Impact of cancer in childhood, adolescence, and young adulthood on death, social security benefit uptake and education

A nationwide population-based cohort study

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Sciencific environment

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NORWEGIAN **CANCER** SOCIETY

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Contents

Abstract

Background: Improved survival for childhood and adolescent cancer patients due to advances in medical and supportive care is a great achievement of modern medicine. As the number of long-term survivors of cancer in childhood and adolescence is growing rapidly, increasing attention is being paid to the possible impact of the disease and its treatment on long-term health and social performance. Impact of cancer in childhood (0–14 years), adolescence (15–19 years) and young adulthood (20–24 years) on early cancer death, uptake of social security benefits and educational attainment has been explored in a national cohort.

Material and methods: All children born alive in Norway during 1965–1985 were identified by the Norwegian Central Population Registry and defined as the study cohort (approximately 1.2 million individuals). By linkage to the Cancer Registry of Norway, all children (N=2,481), adolescents (N=1,289) and young adults (N=2,032) diagnosed with cancer were identified. The cohort was followed from birth into adulthood by further linkage to compulsory national databases; the Cause of Death Registry, the National Insurance Scheme, and the Norwegian National Education Database. These registries include data on mortality, social security benefits, and education which were the main outcomes. Data were analysed by applying various regression models that allow for adjustment for confounders; Cox regression, logistic regression and competing risk model. Standardized incidence ratios were used in cases of rare outcomes.

Results: Differences in overall mortality between the cancer patients and the cancer-free population decreased during our study period. Early cancer mortality (within 5-years after diagnosis) for all cancers also decreased since 1965. Overall, there were relatively fewer cancer-related deaths among female than male patients. Adolescents and young adult

patients had lower risk of cancer death than children in general, except for patients who were diagnosed with leukaemia (all combined).

Overall, 5-year cancer survivors were 4.4 times more likely to receive any kind of social security benefits than the cancer-free population. Survivors from bone and connective/soft tissue tumours, central nervous system (CNS) tumours and leukaemia were most likely to be recipients of social security benefits. After neoplasms, the most common causes of receiving social security benefits were diseases of the nervous system, and injury and poisoning.

In general, completion of education was lower among 5-year cancer survivors than the cancer-free population at all levels i.e. intermediate, under graduate and graduate education. Mainly survivors of CNS-tumours and those assumed to have received CNS-directed therapy were at risk of educational deficits and experienced some delays in completion of an educational level. However, educational impairment diminished at higher levels of education, and consequently choice of educational fields was similar for the cancer survivors and the cancer-free population.

Conclusions: More cancer patients become 5-year survivors today compared to earlier. These survivors are at increased risk of late effects. Medical surveillance and supportive care is therefore of high importance for the cancer survivors. Special attention should be paid to survivors of CNS-tumours, leukaemia and bone and connective/soft tissues tumours since they were at higher risk for late effects compared with other survivors. Careful follow-up of cancer survivors during their education is also recommended in order to maximize educational achievements.

List of publications

1. Ghaderi S, Lie RT, Moster D, Ruud E, Syse A, Wesenberg F, Bjørge T. Cancer in childhood, adolescence, and young adults: A population-based study of changes in risk of cancer death during four decades in Norway. Cancer Causes Control 2012; 23(8):1297-305.

2. Ghaderi S, Engeland A, Moster D, Ruud E, Syse A, Wesenberg F, Bjørge T. Increased uptake of social security benefits among long-term survivors of cancer in childhood, adolescence and young adulthood: A Norwegian population-based cohort study. Br J Cancer 2013; 108(7):1525-33.

3. Ghaderi S, Engeland A, Gunnes MW, Moster D, Ruud E, Syse A, Wesenberg F, Bjørge T. Educational attainment and choice of educational fields among long-term survivors of cancer in childhood and adolescence: A Norwegian population-based cohort study (submitted).

Abbrevations

ALL: Acute Lymphoid Leukaemia

AML: Acute Myeloid Leukaemia

CI: Confidence Interval

CNS: Central Nervous System

CRN: Cancer Registry of Norway

HL: Hodgkin Lymphoma

HR: Hazard Ratio

ICD: International Classification of Diseases

NCPR: Norwegian Central Population Registry

NIS: National Insurance Scheme

NNED: Norwegian National Education Database

NHL: Non-Hodgkin Lymphoma

OR: Odds Ratio

PIN: Personal Identification Number

SHR: Sub-hazard Ratio

SIR: Standardized Incidence Ratio

WAA: Work Assessment Allowance

Definitions

Early cancer death: Death which occurred within five years after a cancer diagnosis.

Late effects: Occurrence of any medical condition of certain severity that qualified for uptake of social security benefits among the 5-year survivors.

Childhood/children: Individuals aged 0–14 years.

Adolescence/adolescents: Individuals aged 15–19 years.

Young adulthood/adults: Individuals aged 20–24 years.

1. Introduction

1.1 Background

The incidence of childhood cancer has been studied worldwide. Reported findings are, however, not consistent. Different trends have been shown in different countries.[1-4] Some studies report an increased incidence of childhood cancer, while other report a reduction, stable rates or no significant change.[1-6] However, the cancer mortality in young individuals has shown a substantial decline in western countries during the past few decades.[7, 8] Long-term survival after childhood cancers has improved dramatically over the last half century and about 75% to 80% become 5-year survivors with the current treatment regimens.[9-11]

Risk factors for cancer among young people are in general unknown; however, certain genetic disorders as well as environmental factors have been shown to play a role.[12, 13] Studies have shown that congenital immune defects, fragile chromosomes (ataxia telangiectasia, Bloom syndrome, etc.), certain birth defects, high levels of ionizing radiation, race, ethnicity and infections are associated with an increased incidence of cancer.[12, 14, 15]

Improved survival for childhood, adolescent and young adult cancer patients is one of the great achievements of modern medicine, and can be credited to advances in medical and supportive care based on research.[16] As the number of long-term survivors is growing fairly rapidly, increased attention is being paid to the possible influences of cancer and its treatment on long-term health and social performance.[17, 18] Morbidity, health status (e.g. subsequent neoplasms), fertility, social outcomes (future employments and marriage) and attained educational level are of particular concerns.[19-26] The risk of specific health related outcomes and physical as well as psychological functioning vary considerably among the survivors.[27-29] Health conditions may be influenced by characteristics of the individual,

the initial diagnosis or age at diagnosis.[30] Health and welfare systems that are country or region specific may also play a role.

1.2 Cancer in early life

Cancer is rare in young ages compared to later in life; however, it is one of the most common causes of death in young people in developed countries.[6, 31, 32] Types of cancers occurring in childhood, adolescence and young adults clearly differ from those developing in older adults.[33]

1.2.1 Incidence

In Europe, the overall incidence trends of cancer among children, adolescents and young adults varied in different countries over the last three decades.[1-6] A report from Norway showed a stable cancer incidence rate for children since 1985.[34] In developed countries, increases in childhood cancer (0–14 years) were observed for most tumour types[35, 36] while for adolescents and young adults (15–24 years), highest increases in incidence were observed for carcinoma, lymphoma, and germ-cell tumours.[35, 37] Among children, incidence rates ranged from 130 (British Isles) to 160 cases (Northern Europe) per million while the corresponding value for those diagnosed between age 15–24 years was about 200 per million[6]. Among children, the incidence rates are highest for leukaemia, central nervous system (CNS) tumours and lymphoma. Osteosarcoma and Ewing's sarcoma present with the highest incidence in the age 15–19 years while gonadal germ cell tumours, and Hodgkin's lymphoma peak at age 20–24 years.[38]

In 2010, 128 cases of cancer among children below 15 years of age were diagnosed in Norway, and about 65 and 116 new cancer cases were diagnosed among adolescents (15–19 years) and young adults (20–24 years), respectively.[39]

1.2.2 Mortality

Although cancer mortality in young people has been substantially reduced in developed countries over the past few decades,[7, 8, 40] it is still one of the most common causes of death in young people (Figure 1).

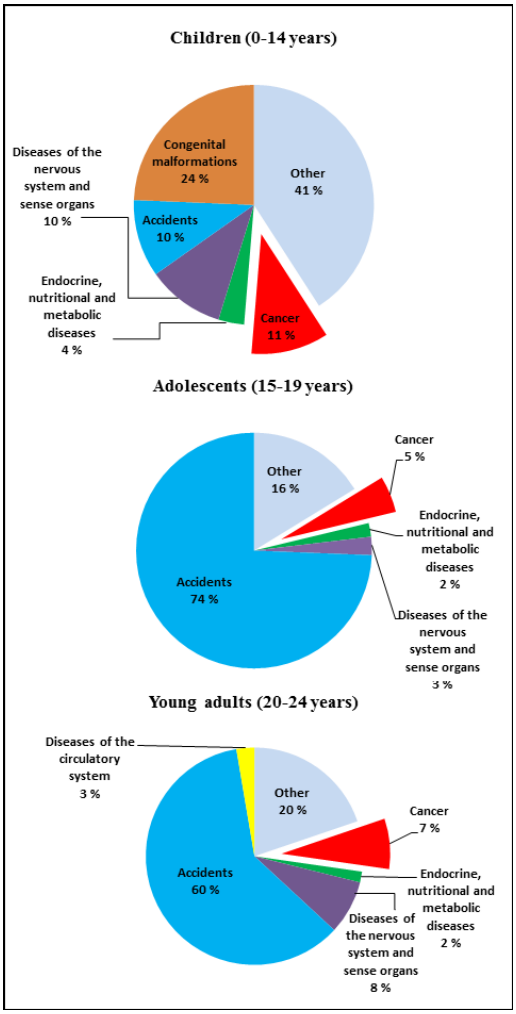

Figure 1: Leading causes of death in Norway, 2011: Children, adolescents and young adults.[41]

Childhood cancer mortality (early and late mortality) from all neoplasms has been declining during the past few decades in the Nordic (Figure 2) and in most other European countries. However, higher rates of death were observed in Eastern Europe than in Western Europe and the United States (US).[8, 31, 42] Highest 5-year survival was seen in Northern Europe (except Denmark) and Austria.[43] Highest reduction in cancer mortality was observed for leukaemia and CNS-tumours among children[9, 32] and Hodgkin lymphoma among adolescence and young adults.[44] Despite the considerable reduction in cancer mortality, cancer continues nevertheless, to represent an important cause of death in young people (0–24) worldwide.[31, 44]

In 2010, the cumulative risk of death in Norway caused by cancer among children, adolescents and young adults were 0.04% (0.02%), 0.02% (0.03%) and 0.02% (0.03%) among males (females), respectively.[39]

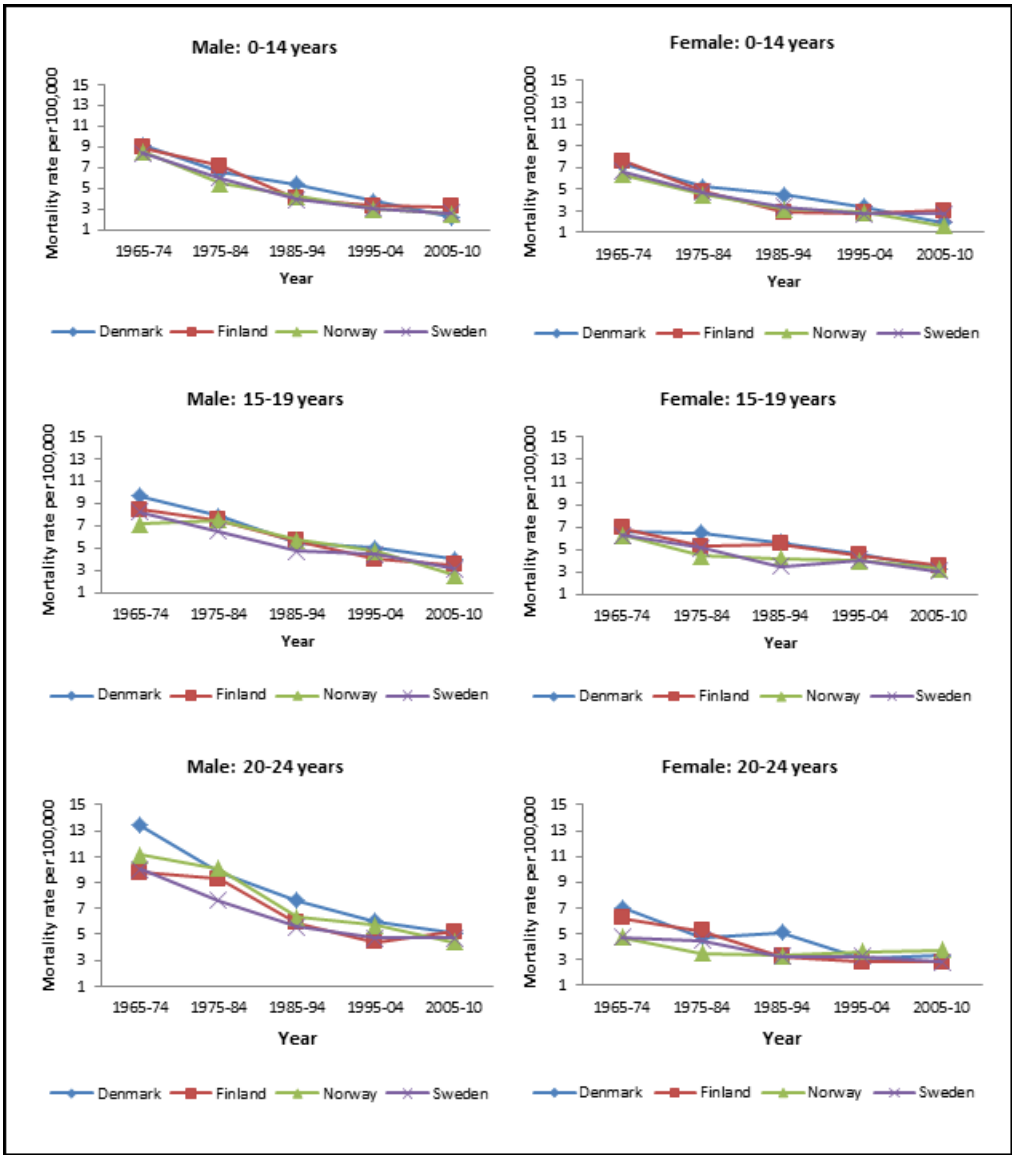

Figure 2: Overall cancer mortality rate per 100,000 for the Nordic counties.[39]

1.2.3 Cancer types

Children

Acute leukaemia is the most common cancer in children. In Norway, 35 to 40 children are diagnosed with acute leukaemia every year. Around 85% of these cases are acute lymphoid leukaemia (ALL) and 15% are acute myeloid leukaemia (AML).[45, 46] Children diagnosed with ALL are typically between two to five years of age, while AML is most common in the first two years of life.[45]

Brain tumours are the most common solid tumour in children. They can be seen through the entire childhood without any particular age peak.[45] Among children, primary brain tumours are commonly located in the posterior cranial fossa.

Lymphoma is another common cancer in young individuals. There are two major kinds of lymphomas, Hodgkin lymphoma (HL) and non-Hodgkin lymphomas (NHL). HL represent approximately 10% of all malignant lymphomas while all others are categorized under NHL.[47] Other common cancer types among children are bone and soft tissue sarcomas, neuroblastoma, Wilms' tumour, retinoblastoma, hepatic tumours and germ cell tumours.[12]

Adolescents and young adults

As the children grow older (after 15 years), they have distinctive medical characteristics which differ from younger children with cancer.[33] Adolescents and young adults are also diagnosed with cancers more common among adults such as melanoma, testicular cancer, or ovarian cancer.

The most common types of cancer in adolescents and young adults are lymphoma, leukaemia, brain and spinal cord neoplasms, soft tissue sarcoma, bone sarcoma, malignant

melanoma, germ cell tumours (including testicular and ovarian cancer), and thyroid cancer. Breast cancer also appears among young adults.[33]

Differences between cancer in children, adolescents and young adults

The distribution of cancer types differs between children, adolescents, and young adults.[10, 48] Among children, NHL is more frequent than HL,[2] however, mortality from NHL is higher among adolescents and young adults compared with children.[49, 50] While tumours like gonadal germ cell tumours, osteosarcoma, Ewing's sarcoma, and HL are most frequent in adolescents and young adults, these cancers occur less frequently in children. Vice versa, the most frequent fetal cancers are absent in adolescents and young adult, including the embryonal malignancies (Wilms' tumour, neuroblastoma, medulloblastoma, ependymoma, hepataoblastoma, and retinoblastoma).[38]

The type of soft-tissue sarcoma that occurs among adolescents differs from those occurring in younger children. Rhabdomyosarcoma accounts for more than 60% of soft-tissue tumours occurring in children younger than 5 years of age, while it accounts only for 25% of cases among adolescents. It is shown that the risk of ALL decreases by age, accounting for only 6% of all cancers in adolescence. On the other hand, the incidence of NHL increases in older patients. The incidence of AML is similar in children and adolescents; however, it is more common in young adults.[38]

Young people with cancer are likely to tolerate and respond better to cancer treatment and their bodies also tend to recover better than adults. However, receiving cancer treatment in young ages may cause a variety of late effects.

1.2.4 Treatment

Norway has a public health care system where cancer treatment and follow-up is provided free of charge for the patients irrespective of social and economic status.[51] Cancer treatment has gone through various changes during the past few decades. Generally, it may include surgery, radiation therapy and/or chemotherapy. For some frequent childhood tumours (i.e. brain tumours), the treatment and prognosis remain mainly unchanged, whereas for other cancers (i.e. leukaemia), there has been a dramatic increase in survival due to improved treatment regimens. These treatment regimens, however, come at a cost, with late effects manifesting later in adult life.[28]

Treatment protocols are determined based on the type of cancer and the age of the patients.[33] The general treatment trends described here, are based on the general knowledge of treatment protocols in Norway for young individuals at the given time periods. In Norway, all children with cancer receive their diagnosis and treatment plan at one of four (previously five) centres.[11] The treatment for various cancers has been nationally agreed upon, which secures equal access to identical treatment regardless of geographic location. Since the mid-1980s, there have been common treatment protocols for children with leukaemia across the five Nordic countries. Since the compliance to these national standards has been high, it was possible to make assumptions of treatment types applied. For adolescents and young adults the structure of cancer treatment has been more de-centralized which make the assumptions regarding treatment in this age group somewhat more uncertain.[52]

Treatment protocols for CNS-tumours differ from the treatment protocols applied for other cancers. CNS-tumour treatment is determined based on morphology, localization of the tumour and the age of the patient. The treatment protocol may consist of one or several modalities including surgery, radiation and chemotherapy.[53]

In the 1970s and early 1980s, more patients with leukaemia received prophylactic CNS-directed therapy in the form of radiation than what is currently the standard for leukaemia treatment. In Norway, the current treatment does not include CNS radiation. This was replaced by intrathecal chemotherapy as well as high-dose chemotherapy with penetrance to the CNS as early as the mid-1970s. Since the mid-1980s, only a very small group of patients have received prophylactic cranial irradiation which is no longer part of the general leukaemia treatment regimen (except for relapses). Intrathecal chemotherapy is kept as an essential part of leukaemia treatment regimens in order to reduce the rate of CNS relapses. Similar to leukaemia patients, CNS-prophylactic therapy (in form of intrathecal chemotherapy) was generally administered for patients with NHL. However, use of cranial irradiation substantially decreased since the early 1980s together with optimized chemotherapy regimens.[54, 55]

1.2.5 Late effects

Due to advances in childhood cancer treatment during the past few decades, today about 75% to 80% of the cancer patients will become 5-year survivors.[10, 34] Studies have shown that long-term cancer survivors have higher risk of late morbidities, chronic diseases and late mortalities compared with the control groups.[18, 56-59] According to previous studies, chronic health problems and a severe or life-threatening condition were reported for more than 50% and 25% of the childhood cancer survivors, respectively.[18, 30, 60, 61] The late effects are due to the specific cancer types, cancer treatment protocols (especially radiation therapy), age at diagnosis or subsequent neoplasms.[30, 61-67] Among late effects affecting childhood cancer survivors, second malignant neoplasms, defects of vision, hearing loss, endocrine and metabolic problems, musculoskeletal abnormalities, activity limitations, dental abnormalities, osteoporosis, chronic fatigue, psychosocial problems, obesity, reduced fertility, mental disorders, decline in intelligence and cardiovascular/pulmonary deaths have been reported frequently.[12, 18, 24, 30, 63-66, 68-72]

Poorer quality of life among cancer survivors has been reported in some studies while others showed minor or no differences.[73, 74] A cross-sectional study on survivors of ALL showed that survivors who received higher dosage of cranial radiotherapy (24 Gy) showed impairments in immediate and delayed memory compared with those who received lower dosages (18 Gy).[75]

1.3 Social security benefits

1.3.1 Norway

To receive social security benefits, an individual should fulfil certain criteria. These criteria are based on health conditions of the individuals and the financial burden caused by such health conditions, irrespective of the general wealth of the individual. The only mandatory condition to be qualified to receive social security benefits is legal residence in Norway for the last 12 months. In case of disability pension, an individual must have been a member of the National Insurance Scheme (NIS) three years prior to the occurrence of disability. An individual may receive more than one benefit due to various health related issues. The duration of benefits varies according to need which is decided by medical personnel together with representatives from the NIS.[76] In 2012, the uptake of basic benefits, attendance benefits and disability pensions among the entire population in Norway was 2.5%, 1.7% and 9.7% (age 18–66 years), respectively.[76] The corresponding value for uptake of medical rehabilitation benefits was 1.0%. Statistics on uptake of medical rehabilitation benefits was only available until June 2009 since it was replaced with another benefit from 2010 (work assessment allowance (WAA)).[77]

Basic and attendance benefits

Basic benefits are awarded to cover (in full or in part) additional expenses as a result of illness, injury or congenital defects and disabilities (bodily defects). These additional expenses may include for instance costs to cover support bandages, running and/or operating technical aids, transport, or a guide dog. Attendance benefit is granted in case of special need for care and supervision as a result of illness, injury or congenital disabilities. This include the need for extra nursing or special care, training, help with getting up/going to bed, eating and personal hygiene.[20, 78] When the need for assistance is being considered, the need for stimulation, education and exercise at home will also be evaluated.[76] There are no age limits for receiving basic or attendance benefits.

Medical rehabilitation benefits and disability pension

The purpose of medical rehabilitation benefits (part of WAA since march 2010)[77] and disability pensions[79] is to provide subsistence allowance to persons who are between 18–67 years and have permanently impaired earning capacity due to illness or injury. The mandatory condition is that a person must have been a member of the NIS during the last three years up until the disability. The medical rehabilitation benefits are relatively short-term and provides up to 66% of yearly income for the period that one is under active treatment with the aim to improve one's working capacity.[76] Disability pensions can only be considered after appropriate rehabilitation, and the earning capacity must be reduced by at least 50%. In case of occupational injury, 30% reduction in earning capacity is sufficient.

1.3.2 Social security benefits among cancer survivors

An association between loss of working ability and cancer and its treatment has been reported from a Norwegian study on cancer survivors diagnosed before age 15. The effect was particularly marked among CNS-tumour survivors.[20] Another Norwegian study on the need for rehabilitation services among cancer patients showed that approximately 63% of the survivors were in need of at least one kind of rehabilitation service such as physical therapy, psychological counselling, consultations with social workers, and occupational therapy. The authors also reported that 40% of the patients who were in need of rehabilitation services did not receive such services.[80]

Individuals who were young at time of diagnosis (before school age), and survivors of brain tumours, leukaemia, lymphoma and other solid tumours were more likely to receive disability pension.[81] Lower social and psychosexual development was also reported among recipients of disability pensions.[82]

A general lack of knowledge about legislation of health insurance among cancer survivors was reported by a US study interviewing 5-year cancer survivors diagnosed before age 21.[83] Despite often high costs, it was shown that survivors were grateful to have any insurance coverage. Increased insurance costs were of major concern among the survivors. Those who were not insured had a general concern about the inability to get required preventive care.

1.4 Education

1.4.1 Norway

Similar to the health care system, all public education in Norway is free of charge and equally available to all individuals. At schools, educational plans are generally adapted to each pupil's abilities. Pupils who are not able to achieve learning yields from the ordinary teaching and are in need of special education are entitled to receive such services, either within ordinary schools or in special education settings outside ordinary schools.[84]

Currently, the levels of education are structured in three main levels, compulsory education (1 to 10 years of education), intermediate education (11 to 14 years of education) and tertiary education (14 to 20 years of education) (Figure 3).

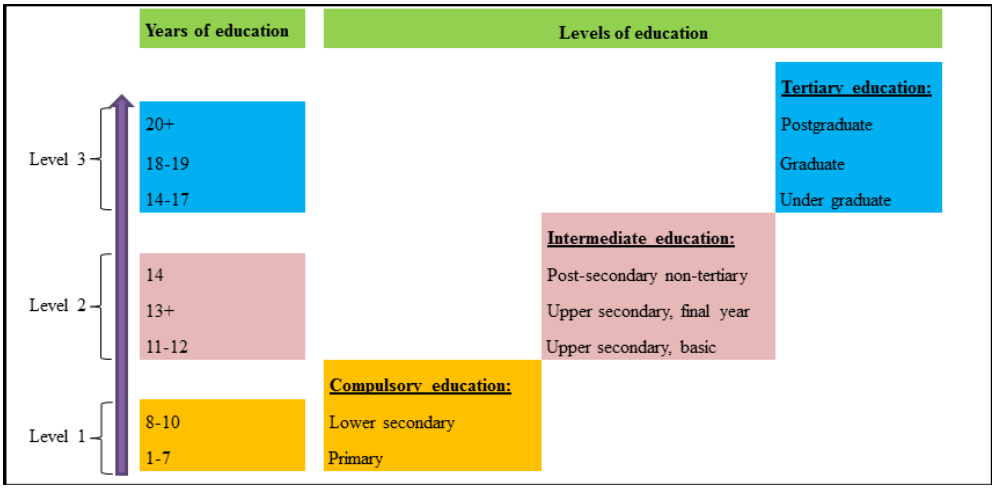

Figure 3: Current classification of education.[85]

However, the educational system has undergone structural changes during the past few decades. The law in 1959 made seven years schooling mandatory. In 1969, primary and

compulsory education was extended to nine years. Further, the Norwegian education system has undergone a number of extensive reforms during the past decades; Reform 94, Reform 97 and Quality Reform of 2003. A reform of secondary education, termed 'Reform 94', gave rights to three years of secondary education. With the 'Reform 97', the curriculum was extended and primary school became 10 years.[51, 86] Unlike Reform 94 and Reform 97, the 'Quality Reform of 2003' mainly affected the structure of tertiary education in Norway. Therefore, the number of years at each level has increased by approximately one to two years over the last 30 years.

The compulsory education consists of two main stages, primary school (class level 1–7) and lower secondary school (class level 8–10). Those who completed compulsory education or equivalent, have right to upper secondary education which leads to admission to higher education, vocational qualifications or to basic skills.[84] Pupils who choose vocational education should take a supplementary programme for general university admission certification to qualify for admission to universities and university colleges. Upper secondary education normally takes three years. Vocational education and training mainly leads to a craft while general studies lead to general university admissions certification.

Tertiary education is built on completed three years of upper secondary education. It consists of a three to four-years bachelor degree (under graduate education), a subsequent two-year master degree (graduate education) and a three-year doctorate degree (postgraduate education). There are eight broad fields of education available at the higher level of education (Figure 4). Broad fields of education are classified according to the academic content of the various educational activities and each field comprises programs that are as academically homogenous as possible.[87]

The State Educational Loan Fund provides financial support for educational purposes in the form of loans and grants which aims to minimize the impact of parental income on students' choices of education. Students in programs for both general and vocational

studies and higher education are entitled to receive such economic support which is made available for everyone regardless of their social and economic background.[87]

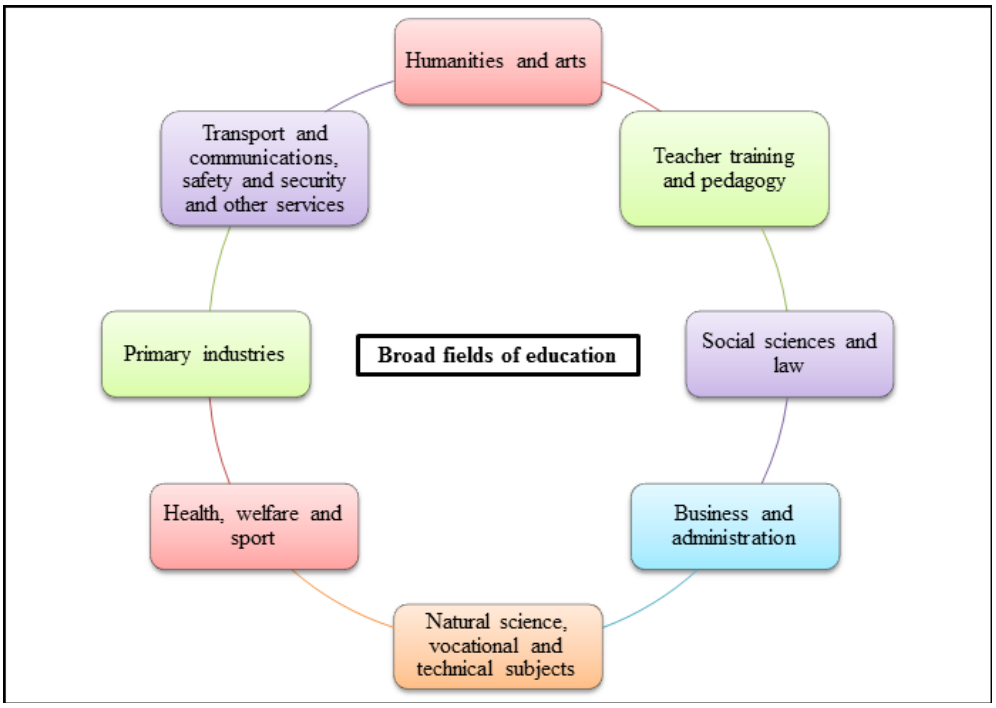

Figure 4: General classification of the academic content at the under graduate and graduate levels (see Appendix I for more information).[85]

Special education is considered when pupils are unable to obtain a satisfactory learning outcome from teaching services provided at schools due to mobility, visual and hearing impairments, physical disabilities, speaking and communication difficulties, as well as brain injuries. The right for special education is granted based on expert assessment carried out by the educational and psychological counselling in the local or regional authority. This evaluation is furthermore used to reach an individual decision on special need education. An individual education plan is then provided for pupils in primary or

secondary education which includes goals and contents of the special education. The educational plan is mandated to be evaluated every six months.[88]

1.4.2 Educational achievements among cancer survivors

Cancer treatment may influence the social development and academic progress of the survivors. In general, gender, treatment with cranial irradiation, age at diagnosis, cancer site, year of diagnosis and parental educational level has been reported to influence educational achievements.[19, 25, 89-92]

Nordic studies have reported that mostly survivors of CNS-tumour experienced reduced educational achievements[91, 93] and that poor academic achievements is likely to affect the chances of finding desirable occupation and reach economical goals.[94] Finnish studies on leukaemia and brain tumour survivors showed that school grades were mostly affected in foreign language studies. They suggested this to be an indication of diminished verbal learning among this group of survivors.[91, 95] Lower school grades were reported in patients with NHL, while similar or better grades were observed among patients with HL. Wilms' tumour patients had similar grades compared to their controls, except for physical education.[19]

A study by Lancashire et al. based on the British Childhood Cancer Survivor Study showed that survivors of bone sarcoma and retinoblastoma were more likely to obtain at least one O'level (equivalent to the Norwegian compulsory education; 1 to 10 years of education) compared to the general population.[89]

Cancer survivors were more likely to repeat a grade and had more often school absences in a study from the US compared to their control group.[92, 96] Female survivors were reported to be less frequently finished with high-school and/or achieved an advanced university degree in a Dutch study.[25] The rate of college graduations was shown to be

lower among survivors of childhood and young adult AML compared to their siblings in the Childhood Cancer Survivor Study. On the other hand, both survivors and their siblings had higher college graduation than the general population.[60]

Increased needs of special education services among cancer survivors compared to their siblings have been reported.[27] A study from the US on 5-year cancer survivors diagnosed before age 21, reported an increased need for special education services among survivors diagnosed before age 6, and diagnosed with a leukaemia, brain tumours or Hodgkin's disease relative to their siblings.[97]

2. Aim of the thesis

The overall aim of this thesis was to assess the impact of cancer in young age (0–24 years) on death, uptake of social security benefits and educational attainment.

The specific aims were to examine:

- Changes in overall and cancer specific early death during the past 40 years among children, adolescents and young adults with cancer born during 1965–1985 (paper I).
- Uptake of social security benefits among survivors of cancers in young ages compared to the cancer-free population (paper II).
- Educational attainment and choice of educational fields among long-term survivors of cancer in childhood and adolescence compared to the cancer-free population (paper III).

3. Material and methods

3.1 Data sources

3.1.1 Norwegian Central Population Registry (NCPR)

The NCPR provides unique 11-digit personal identification numbers (PIN) for individuals in Norway at birth or immigration since 1960. Furthermore, the NCPR registers demographic information on the entire population in Norway based on these PINs. Information such as date of birth, place of residence and date of emigration or death are gathered in the NCPR.[98] Origins of immigrants are also included.

3.1.2 Cancer Registry of Norway (CRN)

All information about cancer cases occurring in Norway has been reported to the CRN since 1953. Pathological and clinical notifications, and death certificates are the main reporting sources. Information about site, histological type and stage of disease at the time of diagnosis are extracted from these sources.[48] Registration of topography was based on a modified version of International Classification of Diseases (ICD-7)[99] until 1992, and ICD-O-2 has been the basis for coding from 1993 onwards. Tumour morphology was coded according to the Manual of Tumor Nomenclature and Coding through 1992 and ICD-O morphology codes were adopted from 1993. Non-solid tumours have been coded according to a separate coding systems from 1986.[48]

3.1.3 Cause of Death Registry

In Norway, providing official statistics on causes of death has been obligatory since 1951 onwards. Such statistics include the entire population in Norway at the time of death irrespective of place of death (in Norway or abroad). Statistics on causes of death are prepared on the basis of medical death certificates by public health officers. Causes of death were registered according to ICD-8 during 1969–1985, ICD-9 during 1986–1995, and ICD-10 from 1996 onwards.[100]

3.1.4 National Insurance Scheme (NIS)

All individuals residing in Norway are insured by the NIS irrespective of their nationality or employment status.[101] Disability benefits are provided by NIS for people whose health conditions are of sufficient severity to be an economic burden. NIS provides for instance attendance benefits, basic benefits, disability pensions and medical rehabilitation benefits (replaced with WAA since 2010).[76] The dates at which the benefits were granted and diagnoses associated with the benefits are recorded. Diagnoses are based on medical examinations and are classified according to ICD-9 and -10. NIS began electronic registration of social security benefit records in 1992. The registration included both already existing and new benefits.

3.1.5 Norwegian National Education Database (NNED)

Since 1970, all individual-level based statistics on education – from completed lower secondary education to tertiary education including doctoral studies – have been gathered in NNED.[87] All information on educational attainment is reported from respective

institutions to NNED annually.[84] Fields of education are coded based on the Norwegian Standard Classification of Education (a 6-digit coding system).

3.2 Study population

This project is based on a population-based cohort. All children born alive in Norway during 1965–1985 (1,216,058 individuals) were identified by the NCPR and defined as our study cohort (625,349 males and 590,709 females). All individuals (both with and without cancer) were followed up into adulthood until they were between 24 and 44 years of age by linkage through the PIN to abovementioned national registries.

All cancer cases were identified by linkage to the CRN and were further grouped as children (0–14 years), adolescents (15–19 years) and young adults (20–24 years) based on age at diagnosis – a total of 5,802 individuals (paper I). Only the first cancer diagnosis was considered. Furthermore, all 5-year cancer survivors (4,031) were included in paper II and paper III (Figure 5).

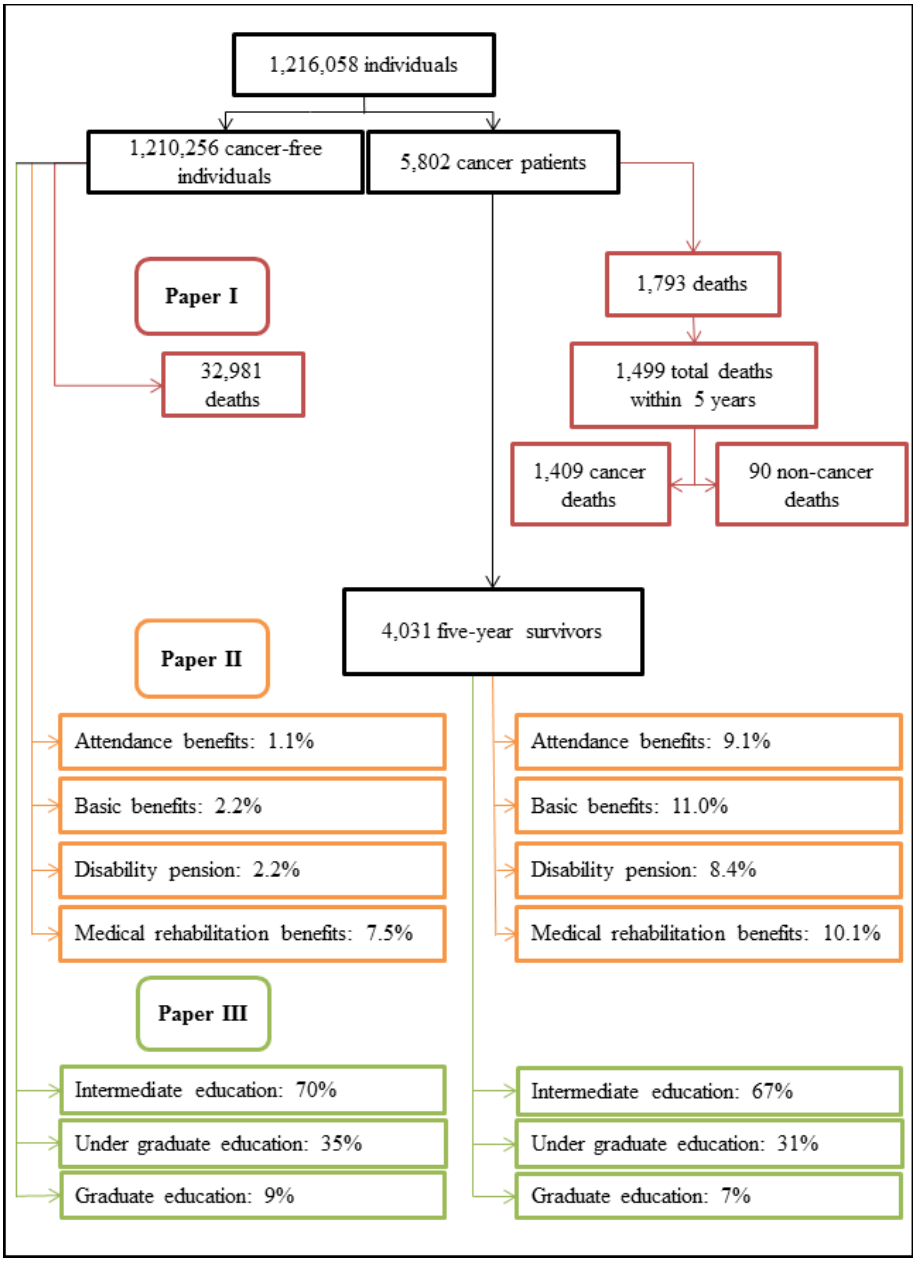

Figure 5: Establishment and follow-up of the study cohort. The comparison group in all three papers were the cancer-free population.

The cohort was followed by linking compulsory national registries, using the aforementioned unique 11-digit PIN assigned to all individuals living in Norway after 1960. A summary of follow-up time for papers I–III are presented in Table 1.

Table 1: Follow-up time of the cancer individuals

	Start of follow-up (whichever occurred last)	End of follow-up (whichever occurred first)
Paper I	• Birth	• Five years after diagnosis • Death • Emigration • 31.12.2009
Paper II [a]	• Five years after diagnosis • 01.01.1992	• Uptake of social security benefit • Death • Emigration • 31.12.2006
Paper III [b]	• Ages 17[c], 20[d], 23[e] • Five years after diagnosis	• Attainment of education in question • Death • Emigration • 31.12.2009

[a] The follow-up time for those who received medical rehabilitation benefits were 2002–2007; [b] Individuals diagnosed with cancer after start of follow-up were censored; [c] For intermediate education; [d] For under graduate education; [e] For graduate education.

3.3 Statistical analysis

To estimate the risk of death (total death) among the cancer patients relative to the cancer-free population (general population), a time-varying Cox regression model with age as the time variable and cancer as a time-varying variable was applied to the entire cohort.[102] A competing risk model[103] with time from diagnosis as the time variable was applied including only the cancer patients and was used for the estimation of cancer death sub-hazard ratios (SHR).[104, 105] SHR is defined as ratios of hazards related to cumulative

incidence in the presence and absence of the risk factor.[106] The primary outcome was defined as death from cancer. Death from a non-cancer cause was considered a competing event (paper I). A description of variables used is presented in Table 2.

Standardized incidence ratios (SIR) were used to describe the prevalence of diseases extracted from NIS. SIR was used to show the occurrence of a specific disease among the 5-year cancer survivors relative to the occurrence of the same disease in the cancer-free population; diseases were identified through social security benefits uptake. The person times were calculated for the years 1992–2006 for all outcomes except for medical rehabilitation benefits for which the person-times were available from 2002 to 2007. Diagnoses retrieved from NIS were coded according to the ICD-10 coding system and were categorized into main diagnostic groups (paper II).

Cox regression models with time from enrolment until attainment of a given educational level as the time variable was applied in paper III. Cox regression was used to estimate the hazard ratio (HR) with 95% confidence interval (CI) of educational attainment among the cancer survivors compared with the cancer-free population. Logistic regression models were used to compare the choice of various educational fields at higher levels of education; odds ratios (OR) with 95% CIs were calculated. Covariates included in the model are shown in Table 2.

Table 2: Overview of the outcomes, statistical models and variables used in this study

Paper I	Paper II	Paper III
Main outcome		
• Early mortality	Uptake of • Attendance benefits • Basic benefits • Disability pension • Medical rehabilitation benefits	• Educational attainment • Choice of educational fields
Statistical model		
• Time-varying Cox regression • Competing risk	• Standardized incidence ratio	• Cox regression • Logistic regression
Covariates		
<u>Time-varying Cox regression</u> • Year of diagnosis o 1965–1974 o 1975–1984 o 1985–1994 o 1995–2004 o 2005–2009 <u>Competing risk</u> • Cancers (ICD-7) o CNS-tumours o Bone and connective/soft tissue tumours o Lymphoma o Leukaemia* • Age at diagnosis o 0–14 o 15–19 o 20–24 • Year of diagnosis o 1965–1974 o 1975–1984 o 1985–1994 o 1995–2004	• Age o 5–9 o 10–14 o 15–19 o 20–24 o 25–29 o 30–34 o 35–39 o 40–44 • Calendar periods o 1970–1974 o 1975–1984 o 1985–1994 o 1995–2004 o 2005–2009 • Gender	• Age at diagnosis o Intermediate level ▪ 0–4 ▪ 5–9 ▪ 10–12 o Under graduate level ▪ 0–4 ▪ 5–9 ▪ 0–14 o Graduate level ▪ 0–4 ▪ 5–9 ▪ 10–14 ▪ 15–18 • Year of diagnosis o 1965–1974 o 1975–1984 o 1985–1994 o 1995–2004 • Cancer survivors o CNS-tumours o CNS-directed therapy o All other survivors

○ 2005–2009 • Gender		
Adjusted for	**Stratified by**	**Adjusted for**
Time-varying Cox regression • Gender • year of birth ○ 1965−1969 ○ 1970−1974 ○ 1975−1979 ○ 1980−1985	• Year of birth ○ 1965–1969 ○ 1970–1974 ○ 1975–1989 ○ 1980–1985 • Age at diagnosis ○ 0–14 ○ 15–19 ○ 20–24 • Year of diagnosis ○ 1965–1974 ○ 1975–1984 ○ 1985–1994 ○ 1995–2004 ○ 2005–2009 • Cancers ○ CNS-tumours ○ Bone and connective/soft tissue tumours ○ Lymphoma ○ Leukaemia • Gender	• Parental education ○ No education ○ Compulsory ○ Intermediate ○ Tertiary • Gender • Year of birth ○ 1965–1969 ○ 1970–1974 ○ 1975–1989 ○ 1980–1985
	Statistical software	
• PASW Statistics 18 • STATA/IC 11	• PASW Statistics 18	• PASW Statistics 18

* Additionally, ALL and AML were considered separately.

4. Results

4.1 Paper I

The study included 3,268 males and 2,534 females diagnosed with cancer. The mean age at diagnosis for both genders was 14.7 (range 0–25 years). The mean age of children at death was 7.0 years for males and 6.9 for females. The mean ages among adolescents and young adults for both genders were 19.0 and 24.1 years, respectively.

In general, cancer occurred more frequently among males than females. The most frequent cancers among children were leukaemia and CNS-tumours. Cancers of the testis and lymphoma were most common among male patients older than 15 years, while malignant melanoma and lymphoma were most frequent among female patients.

Leukaemia was the most common cause of death. The percentage of cancer deaths occurring among male patients was higher than among females. Among children, death from CNS-tumours and leukaemia (also when ALL was considered separately) showed the largest decline during our study period. Among adolescents, deaths from cancer of bone and connective/soft tissue tumours, lymphoma and AML were most pronouncedly reduced. Despite the substantial reductions in mortality among children and adolescents, the risks of cancer death among young adults were reduced moderately in the past 40 years.

The entire study cohort (time-varying Cox regression)

To study the risk of early death, patients were followed for an average of 4.1 years (range 0–5 years). A total of 1,499 patients died within five years after diagnosis. Cancer was the cause of death in 94% of these patients. Overall HR of death for the cancer patients relative to the cancer-free population decreased from 361.5 (95% CI: 313.9–416.2) in 1965–1974 to 19.3 (95% CI: 9.2–40.7) in 2005–2009.

The cancer patients (competing risk)

When all cancer sites were studied combined, the competing risk model showed fewer cancer related deaths among female compared with male patients (SHR: 0.83; 95% CI: 0.75–0.93). Lower mortality was observed among adolescents and young adults.

Except for leukaemia (also when ALL was considered separately), adolescents and young adults had lower mortality than children. Furthermore, adolescents with AML had higher mortality than children (SHR: 1.36; 95% CI: 0.81–2.26); but this difference was not statistically significant.

4.2 Paper II

A total of 4,031 individuals were 5-year cancer survivors (55.4% males). Cancer survivors and the cancer-free population were followed for an average of 13.2 (range 0–39.3) and 34.2 (range 0–45) years, respectively.

Uptake of social security benefits increased with younger age at diagnosis, year of birth and year of primary cancer diagnosis. In total, survivors of bone and connective/soft tissue tumours (SIR: 10.8; 95% CI: 9.1–12.9), CNS-tumours (SIR: 7.7; 95% CI: 6.9–8.6) and leukaemia (SIR: 6.1; 95% CI: 5.3–7.0) had the highest risks of late effects as indicated by uptake of social security benefits.

After extracting diagnoses from the NIS, a total of 29.7% of the survivors were shown to be recipients of social security benefits compared to 10.8% of the cancer-free population. Among the cancer survivors, 9.1% received attendance benefits, 11.0% received basic benefits, 8.4% received disability pensions and 10.1% received medical rehabilitation benefits. The corresponding percentages among the cancer-free population were 1.1%, 2.2%, 2.2% and 7.5%, respectively. Uptake of benefits among the cancer survivors

overall was 4.4 times (95% CI: 4.1–4.6) higher than that of the cancer-free population (all social security benefits combined). The overall SIR for receiving attendance benefit was 17.9 (95% CI: 16.3–20.0) and 9.3 (95% CI: 8.5–10.3) for uptake of basic benefits. The overall SIR for uptake of disability pension was 5.6 (95% CI: 5.0–6.2) while it was 1.3 (95% CI: 1.1–1.4) for receiving medical rehabilitation benefits.

Neoplasm was the main cause of social security benefit uptake. Among survivors, after neoplasm, injury and poisoning and diseases of the sense organs were the most common causes of attendance and basic benefits uptake. Disability pension were commonly granted for endocrine, nutritional and metabolic and immunity disorders and diseases of the nervous system. Diseases of the genitourinary system and infectious and parasitic diseases were the main causes for uptake of medical rehabilitation benefit.

4.3 Paper III

A lower proportion of the cancer survivors completed intermediate (67%), under graduate (31%) and graduate education (7%) compared with the cancer-free population (70%, 35%, and 9%, respectively). Among the cancer survivors, a higher proportion of females completed their education when compared to their male counterparts.

Intermediate level

Educational deficit was observed among survivors of CNS-tumours diagnosed during 1975–1984 (HR: 0.6; 95% CI: 0.4–0.7) and 1985–1994 (HR: 0.6; 95% CI: 0.4–0.7). Survivors of CNS-tumours diagnosed at ages 0–4 (HR: 0.4; 95% CI: 0.3–0.6) and 5–9 years (HR: 0.6; 95% CI: 0.5–0.8) displayed significant educational impairment.

Under graduate level

Survivors of CNS-tumours who were diagnosed during 1975–1984 (HR: 0.5; 95% CI: 0.3–0.7) and 1985–1994 (HR: 0.5; 95% CI: 0.3–0.7) showed a significant educational deficit. Significantly lower educational attainments were seen at all ages of diagnosis.

Among survivors who were assumed to receive CNS-directed therapy, completing under graduate education was lowest in survivors who were diagnosed during 1975–1984 (HR: 0.7; 95% CI: 0.6–0.9). Survivors diagnosed at ages 0–4 (HR: 0.7; 95% CI: 0.6–0.9) and 10–14 years (HR: 0.6; 95% CI: 0.4–0.8) also demonstrated educational deficits.

"Natural science, vocational and technical subjects" was the most common field of education among male individuals. Among females (both the survivors and the cancer-free population), "Health, welfare and sport" was most frequently studied. Female survivors who received CNS-directed therapy chose the field of "Health, welfare and sport" more frequently than females in the cancer-free population (OR: 1.8; 95% CI: 1.1–2.8).

Graduate level

Survivors of CNS-tumours were less likely to complete graduate education compared with the cancer-free population (male: OR: 0.5; 95% CI: 0.3–0.9; female: OR: 0.4; 95% CI: 0.2–0.8). Completing graduate level was also less frequently observed among male survivors assumed to receive CNS-directed therapy (OR: 0.5; 95% CI: 0.3–0.8).

5. Discussion

5.1 Methodological considerations

5.1.1 Study design

All three studies have a prospective cohort design. The cohorts used in these studies were based on a linkage of comprehensive registries with reliable and compulsory information.[107-112] Norway has had a relatively stable population where emigration rates have been minor. The entire population is traced by national registries and statuses of emigration, immigration or deaths are recorded accordingly.[41]

A case-control study or a prospective hospital-based study as alternative designs would probably provide more detailed information about each individual and in particular about treatment regimens encountered. The size of the study population would, however, be considerably smaller. As the outcomes studied are relatively rare (e.g. uptake of certain social security benefits) such designs would be difficult to implement. Furthermore, there would be concerns about the existence of possible biases (in particular information and selection biases). The advantage with a registry-based cohort design[113] is the large population size where the registered information for each individual is almost complete (even though not very detailed) and misclassifications are likely to be non-differential between the cancer survivors and the cancer-free population. Therefore, the cohort design was appropriate for the aims of the current thesis.

5.1.2 Internal validity

Internal validity refers, in this instance, to the correct measurement of the outcome in question (Figure 6). Internal validity may be reduced by the presence of systematic errors which may include selection bias, information bias and confounding.[114]

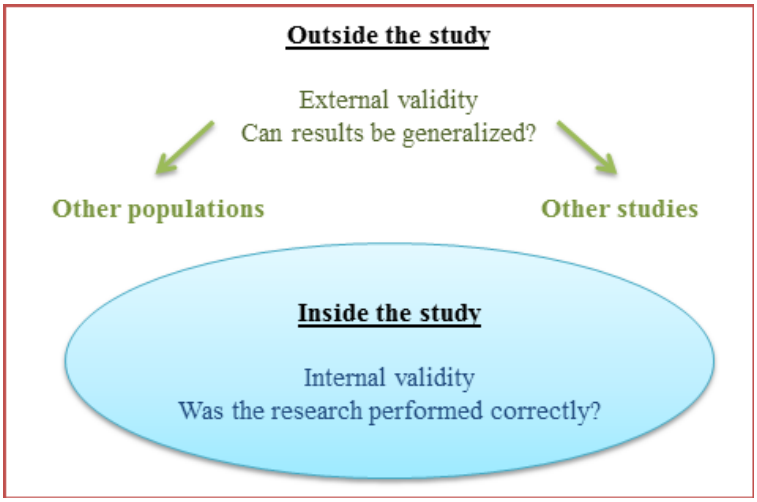

Figure 6: Validity of a study

Selection bias occurs if individuals in exposed and unexposed groups are not truly comparable.[114] One possible cause of selection bias in a cohort study is loss to follow-up. The current study is based on data from registries which are compulsory and selective reporting is minimal. Our study population included the entire population in Norway born alive during 1965–1985 and the comparison group is the entire cancer-free population. The total loss to follow-up was approximately 0.2%. Such a minor percentage is unlikely to cause any serious selection bias, and it thus assumed not to have influenced the results of the present research.

Recall bias and *reporting bias* are two forms of information bias.[114] Recall bias is a systematic error initiated by differences in the accuracy or completeness of the memory recollections reported by study participants regarding an event. Reporting bias is defined as selective revealing or suppression of information by individuals. Occurrences of such biases in the present study are unlikely since the information were collected from registries/databases with compulsory reporting.

Confounding implies that the effect of the exposure of interest is mixed together with the effect of another variable.[114] For confounding to be present, the confounding variable must be associated both with the exposure and the outcome.

In paper I, the time-varying Cox regression was adjusted for gender and year of birth (Table 2). Cancer mortality differed between genders while year of birth could mirror changes in cancer treatment to some degrees.

In paper II, late effects among the cancer survivors were considered in 5-year age-groups (Table 2) since age at diagnosis has been shown to have a pronounced impact on occurrence of late effects.[30] Cancer treatment protocols have undergone significant changes over time, especially at the beginning of our study period. Therefore, we considered the year of diagnosis also as a potential confounder.

In paper III, analyses were adjusted for gender, year of birth, and the highest registered attained level of the parents' education (Table 2). It has been shown that gender plays an important role in the educational achievements of cancer survivors.[91] Year of birth was considered a potential confounder since the educational system has undergone rather radical changes during the study period. Parental level of education has been shown to have a considerable effect on the educational achievement of their offspring.[90, 115] In our study, parental education did not influence the relation between cancer and educational achievement. This is not surprising due to the characteristic of cancer in early ages where causes are mainly unknown. Thus, distribution of individuals with cancer generally varies little across parents' socioeconomic status and educational attainment. As opposed to this,

many adult cancer forms, such as for instance cervical and lung cancer, are associated with socioeconomic status (e.g. educational level).[116-118] Nevertheless, inclusion of parental education in our analysis helped the comparability with results from other studies.

5.1.3 External validity

External validity is the extent to which the results can be generalized to other settings (Figure 6).[114]

Health care, welfare and educational systems vary significantly between countries. This could affect the generalizability of our results. In paper I, difference in risk of death (overall and cancer specific) between the cancer patients and the cancer-free population has been reduced over time. This result is similar to those observed in other studies from developed countries.[3, 8] Hence, the results from paper I could be generalized to countries with similar health care systems and cancer treatment protocols.

In paper II, higher rates of social security benefits uptake was observed among cancer survivors compared with cancer-free individuals. Social security systems are highly country specific. Thus, the results from paper II could only be generalized to countries with similar social and welfare systems such as the other Nordic countries.

In paper III, some educational deficit was observed among the cancer survivors compared with the cancer-free population (especially survivors of CNS-tumours and those assumed to have received CNS-directed therapy). Education in Norway is free of charge, and consequently our results cannot be generalized to countries with educational systems different from Norway.

Health care systems differ across countries. Furthermore, the health status and prevalence of other diseases in children, adolescence and young adults may also vary across

countries, both as a result of health care system differences but also due to differences in welfare levels and/or other factors important for general health.[119] Hence, the results from all three papers could be generalized to countries with similar health care systems and cancer treatment protocols specifically, as well as similar distributions of other diseases and health and welfare measures in general.

5.1.4 Precision

Precision refers to the absence of random errors.[114] A large study sample ensures high precision. In this study, the large population that is retrieved from reliable registries leads to a high precision of the estimates obtained in all three papers. On the other hand, the number of cancer cases and the number of outcomes for the cancer individuals were relatively small. In order to further increase the sample size of cancer individuals, pooling data from similar registries in the Nordic countries is an option.[120]

5.1.5 Choice of statistical methods

Choice of statistical methods depended on the data available and the purpose of each individual study. A time-varying Cox regression model was used in paper I. A Cox regression model is suitable for survival data since it can handle censoring.[121] With a time-varying Cox regression, a variable that was not constant over time could be included adequately. Furthermore, a competing risk model was applied to estimate SHR of early cancer death. The choice of the competing risk model was based on the concern for deaths which were not caused by cancer, even though this was rare. A competing risk model allows one to consider the effect of deaths not caused by cancer.[103, 122] In a Cox regression model individuals dying of other causes would have been censored since the cause of

death was not cancer. In the competing risk model, these deaths were included as competing events.

In paper II, SIRs were used which are relatively easy to apply due to their flexibility in the calculation of person-time. Furthermore, the results obtained from SIR are also easy to understand and can easily be compared to results from other settings.

In paper III, Cox and logistic regression models were applied. As an alternative to the ordinary Cox regression model, a time-varying Cox regression could have been applied to facilitate an easier definition of follow-up time. However, a multivariate Cox regression model without a time-varying variable was applied and the follow-up time was restricted. This model is commonly used and the results could easily be compared to the results from other studies.

Also a linear regression model was applied when studying the delays at attaining a given educational level in paper III. Results from the linear regression were only used as part of the discussions in both paper III and this thesis. By applying a linear regression model, occurrence of delays in educational achievements among the cancer survivors could be evaluated and compared to those of the cancer-free population. Results of the linear regression model are presented in Appendix II.

5.1.6 Other methodological considerations

Missing data occurs when no value is recorded for the variable in an observation.[123] It has been suggested that incompleteness of follow-up may result in overestimations of outcomes.[124] In paper I, death specification was missing for 48 cancer patients. Given the large sample size in our study, it is unlikely to have influenced the results. In Paper III, 2.8% of the population (similar proportions for the cancer and the cancer-free population) lacked educational specifications. Since the proportion of missing values were less than

5–10%, deleting the cases was a reasonable solution and there was no need for imputation.[125, 126] Thus, it is unlikely that removing the individuals with missing educational specifications could have influenced the final results and conclusions.

Grouping of cancer types is a challenge in studies such as the current one with a relatively small number of cancer cases. Hence, main categories were studied here.

In paper I, the cancers were first divided into 11 main categories. Furthermore, the most common cancers were studied in detail among young individuals; CNS-tumours (ICD-7; 193), bone and connective/soft tissue tumours (196–7), lymphomas (206), and leukaemia (207). ALL and AML were considered separately. There were very few deaths among HL and NHL patients, especially during 1965−1974 and 2005−2009. Hence, HL and NHL were not considered separately. Also, Wilms' tumours could not have been studied separately due to the low number of deaths.

Also in paper II, the main 11 cancer categories were considered. In paper III, the grouping of cancers was more challenging. Cancer and its treatments are reported to have a significant effect on educational achievements.[89, 91] One of the main weaknesses of this study was the lack of information on cancer treatment on the individual level. In order to account for this, the cancer survivors were divided into the following groups based on the general knowledge of cancer treatment in Norway; survivors of CNS-tumours, survivors of cancers assumed to have been treated with CNS-directed therapy and all other cancer survivors combined.

5.2 Discussion of results

The risk of early death (paper I) was mainly considered to indicate the efficacy of cancer treatment, while uptake of social security benefits and deficits in educational

achievements (paper II and III) were considered to be consequences of treatment-induced late effects.

5.2.1 Early mortality (paper I)

In line with other studies,[6, 32, 127, 128] the most frequent cancers in our study were CNS-tumours, leukaemia and lymphoma. In paper I, a general decline in risk of early cancer death over time was observed among children, adolescents, and young adults in Norway. These findings were in accordance with studies from Europe,[7, 8, 32] and the USA.[36, 42, 129] Risk of cancer death decreased substantially among children and adolescents during our study period while only a moderate decline was observed among young adults.

Mortality from childhood leukaemia and other childhood cancers has been reduced substantially in western countries in the past few decades.[8, 36] A similar trend was demonstrated in our study. Other studies reported the highest reduction in mortality for leukaemia, lymphoma and brain tumours[8, 36, 40, 42]. Moderate reduction was reported for bone cancers.[42] In our study, except AML, early cancer deaths were reduced for the four major cancers and all cancers combined. Mortality from AML declined during 1965−1984 and after 1995; a slight increase during 1985–1994 was observed when compared with other diagnosis.

In our study, trends in mortality among children compared with adolescents and young adults were somewhat different from that observed in other studies.[31] Adolescents and young adults diagnosed with CNS-tumours, bone and connective/soft tissue tumours and lymphoma, generally had lower risk of mortality as compared with children, even though the differences were not always statistically significant. Results from the US Surveillance, Epidemiology, and End Results (SEER) showed that adolescents and young adults with ALL had higher mortality than children[10] which was similar to our findings. Also, a French study on adolescent cancer (age 15–19 years) showed that adolescents when

compared with children, had higher mortality from ALL, NHL, osteosarcoma, soft tissue sarcoma and Ewing's tumour.[31] Due to the small number of deaths in our study, it was not possible to evaluate each of these cancer sites separately and compare them between age groups.

A study from Pritchard-Jones et al.[124] on European children (age 0–14 years) and adolescents (age 15–19) with cancer showed similar overall 5-year survival among adolescents compared with children. In our study, the mortality among adolescents compared with children varied by cancer site. Adolescents diagnosed with leukaemia, also when ALL and AML were considered separately, had significantly higher risk of early death than children. However, adolescents diagnosed with CNS-tumours had significantly lower risk of death than children. Those diagnosed with bone and soft/connective tissue tumours and lymphoma had similar risk of mortality compared to children. Gatta et al.[43] studied cancer survival among young individuals in Europe (15–24 year) diagnosed during 1990–1994. They showed higher mortality among adolescents compared with young adults for all cancer sites combined. This was similar to our findings (Table 3). The age group variation could be due to differences in the biology of cancer, treatment protocols designed for each cancer at each age group, and period of diagnosis.

Another explanation for the lower mortality among adolescents and young adults as compared with children might be the presence of a higher proportion of less aggressive tumours with more favourable prognosis in adolescents and young adults (such as HL and germ-cell tumours) in our study. Categorizing less aggressive tumours into aggressive tumour groups or coding benign tumours with malignant cases may also affect the mortality rate.[124]

Table 3: Sub-hazard ratios (SHRs) with 95% CI for early cancer death (within 5 years after diagnosis) estimated in a multivariate competing risk model for cancer patients diagnosed at age 15–24 years during 1990–1994[a]

Age at diagnoses	All cancer sites combined
15–19	1.7 (1.2–2.4)
20–24	1

[a] Adjusted for gender.

In our study, there was no overlap of outcomes for different age groups over the same time period. This issue arises when each age cohort reflects a specific diagnosis period and one cannot readily compare all the age groups over similar time periods; thus our results represented the net effect of age in the whole study period. An additional sub-analysis for the diagnostic period 1985–1994 was performed where all the age categories were present. The results were similar to our general findings. Adolescents and young adults had lower mortality compared with children (Table 4).

Table 4: Sub-hazard ratios (SHRs) with 95% CI for early cancer death (within 5 years after diagnosis) estimated in a multivariate competing risk model for cancer patients diagnosed before the age of 25 and during 1985–1994[a]

Age at diagnosis	All cancer sites combined
0–14	1
15–19	0.7 (0.6–0.9)
20–24	0.4 (0.3–0.6)

[a] Adjusted for gender.

Norway has a public health care system where treatments are offered free of charge for the Norwegian residents. Thus, cancer patients at all ages receive adequate treatment and care appropriate to their diagnoses. This may partly explain the difference in our results compared to the research of others from different health care systems. Furthermore,

choice of study population, classification criteria, grouping of cancer sites (detailed or more general) and/or choice of analytic methods could explain further differences. More research is warranted to explore the background for the observed differences in detail.

5.2.2 Social security benefits (paper II)

Similar to previous research, an increased need for assistance and uptake of social security benefits was observed among the cancer survivors compared with the cancer-free population. Increased need for supportive measures has previously been shown to be due to various late effects.[20, 80, 81, 130, 131]

Only a few studies have explored the need for supportive measures such as social security benefits among cancer survivors. Studies by Mulrooney et al.[60] and Oeffinger et al.[18] explored late effects based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCTCAE). Severe late effects were coded as grade 3 and 4 in accordance with NCTCAE. Mulrooney et al. reported that approximately 28% of the long-term survivors (excluding survivors of AML) compared with 6% of the siblings had a severe chronic medical condition. Oeffinger et al. also reported severe and life-threatening health problems among 27.5% of the cancer survivors compared with 5.2% among the siblings. Our results were in line with their findings for severe conditions. The study by Thorsen et al.[80] from Norway showed the need for at least one rehabilitation service among 63% of the individuals. This high percentage compared to our results is probably due to the composition of the study population which included all cancer individuals aged 25–60 years. It may also indicate that the risk of late effects increases further with increasing age. Further research exploring this possibility is therefore necessary.

In line with our findings, a Norwegian study[20] on cancer survivors diagnosed during 1970–1997 (age <15 years) showed that survivors of CNS-tumours more frequently

received social security benefits compared with survivors of malignancies of the haematopoietic system. Hjern et al.[81] explored the effect of cancer and its treatment among adult survivors of childhood cancer (diagnosed <16 years). According to their findings, survivors of CNS-tumours, leukaemia and lymphoma had a high risk of disabilities warranting uptake of benefits. Similar results were observed in our study. Hjern et al. also reported that younger age at diagnosis increased the risk of disability. Similar to our study, uptake of disability pension was highest among children compared to adolescents and young adults (Table 5). Generally, survivors of CNS-tumours and leukaemia were reported to have higher incidence of late effects compared to other survivors.[18, 70, 130-132] This could be due to the intense treatment protocols for these cancers as well as the young age at diagnosis. Although younger patients respond better to treatment, they are at higher risk of developing late effects.

Table 5: Standardized incidence ratio (SIR) for diagnoses obtained for disability pension from social security benefits available from 1992–2006

Diagnoses age	Cancer cases	Cases with disability pension	SIR (95% CI)
0–4	590	67	6.6 (5.1–8.4)
5–9	407	48	6.7 (5.0–8.9)
10–14	473	53	6.2 (4.6–8.1)

A Dutch study on childhood cancer survivors showed that autonomy and social and psychosexual developments could give an indication for the likelihood of applying for disability pension.[82] Mental illnesses were reported frequently as one of the causes for uptake of disability pension in our study. However, to study the subgroups in more detail was not possible due to small number of cases. As mentioned earlier, such studies may be necessary on a Nordic level to ensure a larger number of cases.

Physical performance limitations were reported from other studies.[68, 133, 134] A study by Ness et al.[135] from the US showed that physical performance limitations were more

frequently seen among childhood cancer survivors than their siblings and that the prevalence may increase with younger diagnosis age. They suggested that poor access to health care may be associated with physical disability. This is not applicable to the Norwegian population because the health care system is free of charge in Norway. Thus, health impairments occurring among cancer patients are mainly due to effects of cancer and its treatment on the physical and mental health of the patients. Other studies showed increased risk of physical impairments for female survivors, survivors of bone and brain tumours and Hodgkin's disease.[27, 134] In our study, female patients had a higher risk of attendance benefits and disability pension uptake. Attendance benefits reflect economic burdens while disability pension is an indication of reduced working ability. Survivors of bone and connective/soft tissue tumours and CNS-tumours had the highest risk of uptake when all the different social security benefits were studied combined.

Other studies have shown increased risks of cardiac dysfunction.[136-138] In our study, diagnostic groups retrieved from various uptake rates varied, but diseases of the circulatory system were not a common cause of social security benefit uptake. One problem with using data from NIS is that only individuals with severe conditions may be qualified for uptake of social security benefits. As a result, individuals may have impaired health conditions, but do not qualify for social security benefits. As such, less pronounced but perhaps life inflicting disabilities remain unaccounted for in our study.

Studies have reported that cancer survivors are more likely to be unemployed,[27, 94, 139] living with their parents[140] or be uninsured.[83] Follow-up care and screening may be expensive and cause a financial burden on cancer survivors and their family. If the health care system does not provide such services free of charge, there is a need for health insurance coverage which may be costly and/or not extend fully to cover all the various health expenses.[83] Consequently, cancer survivors may not receive preventive care services that may prevent relapse or the occurrence of late effects. Our results indicated an increased need for help and care provided by the society among the cancer survivors. In Norway, the health care system is public where cancer treatment and follow-up is

provided basically free of charge.[51] Extra medical costs that are caused by late effects are covered by social security benefits.

Other studies have mostly focused on specific cancer sites, usually brain tumours, leukaemia or lymphoma, and fewer possible adverse effects.[130, 132, 141-144] In contrast, access to registry-based data has enabled us to study various late effects using data retrieved from NIS. Although the total numbers of late effects were small, it was possible to provide what was considered to be an overall picture of survivors' health and welfare in Norway.

5.2.3 Educational achievements (paper III)

In line with previous research, some educational deficits were observed among cancer survivors compared with the cancer-free population.[19, 25, 89, 93] Significant deficits among survivors of CNS-tumours and those assumed to have received CNS-directed therapy was displayed in our study. Survivors of "Other" cancers had in general similar educational achievements compared to the cancer-free population. Some educational deficit at the tertiary level was also indicated, but no significant differences in choice of educational fields were observed.

In line with our findings, educational impairments have been reported frequently among survivors of CNS-tumours[91, 93, 145] and leukaemia.[95] Barrera et al.[146] studied the educational and social outcomes among children diagnosed before age 17. They showed that survivors of CNS-tumours, leukaemia and neuroblastoma more often had educational problems. Similarly in our study, survivors of CNS-tumours (at all levels of education) and those assumed to have received CNS-directed therapy (including survivors of leukaemia) had most educational impairments.

Finnish studies[91, 95] showed that foreign language grades of patients with brain tumours and leukaemia at the ninth grade were most pronouncedly affected by cancer and its

treatment. This effect was especially noted among girls. Foreign language was considered as an indication of verbal performances.[91] Another Finnish study[19] showed impaired grades among NHL patients and radiated Wilms' tumour patients. In our study, in order to evaluate differences in various subjects at the intermediate level, pupils' grades similar to that in the Finnish studies should have been accesible.[19, 91, 95] Access to data on grades in our study could have improved the comparability of our results as well as the possibility to evaluate the school performance of pupils at the intermediate level of education in more detail.

A Norwegian cross-sectional study of all young Nordic adult survivors[139] reported similar rates of high school graduation among cancer survivors compared with controls. In our study, only survivors of "Other" cancers had similar educational achievements compared to the cancer-free population. Higher frequencies of repeating a grade and higher rates of school absence among cancer individuals than of that of the control group have been reported from an US study.[96] Although similar data on repeats of grades and school absence was not available in our study, our results showed that survivors completed each level of education less often than the cancer-free population. School absence and repeating a grade could be a possible explanation for the delays observed in our study.

Special education has been examined in other studies,[25, 97, 145] and research shows that cancer survivors are more often in need of such education. The review by Gurney et al. of published studies[27] showed that survivors were more often in need of special education than the control group. Information on special education was not available in our study. Therefore, evaluation of the need for such services among the cancer survivors compared with the cancer-free population was not possible. On the other hand, the Norwegian education system provides services to pupils with special needs. Therefore, cancer survivors in our study are likely to have received special education if considered necessary.

Differences in educational achievements among the cancer survivors and the cancer-free population diminished at higher levels of education in our study. Results from paper I and II indicated that children had higher mortality and were in general more likely to receive social security benefits than adolescents. This could indicate that healthier children survived heavy and aggressive treatments, which may partly explain our results. Another possibility could be that cancers with better prognoses were overrepresented, especially among those diagnosed between 15–18 years. This could potentially result in lower educational differences between the cancer and the cancer-free population.

To our knowledge, choice of educational field at higher level of education has not been studied before. Our results showed no significant differences between cancer survivors and the cancer-free population. A possible explanation could be similar educational achievements at higher levels of education for the cancer survivors and the cancer-free population. Due to relatively small number of survivors, it was not possible to study the differences in choice of educational fields in finer groups (i.e. the narrow fields of education presented in Appendix I).

Results from the linear regression model (Appendix II) indicated only minor delays in completing a level of education among the 5-year cancer survivors despite their intense and prolonged cancer treatments. A lack of delay could partly be explained by improvements in awareness in the Norwegian educational system and thus the provision of better services for pupils with special needs. As discussed earlier, there is a possibility that only patients with less aggressive cancers at the early study period survived, and therefore their educational performances were less affected.

Impact of education on uptake of disability pension among the cancer survivors was studied here. Only survivors that were diagnosed before age 22 and reached age 27 were included, and the highest obtained level of education was then considered. Survivors with university education had a lower risk of disability pension uptake than survivors with lower education (Table 6). The results of paper II showed that cancer survivors were more

likely to receive social security benefits compared to the cancer-free population. This was the case even after adjusting for the effects of education. This could indicate that in spite of educational accomplishment, there is a possibility that cancer survivors may not be able to use their education for getting desirable jobs or equal earnings compared to the cancer-free population. This warrants further research.

Table 6: Hazard ratios (HRs)[a] with 95% CI of uptake of disability pension among cancer survivors diagnosed before age of 22 years and reached age 27 years by level of education

Level of education	HR (95% CI)
Compulsory	1
Intermediate	0.8 (0.4–1.4)
Tertiary	0.2 (0.1–0.5)

[a] Adjusted for gender, year of birth and parental education.

Cancers and treatment protocols have significant effect on survivors' educational achievements.[19, 91] Although adjustment for potential treatment effects was not possible, the general knowledge on cancer treatment protocols applied in Norway during the past few decades was used. In our study, significant differences were mostly observed for those diagnosed during 1975–1984. These patients were diagnosed at the treatment transition period that took place from the 1970s to the 1980s where treatment was fairly intense. They may, therefore, have been over-treated; but studying this effect was not possible.

As mentioned earlier, structural changes (such as Reform 94, Reform 97 and Quality Reform in 2003) have taken place in the Norwegian educational system during the past few decades. Only Reform 94 could have affected our study population. Moreover, most observed delays in our study occurred before 1990, and therefore it is unlikely that our results have been affected by these changes.

6. Conclusion and future perspective

Access to data from population-based registries gave us a unique opportunity to study the impact of cancer on young people in general. Consequently, some important questions regarding the individuals' life prospects after a cancer diagnosis could be clarified.

Cancer mortality among patients diagnosed before age 25 years in Norway has been reduced over time, also relative to the cancer-free population. Consequently, more patients survive and become 5-year survivors. Cancer diagnosis and its treatment may cause severe late effects among survivors that could appear later in life. Our results showed increased rate of social security uptake among 5-year survivors compared with the cancer-free population. Uptake of social security benefits was associated with year of birth, younger age at primary cancer diagnosis and type of cancer. Survivors of bone and connective/soft tissue tumours, CNS-tumours and leukaemia were more likely to be recipient of social security benefits. Further follow-up[147] and long-term medical surveillance of cancer survivors diagnosed in younger years may minimise the occurrence of late effects and increase the health awareness among the cancer survivors.[148-150]

Lower educational achievements among some groups of cancer survivors were observed compared with the cancer-free population. These effects were more pronounced at lower levels of education (intermediate level). Although cancer survivors were less likely to complete their education at university level, choice of educational fields was similar for the cancer and the cancer-free population. Providing supportive educational measures for students, especially at lower level of education, may help improving educational achievements among the individuals diagnosed with cancer at an early age.

Further research on cancer and treatment effects is necessary to improve the long-term survival rate and reduce the occurrence of late-effects with implications for social security uptake and educational attainment. Additionally, providing proper information to the

public and health professionals could improve general knowledge about long-term consequences and need for proper care for these cancer survivors.[134, 147]

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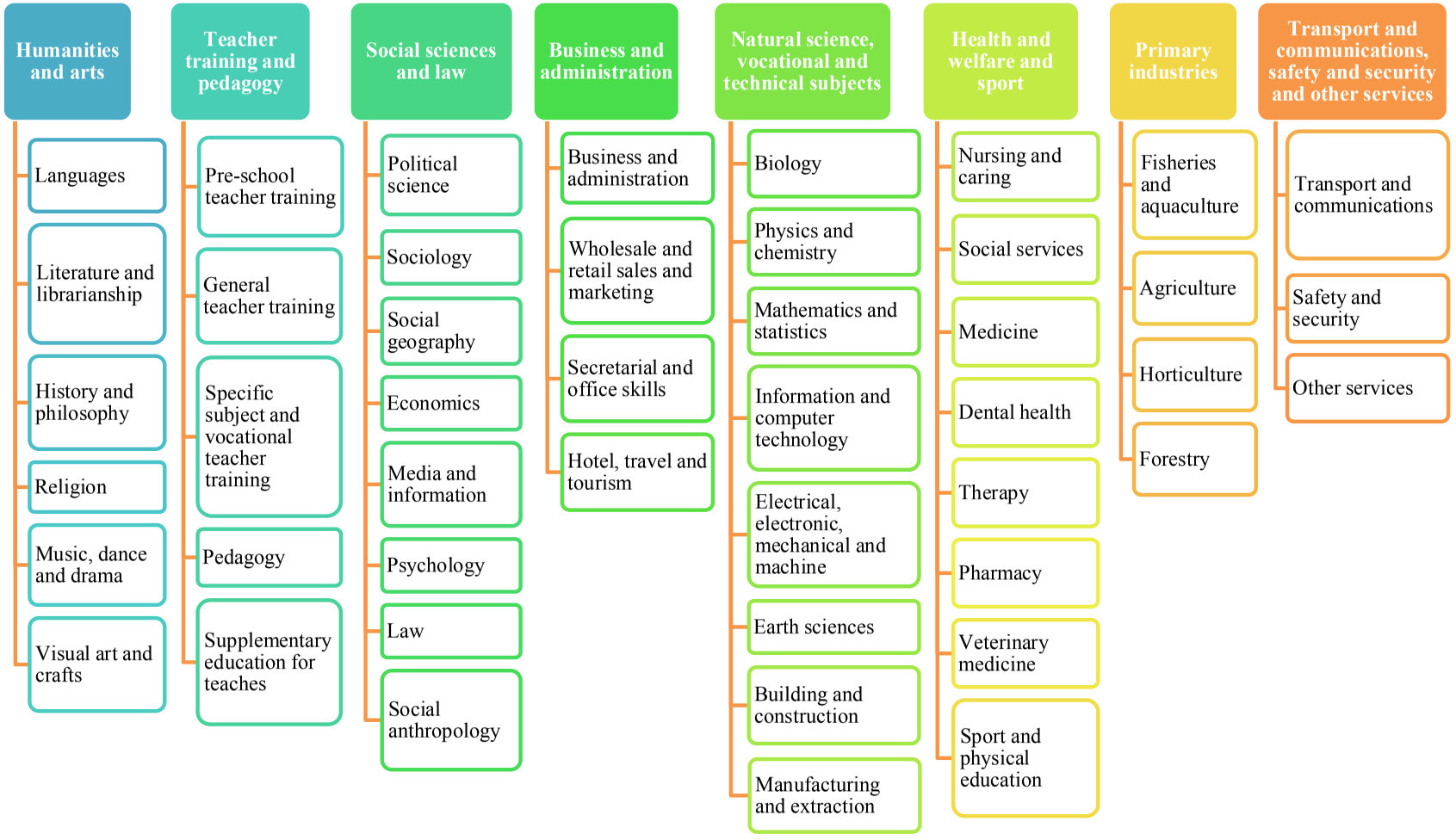
Errata

Paper I:

During the work on our project, we discovered a small programming error. A small population of children who were not born in Norway, especially during the first two years of the study period (1965-1966) was included in the original manuscript. We have repeated all analyses in the published paper. Fortunately, only small differences in numbers were observed, and all conclusions remained unchanged (Appendix III).

Appendix I

An overview of narrow fields of education



Appendix II

Table 1: Linear regression with 95% confidence intervals (CI) of delays in educational attainment for cancer survivors by year and age of diagnosis compared with the cancer-free population [a]

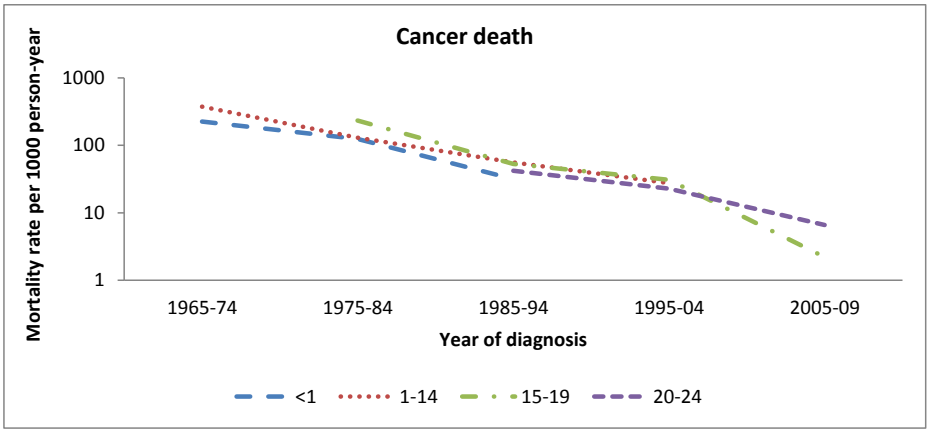
		CNS-tumour [b]	Cancer with CNS directed therapy [c]	Other childhood cancers [d]	All cancer sites combined
Intermediate	**Year of diagnosis**				
	1965-74	2.8 (1.2,4.4)	0.2 (-1.0,1.4)	0.1 (-0.6,0.9)	0.5 (-0.1,1.1)
	1975-84	0.1 (-0.6,0.9)	0.1 (-0.4,0.6)	-0.2 (-0.7,0.2)	-0.1 (-0.4,0.3)
	1985-94	0.7 (-0.1,1.5)	0 (-0.6,0.6)	-0.1 (-0.7,0.6)	0.2 (-0.2,0.5)
	1995-04	0.6 (-2.3,3.6)	-1.2 (-5.4,3.1)	0.1 (-1.8,1.9)	0 (-1.5,1.5)
	Age at diagnosis				
	0-4	1.1 (0.2,2.1)	0.2 (-0.3,0.7)	0.2 (-0.3,0.6)	0.3 (0,0.6)
	5-9	0.4 (-0.3,1.1)	-0.2 (-0.8-0.4)	-0.4 (-1.1,0.3)	-0.1 (-0.5,0.3)
	10-12	0.5 (-0.7,1.6)	-0.2 (-0.8,1.3)	-0.7 (-1.6,0.2)	-0.1 (-0.7,0.5)
Under graduate	**Year of diagnosis**				
	1965-74	-1.8 (-5.2,1.5)	-0.8 (-0.6,1.1)	-0.2 (-1.4,1.0)	-0.4 (-1.3,0.5)
	1975-84	1.3 (0.1,2.5)	0.9 (0.2,1.7)	-0.3 (-0.9,0.4)	0.3 (-0.1,0.8)
	1985-94	-0.3 (-1.5-1.0)	0 (-1.0,0.9)	-0.4 (-1.3,0.4)	-0.3 (-0.8,0.3)
	1995-04	0.1 (-2.4,2.6)	0.2 (-2.5,2.9)	-0.3 (-1.9,1.2)	-0.1 (-1.3,1.0)
	Age at diagnosis				
	0-4	0.4 (-1.6,2.4)	0.2 (-0.7,1.0)	-0.1 (-0.8,0.6)	0 (-0.5,0.5)
	5-9	0.5 (-0.8,1.9)	0.9 (-0.1,1.8)	-0.6 (-1.6,0.5)	0.4 (-0.2,1.0)
	10-14	0.2 (-1.0,1.3)	0 (-1.5,1.4)	-0.4 (-1.2,0.3)	-0.3 (-0.9,0.3)
Graduate	**Year of diagnosis**				
	1965-74	-	5.5 (2.3,8.7)	0.1 (-1.9,2.1)	1.2 (-0.4,2.8)

1975-84	0.1 (-2.0, 2.2)	0.5 (-1.9,1.0)	1.2 (0.3,2.2)	0.7 (-0.1,1.4)
1985-94	0.1 (-1.8,1.9)	0 (-1.8,1.7)	-0.6 (-1.6,0.4)	-0.4 (-1.2,0.4)
1995-04	0 (-3.9,3.9)	-	-0.3 (-1.7,1.1)	-0.3 (-1.6,1.0)
Age at diagnosis				
0-4	-0.5 (-3.7,2.7)	-0.3 (-1.7,1.2)	-0.2 (-1.3,1.0)	-0.3 (-1.2,0.6)
5-9	-0.4 (-3.6,2.8)	2.9 (0.4,5.4)	2.3 (0.3,4.3)	2.0 (0.6,3.4)
10-14	1.3 (-1.0,3.6)	-0.9 (-3.7,1.9)	0.4 (-0.7,1.6)	0.4 (-0.5,1.4)
15-18	-0.6 (-2.9,1.6)	0.9 (-2.2,4.1)	-0.2 (-1.1-0.7)	-0.2 (-1.0,0.7)

[a] The model is adjusted for gender, year of birth and parental education; [b] Including the cancer sites with ICD-7 codes 195.3-5; [c] This group includes survivors of leukaemia and non-Hodgkin lymphoma; [d] Including the cancer sites with ICD-7 codes 193.5-6.

Appendix III

Correction of figures and tables, paper I



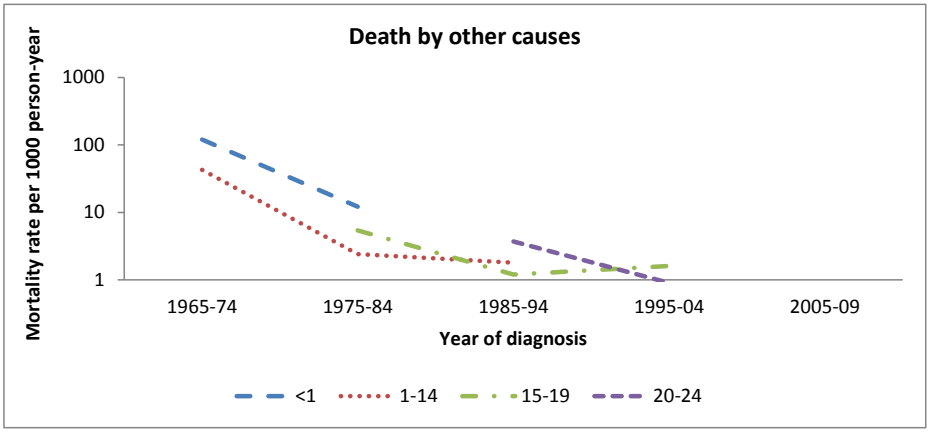


Figure 1: Early death rates (5 years after diagnosis) caused by cancer and other causes among cancer patients by age at diagnosis (<1, 1−14, 15−19 and 20−24 years) per 1,000 person-years. Note that patients diagnosed in the period 2005−2009 were at least 20 years of age at the time of diagnosis. The y-axes are presented in logarithmic scale

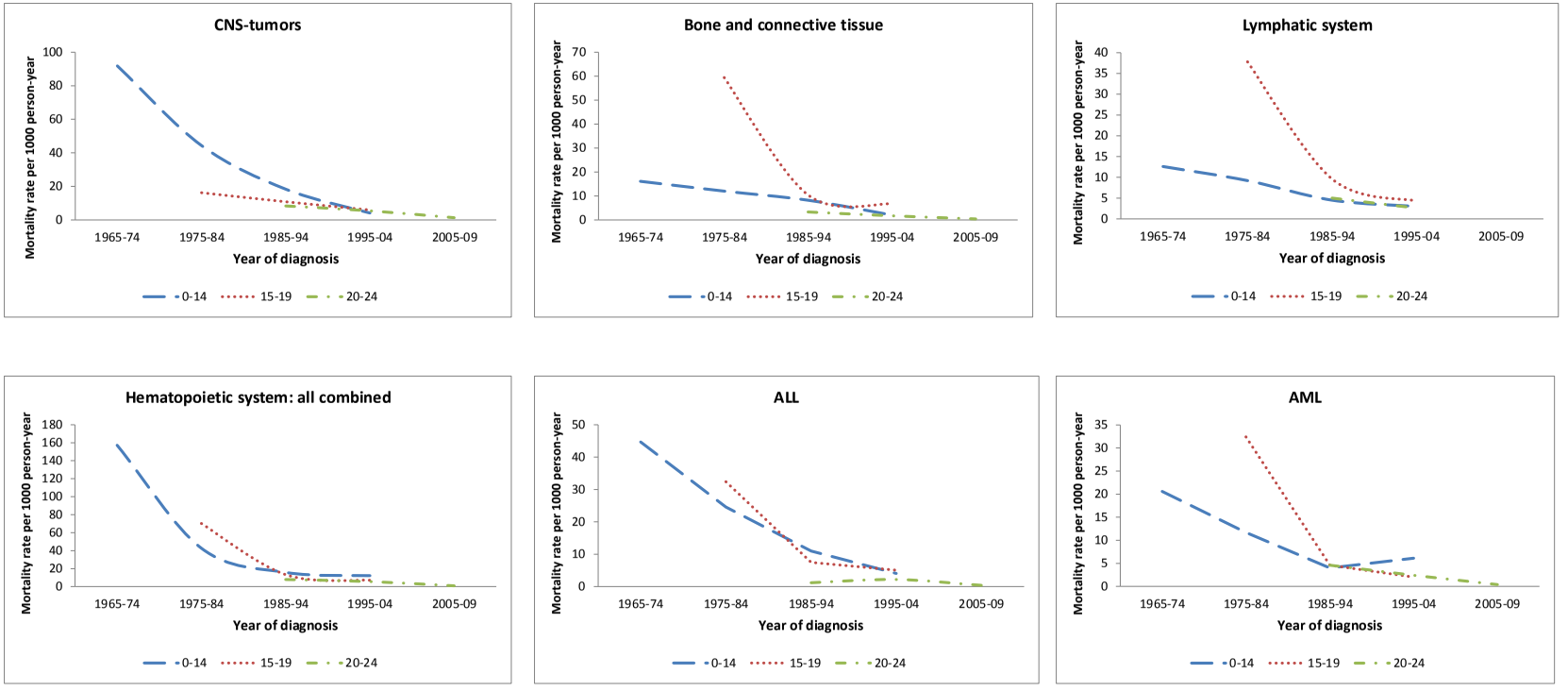


Figure 2: Cause-specific early death rate (5 years after diagnosis) among cancer patients by age at diagnosis (0−14, 15−19, and 20−24 years) per 1,000 person-years for four major cancer sites (including ALL and AML). Note that patients diagnosed in the period 2005−2009 were at least 20 years of age at the time of diagnosis
Abbreviation: ALL: Acute lymphatic leukemia; AML: Acute myelogenic leukemia

Table 1: Characteristics of the cancer patients born in Norway during 1965−1985

	No. of individuals (%)	Total no. of deaths [a] (%)	No. of cancer deaths (%)
Gender			
Male	3,268 (56.3)	889 (59.9)	846 (60.0)
Female	2,534 (43.7)	601 (40.1)	563 (40.0)
Year of birth			
1965-1969	1,504 (25.9)	524 (35.0)	465 (33.0)
1970-1974	1,456 (25.1)	413 (27.6)	403 (28.6)
1975-1979	1,306 (22.5)	276 (18.4)	264 (18.7)
1980-1985	1536 (26.5)	286 (19.1)	277 (19.7)
Age at diagnosis			
0-14	2,481 (42.8)	1,007 (67.2)	938 (66.6)
15-19	1,289 (22.2)	257 (17.1)	249 (17.7)
20-24	2,032 (35.0)	235 (15.7)	222 (15.8)
Year of diagnosis			
1965-1974	534 (9.2)	349 (23.3)	297 (21.1)
1975-1984	1,230 (21.2)	474 (31.6)	462 (32.8)
1985-1994	2,128 (36.7)	441 (29.4)	423 (30.0)
1995-2004	1,639 (28.2)	219 (14.6)	211 (15.0)
2005-2009	271 (4.7)	16 (1.1)	16 (1.1)
Cancer site (ICD-7 codes)			
Kidney (180.0) [b]	154 (2.7)	43 (2.9)	36 (2.6)
Eye (192)	98 (1.7)	7 (0.5)	6 (0.4)
CNS tumor (193)	1,192 (20.5)	407 (27.2)	385 (27.3)
Thyroid gland and other endocrine glands (194-5) [c]	370 (6.4)	57 (3.8)	53 (3.8)
Bone and connective tissue (196-7)	393 (6.8)	156 (10.4)	154 (10.9)
Lymphatic system (206)	742 (12.8)	133 (9)	125 (8.9)
Hodgkin lymphoma	414 (55.8)	23 (17.3)	20 (16.0)
Non-Hodgkin lymphoma	270 (36.4)	92 (69.2)	88 (70.4)

Other	58 (7.8)	18 (13.5)	17 (13.6)
Hematopoietic system (207)	1,008 (17.4)	479 (32.0)	454 (32.2)
Acute lymphatic leukemia (ALL)	625 (61.9)	217 (45.3)	213 (46.9)
Acute myelogenic leukemia (AML)	191 (18.9)	127 (26.5)	121 (26.7)
Other	194 (19.2)	135 (28.2)	120 (26.4)
Cervix uteri (171)	68 (1.2)	10 (0.7)	10 (0.7)
Ovary (175)	100 (1.7)	12 (0.8)	12 (0.9)
Testis (178)	741 (12.8)	45 (3.0)	40 (2.8)
Melanoma (190)	471 (8.1)	20 (1.3)	18 (1.3)
Other	465 (8.0)	130 (8.7)	116 (8.2)
Year of death			
1969-1974 [d]		299 (19.9)	248 (17.6)
1975-1984		454 (30.3)	442 (31.4)
1985-1994		450 (30.0)	437 (31.0)
1995-2004		261 (17.4)	248 (17.6)
2005-2008		35 (2.3)	34 (2.4)
Total	5,802 (100.0)	1,499 (100.0)	1,409 (100.0)

[a] Death cases within 5 years after diagnosis [b] 83.8 % were Wilms tumor cases [c] This site include malignant neoplasm of the thyroid gland (44.6%), suprarenal gland (16.8 %), pituitary gland (20.8 %), pineal gland (8.1 %), cranieopharyngeal canal (9.2 %), and others (0.6 %) [d] 48 patients who died before 1969, lack cause of death specification

Table 2: Hazard ratios (HRs) of death among the cancer patients diagnosed before age 25 relative to individuals without cancer by year of diagnosis, with 95% confidence intervals (CI) estimated by a time-dependent Cox regression model [a]

	5 years follow-up after diagnosis [b] (n [c] =1,499/5,802)	Total follow-up (n=1,793/5,802)
Year of diagnosis [d]		
1965-74	361.5 (313.9,416.2)	79.7 (69.8-91.0)
1975-84	245.2 (216.8,277.4)	46.2 (41.3,51.5)
1985-94	94.1 (83.4,106.1)	28.9 (26.1,32.1)
1995-04	41.3 (34.8,49.1)	26.0 (22.1,30.5)
2005-09	19.3 (9.2,40.7)	25.4 (12.1,53.4)

[a] The analysis was adjusted for gender and year of birth (1965−1969, 1970−1974, 1975−1979 and 1980−1985) [b] The follow-up time was from birth until 5 years after diagnosis [c] N represents the number of deaths / total number of cancer patients [d] The analyses were performed relative to the general population

Table 3: Sub-hazard ratios (SHRs) with 95% confidence intervals (CI) for early cancer death (5 years after diagnosis) estimated in a multivariate competing risk model for cancer patients diagnosed before the age of 25

	CNS tumors (193 [a]) (n [b]=383/1,192)	Bone and Connective tissue (196-7) (n=154/393)	Lymphatic system (206) (n=125/742)	Hematopoietic system: all combined (207) (n=453/1,008)	Acute lymphatic leukemia (ALL) (n=212/625)	Acute myelogenic leukemia (AML) (n=121/191)	All cancer sites (n=1,409/5,802)
Gender							
Male	1	1	1	1	1	1	1
Female	0.82 (0.66,1.01)	0.92 (0.67,1.27)	0.81 (0.56,1.18)	0.86 (0.71,1.03)	0.91 (0.69,1.22)	0.63 (0.43,0.91)	0.83 (0.75,0.93)
Year of diagnosis							
1965-74	1	1	1	1	1	1	1
1975-84	0.69 (0.53,0.92)	0.65 (0.33,1.28)	0.58 (0.27,1.27)	0.43 (0.34,0.54)	0.45 (0.32,0.64)	0.58 (0.32,1.07)	0.60 (0.52,0.70)
1985-94	0.41 (0.30,0.55)	0.41 (0.20,0.82)	0.28 (0.12,0.65)	0.31 (0.23,0.41)	0.32 (0.21,0.48)	0.77 (0.38,1.38)	0.38 (0.32,0.45)
1995-04	0.25 (0.16,0.39)	0.33 (0.16,0.71)	0.17 (0.07,0.40)	0.29 (0.20,0.43)	0.30 (0.17,0.53)	0.48 (0.22,1.06)	0.28 (0.23,0.35)
2005-09	0.05 (0.01,0.23)	0.11 (0.01,0.93)	[c]	0.10 (0.02,0.42)	0.18 (0.02,1.66)	0.22 (0.03,1.46)	0.15 (0.09,0.26)
Age at diagnosis							
0-14	1	1	1	1	1	1	1
15-19	0.69 (0.49,0.97)	0.93 (0.65,1.34)	0.96 (0.59,1.57)	2.16 (1.56,2.89)	2.74 (1.75,4.28)	1.36 (0.81,2.26)	0.73 (0.62,0.86)
20-24	0.88 (0.60,1.30)	0.66 (0.37,1.18)	0.52 (0.29,0.93)	1.92 (1.29,2.87)	2.21 (1.18,4.13)	0.93 (0.53,1.64)	0.46 (0.38,0.56)

[a] ICD-7 codes [b] N represents the number of cancer deaths/ total number of cancer patients [c] There were no death cases