institution, hospital-based setting, were found to be at an elevated risk for preterm delivery and low birth weight (Signorello et al. 2006) (**Table 2**). Other population-based studies have confirmed this result (Chiarelli et al. 2000; Clark et al. 2007; Magelssen et al. 2008; Mueller et al. 2009; Reulen et al. 2009). Perinatal health of offspring of former cancer patients aged 15–45 years at diagnosis was examined in a study that focused on parenthood (Magelssen et al. 2008), reporting both the risk of preterm delivery and of low birth weight of offspring to be increased among female cancer survivors as compared to the risk among the general population retrieved from the Medical Birth Register. In addition to an elevated risk of preterm delivery, one study identifying all post-diagnosis first deliveries of cancer survivors diagnosed under the age of 36 years, found that female cancer survivors were at an elevated risk of operative delivery and post-partum haemorrhage when compared to a randomly selected comparison population (Clark et al. 2007). A recent single-centre study of female childhood cancer survivors, which combined registry and self-reported

data, found, in addition to a higher incidence of preterm deliveries, also elevated risk of post-partum haemorrhage in female survivors treated with abdominal radiotherapy, thus confirming the finding of Clark et al. (Lie Fong et al. 2010).

Several early studies of prematurity risk in offspring of childhood cancer survivors exist. These were restricted to specific diagnoses – namely, acute lymphoblastic leukaemia (Moe et al. 1979; Marradi et al. 1982; Green et al. 1989; Nygaard et al. 1991b), Hodgkin's lymphoma (Holmes et al. 1978; McKeen et al. 1979; Green et al. 1988), and Wilms' tumours (Li et al. 1987; Byrne et al. 1988; Hawkins et al. 1989a). An early study of primarily Wilms' tumour survivors collected information on pregnancy outcomes using a postal survey and found an elevated proportion of adverse pregnancy outcomes (spontaneous abortion and low birth weight) among abdominally irradiated patients as compared to unexposed patients diagnosed with the same malignancy (Hawkins et al. 1989a). A more recent study showed that female Wilms' tumour survivors who have received flank irradiation are, in addition to preterm birth (prior to 37 weeks) and low birth weight, at risk of hypertensive complication during pregnancy, fetal malposition and premature labour (Green et al. 2010b). Other, similar studies have published reports consistent with these (Li et al. 1987; Byrne et al. 1988; Green et al. 2002b; Kalapurakal et al. 2004).

Recent studies with larger cohorts of childhood cancer survivors have found an elevated risk of adverse pregnancy outcomes in patients treated with radiotherapy for a wide range of malignancies (Chiarelli et al. 2000; Signorello et al. 2006; Mueller et al. 2009; Reulen et al. 2009). In a questionnaire-based study, Chiarelli et al. reported that, in addition to preterm birth and low birth weight, infants born to patients who had received abdominal-pelvic irradiation were also at higher risk of perinatal death when compared to offspring of those treated with surgery only (Chiarelli et al. 2000). Signorello et al. found an increased risk of preterm delivery and low birth weight among children of patients treated with high-dose radiotherapy to the uterus (>500 cGy) in comparison with children of survivors who did not receive radiotherapy (Signorello et al. 2006). Mueller et al., using a registry-based approach, reported an increased risk of preterm delivery and low birth weight not only in irradiated patients but also in those receiving chemotherapy only (Mueller et al. 2009). A population-based questionnaire study found female survivors exposed to abdominal irradiation to be at a threefold risk of delivering prematurely, a twofold risk of delivery of a low-birth-weight infant, and a slightly increased risk of miscarriage (Reulen et al. 2009). In addition to low birth weight, Green et al. explored the risk of various other pregnancy outcomes including live births, stillbirths, miscarriages, and abortions following treatment with radiotherapy and a wide range of chemotherapeutic agents (Green et al. 2002a). Although no increased risk of adverse pregnancy outcomes was associated with any chemotherapeutic agent, risk of low birth weight was associated with pelvic irradiation.

Table 2. Summary of results of recent large epidemiological studies on preterm birth (<37 weeks) and low birth weight (<2500g) among female cancer survivors with a mixture of cancer diagnoses.

Reference	Age at diagnosis	Treatment period	Comparison group	N	Data Source	Preterm birth OR (95% CI)	LBW* OR (95% CI)
Mueller et al. 2009	0–19	1973–2000	Population	1,898	Registry linkage	1.54 (1.30–1.83)	1.31 (1.10–1.57)
Reulen et al. 2009	0–15	1940–1991	Population	4,113	Questionnaire	3.20 (2.10–4.70)	1.90 (1.10–3.20)
Clark et al. 2007	0–43	1980–2005	Population	917	Registry linkage	1.33 (1.01–1.76)	1.03 (0.77–1.37)
Signorello et al. 2006	0–20	1970–1986	Siblings	2,201	Questionnaire	1.90 (1.40–2.40)	1.3 (0.90–1.90)
Green et al. 2002a	0–20	1970–1986	Siblings	4,029	Questionnaire	NA	2.05 (1.42–2.95)

*LBW Low birth weight, N number of live births

2.6.1.2 Spontaneous and induced abortions

Female childhood cancer survivors have been reported to be at a slight excess risk of spontaneous abortions, while the proportion of stillbirths was unaffected by previous cancer history (Winther et al. 2008). Another study by the same group showed that female survivors are more likely than sisters and population controls to elect a second-trimester abortion because of physical or mental conditions or foetal abnormality (Winther et al. 2009).

Two earlier studies on Wilms' tumour survivors reported increased risk of spontaneous abortions among females who had received abdominal irradiation (Li et al. 1987; Byrne et al. 1988). Two studies of Hodgkin's lymphoma patients found an elevated risk of spontaneous abortion (Holmes et al. 1978; McKeen et al. 1979), with the risk in the other study being linked to combination treatment with radiotherapy and chemotherapy, independent of whether the radiation was above or below the diaphragm (Holmes et al. 1978). A larger study incorporating more recent treatment protocols and including female survivors with a wide variety of diagnoses reported, among other adverse pregnancy outcomes, an elevated though not statistically significant risk of spontaneous abortions in patients whose ovaries were in or near the radiation therapy field (Green et al. 2002a). Another study with a wide range of primary diagnoses confirmed this result, reporting an association between slightly increased risk of spontaneous abortion among survivors and abdominal radiotherapy (Reulen et al. 2009).

2.6.1.3 Stillbirths and neonatal deaths

Previous studies evaluating the risk of stillbirth among female cancer survivors did not find it to be elevated (Green et al. 2002a; Clark et al. 2007; Winther et al. 2008).

A recent report from the Childhood Cancer Survivor Study found an association between uterine and ovarian radiation and the risk of stillbirth and neonatal death among offspring of female cancer survivors (Signorello et al. 2010), while chemotherapy with alkylating drugs was not associated with an increased risk of the study outcomes.

The subject of neonatal deaths of offspring of cancer survivors has not been extensively explored, although one study did report an elevated though not significant risk (OR 1.37; 95% CI 0.42–4.45) of neonatal mortality in offspring of early onset female cancer survivors (Clark et al. 2007).

2.6.2 Genetic effects of cancer treatment

Although radiotherapy has been found to cause somatic mutations in humans and germ-line mutations in animal models (Boice et al. 2003), whether or not and to what extent mutagenic cancer treatments can introduce germ-line mutations leading to genetic disease in the offspring of survivors is unknown. Cancer predisposition, altered sex ratio, and congenital abnormalities in offspring are considered potential manifestations of treatment-induced transgenerational effects. Studies that have explored sex ratio and genetic disease in offspring of cancer survivors are summarised in **Table 3**.

The majority of studies exploring sex ratio in offspring of childhood cancer survivors reported no significant alterations in the sex ratio of offspring (Hawkins 1991; Byrne et al. 1998; Green et al. 2002a). These studies included childhood cancer survivors treated mainly prior to the use of multi-agent chemotherapy, before 1977 (Hawkins 1991), in 1945–1975 (Byrne et al. 1998), and in 1970–1986 (Green et al. 2002a). Two large epidemiological studies that included patients treated with more recent protocols (Winther et al. 2003; Reulen et al. 2007), confirmed results of previous studies of unaltered sex ratio and found no influence of radiation dose or interval from cancer diagnosis.

In healthy populations, the reported range of major and minor congenital abnormalities is 1–4% and 8–10% respectively (Myriantopoulos et al. 1974; Blatt 1999). Congenital anomalies may be an isolated simple malformation, the result of cytogenetic abnormalities or a single gene disorder. A number of studies have attempted to report the incidence of congenital anomalies in the offspring of cancer survivors, some larger (**Table 3**) (Green et al. 1991; Green et al. 1997; Byrne et al. 1998; Winther et al. 2004) and some focusing on a smaller subgroup of patients (Holmes et al. 1978; Moe et al. 1979; Blatt et al. 1980; Bunday et al. 1982; Li et al. 1987; Byrne et al. 1988; Green et al. 1988; Hawkins et al. 1988; Green et al. 1989; Pajor et al. 1991; Nygaard et al. 1991b; Kenney et al. 1996).

Most studies have shown no significant increase in the number of congenital anomalies. Few studies have focused on chemotherapy exposure and genetic outcomes in offspring (Green et al. 1991; Kenney et al. 1996; Green et al. 1997; Byrne et al. 1998). Although one study suggested an association between dactinomycin and cardiac anomalies in offspring of female survivors (Green et al. 1991), more recent reports failed to support this finding (Green et al. 1997; Byrne et al. 1998). While one smaller study of female acute lymphoblastic leukaemia survivors found an increased risk of birth defects among offspring of patients who had received cyclophosphamide (Kenney et al. 1996), two larger studies failed to confirm an association between alkylator exposure and increased risk of birth defects (Green et al. 1991; Byrne et al. 1998).

Table 3. Summary of results from recent large epidemiological studies exploring sex ratio and congenital anomalies among offspring of female cancer survivors.

Reference	Outcome	Age	Patients	Treatment period	Comparison group	Survivors N	Offspring N	Data source	Results
Reulen et al. 2007	Sex ratio	0–15	Mixed	1940–1991	Population	3,218	6,232	Population registry	Unaltered sex ratio
Winther et al. 2003	Sex ratio	0–19	Mixed	1943–1996	Population	1,100	2,130	Population registry	Unaltered sex ratio
Winther et al. 2009	Congenital anomalies	0–19	Mixed	1950–1996	Siblings	3,963	1,715	Population registry	No significantly increased risk
Byrne et al. 1998	Cytogenetic abnormalities Single-gene defects Simple malformations	0–19	Mixed	1945–1975	Siblings	4,544	2,198	Interview	No significantly increased risk
Green et al. 1997	Congenital anomalies	0–19	Chemo treated	1960–1989	Population	148	280	Medical records Questionnaire	No significantly increased risk
Green et al. 1991	Congenital anomalies	0–19	Chemo treated	1960–1984	Population	306	202	Medical records Questionnaire	Slight increase in cardiac defects among offspring of dactinomycin-treated patients

2.6.3 Cancer in offspring of cancer survivors

Multiple publications from the 1970s and 1980s have investigated the risk of cancer in the offspring of cancer survivors (Li et al. 1979; Marradi et al. 1982; Bunday et al. 1982; Hawkins et al. 1988; Green et al. 1989; Nygaard et al. 1991b). Recent studies exploring cancer risk among patients treated in childhood and adolescence (Mulvihill et al. 1987; Hawkins et al. 1988; Hawkins et al. 1989b; Green et al. 1997; Sankila et al. 1998) are presented in **Table 4**. Of these studies, most included treatments that are now outdated and relied on survivor self-reporting as the source of offspring outcome data (Mulvihill et al. 1987; Hawkins et al. 1988; Hawkins et al. 1989b). Green et al. found no cancers among 230 offspring of cancer survivors but was limited by cohort size (Green et al. 1997). Of two larger studies, one reported no elevation in risk in comparison to the general population (Hawkins et al. 1988) and the other could not make accurate risk estimates (Hawkins et al. 1989b).

Two larger studies on the subject are cited in the literature (Mulvihill et al. 1987; Sankila et al. 1998). Mulvihill and co-workers, reported no increased risk of cancer among 2,308 offspring of survivors (n=7) when compared to offspring of siblings (n=11); however, the majority of patients in this study were only treated with surgery (Mulvihill et al. 1987).

The other, more recent large study was based on Nordic population data and included 5,847 offspring of 14,652 paediatric and adolescent cancer survivors, who were followed up to 1994 (Sankila et al. 1998). There were 44 malignant neoplasms identified in the survivor offspring cohort, yielding a standardised incidence ratio of 2.6 (95% CI 1.9–3.5). After removal of offspring with familial retinoblastoma and other identifiable hereditary cancer syndromes, the risk of cancer in offspring was only slightly elevated (SIR 1.3, 95% CI 0.8–2.0), to a non-significant degree when compared to that in the general population. The age of the survivor parent at diagnosis appeared predictive of offspring cancer risk, as the SIR for offspring of survivors, compared to that expected based on the general population, diagnosed before their 10th birthday was 3.9 (95% CI 2.1–6.7) and was only 1.1 (95% CI 0.6–1.8) among patients diagnosed over the age of 10 years. Despite it being the largest study, with the longest follow-up to date, full pedigrees were not constructed. For this reason, not all hereditary cancer syndromes could be identified and removed from sporadic risk calculations.

A recent study, based on data from the hospital discharge registry records, evaluated hospitalisations among offspring of survivors of childhood and adolescent cancer (Winther et al. 2010), finding a sixfold excess risk of hospitalisation for malignant tumours, the elevation owing largely to the presence of hereditary cancer syndromes. A twofold excess in hospitalisations for benign tumours could not be entirely accounted for by hereditary cases, thus suggesting the possibility of increased surveillance of offspring of cancer survivors. Overall hospitalisation among survivors' offspring was similar to that among siblings' offspring and the general population.

Table 4. Summary of results from previous studies on the risk of cancer in offspring of cancer patients with a mixture of diagnoses.

Reference	Age	Treatment period	Comparison group	Survivors		Offspring		FUP	Data source	Cancer	
				N	N	PY	PY			Heritable	Sporadic
Sankila et al. 1998	0–19	1955-1991	Population	14,652	5,847	86,780	86,780	Median: 14 years	Population registry	22	22
Green et al. 1997	0–19	1960-1989	Population	405	230	NA	NA	NA	Questionnaire	0	0
Hawkins et al. 1989b	0–14	before 1978	Population	2,352	1,192	7,214	7,214	6 years	Questionnaire	0	2
Hawkins et al. 1988	0–14	before 1970	Population	2,001	1,018	NA	NA	NA	Questionnaire	18	2
Mulvihill et al. 1987	0–19	1945-1975	Siblings	2,283	2,308	25,046	25,046	Mean: 10.9 years	Questionnaire	4	3

PY person-years

FUP length of follow-up

3. AIMS OF THE PRESENT STUDY

This study was initiated to investigate the late effects of early onset cancer by means of registry data. The present investigation assessed the endocrine and reproductive health of survivors of early-onset cancer and the health of their offspring, with the following specific aims:

1. to estimate the nationwide prevalence, incidence and patient-related risk factors for hypothyroidism as a late effect of cancer diagnosed in childhood. **(Study I)**
2. to investigate parenthood after cancer in a wide range of cancer survivors, diagnosed in childhood, adolescence, and early adulthood as compared to siblings. **(Study II)**
3. to assess birth outcomes (preterm birth and low birth weight) **(Study III)** and neonatal health (early death, stillbirth and neonatal morbidity) among offspring of female patients as compared to offspring of female siblings. **(Study IV)**
4. to assess cancer risk in offspring of survivors of early-onset cancer as compared to the general population and to offspring of siblings. **(Study V)**

4. SUBJECTS AND METHODS

4.1 Registers

The unique personal identity code was introduced in Finland in the 1960s. Since 1967, every resident of Finland has been given such a personal identity code (PIC). It is this PIC that makes linkage of records from different registries and databases in Finland possible.

4.1.1 *The Finnish Cancer Registry*

The Finnish Cancer Registry (FCR) was founded in 1952 and began systematic registration in 1953. It therefore contains information on all cancer cases diagnosed in residents of Finland since 1953. The National Board of Health requested all physicians, hospitals and laboratories to notify the FCR of all diagnosed or suspected cases of cancer. This notification has been compulsory since 1961. The notifications are further supplemented by death certificate information from Statistics Finland, resulting in almost complete coverage (99% for solid tumours, 92% for haematological malignancies, and 100% for childhood cancers) (Teppo et al. 1994; Korhonen et al. 2002).

The FCR includes patient data (date of birth, personal identity code, gender, name, and residence), cancer data (date of diagnosis, primary site, histology, malignancy, stage, and basis for diagnosis), initial treatment data (dating back to the first four months of treatment), and the date and cause of death (if applicable). In the FCR, information on treatment, when available, is based on clinical notifications and includes data on radiotherapy, chemotherapy, and surgery. Details of the anatomical region irradiated, dose, or (for chemotherapy) dose and agent administered are not, however, included. Coded treatment data, concerning different treatment modalities, include the following details: palliative/radical/radicality unknown and treatment given in the first four months / after the first four months / at an unknown timepoint.

4.1.2 *The Central Population Register (CPR)*

The Population Register Centre hosts a nationwide central population register (CPR). The Population Register Centre, tasked with directing and supervising population registration, was set up in 1969 and the computer-based register introduced in 1971.

Personal data recorded for all Finnish citizens and permanent residents in Finland include name and any former names, PIC, municipality of birth and residence, citizenship and native language, family relations (spouse, siblings, and offspring), and date of birth and either death or emigration (if applicable).

4.1.3 The Medical Birth Register

The Finnish Medical Birth Register (MBR), run by the National Institute for Health and Welfare (THL) and formerly by STAKES (the National Research and Development Centre for Welfare and Health), was established in 1987. Data are reported to THL directly from all delivery units or from the midwife or physician assisting in the delivery. The data provided by hospitals are checked and any missing or seemingly incorrect data are confirmed by contacting the treating hospital and then corrected in the database. The quality of information is high, with data for under 0.5% of all births missing from the register (Teperi 1993; Gissler et al. 2002). Missing information is completed using data compiled by the Population Register Center on live births and data compiled by Statistics Finland on stillbirths and deaths during the first week of life (Gissler et al. 2004). Aimed at improved reliability of the registry, reforms to the data were made in 1990, 1996, and 2004 (Gissler et al. 1995).

The MBR contains data on all mothers who have delivered a child in Finland and on all newborn infants up to the age of seven days. The register includes data on all live births and stillbirths at a weight of at least 500 g or a gestational age of at least 22 weeks. Data on obstetric and neonatal outcomes are available in the MBR.

4.1.4 The Cause-of-Death Register (CDR)

The Cause-Of-Death Register (CDR) is maintained by Statistics Finland with the purpose of identifying all deaths in Finland. The data are compiled from death certificates (written by the clinician who treated the patient or the pathologist who performed the autopsy), which are supplemented with data from the population information system of the Population Register Centre. Death certificates are checked by physicians in the provincial government and at Statistics Finland. Seemingly incorrect information is sent back to the clinicians for review. All people who have died in Finland or abroad and who at the time of death were domiciled in Finland are included in this register. Data on causes of death are available in computerised form from 1969 onward. Causes of death have been classified according to ICD-8 (1969–1986), ICD-9 (1987–1995), and ICD-10 (1996 onward).

4.1.5 The Drug Reimbursement Register

The entire Finnish population is entitled to national health insurance, which is maintained by the state and organised through the Social Insurance Institution (SII) of Finland. The insurance, to which all permanent Finnish residents are entitled, includes a pharmaceutical reimbursement system, which covers some of the costs of prescription drugs.

Maintained by the SII, the Drug Reimbursement Register (DRR) has records of all reimbursable drug purchases. Registration began in 1986, and between 2000 and 2004 the register captured 97% of all special-class reimbursed prescription drugs (Helin-Salmivaara et al. 2003).

Reimbursement is calculated as a percentage of surplus costs beyond a fixed price. Before 2006, drugs were grouped by the Ministry of Health and Social Affairs into three distinct reimbursement categories: none, basic (reimbursement: 50% per payment), and special (reimbursement: 75-100% per payment, depending on diagnosis).

4.1.6 The Drug Purchase Register

The drug purchase register (PR) is held by the SII and keeps a record of all prescription drugs that have been purchased. It began registration in 1993 and includes all purchased drugs belonging to any refund category, with the exception of over-the-counter drugs, medications used in hospitals, and those reimbursed from occupational health-care funds.

The database includes information on personal identity code, anatomic therapeutic chemical code of the drug, date of purchase, package size, and drug cost and refund category. Drug purchases are recorded in the database regardless of whether paid for by the individual or by a private insurance company.

4.2 Study populations

4.2.1 Cancer survivor and offspring cohorts

All studies utilised patient or offspring subcohorts derived from the same main cancer survivor and offspring cohorts. The main cancer survivor cohort was identified from the FCR and included 25,784 males and females diagnosed with invasive cancer in Finland in 1953–2004 and between the ages of 0 and 34 (**Fig. 6**). All liveborn offspring alive in 1969 were identified by linkage to the CPR. Linkage to the MBR gave access to information on all liveborn and stillborn offspring since 1987. A sub-cohort of cancer patients was linked to the DRR and PR to obtain information on prescribed and reimbursed drugs. Registry linkage procedures and the outcome data obtained are presented in **Figure 6**. For purposes of this study, cancer was defined as a malignant neoplasm or a non-malignant brain tumour – i.e., meningiomas and juvenile pilocytic astrocytoma – or a brain tumour of uncertain malignancy. Micro-invasive tumours of the uterine cervix were also included.

In **Study I**, the cohort was a subset ($n = 5,180$) of the main cancer survivor cohort, with the restriction of diagnosis before the age of 16 years, birth year after 1970, and diagnosis with cancer by the end of 2002 (**Fig. 7**).

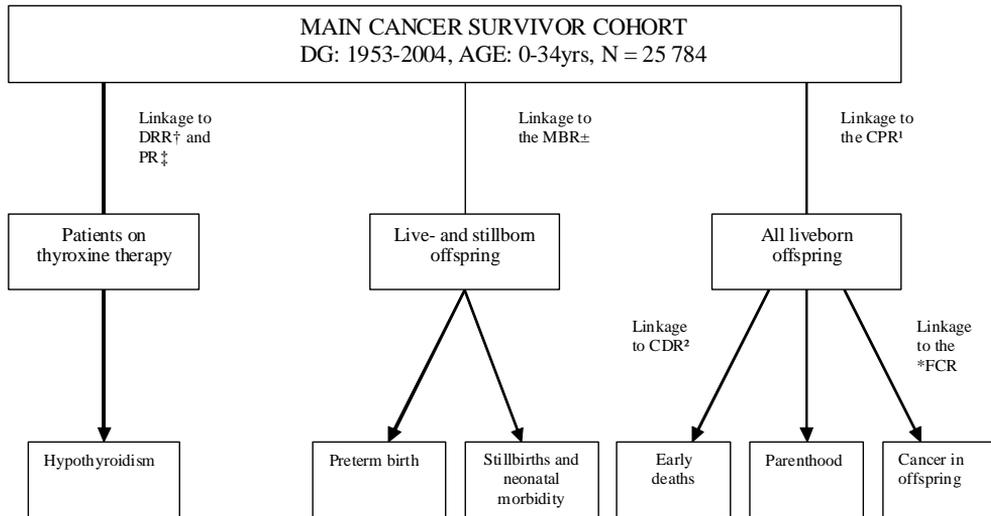


Figure 6. Registry linkage procedures and outcome data obtained. The sibling cohort was identically linked to the MBR and CPR and the siblings offspring cohort to the CDR and FCR.

* FCR Finnish Cancer Registry (1953->)

† DRR Drug Reimbursement Register (1986 ->)

‡ PR Drug Purchase Register (1993->)

± MBR Medical Birth Register (1987->)

¹ CPR Central Population Register (1969->)

² CDR Cause-of-Death Register (1969->)

The cohort in **Study II** was derived from the main cancer survivor cohort, by first identifying those patients who could be followed up for liveborn offspring ($n = 22,465$) – i.e., those reaching reproductive age. Of these, 12,735 survivors became parents. Exclusion of patients with offspring before or within nine months of diagnosis yielded 3,905 survivor parents of at least one child and 2,390 survivor parents of at least two children born after diagnosis (**Fig. 7**).

Linkage to the Central Population Register allowed identification of spouses and offspring of cancer survivors. As offspring are identified by maternal link, offspring of female survivors were directly identified. Offspring of male survivors could be identified via the female spouse. The main offspring cohort included, in all, 26,331 offspring of cancer survivors, of them 15,708 born before, 746 within nine months after, and 9,877 longer after the cancer diagnosis of the survivor (**Fig. 8**).

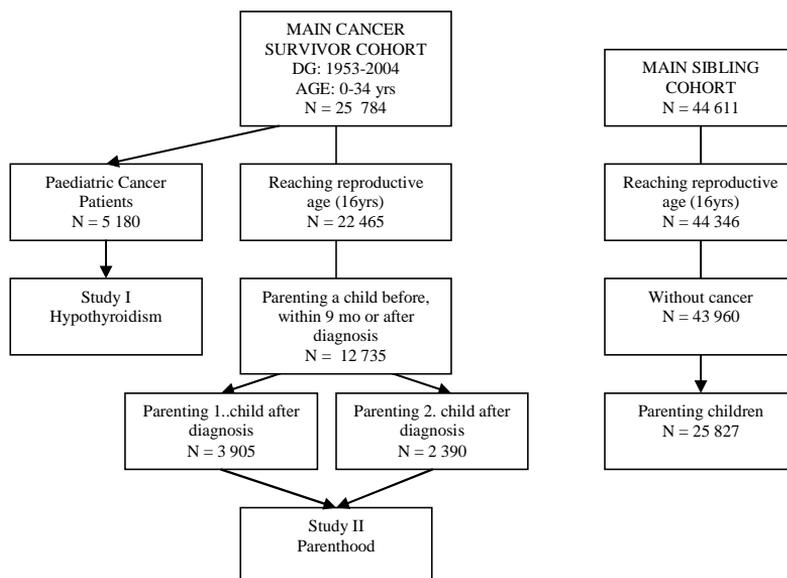


Figure 7. Identification of patient populations for Studies I and II and the sibling comparison cohort for Study II.

In **Studies III and IV**, the study cohorts were derived from the main offspring cohort by inclusion of only the 9,877 offspring born after diagnosis. Of these, 5,303 were offspring of female cancer patients. Restriction of female survivors to those born in or after 1955, for whom siblings could be reliably identified, yielded 3,706 singleton offspring of female survivors, forming the study cohort for the mortality substudy (**Study IV**). Offspring of all female cancer survivors, born since 1987 (3,657 offspring in all) could be linked to the MBR and were thus eligible for the stillbirth and neonatal morbidity substudy (**Study IV**). Subanalyses of the preterm delivery and low birth weight study, included all these post-diagnosis offspring (**Study III**). After exclusion of post-diagnosis offspring born to female survivors parenting offspring before diagnosis and higher-order post-diagnosis offspring from the stillbirth substudy cohort, 1,309 firstborn postdiagnosis offspring were eligible for main analyses in **Study III** (**Fig. 8**). **Study V** included all offspring in the main offspring cohort (**Fig. 8**).

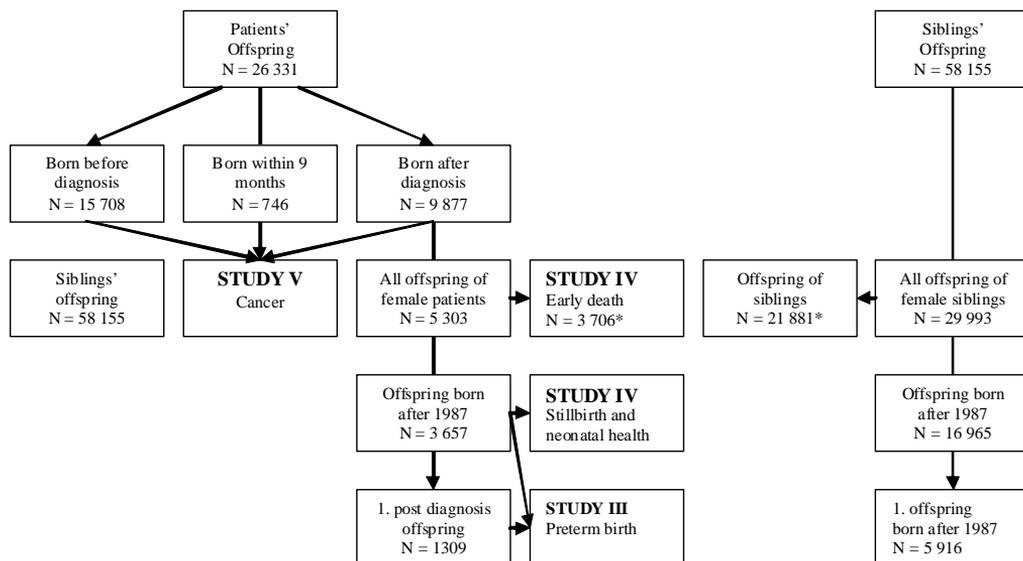


Figure 8. Identification of offspring populations for Studies III–V and the siblings' offspring comparison cohort.

* Only offspring of patients and siblings born after 1955 were included in the early death analysis

4.2.2 Reference cohorts

Half and full siblings of the cancer survivors were identified by linkage to the CPR. Out of a total of 44,611 siblings, 44,346 attained reproductive age and 386 were patients with early-onset cancer, and were excluded from the sibling cohort but not from the survivor cohort (**Fig. 7**). In all, 43,960 siblings were linked to the CPR for identification of offspring. Finally, 25,827 siblings with 58,155 offspring were identified and served as the comparison group for parenthood analyses in **Study II** (**Figs. 7 and 8**).

In total, 29,993 singleton offspring of female siblings could be identified from the CPR. For the early death sub-study (**Study IV**) in which follow-up of offspring was available as early as 1969, only siblings born in or after 1955 and their offspring were included as identification of siblings was only reliable thereafter (**Fig. 8**), thus 21,881 offspring of siblings served as the reference group. Of the 29,993 offspring of siblings, 16,965 were born after 1987 and could therefore be linked to the MBR, serving as a reference group in the sub-analyses of the preterm delivery study, which included all post-diagnosis offspring of patients (**III**), and for the stillbirth and neonatal morbidity substudy (**IV**) (**Fig. 8**); 5,916 first offspring of female siblings were used as the reference group for the main preterm birth analyses, which included only firstborn post-diagnosis offspring of patients (**III**). In **Study V**, offspring of male and female

survivors were compared to the offspring of all male and female siblings and the general population.

The general population was used as a reference cohort in prevalence comparisons in **Study I (Table 5)**. In relative risk estimates concerning hypothyroidism in different diagnostic groups, leukaemia patients were used as the reference group.

Table 5. Description of data obtained from different outcome registries for Studies I–V.

Study	Data source	Years	Study cohort	Comparison group	Outcome
Study I	DRR*	1986–2005	Patients	General population	Hypothyroidism
	PR†	1993–2005	age 0–15 Dg 1986–2002 1993–2002	Leukaemia patients	
Study II	CPR±	1969–2006	Patients age 0–34 Dg 1953–2004	Male and female siblings	Post-diagnosis parenthood
Study III	MBR ¹	1987–2006	Offspring of female patients	Offspring of female siblings of male and female patients	Preterm birth and low birth weight
Study IV	CDR ²	1969–2007	Offspring of female patients	Offspring of female siblings of male and female patients	Early death, stillbirth and neonatal morbidity
	MBR	1987–2007			
Study V	FCR‡	1972–2006	Offspring of patients	Offspring of male and female sibs and the general population	Cancer incidence

Drug Reimbursement Register; † Drug Purchase Register; ‡ Finnish Cancer Registry, ± Central Population Register, ¹ Medical Birth Register, ² Cause-of-Death Register

4.3 Methods

4.3.1 Information on covariates and follow-up status

Information on vital status and emigration of survivors, siblings, and offspring is available through the Central Population Register. As the linkage was completed in early 2007, the information covered vital status at the end of follow-up (31 December 2006), date of birth of children, date of emigration, and date of death (when applicable).

Information on the maternal variables of age at delivery, socio-economic status, smoking, hypertension, infection, gestational diabetes or impaired glucose tolerance, pre-eclampsia, placental problems, delivery year, malpresentation, caesarean delivery and use of artificial reproductive technology, previous history of an early preterm delivery, previous history of stillbirths, and previous history of spontaneous or induced abortions was available from the MBR for survivors and siblings alike since 1987.

Information on offspring such as gender, birth order, number of offspring at birth (singleton/twin/triplet), presentation, and time of birth, has been available in the MBR since 1987. The birth order variable, however, takes into account deliveries prior to 1987.

4.3.2 Information on outcomes

A brief description of the outcome data obtained from different registries is presented in **Figure 6 and Table 5** (page 35 and page 38, respectively).

Patient Outcomes

Data on thyroxine use (**Study I**) were obtained from two outcome registries. Information on thyroxine purchases from 1 January 1993 to 31 March 2005 was obtained from the Drug Purchase Register (PR) maintained by the SII of Finland. Reimbursement data from 1 January 1986 to 31 March 2005 were obtained from the drug reimbursement registry (DRR). Information obtained included name of drug, date of purchase, and issuing date of the reimbursement permit.

Information on live births of survivors and siblings was obtained from the CPR of Finland, including information on dates of birth of liveborn children and possible dates of death (**Study II**) (**Fig. 6 and Table 5**).

Offspring Outcomes

Information on the neonatal health of the offspring of female patients and of siblings was obtained from the MBR. The information covered birth weight (**III**), duration of pregnancy (**III**), use of cardiopulmonary resuscitation or ventilation assistance (**IV**), neonatal monitoring (**IV**), birth asphyxia (**IV**), and stillbirths (**IV**). Mortality data including date and cause of death of offspring were obtained from the CDR (**IV**). Data on malignant disease of offspring of all survivors and siblings, including ICC class and date of diagnosis, were obtained from the FCR (**V**).

Outcome Definitions

Patient Outcome Definitions

A patient was considered to have hypothyroidism if there were records of thyroxine purchase or reimbursement for thyroxine treatment. The date the reimbursement permit was granted was chosen to represent the initiation of replacement therapy. With regard to drug purchase data, the first date of purchase was the incidence date of clinical hypothyroidism (**Study I**).

Parenthood was defined as the first post-diagnosis child in patients with no children before cancer diagnosis. For siblings, the definition of parenthood was siring or mothering the first child. Higher-order parenthood was defined as a second childbirth after diagnosis for patients who had a first child after diagnosis and a second child for siblings (**Study II**).

Offspring Outcome Definitions

In **Studies III–V**, the same outcome definitions were applied for the offspring of survivors and siblings. Preterm birth was defined as a birth occurring at less than 37 weeks of gestation and early preterm delivery as one occurring at less than 34 weeks of gestation (**Study III**). A low-birth-weight (LBW) infant was defined as a neonate weighing less than 2,500 g at birth. Small-for-gestational-age (SGA) was defined as having a birth weight on the $-2SD$ (standard deviation) curve or below, when compared to infants of the same sex born during the same gestational week, according to the national birth weight statistics (Pihkala et al. 1989).

Early neonatal mortality was defined as death occurring during the first week of life; neonatal mortality was defined as death within the first month and infant mortality as any death occurring during the first year of life (**Study IV**). The cause of death was studied in the following groups: deaths from disease and medical conditions or violent deaths (including sudden infant death syndrome (SIDS) and deaths from external causes and poisonings from unintentional and intentional accidents and injuries). Causes of death related to diseases and medical conditions were grouped in the

categories: congenital anomalies and disease, prematurity and delivery complications, infections and malignancy.

In **Study V**, examining cancer among offspring of cancer survivors, we first identified all known cancer syndromes among offspring and their parents. For all parent–offspring pairs in which both the parent and the child had cancer, histology was checked from pathology reports and pedigrees were constructed to identify possible familial cancer susceptibility syndromes. For parent–offspring pairs suggestive of Li-Fraumeni-like syndrome, pedigrees were constructed and the grandparents were checked by linkage to the FCR for neoplasms confirmatory of Li-Fraumeni syndrome. In the case of pairs in which the offspring of a patient was diagnosed with cancer, also the offspring of siblings were identified, to spot possible syndromes of incomplete penetrance. However, we did not identify any affected offspring among the children of these siblings, and, therefore, no hereditary cases were identified among the siblings' offspring.

4.3.3 Statistical analysis

In incidence calculations in **Study I**, the group of paediatric cancer patients diagnosed at 0 to 15 years of age was categorised into 11 diagnostic subgroups. In **Studies II–V** separate models were fitted to three diagnostic age categories: childhood (0–14 years), adolescent (15–19 years), and young adult (20–34 years).

Study I

Patients were classified into 11 diagnostic subgroups with consideration of proximity of treatment to the thyroid gland as follows: leukaemia, Hodgkin's lymphoma, non-Hodgkin lymphoma, gastrointestinal tract and liver, genitourinary system, skin, eye, central nervous system, neuroblastoma, thyroid, and bone and soft tissue tumours.

Due to availability of data in the outcome registries, only patients diagnosed with cancer after 1 January 1986 and after 1 January 1993 were included in the linkages with the thyroxine reimbursement and thyroxine purchase data, respectively, and thus were included in the incidence calculations and life-table analyses. Person-time at risk for HT after cancer diagnosis was computed for each study subject. Follow-up began at the time of cancer diagnosis and ended either on the date of first thyroxine purchase or at reimbursement, death, or closing of the study, 31 March 2005, whichever came first. The incidence rate of HT in each diagnostic group was calculated by dividing the number of patients with HT by the sum of person-months. Cumulative incidence rates were calculated by diagnostic group. Ninety-five per cent confidence intervals (95% CI) for incidence rates were calculated based on the assumption that the number of patients with HT followed a Poisson distribution.

The relative risk of hypothyroidism by diagnostic group was estimated by survival analysis. Leukaemia patients were chosen as the reference group, as this diagnostic group was the largest. Survival curves were produced by the Kaplan-Meier log-rank-

test. Differences in the risk of HT between the above-mentioned 11 diagnostic groups were assessed by means of a Cox proportional hazard model (Cox 1972), with sex as a covariate.

Prevalence was calculated at the date of closing of follow-up, 31 March 2005 for the whole group of childhood cancer patients identified from the FCR. Prevalence of HT in the general population was calculated at the end of 2004 according to the population figures extracted from the CPR and the number of persons in Finland on thyroxine replacement (SII data).

Study II

The probability of post-diagnosis parenthood was studied in survivors who were childless at diagnosis. The probability of parenthood among patients was compared to that of siblings through Cox proportional hazards modelling. Separate analyses were performed for first and second liveborn children.

For patients, follow-up began either at the 16th birthday or nine months after the date of cancer diagnosis for those diagnosed with cancer after the age of 15 years and three months. For siblings, follow-up started on the 16th birthday. The end of follow-up was defined for both patients and siblings as the date of birth of a child, the possible date of death, permanent emigration, or the end of December 2006, whichever came first. In the analyses for the second liveborn child, follow-up began at the time of delivery of the first child and ended at the delivery of the second child, or death, emigration, or the end of December 2006.

Cox proportional hazards models with age as a time variable were used in assessment of the effects of various variables (Cox 1972). The relative risk expressed the relative probabilities of parenthood. Statistical significance was obtained by comparing hierarchical models. The final results are presented by comparing each set of cancer patients defined by gender, age at diagnosis and site category (including all sites combined) with the total group of siblings of the same gender. All models included calendar time of birth (birth cohort) as a categorical variable, classified as follows: 1) before 1951, 2) 1951–1959, 3) 1960–1969, 4) 1970–1979 and 5) 1980 or after. An additional analysis using the abovementioned model was used to assess the effect of diagnostic era on parenthood probability with diagnostic era categorised as follows: 1) 1953–1962, 2) 1963–1972, 3) 1973–1982, 4) 1983–1992 and 5) 1993–2004.

Parenthood calculations were performed for all sites and separately for each diagnostic class. The patient classification used in this study was largely based on the International Childhood Cancer Classification (ICCC) (Kramarova et al. 1996), which, as the majority of paediatric cancers are disseminated when they are diagnosed, is primarily based on histology. To take into account the predominance of epithelial tumours (carcinomas) in adolescents and young adults, we further subdivided the ICCC

subgroup XI (carcinomas and other malignant neoplasms) into major sub-sites, using the ICD10 coding.

Study III

Relative risk of preterm birth and low birth weight (LBW) among offspring of female cancer survivors as compared to offspring of female siblings was estimated using multiple logistic regression modelling.

Main analyses for all outcomes were performed for first post-diagnosis offspring and first offspring of siblings. An additional analysis, including all post-diagnosis offspring of cancer patients and all offspring of siblings, was performed for the preterm birth outcome.

As data were available on a large number of maternal exposures that are potential risk factors for an adverse pregnancy outcome and therefore possible confounders, the log-likelihood ratio test was used to identify those explanatory variables to be included in the final model. Despite the *a priori* suggestion to include maternal infection, maternal diabetes or impaired glucose tolerance, pre-eclampsia, and diagnostic decade, in our data, these did not prove to have an effect on the outcomes of interest and were therefore not included in the final model.

All models were adjusted for maternal age, maternal smoking, maternal hypertension, delivery year, child gender, placental problems, caesarean section, use of in-vitro fertilisation or assisted reproductive technologies, and malpresentation of the foetus. Models for assessing LBW were also adjusted for full gestational weeks at delivery. We additionally checked the models, adjusting for socio-economic status, but did not include this variable in the final models, as the fit did not improve significantly with inclusion of this variable and there was a large number of missing values. Sub-analyses including all post-diagnosis offspring were additionally adjusted for birth order, previous history of an early preterm delivery at <34 weeks, previous history of stillbirth, and spontaneous or induced abortion. Checking for possible interaction between the variables in each model was based on the likelihood ratio test. All interactions among the variables in the final model were checked, and none were found to be significant. Estimates of model parameters and 95% confidence intervals were computed according to the maximum likelihood technique.

Only singleton births were included in all analyses, as twin and triplet deliveries are strongly associated with the outcomes studied. As parity is expected to have an influence on birth weight and primiparity is a known risk factor for preterm delivery, the main analyses for all study outcomes were restricted to first post-diagnosis offspring. Because more than one pregnancy was included per subject in the sub-analysis, conditional fixed-effects logit models (Allison 2009) were applied to take into account the dependent nature of the data for children born to the same mother.

An additional model calculated the risk of preterm delivery by time from diagnosis to delivery. The variable of time from diagnosis to delivery was divided into two categories: deliveries occurring within 10 years of diagnosis and those taking place later than 10 years from cancer diagnosis.

By combining the available information on the site of the tumour and whether the initial treatment included radiotherapy, survivors were classified into four mutually exclusive groups: no radiotherapy, abdomino-pelvic radiation, cranial radiation, and radiotherapy other than to the brain or the abdomino-pelvic region. To study the possible effect of treatment other than radiotherapy, separate analysis of the patients who had not received ionising radiation as part of their therapeutic exposure was conducted. This resulted in the following groups: chemotherapy with or without surgery and surgery only.

Study IV

Multiple logistic regression modelling was used to calculate odds ratios for the outcomes of early death, stillbirth and various neonatal morbidity outcomes in offspring of female patients in comparison to offspring of female siblings.

Models exploring neonatal mortality were adjusted for previous history of a neonatal death, gender of infant, maternal age, calendar time (delivery year grouped by decade) and birth order. Multiple deliveries (twin and triplet) were excluded from the analyses, as they have been associated with the outcomes of interest. Models calculating ORs for adverse neonatal outcomes included the following basic set of explanatory variables: child gender, birth order, duration of pregnancy in full weeks, year of delivery, maternal age, maternal hypertension, maternal smoking, pre-eclampsia, maternal infections, gestational diabetes or impaired glucose tolerance, and placental problems (including premature detachment and placenta praevia). Maternal age was treated as a categorical variable with the following categories: 1) <20 years; 2) 20–34 years, and 3) >35 years. Birth order and year of delivery were treated as continuous variables, while all other variables were dichotomous. Multiple pregnancies of the same women were included in the analyses using conditional fixed-effects logit models (Allison 2009) to take into account the dependent nature of the data on children born to the same woman.

Study V

The risk of cancer in offspring of cancer survivors and siblings was calculated using standardised incidence ratios (SIRs). All offspring of patients and their healthy siblings were followed up for cancer between 1972 and 2006. The vital status was checked for every cohort member. Follow-up ended on the date of death or emigration or the closing date of the study, 31 December 2006. Person-years were counted accordingly.

For SIR calculations, the numbers of observed cases and person-years at risk were counted, by five-year age groups and gender, separately for five calendar periods: 1)

1972–1978, 2) 1979–1985, 3) 1986–1992, 4) 1993–1999, and 5) 2000–2006. The expected numbers of cases for total cancer and for specific cancer types were calculated by multiplying the number of person-years in each age group and gender by the corresponding average cancer incidence in the whole of Finland during the period of observation. SIRs were calculated for all cancer cases as well as for sporadic cancers only. SIRs for sporadic cancer were calculated by excluding the identified hereditary cases. The malignant neoplasms of the offspring were classified according to the International Classification of Childhood Cancer (Kramarova et al. 1996). Multiple primary neoplasms present in one child were considered separate cancers. Clinical details of the cancers of the survivor parents and of the offspring were based on FCR data including histology of tumours.

The offspring of cancer survivors were classified according to their date of birth relative to the parent's diagnosis as follows: 1) born before diagnosis; 2) born within nine months and, 3) born later than nine months after diagnosis. SIRs were calculated for each offspring group separately, as well as for all offspring of survivors together. For the group of offspring born after the parent's diagnosis, separate analyses were conducted by primary site and gender of the survivor parent as well as by radiotherapy treatment (Yes/No).

5. RESULTS

5.1 Late effects in patients treated in childhood

5.1.1 Hypothyroidism

The prevalence, incidence, relative risk, and time frame for development of hypothyroidism were studied in patients diagnosed with cancer before their 16th birthday. Thyroxine purchase data captured 149 cases of hypothyroidism in the available follow-up period of 11 years (1993–2005), while the reimbursement database captured 157 cases of hypothyroidism in 18 years of registration (1986–2005). Thus, thyroxine purchase data proved more accurate in catching patients on thyroxine replacement therapy, and results using these data are presented (**Table 6**).

The prevalence of hypothyroidism in former cancer patients (10,509/100,000) at the end of the follow-up period was found to exceed that in the general population, in comparison both to figures for the entire population (1,573/100,000) and to those for persons below 35 years (240/100,000). Under 35-year-olds were used as the comparison group because this was the highest age reached by survivors in follow-up. With the exception of former thyroid cancer patients, prevalence at the end of follow-up was highest among Hodgkin's lymphoma (HL), central nervous system tumour, non-Hodgkin lymphoma (NHL), and neuroblastoma survivors.

With thyroid cancer patients excluded, the cumulative incidence of hypothyroidism was highest in central nervous system tumour, HL, neuroblastoma, NHL, and leukaemia survivors.

Diagnostic group ($p < 0.001$) and gender ($p < 0.0025$) were found to have a significant effect on the risk of developing hypothyroidism. Males were less prone to development of hypothyroidism (M/F HR 0.6; 95% CI 0.43–0.83). Age at diagnosis did not appear to have a significant effect on development of abnormal thyroid function ($p = 0.44$) among childhood cancer survivors. The risk of hypothyroidism was significantly higher than in the reference group (leukaemia patients) in thyroid cancer, CNS tumour, HL, and neuroblastoma patients.

The median time for the development of HT varied from 1.5 to 4.6 years, except for thyroid cancer patients, who developed HT at a median time of 4.5 months. In our study, HT developed at a median of 19 months for CNS tumour survivors, with the majority (75%) of events occurring within the first 32 months (2.7 years). The schedule for HT development among HL patients was with a median of 4.3 years, with 75% of cases developing by 6.5 years, and at a median of 2.8 in leukaemia survivors, with 75% of events occurring in 5.6 years. No obvious plateau in occurrence was observed in HL patients during the follow-up period (**Figure 9**).

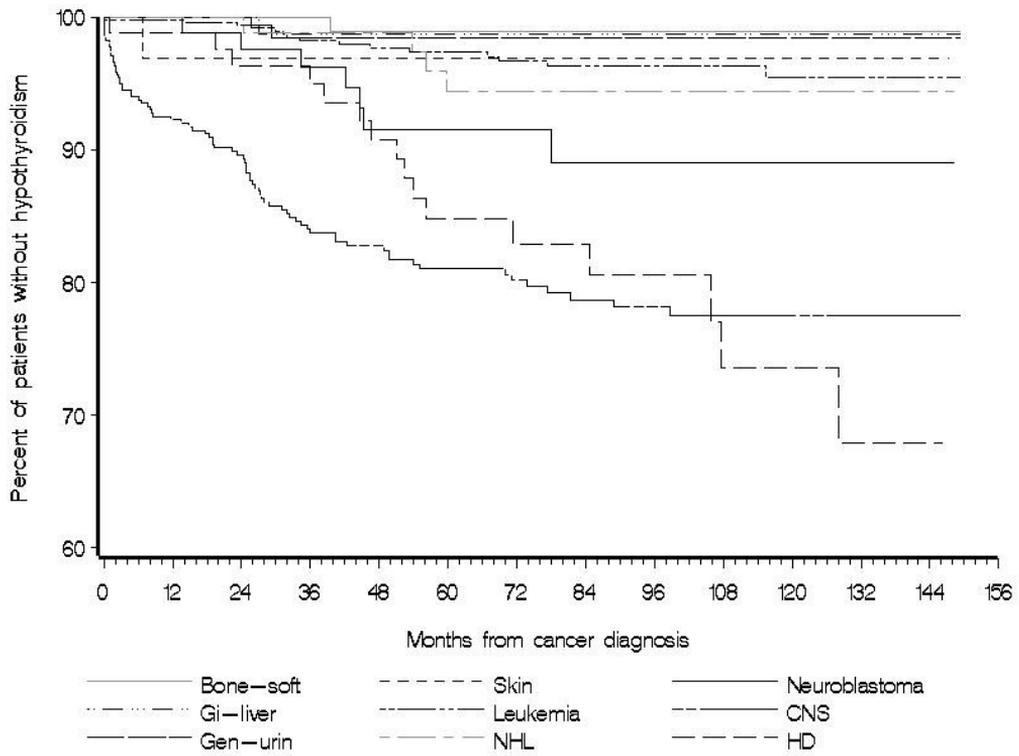


Figure 9. Time frame for development of hypothyroidism. The proportion of patients with normal thyroid function by time from diagnosis in different diagnostic groups (excluding the thyroid cancer group)

Table 6. Prevalence, cumulative incidence, relative risk, and time from diagnosis to development of hypothyroidism after cancer in childhood (0–15 years).

Diagnostic group	N	HT	Prevalence* (/100,000)	Incidence†	95% CI	Relative risk HR	95% CI	Time from diagnosis‡	
								Median	Q1-Q3
Leukaemia	509	15	4100	3.9	2.4-6.5	referent		34.1	29.3-66.9
NHL	93	4	6900	5.4	2.0-14.4	1.46	0.49-4.42	54.9	39.1-57.7
Hodgkin's lymphoma	84	16	28 800	24.6	15.1-40.2	6.32	3.12-12.78	51.7	37.1-77.9
GI and liver	89	1	2200	1.5	0.2-10.8	0.38	0.05-2.86	27.0	NA
Genitourinary	134	2	2400	1.7	0.4-6.8	0.46	0.11-2.02	27.4	25.6-29.2
Skin	33	1	1300	4.5	0.6-32.3	1.07	0.14-8.09	6.7	NA
Eye	43	0	2400	0	NA	NA	NA	NA	NA
CNS	445	79	18 900	29	23.3-36.2	7.32	4.22-12.73	19.1	2.5-32.4
Neuroblastoma	104	7	5700	11.2	5.3-23.5	2.66	1.08-6.52	42.2	24.0-45.4
Thyroid	24	23	95 000	1293.5	859.6-1946.5	147.76	73.25-298.06	4.5	3.0-8.3
Bone and soft tissue	120	1	2900	1.1	0.1-7.7	0.28	0.04-2.12	39.6	NA

*Prevalence expressed as cases per 100,000 persons

† Cumulative incidence rate per 10,000 person-months

‡ Time in months from diagnosis of cancer to first thyroxine purchase

CNS = central nervous system

HT = hypothyroidism

HR = hazard ratio

NHL = non-Hodgkin's lymphoma

N = Total number of patients

NA = not applicable

Q1 = 25 th percentile

Q3 = 75 th percentile

5.1.2 Parenthood

When parenthood was studied among childhood cancer survivors, the probability for parenting of the first child after diagnosis was reduced among males and females, RR 0.51 (95% CI 0.46–0.57) and RR 0.62 (95% CI 0.56–0.68) respectively, when compared to siblings, with the reduction being slightly, albeit not significantly, more pronounced in males (**Table 7**). No clear or significant trends in first parenthood could be observed among male or female childhood cancer survivors over calendar periods (**Table 8**).

The lowest first parenthood rates in males were in the CNS tumour and HL groups and the CNS and germ cell malignancy groups in females. Though not significantly different, reduction in parenthood rates of female leukaemia and HL survivors appeared less pronounced than among males with the same diagnoses. Probabilities of parenting a second child were not reduced for either gender (females 0.99, 95% CI 0.88–1.11 and males 1.03, 95% CI 0.90–1.81) (**Table 7**).

Table 7. Parenthood after childhood cancer – relative risks (RR) with 95% confidence intervals (CIs) estimated using a Cox proportional hazards model with age as a time variable and adjusting for birth cohort, for parenting of the first child and second child at least nine months after diagnosis.

	Males				Females			
	N	N1	RR	95% CI	N	N1	RR	95% CI
Overall								
First child after diagnosis	1476	346	0.51	0.46-0.57	1334	473	0.62	0.56-0.68
Second child after diagnosis		233	1.03	0.90-1.18		319	0.99	0.88-1.11
Diagnostic group								
Leukaemia	300	43	0.48	0.35-0.64	323	103	0.74	0.61-0.89
Hodgkin's lymphoma (HL)	101	20	0.41	0.27-0.62	67	22	0.65	0.43-0.99
Non-Hodgkin's lymphoma	118	38	0.72	0.53-0.99	64	16	0.56	0.34-0.92
Central nervous system	387	59	0.28	0.22-0.37	337	90	0.39	0.32-0.48
Sympathetic nervous system	59	12	0.48	0.27-0.84	52	25	0.85	0.58-1.26
Retinoblastoma	69	23	0.58	0.38-0.87	53	26	0.69	0.47-1.01
Renal tumours	102	30	0.65	0.46-0.93	90	36	0.69	0.50-0.96
Hepatic tumours	12	1	0.27	0.04-1.93	6	0	NA	NA
Malignant bone tumours	72	30	0.81	0.57-1.16	59	27	0.64	0.44-0.93
Soft tissue sarcomas	138	46	0.71	0.53-0.95	94	41	0.88	0.65-1.19
Germ cell, trophoblastic and other gonadal neoplasms	30	6	0.44	0.20-0.98	42	9	0.27	0.14-0.52
Carcinomas	74	30	0.69	0.49-0.99	133	71	0.86	0.68-1.08

N = total number of survivors in analysis

N1 = number of survivors with a child after diagnosis

Table 8. Probability of first parenthood following treatment for childhood cancer (0–14 years) in different diagnostic eras compared to siblings: relative risks (RR) with 95% confidence intervals (CIs), estimated by means of a Cox proportional hazards model for parenting of the first child express all sites combined.

Diagnostic era	Males		Females	
	RR	95% CI	RR	95% CI
1953–1962	0.61	0.49–0.76	0.70	0.56–0.87
1963–1972	0.48	0.38–0.59	0.58	0.48–0.70
1973–1982	0.47	0.38–0.57	0.58	0.49–0.69
1983–1992	0.50	0.40–0.64	0.65	0.54–0.77
1993–2004	0.57	0.31–1.04	0.67	0.43–1.05

5.2 Late effects in patients treated in adolescence and adulthood

5.2.1 Parenthood

Among adolescent survivors (aged 15–19 years at diagnosis), compared to siblings, the overall probability of parenting a first child after diagnosis was reduced in male (RR 0.70; 95% CI 0.63–0.79) and female (RR 0.64; 95% CI 0.58–0.70) survivors (**Table 9**). A significantly reduced relative probability of parenthood could be seen in the CNS, leukaemia, HL, and germ cell malignancy groups for both genders as well as in the malignant bone tumour and carcinoma groups among females. No clear trends in first parenthood could be observed among male or female adolescent survivors over calendar periods (**Table 11**).

In the young adult (20–34 years) age group, the parenthood disadvantage relative to siblings was significantly more reduced in females (RR 0.37; 95% CI 0.34–0.39) than in males (RR 0.56; 95% CI 0.53–0.60) (**Table 10**), this difference being most pronounced in the malignant bone tumour, carcinoma (particularly breast carcinoma), and germ cell malignancy groups. Among adult male survivors, the relative probability of parenthood was lowest among leukaemia and HL patients. In female survivors, reductions were most pronounced among leukaemia, germ cell malignancy, and breast cancer patients. Relative probabilities of parenthood were highest among male thyroid cancer, malignant bone tumour, and soft-tissue sarcoma survivors. Among females, the probabilities were least affected among thyroid cancer, NHL, and soft-tissue sarcoma survivors. There was a significant trend of an increasing probability of first parenthood over calendar periods of diagnosis among young adult male and female survivors (**Table 11**). The relative probability of parenting a second child after diagnosis was

also significantly reduced in the young adult diagnostic age-group. Though the difference was not significant, this reduction seemed slightly more pronounced among females than among males: RR 0.84; 95% CI, 0.77–0.91 and RR 0.92; 95% CI, 0.85–0.99, respectively (**Table 10**). In females, the reduction was visible in the carcinoma subgroup, mainly thyroid cancer, whereas in males no significant reductions in probability of parenting a second child by site could be seen.

Table 9. Parenthood after adolescent cancer – relative risks (RR) with 95% confidence intervals (CIs) estimated using a Cox proportional hazards model with age as a time variable and adjusting for birth cohort, for parenting of the first child and second child at least nine months after diagnosis.

	Males				Females			
	N	N1	RR	95% CI	N	N1	RR	95% CI
Overall								
First child after diagnosis	1338	327	0.70	0.63–0.79	1254	425	0.64	0.58–0.70
Second child after diagnosis	1338	213	0.97	0.84–1.11	1254	281	1.00	0.89–1.13
Diagnostic group								
Leukaemia	197	21	0.60	0.39–0.94	119	15	0.53	0.32–0.88
Hodgkin's lymphoma	223	68	0.77	0.61–0.98	211	74	0.64	0.51–0.80
Non-Hodgkin's lymphoma	96	33	1.18	0.84–1.67	60	19	0.76	0.48–1.19
Central nervous system	234	50	0.42	0.32–0.56	185	47	0.47	0.36–0.63
Malignant bone tumours	136	26	0.84	0.58–1.23	86	20	0.49	0.32–0.76
Soft tissue sarcomas	108	32	0.80	0.57–1.12	115	45	0.89	0.66–1.18
Germ cell, trophoblastic and other gonadal neoplasms	139	27	0.67	0.46–0.97	100	32	0.44	0.31–0.63
Carcinomas	163	61	0.86	0.67–1.11	338	116	0.75	0.65–0.88
Breast	1	1	2.10	0.30–14.9	6	5	1.27	0.53–3.04
Thyroid	27	16	1.04	0.64–1.71	136	72	0.67	0.53–0.85

N = total number of survivors in analysis; N1 = number of survivors with a child after diagnosis

Table 10. Parenthood after young adulthood cancer – relative risks (RR) with 95% confidence intervals (CIs) estimated using a Cox proportional hazards model with age as a time variable and adjusting for birth cohort, for parenting of the first child and second child at least nine months after diagnosis.

	Males				Females			
	N	N1	RR	95% CI	N	N1	RR	95% CI
Overall								
First child after diagnosis	6471	1161	0.56	0.53–0.60	8732	1173	0.37	0.34–0.39
Second child after diagnosis		695	0.92	0.85–0.99		649	0.84	0.77–0.91
Diagnostic group								
Leukaemia	486	23	0.29	0.19–0.44	348	12	0.14	0.08–0.25
Hodgkin's lymphoma	765	149	0.45	0.38–0.53	573	124	0.40	0.33–0.47
Non-Hodgkin's lymphoma	544	89	0.51	0.41–0.63	334	56	0.47	0.36–0.61
Central nervous system	832	133	0.52	0.43–0.61	859	99	0.31	0.25–0.38
Malignant bone tumours	202	51	0.70	0.53–0.92	124	18	0.28	0.18–0.44
Soft tissue sarcomas	538	120	0.66	0.55–0.79	526	103	0.43	0.36–0.53
Germ cell, trophoblastic and other gonadal neoplasms	1003	201	0.50	0.44–0.58	623	63	0.21	0.16–0.27
Carcinomas	1859	361	0.66	0.60–0.74	5075	665	0.36	0.34–0.40
Breast	5	0	NA	NA	1591	83	0.17	0.14–0.21
Thyroid	243	78	0.71	0.57–0.88	974	229	0.46	0.40–0.53

N = total number of survivors in analysis; N1 = number of survivors with a child after diagnosis

Table 11. Probability of parenthood among former adolescent (15–19years) and young adult (20–34 years) patients following cancer treatment in different diagnostic eras. Relative risks (RR) with 95% confidence intervals (CIs), estimated using a Cox proportional hazards model for parenting the first child, expressed for all sites combined.

Diagnostic era	Males				Females			
	Adolescents		Young adults		Adolescents		Young adults	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
1953–1962	0.82	0.59–1.14	0.62	0.50–0.78	0.70	0.52–0.94	0.22	0.16–0.28
1963–1972	0.84	0.66–1.08	0.43	0.36–0.52	0.51	0.40–0.64	0.20	0.17–0.25
1973–1982	0.66	0.53–0.82	0.48	0.42–0.55	0.59	0.49–0.71	0.28	0.24–0.32
1983–1992	0.75	0.61–0.91	0.56	0.50–0.63	0.74	0.61–0.88	0.42	0.38–0.47
1993–2004	0.52	0.39–0.70	0.70	0.63–0.78	0.69	0.56–0.86	0.51	0.46–0.57

5.3 Health of offspring

5.3.1 Preterm birth

Overall, the risks of preterm delivery (OR 1.59; 95%CI 1.26–2.01) and early preterm delivery (OR 2.0; 95%CI 1.30–3.06) were elevated among female cancer survivors when compared to female siblings. This elevation was still significant after adjustment for the main confounders, OR 1.46 (95% CI 1.14–1.85) and OR 1.75 (95% CI 1.12–2.72), respectively. The crude risk of delivering a low birth weight (LBW) infant was significantly increased (OR 1.68; 95% CI 1.29–2.18) but not after adjustment for duration of pregnancy (OR 1.11; 95% CI 0.76–1.64), suggesting that these LBW infants were nevertheless adequate weight for their gestational age.

Table 12. Risk of preterm delivery by cancer site of survivor mother compared to siblings.

Primary site	Outcome			
	Preterm delivery (<37wks)		Early preterm delivery (<34wks)	
	Patients (n=1,309)	OR (95%CI)	Patients (n=1,309)	OR (95%CI)
Leukaemia	9/119	1.47 (0.73–2.96)	2/119	1.32 (0.31–5.60)
Lymphomas	16/214	1.38 (0.80–2.36)	3/214	1.04 (0.32–3.41)
Brain and CNS	10/141	1.33 (0.69–2.59)	5/141	2.67 (1.04–6.87)
Sympathetic nervous system	2/20	2.19 (0.50–9.70)	1/20	4.30 (0.53–34.93)
Retinoblastoma	1/12	1.80 (0.23–14.30)	0/12	NA
Kidney	8/33	5.50 (2.39–12.64)	4/33	9.31 (2.93–29.57)
Malignant bone	2/29	0.99 (0.22–4.37)	0/29	NA
Soft tissue sarcomas	6/97	1.15 (0.49–2.69)	0/97	NA
Germ cell	9/56	2.94 (1.38–6.25)	3/56	3.26 (0.91–11.69)
Carcinomas	38/574	1.22 (0.86–1.76)	13/574	1.68 (0.90–3.11)
Other	1/14	1.52 (0.20–11.82)	0/14	NA

As numbers by diagnostic age-group were small, the effect of primary site of diagnosis (**Table 12**) on the risk of preterm delivery was studied in the entire population of female cancer survivors. Despite the small numbers for most cancer sites (**Table 12**), significance was established for an elevated risk of preterm delivery among survivors of kidney tumours (OR 5.50, 95% CI 2.39–12.64) and germ cell tumours (OR 2.94, 95% CI 1.38–6.25). In addition, the risk of early preterm delivery was increased in survivors of brain and central nervous system tumours (OR 2.67, 95% CI 1.04–6.87) as well as kidney tumours (OR 9.31, 95% CI 2.93–29.57). The risk of LBW was elevated, though not significantly, in survivors of kidney tumours (OR 2.74, 95% CI 0.63–12.03). All kidney tumour patients delivering prematurely had been diagnosed in childhood with Wilms' tumours (WT), whereas three out of nine germ cell tumour survivors with a preterm delivery were diagnosed in adolescence and six in adulthood. In total, early preterm delivery occurred in five CNS tumour survivors, two of whom were diagnosed in childhood, two in adolescence, and one in adulthood.

Due to small numbers, the effect of treatment on the risk of preterm delivery was also explored without diagnostic age categorisation. Overall, patients receiving radiotherapy treatment were at an increased risk of preterm delivery when compared to siblings (**Table 13**). Abdomino-pelvic irradiation increased the risk of preterm delivery. Cranial irradiation and irradiation directed at other sites were not associated with an increased risk of the outcomes studied (**Table 13**). Among patients who did not receive radiotherapy, chemotherapy was associated with a significantly elevated risk of preterm delivery, as 19/155 receiving chemotherapy had a preterm delivery (OR 2.42, 95% CI 1.45–4.05). Out of 598 patients receiving surgery alone, however, only 43 had

a preterm delivery and were not at a significantly elevated risk of preterm delivery (OR 1.33, 95% CI 0.95–1.87).

Table 13. Effect of radiotherapy on risk of preterm delivery and low birth weight.

Treatment	Preterm delivery <37weeks		Early preterm delivery <34weeks		LBW	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
No radiotherapy	64/761	1.58 (1.18-2.11)	23/761	2.24 (1.38-3.66)	50/761	1.26 (0.84-1.90)
Chemotherapy	19/155	2.42 (1.45-4.05)				
Surgery only	43/598	1.33 (0.95-1.87)				
Radiotherapy	36/434	1.49 (1.03-2.16)	11/434	1.81 (0.94-3.51)	28/434	1.14 (0.66-1.98)
Abdomino-pelvic	13/72	3.81 (2.02-7.19)	4/72	4.51 (1.54-13.20)	11/72	2.01 (0.75-5.39)
Cranial	7/151	0.78 (0.36-1.70)	3/151	1.34 (0.41-4.44)	3/151	0.46 (0.12-1.69)
Other	16/211	1.35 (0.79-2.31)	4/211	1.35 (0.48-3.82)	14/211	1.26 (0.58-2.77)

Offspring of childhood cancer survivors

Preterm birth risk was explored among female childhood cancer survivors. Offspring of these survivors were found to have a 1.6-fold increased risk of preterm birth (<37 weeks) and a 2.4-fold risk of early preterm birth (<34weeks) in comparison to offspring of female siblings (**Table 14**). Offspring of patients were, however, adequate for gestational age, as the seemingly elevated crude risk of being born weighing less than 2500g (OR 1.96; 95% CI 1.23–3.12) disappeared after adjustment for gestational age (OR 1.61; 95% CI 0.80–3.21).

In survivors delivering more than 10 years after diagnosis, the risk of preterm delivery was nearly double that among siblings (**Table 14**). Furthermore, the risk of early preterm delivery was elevated among those delivering later than 10 years from diagnosis (OR 2.48; 95% CI 1.15–5.36). Similarly, the risk of delivering a low-birth-weight infant was elevated for those survivors delivering at 10 or more years after diagnosis, though non-significantly (OR 1.74; 95% CI 0.84–3.62). Paediatric patients who received abdomino-pelvic irradiation were at a fourfold and sixfold increased risk of preterm and early preterm delivery, respectively.

In view of the small numbers, risks of the outcomes by the mother's primary site were calculated for all three diagnostic age-groups combined (**Table 12**). The risks of preterm delivery (OR 5.50, 95% CI 2.39–12.64) and low-birth-weight (OR 2.74, 95% CI 0.63–12.03) were elevated among WT survivors, however; the risk of low birth weight was not significantly elevated. The preterm birth analysis was performed without this high-risk group, and the risk among childhood cancer survivors overall was no longer significantly elevated after exclusion of WT patients (OR 1.26, 95% CI 0.76–2.08).

Table 14. Risk of preterm birth and low birth weight in offspring of female childhood cancer survivors compared to offspring of female siblings overall, by time from diagnosis to delivery and abdomino-pelvic radiation treatment, expressed as adjusted odds ratios (ORs).

Outcome	Overall		Time from diagnosis						Abdomino-pelvic irradiation			
	N	N1	OR (95% CI)‡	<10 years			≥10 years			N	N1	OR (95% CI)
				N	N1	OR (95% CI)	N	N1	OR (95% CI)			
Preterm birth <37wks*	297	25	1.62 (1.05–2.51)	54	3	1.11 (0.34–3.64)	243	22	1.73 (1.08–2.75)	37	7	4.01 (1.71–9.40)
Early preterm birth <34wks*	297	9	2.38 (1.15–4.94)	54	1	1.81 (0.24–13.93)	243	8	2.48 (1.15–5.36)	37	7	6.09 (1.70–21.82)
Low birth weight†	297	21	1.61 (0.80–3.21)	54	2	0.89 (0.11–7.35)	243	19	1.74 (0.84–3.62)	37	6	1.96 (0.54–7.07)

* Adjusted for maternal age, delivery year, child gender, maternal smoking, maternal hypertension, placental problems, use of assisted reproductive technologies, malpresentation and caesarean section

† Additionally adjusted for gestational weeks

‡ 95% confidence interval

N = total number of births

N1 = number of births with an outcome

Offspring of adolescent and young adult survivors

Among offspring of survivors of adolescent cancer, the risk for being born earlier than 37 weeks was elevated, although not significantly (OR 1.56; 95% CI 0.96–2.55) as was the case for the early preterm delivery outcome (**Table 15**). However, the risk of preterm delivery was fivefold and significantly elevated among adolescents who had received abdomino-pelvic irradiation.

Offspring of mothers diagnosed as young adults were at a significantly increased risk of preterm delivery as compared to offspring of siblings (OR 1.36; 95% CI 1.01–1.85) (**Table 16**). A significantly elevated risk of LBW was observed among young adult cancer survivors in crude analyses (OR 1.61; 95% CI 1.16–2.24). After adjustment for gestational age, the association disappeared in this age group. In young adult cancer survivors delivering more than 10 years from diagnosis, the risk of preterm delivery was nearly triple that among siblings. It is noteworthy, however, that in this subgroup the proportion of those receiving radiotherapy among those delivering prematurely was eight out of 10. The risk of preterm delivery was significantly elevated among survivors of germ cell tumours (OR 2.94, 95% CI 1.38–6.25) (**Table 12**). Three out of nine germ cell tumour survivors with a preterm delivery were diagnosed in adolescence and six in adulthood. The risk of preterm delivery among adulthood cancer survivors was no longer significantly elevated after exclusion of the high-risk subgroup of germ cell tumour patients (OR 1.29, 95% CI 0.94–1.77). Risks of preterm delivery and low birth weight were elevated among patients receiving abdomino-pelvic irradiation, though significantly only for low birth weight. Interestingly, in the young adult age group, the risk of preterm delivery was significantly increased among 37 of the 452 patients whose treatment regimens did not include radiotherapy.

Table 15. Risk of preterm birth and low birth weight in offspring of female adolescent cancer survivors compared to offspring of female siblings by time from diagnosis to delivery and abdomino-pelvic radiation treatment, expressed as adjusted odds ratios (ORs).

Outcome	Overall		Time from diagnosis						Abdomino-pelvic irradiation			
	N	N1	OR (95% CI)‡	<10 years		≥10 years		N	N1	OR (95% CI)		
				N	N1	OR (95% CI)	OR (95% CI)					
Preterm birth* <37wks	249	19	1.56 (0.96–2.55)	176	12	1.46 (0.80–2.67)	73	7	1.78 (0.79–3.98)	14	3	5.44 (1.45–20.48)
Early preterm birth* <34wks	249	5	1.74 (0.68–4.40)	176	3	1.58 (0.49–5.17)	73	2	2.04 (0.48–8.76)	14	1	9.15 (1.11–75.33)
Low birth weight†	249	14	0.88 (0.38–2.04)	176	9	0.97 (0.36–2.56)	73	5	0.68 (0.14–3.30)	14	1	0.33 (0.03–4.16)

*Adjusted for maternal age, delivery year, child gender, maternal smoking, maternal hypertension, placental problems, use of assisted reproductive technologies, malpresentation and caesarean sections

†Additionally adjusted for gestational weeks

‡ 95% confidence interval

N = total number of births

N1 = number of births with an outcome

Table 16. Risk of preterm birth and low birth weight in offspring of female adult cancer survivors compared to offspring of female siblings by time from diagnosis to delivery and abdomino-pelvic radiation treatment, expressed as adjusted odds ratios (ORs).

Outcome	Overall		Time from diagnosis				Abdomino-pelvic irradiation						
	N	N1	OR (95% CI)‡	<10 years		≥10 years		N	N1	OR (95% CI)	N	N1	OR (95% CI)
				N	N1	OR (95% CI)	N						
Preterm birth* <37wks	763	58	1.36 (1.01–1.85)	705	48	1.26(0.91–1.74)	58	10	2.66 (1.26–5.63)	21	3	2.44 (0.67–8.92)	
Early preterm birth* <34wks	763	17	1.53 (0.87–2.67)	705	16	1.63 (0.92–2.88)	58	1	0.72 (0.09–5.62)	21	0	NA	
Low birth weight†	763	45	1.03 (0.63–1.67)	705	36	0.91 (0.53–1.55)	58	9	2.05 (0.70–6.05)	21	4	6.94 (1.35–35.73)	

*Adjusted for maternal age, delivery year, child gender, maternal smoking, maternal hypertension, placental problems, use of assisted reproductive technologies, malpresentation and caesarean sections

†Additionally adjusted for weeks of gestation

‡ 95% confidence interval

N = total number of births

N1 = number of births with an outcome

5.3.2 *Early death, stillbirth, and neonatal morbidity among offspring*

In total there were 17 early deaths among offspring of patients compared to 106 among offspring of siblings. In both groups the majority of deaths occurred in the neonatal period 15/17 (88%) and 67/106 (63%), for patients and siblings offspring, respectively. After 1987, there were 12 stillbirths among former patients and 50 among siblings.

Overall, offspring of female cancer survivors did not have a significantly elevated risk of early death before the age of one year compared to offspring of siblings (**Table 17**). Though non-significant, our results suggest an increased risk for early neonatal deaths (first week of life).

In all, deaths from diseases and medical causes within the first year of life were evenly distributed between offspring of survivors and siblings (17/3,706 (0.46%) vs. 93/21,881 (0.43%)). The largest categories of early death causes were delivery complications and prematurity as well as congenital anomalies and conditions. There were 9 (0.2 %) deaths due to prematurity or delivery complication among offspring of patients and 8 (0.2 %) due to congenital anomaly or congenital disease. Among offspring of siblings 36 (0.2 %) deaths were due to prematurity or delivery complication and 47 (0.2 %) due to congenital anomaly or congenital disease. Additionally, there were 13 violent deaths (accidental or due to sudden infant death syndrome) among offspring of siblings, whereas among patients' offspring there were none in this category.

The risks of stillbirth and birth asphyxia were not elevated in offspring of patients compared to offspring of siblings but there was a significantly increased risk (OR 1.44, 95% CI 1.25–1.66) for the need for neonatal monitoring or intensive care in patients' offspring compared to siblings' offspring (**Table 18**). Though risk for cardiopulmonary resuscitation (CPR) or respirator care appeared significantly elevated in crude analyses, these associations disappeared after adjustment for confounders.

5.3.3 *Cancer in offspring*

In total, 26,331 patients' offspring and 58,155 siblings' offspring could be followed up for cancer. They contributed 560,611 and 998,517 person-years, respectively. Among all offspring of patients the overall incidence rate of cancer for all sites combined was elevated, SIR 1.43 (95% CI 1.27–1.59). After exclusion of hereditary cases, however, the SIR dropped to 1.08 (95% CI 0.94–1.22), similar to that among offspring of siblings SIR 1.07 (95% CI 0.94–1.21) (**Table 19**).

Among the 9,877 children born after their parent's diagnosis, 65 were diagnosed with cancer, yielding an increased risk of cancer (SIR 1.67; 95% CI 1.29–2.12) (**Table 19**). By sub-site of cancer in offspring, significant increases in risk were seen in the brain and CNS tumour (SIR 2.27; 95% CI 1.37–3.55) and retinoblastoma (SIR 8.98, 95% CI 2.91–20.94) groups (**Table 20**). From 65 affected offspring born nine months after their parents' diagnosis or later, 25 hereditary cancers were identified – six cases with

Li-Fraumeni syndrome, six of retinoblastoma, three of von Hippel Lindau, one MEN 2, one HNPCC, six neurofibromatosis, one familial Hodgkin's lymphoma syndrome, and one hereditary kidney cancer (**Appendix Table A1, Publication V**). After removal of these 25 hereditary cancer syndromes, the observed increase in risk disappeared (SIR 1.03; 95% CI 0.74–1.40). By sub-site, a slight elevation in risk of brain and CNS tumors (SIR 1.2; 95% CI 0.58–2.21) remained, albeit non-significant (**Table 20**).

The risk of cancer in offspring born ($n = 15,708$) prior to their parent's cancer diagnosis was elevated (232 cases, SIR 1.37, 95% CI 1.20–1.54), but removing 49 hereditary syndromes resulted in a diminished and non-significant association (SIR 1.08, 95% CI 0.93–1.25). Similar criteria were used to identify hereditary cases among offspring born before their parent's diagnosis to those used for offspring born after diagnosis. Among sporadic cases, it appeared that only the risk of thyroid cancer was significantly elevated among offspring born before the parent's diagnosis (**Table 21**). All 17 sporadic cases of thyroid cancer in offspring were either papillary ($n = 15$), follicular ($n = 1$) or medullary ($n = 1$) adenocarcinomas. The distribution of malignancies in their parents was heterogeneous.

Among the 746 offspring born within nine months of their parent's diagnosis, there were eight malignant neoplasms diagnosed, of which six were sporadic. One woman diagnosed at the age of 37 years with both an endometrial adenocarcinoma and an adenocarcinoma of the transverse colon was removed as a hereditary case due to hereditary non-polyposis colorectal cancer syndrome, as the father had also been diagnosed with adenocarcinoma of the transverse colon at 32 years of age. The overall risk of sporadic cancer in this subgroup was not significantly elevated (SIR 1.23, 95% CI 0.45–2.67).

Overall, the risk of sporadic cancer was not elevated in offspring of male (SIR 0.54 95% CI 0.01–3.01) or female cancer survivors (SIR 1.91; 95% CI 0.62–4.45). Radiotherapy treatment did not affect the risk (SIR 0.91 95% CI 0.51–1.49) of cancer in post-diagnosis offspring. With all sites considered, sporadic cancer risk in offspring born more than nine months after their parent's diagnosis was not affected by the primary site in the parent. Although diagnosis of Hodgkin's lymphoma in the parent did not significantly increase the overall risk of a cancers in offspring ($n = 6$, SIR 1.42, 95% CI 0.52–3.09), the risk of thyroid cancer was significantly elevated in their offspring ($n = 2$, SIR 9.65, 95% CI 1.17–34.84). Age of the parent did not affect the risk of sporadic cancer in offspring.

Table 17. Risk of early neonatal death (within one week), neonatal death (within one month, first week included), and infant death (up to one year) from the Cause-of-Death registry (1969-2007) among offspring of female cancer survivors born nine months after diagnosis or later as compared with offspring of female siblings

Birth outcome	Offspring of female		Crude OR	95% CI‡	Adjusted OR*	95% CI
	Patients (N=3,706)	Siblings (N=21,881)				
Early neonatal death (<7d)	12	56	1.27	0.66–2.46	1.81	0.89–3.65
Neonatal death (<28d)	15	67	1.34	0.74–2.44	1.65	0.84–3.24
Infant death (<1yr)	17	106	0.95	0.56–1.62	1.30	0.71–2.36

*Adjusted for maternal age, delivery year, child gender, birth order, previous history of neonatal death

‡ 95% Confidence interval

Table 18. Crude and adjusted odds ratios (ORs) for stillbirths and neonatal morbidity outcomes among offspring of women with a history of cancer compared with offspring of female siblings from the Medical Birth Registry data

Birth outcome	Offspring of female				Crude OR	95% CI	Adjusted OR	95% CI**
	Cancer survivors N= 3 504 ‡ (%)	Siblings N= 16 915 ‡ (%)						
Stillbirth*	12/3516 (0.3)	50/16965 (0.29)			1.15	0.61–2.19	0.77	0.33–1.78
CPR or respirator care*	60 (1.7)	182 (1.1)			1.63	1.20–2.23	1.12	0.76–1.65
Monitoring or NICU care*	450 (12.8)	1312 (7.8)			1.90	1.64–2.19	1.44	1.25–1.66
Birth asphyxia*	79 (2.3)	322 (1.9)			1.21	0.92–1.59	0.92	0.70–1.22

* Adjusted for maternal age, delivery year, child sex, maternal smoking, maternal hypertension, placental problems maternal infections, gestational age, birth order, maternal diabetes or impaired glucose tolerance, pre-eclampsia

**95% Confidence interval

‡Only livebirths included in analyses of all neonatal morbidity outcomes

Table 19. Standardised incidence ratios (SIR) for overall cancer among offspring born at different time-points relative to their parent's cancer diagnosis, as well as among offspring of siblings

	Offspring of Patients										Offspring of Siblings			
	All cases					Sporadic					Exp	SIR	95% CI	
	Obs	Exp	SIR	95% CI	N	Exp	SIR	95% CI	N					
All offspring	305	213.7	1.43	1.27–1.59	229	212.61	1.08	0.94–1.22	239	222.67	1.07	0.94–1.21		
Born >9 months after dg	65	38.95	1.67	1.29–2.12	40	38.76	1.03	0.74–1.40						
Born within 9 months	8	4.92	1.63	0.70–3.20	6	4.89	1.23	0.45–2.67						
Born before dg	232	169.84	1.37	1.20–1.54	183	168.97	1.08	0.93–1.25						

Table 20. Standardised incidence ratios (SIRs) with 95% confidence intervals (CI) for malignant neoplasms, including and excluding hereditary cases, observed among offspring born >9 months after parent's cancer diagnosis.

Primary cancer among offspring	Offspring born > 9 months after diagnosis											
	All cases					Sporadic cases						
Primary site	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
Person-years			146,794				146,352					
All sites	65*	38.95	1.67	1.29-2.12	40*	38.76	1.03	0.74-1.40				
Leukemia	11	6.55	1.68	0.84-3.00	11	6.54	1.68	0.84-3.01				
Non-Hodgkin lymphoma	2	2.51	0.80	0.10-2.87	2	2.50	0.80	0.10-2.89				
Hodgkin lymphoma	2	2.35	0.85	0.10-3.07	1	2.34	0.43	0.01-2.38				
Brain and CNS	19	8.36	2.27	1.37-3.55	10	8.33	1.20	0.58-2.21				
Neuroblastoma	1	1.17	0.86	0.02-4.76	1	1.17	0.86	0.02-4.77				
Eye	5	0.56	8.98	2.91-20.94	0	0.56	0	0-6.64				
Kidney	2	1.43	1.40	0.17-5.04	0	1.43	0	0-2.58				
Liver	1	0.33	2.99	0.08-16.66	1	0.33	3.00	0.08-16.73				
Bone	1	0.81	1.24	0.03-6.88	1	0.81	1.24	0.03-6.90				
Soft tissues	3	1.12	2.68	0.55-7.84	1	1.11	0.90	0.02-5.00				
Thyroid gland	4	1.82	2.19	0.60-5.61	3	1.81	1.65	0.34-4.83				
Skin, non-melanoma	1	0.37	2.71	0.07-15.11	0	0.37	0	0-10.06				
Breast	5	3.19	1.57	0.51-3.66	3	3.15	0.95	0.20-2.78				
Testis	3	1.77	1.70	0.35-4.95	3	1.76	1.70	0.35-4.97				
Colon and rectum	2	1.55	1.29	0.16-4.66	1	1.54	0.65	0.02-3.62				

*All sites includes 2 sporadic tumors of 'Other sites': 1 stomach and 1 urinary bladder. Additionally there is one hereditary case of cortical carcinoma of the adrenal gland in a survivor-offspring pair with Li Fraumeni syndrome.

Table 21. Standardised incidence ratios (SIRs) with 95% confidence intervals (CI) for malignant neoplasms, including and excluding hereditary cases, observed among offspring born before diagnosis

Primary cancer among offspring	All cases					Offspring born before diagnosis				
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	SIR	95% CI
Person-years			398,558						397,432	
All sites	232	169.80	1.37	1.20–1.54	183	168.97	1.08	0.93–1.25		
Leukemia	13	13.99	0.93	0.49–1.58	13	13.96	0.93	0.50–1.59		
Non-Hodgkin lymphoma	9	9.71	0.93	0.42–1.76	9	9.67	0.93	0.43–1.76		
Hodgkin lymphoma	9	8.31	1.08	0.50–2.05	8	8.28	0.97	0.42–1.90		
Brain and CNS	46	24.37	1.89	1.38–2.52	33	24.29	1.36	0.94–1.91		
Neuroblastoma	1	1.71	0.58	0.01–3.24	1	1.71	0.58	0.01–3.25		
Eye	3	1.19	2.52	0.52–7.37	3	1.19	2.53	0.52–7.39		
Kidney	7	4.70	1.49	0.60–3.06	5	4.68	1.07	0.35–2.49		
Liver	1	1.12	0.90	0.02–4.98	1	1.11	0.90	0.02–5.01		
Bone	2	2.67	0.75	0.09–2.70	1	2.66	0.38	0.01–2.09		
Soft tissues	9	3.42	2.63	1.20–4.99	7	3.41	2.05	0.83–4.22		
Thyroid gland	23	9.50	2.42	1.53–3.63	17	9.45	1.80	1.05–2.88		
Skin, melanoma	12	10.03	1.20	0.62–2.08	12	9.98	1.20	0.62–2.10		
Breast	30	28.67	1.05	0.71–1.49	21	28.42	0.74	0.46–1.12		
Cervix	4	3.59	1.11	0.30–2.84	4	3.57	1.12	0.31–2.86		
Ovary	5	4.12	1.21	0.39–2.83	5	4.09	1.22	0.40–2.85		
Testis	6	6.51	0.92	0.34–2.00	6	6.49	0.92	0.34–2.01		
Colon and rectum	23	9.23	2.49	1.58–3.73	13	9.18	1.42	0.75–2.42		

6. DISCUSSION

6.1 Late effects of cancer in childhood

Diagnostic subgroup, mode of treatment, and time elapsed from treatment are modifiers of risk in a wide range of outcomes studied in childhood cancer survivors.

In **Study I**, we evaluated the incidence and prevalence of hypothyroidism in the cancer survivor population in Finland. Previous studies exploring hypothyroidism as a late effect focused on HL (Hancock et al. 1991; Bhatia et al. 1996a; Sklar et al. 2000; Metzger et al. 2006) and CNS (Livesey et al. 1989; Ogilvy-Stuart et al. 1991; Heikens et al. 1998; Schmiegelow et al. 2003a; Schmiegelow et al. 2003b; Mulhern et al. 2004) tumour patients as well as patients receiving stem cell transplants for haematological malignancies (Bakker et al. 2004; Steffens et al. 2008; Savani et al. 2009) or cranial irradiation (Chow et al. 2009).

Hypothyroidism if untreated can cause stunted growth or developmental delay in children and infertility in adolescence and adulthood. Subclinical hypothyroidism, that manifests as prolonged elevated thyroid stimulating hormone levels, may increase the risk of thyroid gland nodules and even lead to thyroid malignancy (Sklar et al. 2000; Acharya et al. 2003). Therefore, hypothyroidism is recognised as an important treatable late-effect of childhood cancer, and our goal was to evaluate how common a problem this is and the time point of occurrence after treatment for childhood cancer as well as to identify possible patient groups at risk, thus providing information applicable in the planning of surveillance and screening of cancer survivors.

In our study, the incidence of hypothyroidism was found to be higher among childhood cancer survivors than the general population. The main risk factors identified were diagnostic group and female gender. The results concerning differences between diagnostic groups supported the results of previous studies (Schmiegelow et al. 2003a) with thyroid carcinoma, brain and central nervous system tumours and Hodgkin's lymphoma survivors being at highest risk, reflecting the thyroid effects of radiotherapy-based treatment modalities. The female predisposition to thyroid hypofunction is supported by other studies (Sklar et al. 2000; Madanat et al. 2007). Neck and mediastinal radiotherapy in the case of Hodgkin's lymphoma patients results in peripheral HT, while cranial or craniospinal radiotherapy in CNS tumour patients most likely results in central HT by affecting the hypothalamo-pituitary-thyroid axis. In the case of thyroid cancer, surgery and pharmacological intervention result in hypothyroidism. Incomplete treatment data in the FCR did not allow for direct analysis of treatment; however, 20/149 patients who developed HT had received only chemotherapy according to the records of the cancer registry, suggesting possible toxicity of chemotherapy to the thyroid gland. The high cumulative incidence of HT among neuroblastoma survivors is most likely explained by intensive therapies including stem cell transplant with TBI as conditioning as well as radiotherapy to the

primary tumour, both of which cause HT by scatter to the thyroid. A hospital-based study by our group (Madanat et al. 2007) further explored the effects of treatment on the risk of hypothyroidism. Detailed treatment data could be extracted from hospital records of 291 former childhood cancer patients. Hypothyroidism occurred in about half of the central nervous system and Hodgkin's disease patients, while the equivalent figure with the registry-based approach was only 20%, indicating the superiority of the hospital-based record study in capturing HT cases. CNS tumour survivors developed hypothyroidism earlier than did other patient groups. Radiotherapy, both on its own and in combination with chemotherapy, was associated with a higher risk than chemotherapy alone.

In the overall analysis, age at diagnosis was not a risk factor for HT, a finding in agreement with the previous abovementioned hospital-based study (Madanat et al. 2007). Two other studies explored the time frame for HT development after CNS tumours. One was in agreement with our result concerning early development of hypothyroidism after brain and central nervous system tumours (median 1.5 years) and reported a median time of 1.7 years (Madanat et al. 2007). The other, not directly comparable as it focused on medulloblastoma survivors, reported development of abnormal thyroid function between six months and six years after therapy (Oberfield et al. 1986). The result of schedule for development of thyroid hypofunction after Hodgkin's lymphoma (median 4.3years Q1–Q3 3.1–6.5) was in agreement with results from two other studies one reporting a median of 5.7years (Q1–Q3 1.5–8.0)(Madanat et al. 2007) and the other a median of 2.9years (range 0.7–11.3) (Metzger et al. 2006). Although hypothyroidism presents quite soon after cancer diagnosis in thyroid and brain tumour patients, the time for appearance of hypothyroidism is long in most diagnostic groups for childhood cancer, justifying the need for long-term follow-up of survivors for thyroid abnormalities.

The probability of parenthood among childhood cancer survivors was around half of that among healthy siblings, with CNS, HL and germ cell tumour survivors suffering the largest disadvantage and males seemingly more affected than females. Because of the physiological depletion of the follicular pool with age (Faddy et al. 1992; Gosden et al. 1994), younger age at diagnosis is thought to be a protective factor with regard to effect on female reproductive function (Wallace et al. 2003; Wallace et al. 2005a), which may explain the subtle difference in parenthood probability rates in favour of female gender in this age group. Furthermore, the pre-pubertal testis is particularly susceptible to the adverse effects of chemotherapy and radiotherapy (Whitehead et al. 1982; Chatterjee et al. 1994; Mackie et al. 1996; Papadakis et al. 1999; Jahnukainen et al. 2007).

Generally, treatment in childhood rather than later in life is more likely to affect parenthood, for various reasons. Psychological effects of treatment given in childhood may have different implications than if given later in life, especially if diagnosed close to puberty. It is known that former CNS tumour patients are the most vulnerable, particularly those diagnosed at an early age (Ross et al. 2003; Bhat et al. 2005; Turner

et al. 2009). Cognitive, physical and emotional special needs endanger these patients and affect their ability to adapt to society and lead productive lives. Physical sequelae such as handicap associated with CNS tumour survivorship may also hinder the psychosocial well-being of a cancer survivor. A recent study reported the lowest marriage rates to be among male CNS tumour survivors (Frobisher et al. 2007). Also, direct effects of treatment (namely, alkylator sensitivity of testicular tissue) may explain a large part of the male disadvantage in this group (Whitehead et al. 1982; Watson et al. 1985; Wallace et al. 1989c; Mackie et al. 1996). Although scatter from craniospinal irradiation may directly affect ovarian function, the most common mechanism underlying reduced fertile potential following cranial irradiation is central as both craniospinal and cranial irradiation, typically used in the treatment of some brain tumours and earlier in ALL with CNS involvement, cause hypogonadotrophic hypogonadism (Littley et al. 1989; Bath et al. 2001). Thus both direct effects of therapy, with the resulting infertility, and psychosocial effects that may impair independence in adolescence and later finding of a partner could play a role in low parenthood rates among both male and female CNS cancer survivors.

The low parenthood rates in male HL patients are explained by the gonadotoxicity of chemotherapy. Alkylator-based regimens (e.g., MOPP, MVPP, ChIVPP, and COPP) used in HL treatment have been reported to cause azoospermia in 85% of adult males (Wallace 2004a). In females, low parenthood rates among germ cell tumour survivors are explained by surgical and other treatment directly involving the ovaries or the hypothalamo-pituitary axis in the case of intracranial tumours.

Other factors that may underlie lower parenthood rates in childhood cancer survivors are linked to psychosocial well-being. A recent report from the childhood cancer survivor study reported 1.5 times higher rates of anxiety and depression among adolescent cancer survivors in comparison to siblings and showed survivors to be 1.7 times as likely to display antisocial behaviours (Schultz et al. 2007). Another recent report which investigated leaving home as a measure of social independence of survivors of cancer in childhood and adolescence found that the psychosocial effects of cancer treatment impeded achievement of social independence among CNS tumour survivors (Koch et al. 2006). Yet another study described delayed development of sexual identity/esteem and reported delayed separation from parents in survivors of childhood cancer (Kokkonen et al. 1997).

Two studies explored body image and sexual self-image in female leukaemia survivors and found them to be more negative than those of controls (Puukko et al. 1997a; Puukko et al. 1997b). These kind of psychosocial outcomes may hinder a survivor from finding a partner and/or establishing a family.

As employment status may influence decisions about parenting, childhood cancer survivors may be more likely to refrain from having children for financial reasons, as the risk of unemployment has been shown to be elevated among cancer survivors (de Boer et al. 2006; Pang et al. 2008).

6.2 Late effects of cancer in adolescents and young adults

For males, the relative probability of parenthood was highest among patients treated in adolescence. The parenthood advantage among adolescent cancer patients could be explained by the likelihood of sperm banking increasing after puberty. Despite this equal possibility in adolescent and adult cancer patients, adolescents were more likely to parent children, which could be explained by malignancy type and treatment regimens. The largest groups were lymphomas at 23.9% (HL 15.5%, NHL 8.4%) CNS tumour (17.8%) and leukaemia (15%) patients among adolescent males, with the equivalent-sized groups being carcinomas at 29.7%, lymphomas at 20% (HL 12.0%, NHL 8.0%) and germ cell tumours at 15.3% (14.8% testicular carcinomas) in young adults. Since HL and testicular cancer as disease processes influence spermatogenesis even prior to treatment (Rueffer et al. 2001; Magelssen et al. 2006), this may rule out the possibility of sperm banking and it may be expected that adult male fertility is more likely to be affected, which would then be reflected in lower parenthood rates. Other factors reducing fertility in testicular cancer patients include testosterone deficiency (Petersen et al. 1998) and local effects of paracrine action of the substances originating from the tumour itself (Paduch 2006). The lowest parenthood rates in adult males were found among leukaemia, HL, and testicular cancer patients. Parenthood rates in adult males with HL were similar to those observed in a previous study (45%) (Kiserud et al. 2007). A study of testicular cancer patients in Norway (Brydoy et al. 2005) reported parenthood rates of 71%, ranging from 48% in patients treated with high-dose chemotherapy to 92% in patients undergoing mere surveillance after orchiectomy. Our lower overall rate of 50% reductions for testicular cancer patients may be due to the fact that we did not differentiate between bi- and unilateral disease, whereas Brydoy et al. restricted their study to unilateral cases.

Among females, young adults had the lowest overall probability of parenthood, easily explained by higher susceptibility to effects of treatment – namely a higher incidence of complete ovarian failure and permanent infertility – due to their limited primordial follicle reserve. The parenthood disadvantage was most pronounced in the leukaemia and breast cancer groups. A large proportion of young adult leukaemia patients have undergone stem cell transplantation in recent decades (Gratwohl et al. 2008). The high-dose treatments related to stem cell transplantation, such as total-body irradiation, could explain the lowered parenthood rates. Systemic treatment in the form of high-dose chemotherapy for breast cancer interferes with the fertility of these women by causing temporary or permanent premature ovarian failure. Classic cyclophosphamide-containing regimens (CMF, FEC and AC) are associated with a reported incidence of amenorrhoea varying between 33% and 82%, depending on treatment duration, cumulative dose, and the patient's age (Maltaris et al. 2008). Previous population-based studies have reported similarly reduced pregnancy rates, ranging from 3–8% (Sankila et al. 1994; Mueller et al. 2003; Kroman et al. 2008). This reduction is not, however, purely a reflection of treatment-induced lowered fertility. Population-based Danish data show a considerably higher induced abortion rate (Kroman et al. 1997; Kroman et al. 2008) among breast cancer patients aged less than 45 years than in the

general population of similar age, reflecting uncertainties of patients and physicians about the safety of pregnancy after breast cancer. Also, until recently, in consequence of absence of adequate data, women were generally discouraged from further pregnancies after hormone-dependent tumours such as breast cancer, because of the gestational high oestrogen load and presumed related risk of recurrence (Russo et al. 2006). This may explain part of the low parenthood rates observed among breast cancer survivors in this study.

Similarly lowered parenthood rates were observed among males and females in the adolescent age group, despite the fact that pubertal gonadal tissue is differentially sensitive to the deleterious effects of cancer therapy in the sexes. This may be explained by the reversibility of male gonadal damage, despite higher incidence of sterility immediately after treatments than among females. Though female gonadal tissue is less sensitive to deleterious effects of treatment, resulting early menopause and thus a truncated fertile window explains the reductions in parenthood rates. The low rates in CNS, leukaemia, and HL groups are most likely attributable to similar causes as in the paediatric age group, as treatments are similar and psychological factors are likely to affect identity and independence in a similar way.

The probability of having a second child was significantly reduced only among young adult survivors, and slightly more so among female survivors. A similar pattern of a female disadvantage was noted by Syse et al., reporting reduced higher-order births among males and females (OR 0.78; 95% CI 0.75–0.81 and OR 0.64; 95% CI 0.61–0.67, respectively). The more pronounced reduction in odds ratios in this Norwegian study may be due to the inclusion of third-order births and the different diagnostic age range of patients (17–44 years). In adult females, the reduction in second-order parenthood may be due to the age-dependent depletion of the follicular pool, with adults being more likely to have experienced premature ovarian failure, attributable largely to the deleterious effects of chemotherapy and abdomino-pelvic irradiation (Sklar et al. 2006; De Bruin et al. 2008). That paediatric and adolescent cancer survivors are as likely as siblings to parent a second child may be due to the so-called ‘healthy mother effect’ (Sankila et al. 1994), i.e., patients who mothered or sired one child after diagnosis could have more favourable characteristics (preserved fertility due to locoregional treatment, longer survival) than those who did not, with the second parenthood rates therefore representing the subset of patients with limited disease.

Among young adult survivors, a significant trend of increasing relative parenthood probability with diagnostic era was visible. Both Cvancarova et al. (Cvancarova et al. 2009) and Syse et al. (Syse et al. 2007) reported a significant influence of diagnostic era on parenthood rates. This may reflect the expanding use of chemotherapy among adults; this has replaced radiotherapy as the main treatment option during the last two decades. Thus, the possibility of having children after cancer treatment has increased, as chemotherapy is more fertility-preserving than radiotherapy treatment used to be. Among paediatric patients, however, the use of chemotherapy has been common practice for a longer time already and there was no clear improvement to be seen by

diagnostic era. Among adults, the development of assisted reproductive technologies in the last two decades may also explain some of the increase.

6.3 Health of offspring

While the number and depth of studies examining offspring of childhood cancer survivors both are limited (Nagarajan et al. 2005), even less is known of the health of offspring of young adult survivors of malignancies.

6.3.1 Preterm Birth

Overall, having a previous history of cancer placed females at an elevated risk of preterm delivery. In our study, cancer patients had a 50% increased risk of delivering before 37 full weeks of gestation. Neonates of cancer survivors were, however, adequate for gestational age. Age at cancer diagnosis was an important determinant of the risk of preterm delivery.

Paediatric cancer survivors had a high risk of both preterm and early preterm delivery. Wilms' tumour patients accounted most of the increased risk. All 25 Wilms tumour patients in our study were diagnosed under the age of eight years and were most likely pre-pubertal when treated. Paediatric cancer survivors also had an increased risk of delivery earlier than 34 weeks, and there was a non-significant increased risk of LBW infants even after adjustment for duration of pregnancy. However, there was no increase in the risk of delivering an SGA infant, according to the internationally accepted definition of SGA.

Results of analyses by treatment were generally in agreement with previous studies (Chiarelli et al. 2000; Signorello et al. 2006; Mueller et al. 2009; Reulen et al. 2009), as the risk of preterm delivery was elevated among paediatric and adolescent patients receiving abdomino-pelvic irradiation. Previous studies have reported significantly elevated risks of preterm delivery and of LBW, ranging from 1.3–3.6 and 1.3–2.1, respectively (**Table 2**). Other than chance, several methodological differences may explain small differences in risk estimates. Paediatric patients in the previous studies were aged less than 21 years at diagnosis, whereas our study's age group was restricted to patients diagnosed at less than 15 years of age. Comparison groups varied, and the majority of studies used the general population. However, in one study the risks were compared to those for patients treated with non-sterilising surgery.

The risk of preterm delivery was elevated among adolescent and young adulthood cancer survivors. Despite no overall significant increase in risk among adolescents, a fivefold significant elevation in risk was seen among the subgroup of these patients receiving abdomino-pelvic irradiation. Although the exact mechanisms underlying the deleterious effects of radiotherapy on uterine function are unclear, reduced elasticity of the uterine musculature and uterine vascular damage have been suggested (Critchley et al. 1992; Sanders et al. 1996). As the uterus continues growing for several years after menarche, the pubertal or prepubertal uterus is more susceptible to the deleterious

effects of treatment than is the uterus of an adult. In young adults, however, risk of preterm delivery was not associated solely with radiotherapy exposure. Previously, most reports have addressed only survivors of cancer in childhood or an otherwise restricted subgroup of survivors (Green et al. 1989; Green et al. 2002b). Two recent studies, however, extended the age range of cancer survivors examined by including patients aged 15–35 years (Magelssen et al. 2008) and 0 to 43 years (Clark et al. 2007) at diagnosis, though results for young adults were not reported separately. In our study, adult cancer survivors were found to be unlikely to deliver LBW infants, after adjustment for gestational age. That risk of preterm delivery was also elevated in adult patients would suggest an additional pathophysiology, possibly vascular damage, in addition to that of the growth and volume restriction presumed to underlie preterm deliveries in the developing uterus.

Among young adults, deliveries occurring more than 10 years after diagnosis were more likely to be preterm. Radiation-induced fibroatrophy is a late effect of radiotherapy, which may take years to develop (Delanian et al. 2004). This may explain the finding, as the elasticity of the uterus is more likely to be restricted by fibroatrophic changes a decade or more after treatment. In this patient subgroup, radiotherapy may explain the elevated risk observed with increasing time from diagnosis to first delivery as the majority of young adult patients delivering prematurely were irradiated. Another possible explanation is the differential effect of age on obstetric risk factors. Although adjustment for age at delivery takes into account the observed higher age of patients at first delivery, the possibility that increased maternal age poses a higher obstetric risk for patients than for siblings cannot be dismissed. This is implied by previous studies showing that cancer survivors suffer a wide range of metabolic problems over time (Talvensaari et al. 1996; Chow et al. 2007). Another contributing factor may be that women in this subgroup, because of higher maternal age, experience more problems with conception and achieving pregnancy, possibly requiring more assistance from reproductive technologies, which themselves have been associated with the outcomes studied (Fernando et al. 2009).

We found an increased risk of preterm delivery among mothers who survived a germ cell tumour. Among the 56 cancer survivors with germ cell malignancies (45 with ovarian cancer), all seven mothers with preterm deliveries had received chemotherapy and none were irradiated. Furthermore, the overall result of an elevated risk of preterm delivery among survivors receiving chemotherapy is consistent with this observation. The underlying pathophysiology for preterm delivery in this patient group remains unknown, but effects of treatments other than radiotherapy cannot be dismissed as a possibility, nor can effect of the malignancy being treated.

The limitations of previous epidemiological studies include issues of data collection (use of self-administered questionnaires to obtain obstetric history) and selection of comparison groups. Several were limited to only paediatric and adolescent survivors; others grouped all patients together and reported overall rates, thus neglecting the possible effect of age at diagnosis on the outcomes.

6.3.2 *Early death, stillbirth and neonatal morbidity of offspring*

Our results indicated that the offspring of cancer survivors had an elevated risk, though not significantly, of early neonatal death (almost twofold), neonatal death or infant death in comparison with offspring of female siblings. One previous study (Signorello et al. 2010) explored neonatal death in relation to cancer treatment received by the mother and found neonatal death to be elevated among offspring of patients who had received high doses of uterine or ovarian irradiation ($>10\text{Gy}$). Another study explored overall risk of neonatal death and did not find it to be significantly elevated. Our results were in agreement with the latter study, which reported an elevated, though not significant risk of neonatal death (OR 1.37; 95% CI 0.42–4.45) (Clark et al. 2007). This study was also methodologically more similar to our study as it was population based like our study. Previous studies on mortality risk estimates are limited to the neonatal period, and our study is, to the best of our knowledge, the first study reporting later deaths up to one year of life. Our finding, although not significant, of increased risk for death during the first week and month of life may be due to the higher incidence of preterm birth among offspring of cancer patients (Signorello et al. 2006).

Our result of no increased stillbirth risk in offspring of cancer survivors compared to offspring of siblings was generally in agreement with previous studies (Green et al. 2002a; Clark et al. 2007; Winther et al. 2008). As data on treatment are incomplete in files of the Finnish Cancer Registry, comparisons to the results of a recent study indicating elevated risk in patients treated with uterine or ovarian radiation cannot be made. Clark et al. reported an adjusted OR of 0.85 (95% CI 0.34–2.13) for stillbirth among former cancer survivors (aged 0–43 years at diagnosis) compared to healthy population controls (Clark et al. 2007). Our result of an odds ratio of 0.77 (95% CI 0.33–1.78) for stillbirth was similar. A Danish study (Winther et al. 2008), which included only childhood cancer survivors, reported a stillbirth proportion ratio of 1.1 (95% CI 0.40–2.9) compared to siblings.

Etiology of stillbirth is multifactorial (Fretts 2010). According to some estimates in one fourth the underlying etiology is genetic (Wapner 2010), consisting mainly of karyotypic abnormalities 45X, trisomy 21 and trisomy 18 and 13, though single gene disorders and sporadic multiple malformation syndromes may also result in stillbirth. Cord complications and placental etiologies have been implicated in one out of four cases. Other maternal risk factors include maternal pre-eclampsia, maternal infection, nulliparity, smoking and high maternal age (Smith 2010). Due to the reported association between previous preterm delivery and subsequent stillbirth (Rasmussen et al. 2009), there is basis for the hypothesis of increased risk of stillbirth among cancer patients.

In our study, neonatal monitoring of the infant was significantly more likely among offspring of cancer survivors, even after adjustment for duration of pregnancy. Duration of pregnancy and the distribution of Apgar scores among these infants was similar as among siblings' offspring. Maternal history of cancer may place these infants under closer observation. There is, thus, a possibility of a surveillance bias as

healthcare professionals may express exaggerated concern for the health of a child of a former cancer patient. Clark and co-authors (Clark et al. 2007) explored admittance to neonatal intensive care unit as one outcome and did not find the risk to be elevated for offspring of Scottish cancer survivors. The difference may reflect differences in healthcare practices in the two countries and thus supports the theory of a surveillance bias rather than true infant morbidity underlying this excess risk observed in our study.

In our study, risk of birth asphyxia was not elevated among offspring of cancer survivors and they were not more likely to need cardiopulmonary resuscitation or ventilation assistance. These results are in accordance with a study on hospitalizations of offspring of cancer survivors, which found the risk of hospitalization due to perinatal causes (including asphyxia and respiratory distress) to be similar among offspring of survivors and siblings (Winther et al. 2010).

Cancer survivors were not at an increased risk for a pregnancy to end in stillbirth, according to our data. The similar distribution of causes underlying neonatal deaths (especially congenital anomalies and congenital diseases) among survivors and siblings is reassuring. Although this result fails to imply transgenerational effects of cancer and its treatment, further studies exploring etiology of stillbirth and the incidence of congenital malformations in the offspring of cancer survivors are needed to rule out a genetic effect.

The possibility of an excess in early mortality among offspring of former cancer patients cannot be ruled out based on our results. Further studies exploring cause specific early mortality may shed more light on this. However, the overall results regarding neonatal health and stillbirth among offspring of cancer survivors are reassuring.

6.3.3 Cancer in offspring

We found no increase in the risk of sporadic cancer among the children of survivors of non-hereditary cancer. The risk among the offspring of survivors was also similar to that for the offspring of their healthy siblings. Cancer risk in offspring born after the parent's diagnosis was similar to that in offspring born prior to the diagnosis. Among offspring born after the parent's cancer diagnosis, neither radiotherapy treatment of the parent nor the primary site could be shown to elevate the risk of cancer in offspring. In addition, offspring born within nine months of the parent's cancer diagnosis (for female survivors, thus, possibly exposed to cancer treatments *in-utero*; for males, possible exposure during sperm maturation), the risk of cancer in offspring was not found to be elevated when compared to that of the general population. The results of our study are in agreement with the other population-based study, which found a slightly elevated though non-significant risk (SIR 1.3, 95% CI 0.8–2.0) of cancer in the offspring of cancer patients (Sankila et al. 1998).

As cancer patients were identified for cancer diagnosis at 0–34 years and similarly cancer in siblings was only defined as a diagnosis occurring in this age range. Thus cancer cases occurring at age 35 or older were not included so some hereditary cases

may have been missed. However, as most tumours resulting from hereditary cancer syndromes present in early adulthood and as similar criteria were used for patients and siblings, we do not believe a substantial bias has been introduced.

The recent treatment period and the registry-based approach distinguish this study from most prior investigations (Mulvihill et al. 1987; Hawkins et al. 1989b; Hawkins et al. 1995; Green et al. 1997). Longer follow-up, exclusion of hereditary cancer syndromes, and access to siblings as a second comparison group are unique aspects of our study of cancer risk in offspring when compared to the previous report (Sankila et al. 1998). Inclusion of young adults also allowed for evaluation of children born before and after treatment.

6.4 A registry-based approach to studying late-effects of cancer: Strengths and limitations

Large population-based studies of late-effects of cancer are rare. Most studies have been based on clinical records, often lacking an adequately selected reference cohort and date back to an era of treatments that are no longer current (Hawkins et al. 2008; Leisenring et al. 2009; Robison et al. 2009). Furthermore, previous large late-effects studies have addressed the effects of cancer and its treatment in patients treated in childhood, excluding adolescent and young adult patients in whom longevity is as important and thus the study of late effects as relevant.

Two large studies of late effects have been established. One, the Childhood Cancer Survivor Study (CCSS), is a multi-institution US hospital-based study of over 14,000 five-year survivors of cancer in childhood and adolescence treated between 1970 and 1986. Information on various outcomes is collected by means of a questionnaire and medical records. The study uses siblings as a reference cohort. Recruitment of siblings is based on participation of the survivor, with a random sample of CCSS participants asked for permission to contact their nearest-age full siblings. Furthermore, information on deliveries of both patients and a sample of siblings was self-reported using questionnaires. The British Cancer Survivor Study, also a questionnaire-based study, recruited 13,000 five-year survivors of childhood (0–14 years at diagnosis) cancer treated between 1940 and 1991. The general population served as the reference population.

This study, by contrast to both, was entirely registry-based: all information used was obtained from Finnish population statistics and health registers. This approach enabled us to conduct a large, population-based study with the entire sibling cohort, comprehensive information on the children born, and several health outcomes among the patients and their offspring. The coverage and completeness of the Finnish health registers are high (Teperi 1993; Gissler et al. 2002; Gissler et al. 2004). Identification of the study cohort, as a result of the completeness of the Finnish Cancer Registry data (Teppo et al. 1994; Korhonen et al. 2002), is population-based. The computerised record linkage procedure is exceptionally precise; therefore, methodological

deficiencies in the registration or linkage procedures are unlikely to have biased study results. One shortcoming is the unreliable and often missing information on paternity in the central population register and the lack of detailed treatment data in the Finnish Cancer Registry.

Record linkages were conducted with permission from the Ministry of Social Affairs and Health and Statistics Finland. As the information from the registries was merged through record linkage with the personal identity code as a key, the study subjects were not contacted; therefore informed consent to participation was not required. A registry-based study was relatively cost-effective and fast to conduct. In this way, the study cohort and reference cohort could be identified reliably and completely. Our data were then less susceptible to biases associated with participation and response. Also, study outcomes were obtained from the same nationwide registry sources for both patients and siblings. Our data were therefore free of recall or reporting bias, as they were not based on self-reporting. Recall bias and low participation rates, which are probable when, for example, the information is obtained from interviews, could be avoided with the register-based approach used in this study.

In the case of **Study I**, since information on drug intake was not available, information on prescribed drug purchases and reimbursement data were used as proxies for thyroxine use. The drug purchase registry, though established later than the reimbursement database (1993 vs. 1986), captured more annual cases of thyroxine use per year by 2005 than the reimbursement database and therefore proved more reliable in capturing cases of hypothyroidism. Some patients may be reluctant to apply for reimbursement on account of the low cost of thyroxine, so data on drug reimbursement may be more reliable in the case of more expensive drugs. Also, information on drug purchase is only a reflection of the information on true drug intake. For example, non-compliance cannot be assessed from these sources. As hypothyroidism does not cause acute, life-threatening symptoms, some patients may neglect instructions to take thyroxine and may therefore never purchase the drug.

Also subclinical cases of hypothyroidism, known to be harmful in the long term, cannot be identified in this registry linkage approach. The time point of initiation of therapy initiation is also only a proxy for malfunction of the HP-T axis. Clinical hypothyroidism visible as low T4V or T3 may be preceded by years of a preclinical condition of elevated TSH, so the time point of drug purchase may overestimate the time for development of thyroid late effects following cancer therapy. Furthermore, our registry-based approach does not distinguish between patients with central or primary hypothyroidism.

In **Study II**, parenthood was most likely a surrogate for fertility, though not a reflection of fertile potential alone. Lower marriage rates have been reported among former paediatric cancer patients, especially among male CNS tumour survivors (Rauck et al. 1999). It is possible that parenthood may be restricted by difficulty in finding a spouse, in which case childlessness does not necessarily reflect infertility. Female patients may

be discouraged by their physicians from becoming pregnant on account of a lack of knowledge of birth outcomes and through fear of an impact on recurrence, as has been the case with breast cancer patients. By our method, it was not possible to distinguish spontaneous pregnancies from those requiring assisted reproductive technologies. Also, as paternity is more difficult to confirm, it is possible that the parenthood rates noted among male cancer survivors were more optimistic than in reality.

Registry-based methods would not allow for the evaluation of contraception use or time from cessation of contraception to successful conception. Also, fertility or infertility may be male or female, and we assume in our study that any infertility was due to the partner with a previous history of cancer, without information on semen quality or female fecundity of the spouse. Information on semen quality or female fecundity was not included, and information on incentive to conceive, contraceptive use, and lifestyle-related factors (e.g., alcohol consumption or smoking) affecting time to pregnancy was not available.

In our registry-based approach to studying parenthood probability we had no data on desire to become a parent. This is relevant, as cancer survivors have concerns that their children may be at an elevated risk of cancer (Schover et al. 1999; Schover et al. 2002). According to one survey, nine per cent of cancer survivors reported this fear as the reason for not having children (Reinmuth et al. 2008). Young women who have survived cancer appear to be overly concerned about the risk of birth defects and cancer in their children (Schover et al. 1999). Thus, the health of offspring is an important factor influencing the family planning and reproductive choices of cancer survivors. In some cases lower economic status may influence decisions to refrain from having children.

Clinical studies allow for absolute evaluation of fertility by defining serum hormone levels and sperm counts. Questionnaire studies can identify social, economic and other reasons behind low parenthood rates.

Socio-economic status has previously been shown to influence the risk of preterm delivery. In our study, results from models adjusting for socio-economic status did not, however, differ materially from the results with non-adjusted models. Although final models did not adjust for socio-economic status, this cannot be considered a substantial source of bias, as socio-economic differences in perinatal health have been shown to be small and are still diminishing in Finland. Other factors not easily accounted for are anxiety and depression, both of which have been associated with increased risk of preterm delivery – and cancer survivors are known to suffer more psychosocial problems than members of the general population do. Surveillance bias should also be considered; history of cancer may influence obstetric decisions and may place these individuals under increased surveillance.

As incidence of preterm delivery is low in Finland, thanks to the high quality of prenatal care and preventive measures, the figures in our study may not be applicable to women elsewhere in the world.

In the study of cancer in offspring, registry-based methods presented difficulties in studying cancer in offspring and identifying hereditary syndromes. For example due to the establishment of the cancer registry in 1953 meant that the screening of grandparents was incomplete and, therefore, pedigrees could be constructed to three generations for only some families.

Also, there is a possibility of a screening bias when one is interpreting registry data of cancer reports without clinical information; if a parent is diagnosed with thyroid cancer, it may be that the offspring are more easily screened and treated for a thyroid lump, which may not necessarily histologically qualify as a malignant tumour.

Although age and gender appear to influence the risk of the late effects studied, the effect of an important risk factor, namely treatment, cannot be assessed in detail through the use of registry data and would require a hospital-records-based approach for more comprehensive assessment. Although the Finnish Cancer Registry collects information on treatment, this is limited to the first four months of treatment and does not include details of the site of radiotherapy or the dose or agent of chemotherapy used. By combining information on treatment and site of tumour, we could make a rough estimate of the region irradiated; however, evaluation of dose-response still cannot be conducted.

Use of registries and record linkage methodologies is a cost-effective and comprehensive means for conducting survivorship research. The frequency and severity of many late effects can be lessened through survivor-focused health-care.

6.5 Future Aspects

With constantly developing treatments and a trend towards combination of treatment modalities in an attempt to lower the radiation doses administered, further studies are needed to explore possible combined effects of chemotherapy and radiotherapy.

For greater understanding of fertility and to distinguish other factors influencing birth rates in cancer patients, a survey study could be conducted. Information on contraceptive use, conception efforts, and possible adoption or motives to refrain from planning to have children could be obtained

A registry-based study of use of assisted reproductive technologies among cancer patients would be informative as to which diagnostic groups benefit from these technologies and what percentage of cancer patients have subfertility problems, that

can be solved with current technologies that preserve patient fertility. Knowledge of insemination and donor sperm would give a more accurate estimate of paternity rates.

Our study was extensive enough in terms of time span and cohort size to evaluate the incidence of cancer in the offspring and assess perinatal and neonatal health. A future study to evaluate the health of offspring of cancer survivors later in life as well as to evaluate the risk of congenital malformations is needed to rule out the risk of transgenerational effects of therapy.

Results of this study have clear implications for clinical practice in the setting of follow-up and counselling of cancer survivors. Tailored follow-up on the thyroid function of paediatric cancer survivors is strongly recommended, as risks vary based on primary cancer diagnosis. Patients can be advised about their fertile potential following cancer and given an estimate of the possibility of parenthood after cancer, with those who have lowered potential selected as candidates for newer fertility preservation techniques. Patients considering parenting a child can be reassured with regard to the health of potential offspring and should not be discouraged from having children, as despite the increased risk of preterm delivery associated mainly with radiotherapy treatment of the mother, our results indicate that offspring are not at an elevated risk of early neonatal or infant death, nor of sporadic cancer later in life. Our results also suggest that female cancer survivors capable of becoming pregnant should be monitored closely for risk of preterm delivery.

7. CONCLUSIONS

On the basis of the present investigation, the following conclusions can be made:

1. Former cancer patients diagnosed in childhood are at an increased risk of developing hypothyroidism. The prevalence of hypothyroidism exceeded that in the general population. Females as well as survivors of HL and CNS tumours were at highest risk of developing hypothyroidism.
2. Compared to siblings, both male and female cancer survivors were less likely to parent at least one child after diagnosis. The relative probability of parenthood was especially low in male childhood cancer survivors and female young adult cancer survivors.
3. The risk of preterm birth among offspring of female cancer survivors was elevated as compared to offspring of siblings. This elevated risk was seen in survivors of childhood, adolescence and early adulthood cancer. The risk of low birth weight was also significantly increased but not after adjustment for duration of pregnancy. No significant difference in risk for neonatal or infant deaths or stillbirth was found among offspring of female cancer survivors in comparison to offspring of female siblings. However, the risk of neonatal intensive care or monitoring was elevated.
4. The risk of sporadic cancer among offspring of cancer survivors was not elevated as compared to the general population or the offspring of siblings.

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