A statistical approach to cancer survivorship —statistical methods applied on registry-based data for computing reproduction rates, cure proportion and survival

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Abbreviations

ART	Assisted Reproduction Technologies
BC	Breast Cancer
CI	Confidence Interval
CRN	Cancer Registry of Norway
CumInc	Cumulative Incidence
DCO	Death Certificate Only
EOD	Extent of the Disease
HL	Hodgkin's lymphoma
HR	Hazards Rates Ratio
KM	Kaplan-Meier Estimator
MBRN	Medical Birth Registry of Norway
NCI	National Cancer Institute
NAa	Nelson-Aalen Estimator
NRH	Norwegian Radium Hospital
PDR	Post-diagnosis Reproduction
POF	Premature Ovarian Failure
QoL	Quality of life
RPLND	Retroperitoneal Lymph Node Dissection
RT	Radiotherapy
SEER	Surveillance Epidemiology and End Results registry
SES	Socio-economic Status
SSB	Statistics Norway
TC	Testicular Cancer
TGCT	Testicular Germ Cell Tumour

Cancer Treatment Therapies

ABVD	adriamycin, bleomycin, vinblastine, dacarbazine
ABOD	adriamycin, bleomycin, vincristine, dacarbazine

CHOP	cyclophosphamide, adriamycin, vincristine, prednison
MOPP	mechlorethamine, vincristine, procarbazine, prednison
CAOS	cyclophosphamid, adriamycin, vincristine, actinomycin D
BEP	cisplatin, etoposid, bleomycin
BEACOPP	cyclophosphamid, adriamycin, vincristine, etoposide, procarbazine, bleomycin, prednisone
CVB	cisplatin, vinblastin, bleomycin

Acknowledgement

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I am indebted to my co-authors for their support and cooperation and I want also to thank my co-workers at the Cancer registry and the NRH for creating a friendly and stimulating work environment. In particular, I'd like to thank Hanne Stensheim for interesting and stimulating discussions on fertility issues and for helping me with the medical aspects of my work, and Jan Oldenburg and Cecilie Kiserud for all the useful comments to this manuscript. Special thanks go to Kristine Engen Andreassen, you have been a great friend when I needed it the most.

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List of papers

I: Cvancarova M, Aagnes B, Fosså SD, Lambert P and Bray F

Proportion Cured Models Applied to 23 Cancer Sites in Norway

[Submitted: International Journal of Cancer, October 2010]

II: Fosså SD, Cvancarova M, Chen L, Allan AL, Oldenburg J, Peterson DR and Travis LB.

Adverse prognostic factors for testicular cancer-specific survival: a population-based study of 27,948 U.S. patients

[Submitted: Journal of Clinical Oncology, accepted October 2010, pending minor revissions]

III: Cvancarova M, Samuelsen SO, Magelssen H and Fosså SD.

Reproduction Rates After Cancer Treatment: Experience From the Norwegian Radium Hospital

Journal of Clinical Oncology, Vol 27, No 3 (January 20), 2009: pp. 334-343

IV: Stensheim H, Cvancarova M, Møller B, and Fosså SD.

Reproduction after Cancer: a Population-based matched cohort study

[Submitted: Journal of the National Cancer Institute, October 2010]

I. Background

A larger proportion of cancer patients survives their initial diagnosis and remains tumour-free for longer periods than has been observed in previous decades (Janssen-Heijnen, et al., 2010). Hand in hand with this favourable development goes also an increased interest in 'life after cancer'. In other words, while *survival* has been a topic of major attention for many years, *survivorship issues* dealing with other aspects of life after cancer beyond survival have gained increasing interest in the oncological community during the last two decades.

1 Cancer Survival and sources of information

1.1 Cancer statistics worldwide

Data on incidence and mortality after cancer worldwide can be accessed by public databases (Parkin, et al., 1997). For Europe, relevant data on cancer survival have been published in EUROCARE-4 (Verdecchia, et al., 2007). This report comprises survival data for patients diagnosed with cancer in 2000–02, collected from 47 of the European cancer registries participating in the EUROCARE-4 study. Mean five-year relative survival was estimated for the European mean and for five European regions, and findings were compared with those from the US SEER registry (SEE). Survival for patients diagnosed in this time period was generally highest for those in northern European countries and lowest for those in eastern European countries. The pronounced differences in survival are only partly due to cancer treatment and access to diagnostic and treatment facilities but can also be attributed to other factors such as prevention, screening programs and socio-economic status.

Concerning cancer care in the Nordic countries, the NORDCAN database and program (Engholm, et al., 2010) includes detailed information and results on cancer incidence, mortality and prevalence in each of the Nordic countries (Denmark, Faroe Island, Finland, Iceland, Norway and Sweden) over five decades. The NORDCAN database has lately been supplemented with predictions of cancer incidence and mortality. Age-specific mortality and incidence rates are similar in all the Nordic countries (Engholm, et al., 2010).

1.2 Cancer statistics in Norway

In 2008, 26,121 new cases of cancer were recorded in Norway (Cancer of Norway, 2008), of which 14,000 occurred among men and 12,121 among women. As of December 2008, over 190,000 persons were alive and previously diagnosed with cancer in Norway (4.0% of the whole population of 4.8 million) and 115.030 (2.4%) were alive at least five years after their cancer diagnosis.

Today, about two thirds of patients with first-time cancer diagnosis can expect to survive five years, with or without tumour activity (Figure 1 and Figure 2, both from Cancer in Norway 2007).

This positive development of increased cancer survival in general and in particular for selected diagnoses (Armitage, 2010; Kuruvilla, 2009; Horwich, et al., 2006) is related to improved cancer treatment. Further, malignancies tend to be earlier and more correctly diagnosed than some decades ago due improved diagnostic possibilities. Establishment of screening programs - such as mammography screening (Kalager, et al., 2010) for breast cancer and PSA testing for prostate cancer (Andriole, et al., 2009; Schroder, et al., 2009) aims to detect cancers at a very early stage and may contribute to an increased public awareness of the risk and clinical signs of cancer. The increased survival rates have contributed to an increased activity in the field of cancer survivorship, among other aspects dealing with long-term morbidity, cure rates and non-medical factors with impact on survival.

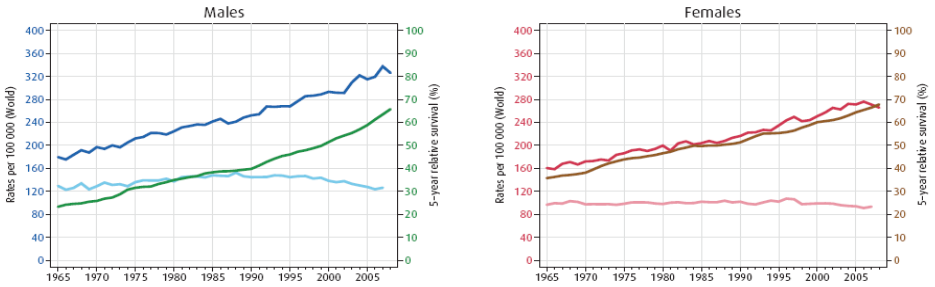


Figure 1: Trends in incidence, mortality and 5-year relative survival by gender (1965-2008)
Males: blue line: incidence; light blue line: mortality; green line: survival

Females: dark red line: incidence; light red line: mortality; brown line: survival.

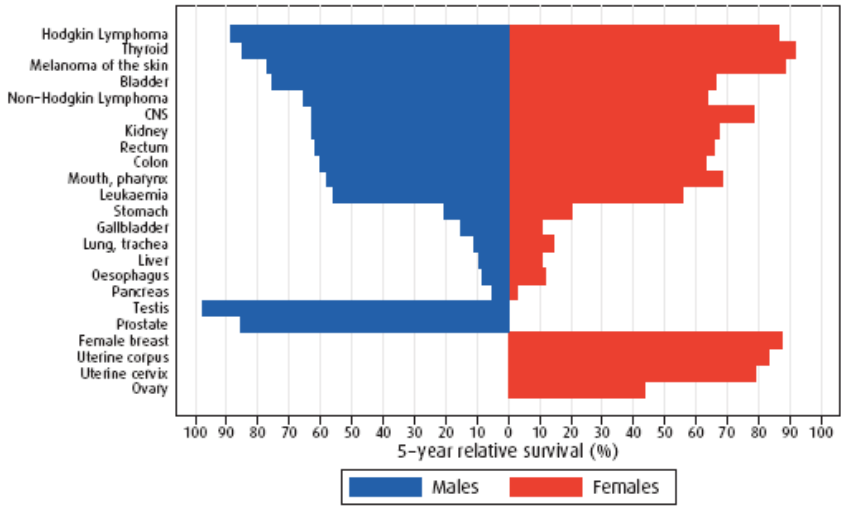


Figure 2: 5-year relative survival by cancer and sex, sorted in descending order of male survival.

1.3 Population- and hospital-based registries

Each individual living in Norway is assigned a unique 11 digit identification number at birth which enables merging of data and linkage of information from different registries. The data required for the projects of this thesis have been retrieved information from the registries described below.

Cancer Registry of Norway (CRN)

Each patients newly diagnosed with a neoplasms or certain precancerous lesions has to be reported to the Cancer Registry of Norway (CRN) following a directive from the Ministry of Health and Social Affairs in 1951, further strengthened by the Health Registry Act in 2002 that included statutory regulations and the requirement that relevant institutions report new cases to the Registry. A recent evaluation suggests that multiple source reporting and effective trace-back has meant that the Registry has retained a high level of overall completeness for many years (Larsen, et al., 2009). In terms of validity, the Registry's effective use of reports from pathology

laboratories, clinical records and death certificates has been shown to provide reasonable and comparable accuracy. Only a small fraction of cancer registrations was solely obtained from death certificate sources (DCO) (Larsen, et al., 2009). A review of registrations from 2001 to 2005 showed that three-quarters of the main cancer sites had a DCO proportion of less than 1%. However, for certain sites, including pancreatic and liver cancer, the percentages were higher, ranging from 3 to 4%.

Cancer type, date of diagnosis, extent of the disease (EOD), at diagnosis and initial treatment in broad terms are recorded at the CRN. Unfortunately, specific information on the type of chemotherapy, radiotherapy doses or target fields is not available, nor date of eventual recurrence or treatment of this. In general, extent of disease of solid tumours is classified as localized, with regional spread, with distant spread, or of unknown extent.

Statistics Norway (SSB)

Statistic Norway (SSB) provides statistics on the Norwegian population. For this thesis, data on vital status, emigration, eventual date of death and education level were retrieved.

The patient registry of the NRH

The Norwegian Radium Hospital (NRH) is a tertiary referral hospital for malignancies requiring radiotherapy and/or intensive chemotherapy. Up to 1980, patients with Hodgkin's lymphoma (HL), testicular (TC), cervical or ovarian cancer from the whole country (except for Bergen region) were referred to the NRH for primary treatment. After 1980, along with the establishment of four other Norwegian oncological academic units in the country, referral was mostly restricted to patients living in the Southern Norway. An electronic patient registry contains demographic and limited medical information for patients treated after 1970.

Surveillance Epidemiology and End Results (SEER) registry

The SEER program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States (US). Data collection on cancer cases has begun on January 1, 1973. Currently it collects and publishes cancer incidence and survival data from population-based registries covering approximately 28% of the whole US population. SEER coverage includes 25% of white Americans, 26% of African Americans, 41%

of Hispanics, 43% of American Indians and Alaska Natives, 54% of Asians, and 71% of Hawaiian/Pacific Islanders.

The SEER Program registries routinely collect data on patient demographics (birth year, age at diagnosis, gender, and marital status), primary tumour site, tumour morphology and EOD, initial surgery and/or radiotherapy. The SEER Program is the only comprehensive source of population-based information in the US that includes stage of cancer at the time of diagnosis and patient survival data. The mortality data that are reported to SEER are provided by the National Centre for Health Statistics.

Medical Birth Registry of Norway (MBRN)

MBRN was established in 1967, and collects data on pregnancies lasting of at least 16 weeks (from 1999 all gestations with a duration of at least 12 weeks), which are compulsorily reported by all doctors and midwives. Regarding data of interest for this thesis, the MBRN provides information on demographic data of the parents, their reproductive history, mortality and possible emigration date. In addition, this registry provides information regarding the pregnancy, such as date of the last menstruation and gestational duration and whether the pregnancy was initiated by assisted reproductive technologies (ART). Date of birth of the newborn is registered, together with measurements such as weight and length and vital status. Adoptions are not registered.

1.4. Survival estimates derived from large registries

Cancer registries usually base their survival analyses on death certificates whose validity concerning causes of death may be questioned. Estimates from survival analyses with the cause of death as the end-point can therefore be debated. However, several studies from Scandinavia and recently also related to the SEER registry were able to document correctness of the cause of death in at least 80% of the death certificates (Johansson, et al., 2000; Johansson, et al., 2002; Lund, et al., 2010).

Overall survival

When estimating overall survival, death of all causes is considered as an endpoint of survival analyses. The different causes of death are not distinguished from one another and patients are censored only at the end of follow up or when lost to follow up.

Cause specific survival

Cause-specific survival can be calculated when reliable information on a cause of death is available (Pandey, 2002). It is calculated in the same manner as overall survival but only death caused by an event of interest (meaning a pre-specified cancer) is considered as an event while other causes of death are treated as censored observations. Estimation of cause-specific survival can be obtained using the Kaplan-Meier method.

However, it may be difficult to pinpoint a particular cause of death, especially for cancer patients with several severe co-morbidities, and to classify the cause of death as due to cancer or other causes.

Relative survival

In order to circumvent the above-mentioned problems regarding reliability of causes of death, Cancer Registries most often report relative survival where the duration of survival in cancer patients is related to that of the general population.

Relative survival was defined by Bergson-Gage (Bergson-Gage, 1950) as the ratio of the observed survival in a group of cancer patients and the expected survival of the general population. Cancer registries most often report relative survival, most frequently as 5- or 10-year survival. Stratifications are performed by age, sex and calendar year and when possible, other factors as race and socioeconomic status.

The main advantage of this method is the fact that information on cause of death is not required. The problems with the inaccuracy or non-existence of death certificates can therefore be avoided and all deaths occurring during the study period can be included in the analysis. The availability of a comparable group from the general population is crucial for estimating the expected survival correctly. Hence population-based mortality tables have to be available.

Conditional relative survival

Conditional relative survival is defined as the probability of a cancer patient to survive an additional number of years given he/she has survived a given number of years since diagnosis. This estimate is more informative compared to the conventional relative survival. The longer a cancer patient survives after his/her diagnosis the more informative is such an estimate compared to the conventional relative survival. For example when a 5-year conditional relative survival reaches 100% fifteen years after the cancer diagnosis, it indicates that after this time there is little or no excess mortality among this patient group and their mortality is the same as observed in the general cancer-free population (Cancer of Norway, 2008).

Proportion cured and median survival of fatal cases

The favourable trend in cancer survival has warranted the development of novel statistical tools to monitor the effectiveness of early-detection strategies and the quality of clinical care and cancer management, including procedures to estimate the *proportion of cured patients* alongside the *median survival of fatal cases* using so-called *cure* models (de Angelis, et al., 1999; Heinavaara, et al., 2006; Verdecchia, et al., 2002). Possible scenarios in terms of trends in median survival of fatal cases and survival of those considered cured are depicted in Figure 3 (after (Verdecchia, et al., 2007)). According to Lambert et al (Lambert, 2007), scenario

a. (a) represents a general improvement, an increased proportion of patients is cured and those patients we are unable to cure have a longer median survival time than those treated earlier.
b. Scenario (b) suggests selective improvement: previously incurable patients are now cured, i.e. so the proportion of cured patients is higher but the median survival time of fatal cases is reduced.
c. Scenario (c) might occur following improved palliative care of fatal cases but, alternatively, could arise if new diagnostic techniques were brought into the health care system, so that patients are diagnosed earlier without affecting the time of death (lead time bias).
d. Finally, scenario (d) might occur when a specific diagnostic procedure is introduced and one is able to diagnosed patients who would have most likely died of other causes before

their cancer would give symptoms. These patients have no excess risk relative to the general population.

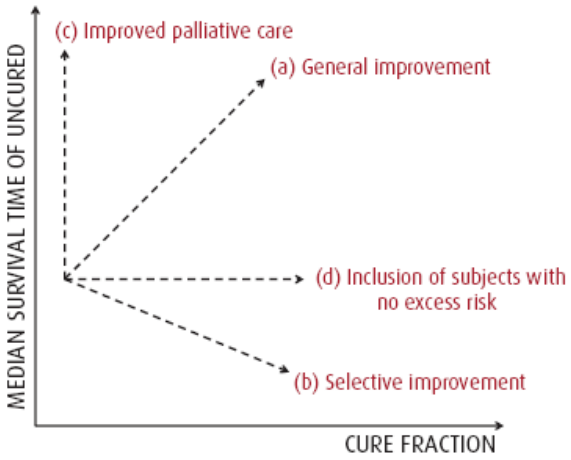


Figure 3: Scenarios for trends in proportion cured and median survival of the uncured.

The inherent differences between the concepts of clinical versus statistical cure need to be understood. *Statistical cure* is applicable to observations examined at the group level, and is distinct from *medical cure* of the individual, as commonly determined in a clinical setting on the basis of lack of specific symptoms of the patients, achieved, for example, when there is no longer any evidence of residual malignant cells. (Lambert, 2007). The models, when applied to population-based cancer survival data, serve to provide estimates of the proportion of statistically-cured individuals, that is, a group of cancer patients who, after a certain time period, are observed to have little or no excess mortality relative to the general population.

Such models have been applied to aid clinical interpretation of survival trends for specific cancer sites in one or more population. A recent EUROCARE study presented estimates of the cured proportion for a limited number of cancer forms (lung, stomach, colon, rectum and breast) for a subset of European cancer patients diagnosed from 1988 to 1999 (Francisci, et al., 2009). Lambert et al have reported the long-term survival trends among colorectal cancer patients in Finland, in terms of the proportion cured and median survival of fatal cases (Lambert, 2007),

while trends in the proportion of childhood cancer patients with leukaemia have been studied in British children diagnosed between 1971 and 2000 (Shah, et al., 2008).

1.5 Prognostic and predictive factors

Identification and assessment of prognostic and predictive factors is one of the major tasks in clinical cancer research. The goal of prognostic studies is to determine survival or in more general terms to attempt to predict the course of the disease for groups of patients defined by the values of prognostic factors and to rank the relative importance of the various prognostic factors (Crowley, et al., 2006). One has to distinguish between prognostic and so-called predictive factors; the latter term is used when one investigates whether a specific treatment works in a particular subgroup of patients. In contrast to studies designed to evaluate predictive factors for which statistical methods and principals are well-developed and generally accepted, this is not the case for studies that aim to evaluate prognostic factors.

Although there has been some positive development in this field in the recent years, most of the studies investigating prognostic factors are based on historical data and the sample sizes are often too small to provide reliable results. Statistical aspects of prognostic factor studies have been addressed in textbooks on survival analysis (Marubini, et al., 1995; Parmar, et al., 1995), and recently in a monograph on prognostic factors in cancer (Gospodarowicz, et al., 2001). These authors interpreted the three major criteria for prognostic factors as established by The American Joint Committee on Cancer (AJCC) (Burke, et al., 1993). The factors have to be significant, independent, and clinically relevant: “significant” means that the prognostic factor rarely occurs by chance; “independent” implies that such factor retains its prognostic value even in presence of other prognostic factors; and “clinically important” means that such a factor has an influence on patients’ management and possible outcome.

1.6 Demographic and socio-economic variables

During recent years there has been an increasing interest in studying the significance of health disparity for survival of cancer patients. Patient’s age, race and socio-economic status have been

investigated as prognostic factors together with inequalities of the healthcare system (Murphy, et al., 2010; Boyle, 2003).

In this thesis the term "socio-economic status" (SES) covers civil status and educational level of the individual person or a group of individuals, whereas factors such as age, race and place of residence are viewed as demographic factors. Data on financial income and assets are other important socio-economic factors, but were not available for our analyses. However, the educational level related to the place of residence (county) was viewed as a surrogate factor for the socio-economic situation of the individuals as also done by Hofmann et al (Hoffman, et al., 2008) in an analysis of TC patients.

Age

In general: for most patients with adult-onset cancer, increasing age represents an independent prognostic factor for cancer-specific survival, even when initial extent of the disease is considered (Gorey, 2009; Rowe, 2010; Ramirez, et al., 1999; Group, 2000). Most often this relates to reduced treatment-intensity, based on the experience of increased risk of treatment-related complications in the older population. However, in the clinical settings there is a growing understanding that the cut-off point between "young" and "old" patients should not be based on chronological, but on biological age, taking into account the patient's performance status and eventual co-morbidities.

Testicular cancer (TC) patients: Though (TC) is a malignancy of young men, males up to the age of 90 years can be diagnosed with TC (Andreassen, et al., 2010). Clinicians have experienced that advancing age increases the risk of unfavorable outcome both after bleomycin-containing chemotherapy and after other chemotherapy regiments (Simpson, et al., 1998) (O'Sulivan, et al., 2003) and RPLND complications (Capitanio, et al., 2009) in metastatic patients. Further, improved renal function and reduced bone marrow reserves may lead to suboptimal dose modifications in older patients (Inci, et al., 2007).

As of 2008 no large survival analyses have compared survival between older and younger TC patients, which is the main reason why paper II was initiated. At that time one was aware of the excellent prognosis of TC patients and that one would require access to large registry-based databases to detect potential differences in survival between patients' groups.

Civil status

In general: the prognostic role of civil status for cancer survival is uncertain. Some studies have shown that single cancer patients in univariate analysis display decreased survival rates compared to married ones. For example, single individuals do more rarely participate in screening programs and sometimes lack sufficient social support during their treatment period (Quaglia, et al., 2005; Boffetta, et al., 1993). On the other hand Ramirez et al (Ramirez, et al., 1999) could not identify any relationship between breast cancer survival and civil status.
TC patients: the prognostic role of civil status has not yet been assessed in population-based analysis in this group of patients.

Race

In general: race has been shown to be an important prognostic factor for many cancer sites though the reasons for this observation are not clearly understood. Sometimes an underlying biological difference between Caucasians and non-Caucasians is discussed as the cause for survival differences. The prognostic significance of race is often reduced when socio-economic factors, life style, extent of the disease and treatment are in multivariate analysis considered as co-variates together with race. Most studies have compared Afro-Africans with Caucasians living in the US (McKenzie, et al., 2009; Williams, et al., 2009; Alexander, et al., 2007).
TC patients: in a hospital-based series of TC patients Bridges et al in 1998 observed that 5-year cancer specific survival among African Americans was decreased by 17% lower (Bridges, et al., 1998). In 2004 Biggs et al (Biggs, et al., 2004) confirmed these findings based on SEER series including 16 086 patients treated from 1973 to 1999. Based on SEER (1973-2000) Nguyen and Ellison (2005) (Nguyen, et al., 2005) demonstrated lower unadjusted survival rates for Asian-American males with TC than for Caucasian ones, the difference disappearing after adjustment for extent of the disease and histology. Gajendran et al. reported similar results for African-American TC patients, indicating that African-American men's survival inferiority was related to higher extent of the disease at diagnosis (Gajendran, et al., 2005).

Place of residence, calendar year of treatment and public health care service

In general: in cancer patients, the place of living and calendar year of diagnosis are highly related to the selection of treatment by the health care service.

TC patients: for these cancer patients this relationship has been clearly shown for men living in Eastern Germany (Boyle, 2003) and in the EUROCARE study from 2007 (Sant, et al., 2007). Additionally, the results were principally confirmed by Aareleid et al in 2010 (Aareleid, et al., 2010) , in a study of TC patients from Estonia. For Norwegian testicular cancer patients significant survival improvement has been observed for patients diagnosed early in the 1980ies. The positive development is explained by the advent of cisplatin-based chemotherapy as the initial treatment of patients with metastatic TC from the beginning of the 80ies (Figure 4, after Cancer in Norway 2008).

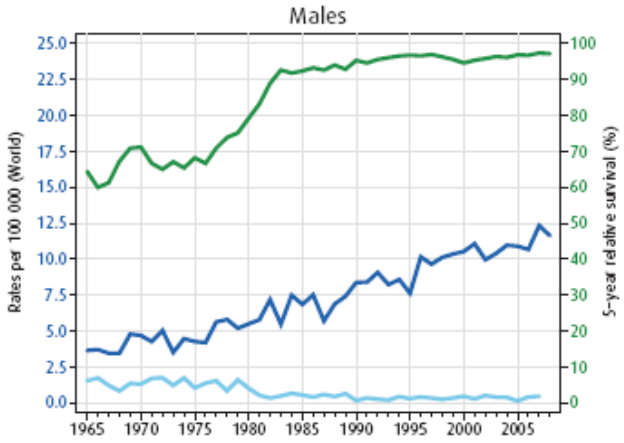


Figure 4: TC patients diagnosed 1965-2008 in Norway. Dark blue: incidence; light blue: mortality, green: survival

Socio-economic status

The association between socio-economic status (SES) and cancer survival has been examined in several epidemiologic studies within a variety of study designs (Kravdal, 2000; Rosso, et al., 1997; Cella, et al., 1991). A number of these are ecologic studies using geographical-area based measures based on the geographical area as SES indicators (comparing richer with poorer areas). Others are hospital-based or record linkage cohort studies with individual information on socioeconomic status measured by socioeconomic group, income or level of education.

Regardless of study design, a number of studies have found improved cancer survival by increasing SES, both overall and for specific anatomic sites, especially for cancers of relatively good prognosis such as female breast, corpus uteri, and bladder cancer. A few studies found no association between SES and overall cancer survival. In general, the observed differences in survival by SES seem to be lower in ecologic studies than in studies with individual assessment of SES. Tumour characteristics as EOD have been claimed to contribute to the SES variation in cancer survival, whereas the limited information on lifestyle factors in previous studies leaves the role of patient characteristics unclear.

Further, one has discussed a possible inter-relationship between SES and race. For patients living in Ontario (Canada), Mackillop et al had shown in 1997 that the economic situation of the area of a testicular cancer patient's residence was positively related to their five years survival (diagnosis in 1982 – 1991; (Mackillop, et al., 1997). This report however did not analyze histology and extent of the disease.

A study on Norwegian women from 2009 found an overall negative socioeconomic gradient in cancer survival when SES was measured as years of education or gross household income. In addition, smoking status prior to diagnosis was an important predictive factor for socioeconomic variation in survival. (Braaten, et al., 2009). Although the wide gap in life expectancy between the affluent and the relatively poor citizens in modern societies is well-documented, such differences can be detected also in supposedly equalitarian Nordic countries. In a study based on a Norwegian sample aged over 40 years and observed from 1960-1991 the excess all-cause mortality among cancer patients compared with similar persons without a cancer diagnosis was significantly related to education, occupation, and income (Kravdal, 2000). Excess mortality was, on the whole, about 15% lower for men or women who had completed a post-secondary education than for those with only compulsory schooling, taking into account age, period and registered differences in tumour characteristics and stage at the time of diagnosis.

In TC patients: Power et al (Power, et al., 2001) found a significant negative effect of socio-economic deprivation on relative 5-year survival of TC patients living in Wales UK, the differences decreased comparing men diagnosed from 1991–1995 with those diagnosed from 1986–1990. No separation was done between seminoma and non-seminoma, and EOD was not considered.

2 Cancer survivorship

2.1 Cancer patients versus cancer survivors

The term *'cancer survivor'* was introduced in 1985 by Mullan who outlined three stages of survival: 'acute survival'—usually taking place in the first year after treatment; 'extended survival'—the few years after active treatment; and 'permanent survival'—long-term survival, when the risk of recurrence is significantly reduced, but there may still be risks of late consequences of treatment, including secondary malignancy (Mullan, 1985).

Among health professionals, people with a cancer history, and the general public, views differ as to when a person with cancer becomes a survivor. The Institute of Medicine in the USA (htt) prefers to consider a person to be a survivor from the moment of diagnosis. Others consider a person with cancer to be a survivor if he or she lives 5 years beyond diagnosis.

The term '*cancer survivor'* has thus been defined differently by different groups. In this summary of the thesis we will not distinguish between "cancer survivors" and "cancer patients" but we will prefer the latter term.

2.2 Long- term treatment-related morbidity in cancer patients

Any treatment-related morbidity persisting or developing for at least one year after cancer treatment will in this thesis be described as 'Long-term'. Post-cancer long-term morbidity may be life threatening e.g. cardiovascular disease (Aleman, et al., 2007; Haugnes, et al., 2010) or second cancer (Hudgson, et al., 2007; Travis, et al., 2005), or can reduce the patient's quality of life (QoL) and general well-being by inducing side effects such as neurotoxicity (Brydøy, et al., 2009), mental distress or involuntarily-reduced reproduction (Schover, 2009; Foster, et al., 2009), the latter being one of the issues of the present thesis.

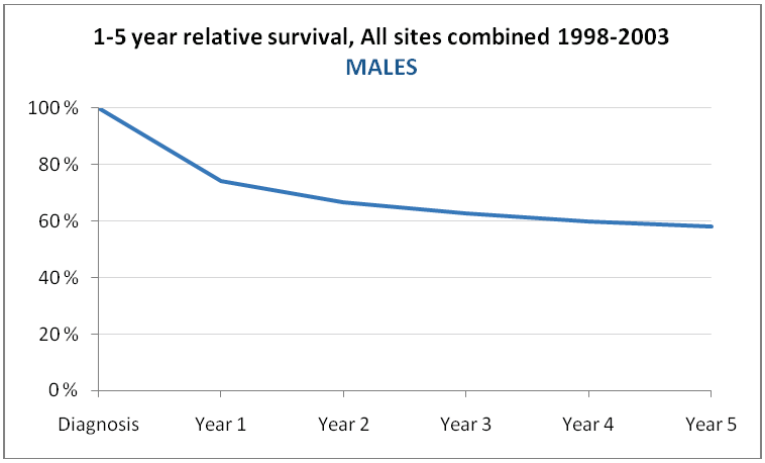
However, the unbiased assessment of morbidity in cancer patients and its causes represent major problems due to the frequent lack of suitable populations-based registries, which record non-fatal medical events in identifiable individuals and allow comparisons with general population data. In the Nordic countries and in some other European countries (Sousa, et al., 2006) there has been a growing interest in using existing databases such as Discharge registries, Prescription registries (Furu, et al., 2009) and established disease specific registries, for example the Norwegian Arthroplasty register, as sources of information on morbidity after cancer.

2.3 Young cancer patients

Cancer is generally a disease of individuals beyond the age of 50 years. In this phase of life most patients have had the number of children they want, and post-diagnosis reproduction is a minor concern when diagnosed with cancer. Further, beyond the age of 50 most women are no longer able to conceive. On the other hand, changes in the society with an increasing proportion of divorces and second and third marriages have led to an increasing number of men who become fathers after the age of 50 years. According to the MBRN, 0.42% of all men fathering a child during 1980 to 1987 were aged ≥50 years. This figure increased to 1.1% for the period 2000-2007 (Vernar Sundvor, personal communication).

About 6 % of patients diagnosed between 2004 and 2008 were aged 15–44 years and TC and BC diagnoses were the most frequent ones among respectively males and females (Table 1). These patients are defined here as *adult-onset cancer* patients (excluding childhood cancer survivors). The majority of such patients can expect to be survivors for at least 5 years as illustrated in Figure 5. For these adolescent and young adult cancer patients post-diagnosis reproduction and the chance of future parenthood represent an important concern.

Figure 5: 5-year relative survival for patients (males/females) aged 15-44 in Norway.



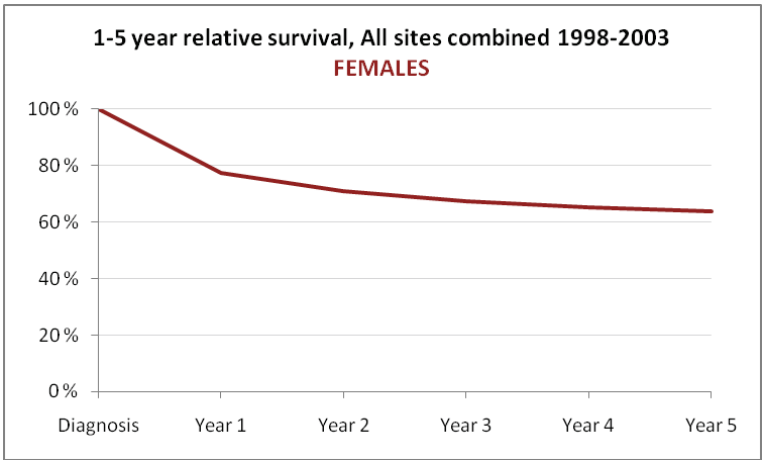


Table 1: New cancer cases aged 15–44 and diagnosed 2004-2008
(Data available online http://www.kreftregisteret.no/no/Registrene/Kreftstatistikk)/

Males	**New cases diagnosed 2004-2008**	**Females**	**New cases diagnosed 2004-2008**
All diagnosed patients 15-44 years old at diagnosis	**749**	**All diagnosed patients**	**1053**
Selected most common diagnoses			
Testicular cancer	223 (30%)	**Breast cancer**	**292 (28%)**
Brain tumours (CNS)	81 (11%)	**Malignant Melanoma**	**132 (13%)**
Malignant melanoma	74 (10%)	**Cervical cancer**	**119 (11%)**
Malignant lymphoma (Hodgkin's and Non-Hodgkin's)	64 (9%)	**Brain tumours**	**82 (8%)**
Leukemia	28 (4%)	**Malignant lymphoma** (Hodgkin's and Non-Hodgkin's)	**46 (4%)**
		Thyroid cancer	**43 (4%)**
		Ovarian cancer	**35 (3%)**
		Leukemia	**24 (2%)**
Others	**279 (37%)**	**Others**	**280 (27%)**

2.4 Testicular cancer

Testicular cancer patients are in the focus of this thesis as they represent a group of patients with a very good prognosis and the majority is diagnosed at a young age. Thus post-diagnosis reproduction is therefore of particular importance.

Incidence: Testicular germ-cell cancer represents about 96% of all malignant testicular tumours and is the most frequent malignancy in men between the 20–40 years. The incidence is increasing in the Western countries, with Norway and Denmark displaying the highest incidences worldwide (10/100 000) (Chia, et al., 2010). Among Caucasians Americans 15–49 years old, the incidence was 6.3/100 000 in 2004, 0.8/100 000 among black African-Americans and was 1.7/100 000 among other non-whites (Holmes, et al., 2008). In spite of the overall

excellent prognosis, small though important differences may be associated with prognostic factors which might be identifiable in large registry based samples.

Histology/staging: Seminoma is distinguished from non-seminoma, the latter with several subtypes of minor therapeutic importance. According to the CRN (1953-2007) approximately 55 % of all new TC patients present with a seminoma, and 45% with a non-seminoma (Andreassen, et al., 2010). The median age of patients with seminoma was 36 years (range: 1-91) in Andreassen et al's study, as opposed to median 30 years in men with non-seminoma (range: 1-85 years). Following recommendations from the Royal Marsden Hospital, UK, the clinical stages (CSs) are defined as follows (Peckham, 1988):

I	Testicular tumour only
IM	Elevated levels of AFP and/or HCG without visible metastases
II A: < 2cm B: 2-5cm C: >5cm	Infra-diafragmal lymphadenopathy
III A: < 2cm B: 2-5cm C: >5cm	Supra-diaphragmal lymphadenopathy
IV	Extra-lymphatic metastases (lung, liver, bone, etc.)

With background in changes in the registration routines in CRN and SEER during several decades, in this thesis localized non-metastatic testicular cancer (stage I) is distinguished from *all* metastatic stages (stage II-IV). A majority (75-80%) of the seminoma patients have a localized disease as compared to 50-60% of men with non-seminoma (Horwich, et al., 2006).

At the end of the 1970ies the relevance of serum tumour markers (alpha foetoprotein [AFP], human chorio- gonadatropin [HCG]) for diagnosis, treatment and follow-up of testicular cancer patients was established. An international consensus group was then able to define a staging classification with improved prognostic significance (Group, 1997)

Treatment: All patients undergo unilateral orchiectomy to provide the histological specimen.

After orchiectomy European and US patients with localized seminoma have traditionally received adjuvant abdominal pelvic radiotherapy (Zagars, 1996; Fosså, et al., 1988) although field size and target dose have gradually been reduced (Fosså, et al., 1999; Jones, et al., 2005) (Table 2). This tradition has been maintained in the United States until recently in the majority of patients, whereas new treatment modalities have been introduced in Europe and Canada with surveillance (Warde, et al., 2002) or adjuvant chemotherapy with carboplatin (Oliver, et al., 2005). In patients with localized non-seminoma, retroperitoneal lymph node dissection (RPLND) was used in the US as a staging procedure and definite treatment as non-seminoma which is less radio-sensitive than seminoma. (Fraley, et al., 1979a; Fraley, et al., 1979b; Steele, et al., 1999). Surveillance of stage I patients with non-seminoma has become a frequently used alternative treatment during the last 15 years both in Europe and North America (Hotte, et al., 2010; Schmoll, et al., 2009; Tandstad, et al., 2009).

Up to the late 1980ies the treatment of metastatic TC has consisted of available chemotherapy: cyclophosphamide, methotrexate, actinomycin D, vinblastine, bleomycin, adriamycin and oncovin ((Klepp, et al., 1977; Katz, et al., 1978). In 1977 Einhorn and Donohue demonstrated the excellent survival response rates in metastatic patients treated with cisplatin combinations (Einhorn, et al., 1977). Since then, cisplatin-based chemotherapy has become the cornerstone for patients with metastatic testicular cancer often combined with post-chemotherapy retroperitoneal lymph node dissection (RPLND) (Horwich, et al., 2006; Heidenreich, et al., 2009; Oldenburg, et al., 2009; Janssen-Heijnen, et al., 2010; Oliver, et al., 2005).

Table 2: Strategies of post-orchiectomy treatment of testicular germ cell tumours (TGCT) in Norway. Similar routines are applied in the USA though with more use of retroperitoneal surgery in non-seminoma)

Extent of the disease	**1953-1979**		**1980-2007**	
Localized	Seminoma	Non-seminoma	Seminoma	Non-seminoma
	RAD [1](30-40 Gy)	RAD [1] (40-50 Gy)	RAD [1] (20-30 Gy) Surveillance or adjuvant chemotherapy (2005+)	Retroperitoneal surgery or surveillance (1990+) or adjuvant low-dose chemotherapy
Metastatic	Chemotherapy[2] RAD[3]	Chemotherapy[2] RAD[3]	Chemotherapy[4] +/- RAD[3]/surgery	Chemotherapy[4] +/- surgery

[1]Abdominal radiotherapy.

[2]Alkylating drugs, anthracyclines, vinca alkaloids, metothrexate

[3]Involved field radiotherapy.

[4]Cisplatin-based chemotherapy

Survival: Today the mean 5-year relative survival rate is 97.3% in Europe, and 95.4% for patients from SEER (13 registries) (Verdecchia, et al., 2009). Of note, the overwhelming majority of patients are rendered tumour-free within the first 2-3 years. Recurrences after two years, i.e. late relapses, are rare (Oldenburg, et al., 2006). Testicular cancer survivors who had survived for five years had a similar survival rates as the age-matched general population (Janssen-Heijnen, et al., 2010).

2.5 Human reproduction

2.5.1 Physiology of reproduction

Males:

Reproduction in males requires the post-pubertal production of mature sperm cells regulated by testosterone and hormones from the pituitary gland. From the testis the sperm cells have to be transported through the male genital tract, a process ending with antegrad ejaculation during

erection. Disruption of any of these transport mechanisms has obviously negative consequences for reproduction.

Females:

At birth the ovaries contain 1–2 million immature oocytes (primordial follicles), which are progressively lost from 400 000 at puberty to about 1000 at the age of 50 (menopause). During the first half of a menstrual cycle the immature oocytes mature, the process ending with ovulation. During the second half of the menstrual cycle, hormonal influences (estrogens, progesterone) prepare the uterus for nidation of the fertilized ovum. Any intervention that reduces the number of immature oocytes, for example due to ovarian surgery, radiotherapy or systemic chemotherapy increases the risk of early menopause, in spite of transient post-diagnosis recovery of the menstrual cycle. Furthermore, any cancer surgery or radiotherapy which disturbs transportation, nidation and maturing of the fertilized ovum reduces the chance of post-diagnosis reproduction.

2.5.2 Cancer therapy and post-diagnosis reproduction

Definitions:

Post-diagnosis reproduction in cancer patients is one of the main topics of the present thesis. The term post-diagnosis reproduction is used to describe whether or not a patient diagnosed with adult-onset cancer has become a father or mother of at least one child after his/her cancer diagnosis and with an estimated date of conception after the date of diagnosis. The expression “gonadal function” describes the ability of the testis and ovaries to produce sex-hormones and mature eggs or sperm cells. The term “fertility” addresses a person’s ability to become a parent thus requiring the normal function of ovaries or testes and other genital organs.

Cancer treatment may transiently or permanently reduce or abolish spermatogenesis, reduce the number of oocytes with the consequence of early menopause, or it may lead to hormonal disbalance and/or disturb the normal function of the genital organs required for physiological transport of the ovum and sperm cells.

In addition to any somatic aspects of reproduction, the diagnosis and treatment of a life-threatening malignancy may cause psychosocial and socioeconomic problems, the latter

theoretically associated with reduced reproduction even in somatically healthy individuals (Joffe, et al., 1995; Dehlendorf, et al., 2010).

This thesis does not aim to discern these possible causes of impaired reproduction in cancer patients. Further, post-diagnosis sub-/infertility in cancer patients may be an inherent component of malignancy as is the case in a few females with ovarian germ cell cancer (androgen insensitivity syndrome) (Lukusa, et al., 1991). Pre-treatment infertility has also been claimed to be a component of the testicular dysgenesis syndrome (Wohlfahrt-Veje, et al., 2009) which has been linked to the etiology of testicular cancer. However, the correlation between pre-treatment sub-/infertility and TC and the existence of a testicular dysgenesis syndrome and decreased pre-diagnosis fertility in TC patients have recently been challenged (Akre, et al., 2009; Kim, et al., 2010).

Surgery

Males: Except for the obvious negative effect of surgical removal of genital organs on post-diagnosis reproduction, the transport of sperm cells is threatened by any pelvic or retroperitoneal operation which carries the risk of resection of nerves. This is for example the case after retroperitoneal lymph node dissection (RPLND), frequently performed in patients with TC, who experience post-operative "dry ejaculation" (Brydøy, et al., 2009; Grigor, et al., 1993)

Females: Removal of the genital organs (uterus, ovaries, and vagina) is often required in case of invasive genital cancer and obviously eliminates the possibility of post-diagnosis motherhood.

Radiotherapy

Males: The spermatogenesis is highly affected by irradiation. Fractionated testicular radiation at doses between 0.2 – 0.7 Gy, as commonly applied during abdomino-pelvine radiotherapy of patients with Hodgkin's lymphoma (HL) and TC, results in transient reduction in sperm cell concentrations. Testicular radiation doses of more than two Gy usually lead to permanent infertility. (Jacobsen, et al., 1997).

Females: Depending on the age of the patient, radiotherapy causes cell death of the immature oocytes and radiation doses of about 4 Gy lead to oocyte reduction by 50 %. At the woman's age of 30 the effective sterilizing radiation dose is 14.3 Gy (Wallace, et al., 2005).

Chemotherapy

Depending of the choice of the cytostatic agents, their combination and cumulative doses and the age of the patient, there is a risk of post-chemotherapy infertility (Lee, et al., 2006)

Males: The most gonado-toxic cytostatic drugs are procarbazine and alkylating agents (such as cyclophosphamide), Prior to 1987, procarbacin was used in patients with Hodgkins lymphoma, as a part of their standard chemotherapy (MOPP: metocloretamin, vincristine, procarbacin, prednisolone) (De Vita, et al., 1987). The ABVD combination (adriamycin, bleomycin, vinblastine, and dacarbazine) was developed during the 1980ies and is less toxic than the MOPP regime (Bonadonna, et al., 1982).Recovery of spermatogenesis can be expected in the majority of patients after treatment with ABVD (Viviani, et al., 1991).The standard treatment of non-Hodgkins lymphoma (CHOP: cyclophosphamide, adriamycin, vincristine, prednisolone) (Juliusson, et al., 1989). is in general less gonadotoxic than the MOPP chemotherapy for HL patients (Kiserud, et al., 2009). Before 1970, chemotherapy for TC mostly consisted of high cumulative doses of cyclophosphamide, eventually combined with methotrexate. In the 1970ies, bleomycin, vinblastine or vincristine, actinomyacin D and adriamycin were used; the gonadotoxic effect of these agents and their combination mostly depend on their cumulative doses (Klepp, et al., 1977).

Cisplatin-based chemotherapy, used as the initial treatment in testicular cancer patients in Norway after 1980, results in temporary azoospermia in most men with the recovery in about 50–80 % of them (Lampe, et al., 1997; Brydøy, et al., 2005),depending on the patients age and cumulative dose.

Females: The MOPP regimen previously used in patients with HL leads to premature menopause and infertility in most females with improvement of the reproduction rates after introduction of the ABVD regimen. Adjuvant chemotherapy in treatment of breast cancer causes early menopause with high dependency on the woman's age (Zervoudis, et al., 2010). Anti-estrogen treatment for 2–5 years used in the treatment of breast cancer has by itself no direct gonadotoxic effect, but delays the prospect of a pregnancy for several years (Liebens, et al., 2008).

2.5.3 Fertility saving tasks

As it is not possible to predict the recovery of gonadal function and the ability of post-treatment reproduction in the individual patient, fertility-saving tasks should be offered before and during cancer therapy in any patients who considers post-treatment parenthood.

Males: In Norway, cryopreservation of semen has been offered to male cancer patients since 1980. Semen cryopreservation should always be offered, though only less than 10 % of Norwegian cancer patients who have stored pre-treatment semen sample ever use their deep-frozen semen (Kiserud, et al., 2007; Magelssen, et al., 2005). Nerve-sparing RPLND techniques have been developed during the 1980ies in patients with TC (resulting in perseveration of antegrade ejaculation in 90 % of the operated patients (Foster, et al., 1993). In case of disturbed transport of sperm cells, microsurgical epidermal aspiration of testicular sperm extraction can be considered. During pelvic radiotherapy testicular shielding should always be performed to reduce scattered testicular irradiation (Jacobsen, et al., 1997).

Females: Embryo cryopreservation has been offered in Norway since early in the 1980s. Today pre-treatment cryopreservation of ovarian tissue and of unfertilized eggs is performed in Norway, but is still an experimental task (Oktem, et al., 2009; Hulvat, et al., 2009). Fertility-saving surgical procedures have been introduced for early stages of gynecological cancer, such as conisation and trachelectomy in women with early cervical cancer. Fertility-saving surgical procedures have also been developed for early ovarian cancer

In women post-diagnosis fertility and gonadal function have mostly been analyzed for patients with Hodgkin's lymphoma, ovarian germ cell cancer, early cervical cancer and choriocarcinoma.

2.5.4 Fertility and reproduction in patients with selected cancer sites

Males

Testicular cancer

The chemotherapy applied in TC patients before the cisplatin era was often followed by permanent azospermia in survivors, whereas abdominal radiotherapy had a less deleterious effect (Fosså, et al., 1986). Bilateral radical retroperitoneal lymph node dissection (RPLND), as frequently viewed necessary in non-seminoma patients diagnosed in USA before the 80s, always lead to "dry ejaculation" and permanent infertility. Approximately two years after modern Cisplatin-based standard chemotherapy spermatogenesis has recovered in at least 80% of testicular cancer survivors (TCSs) with sperm counts sufficient for initiation of a pregnancy (Huddart, et al., 2005). These observed sperm counts are comparable to the 80% 15-year paternity rate in TCSs with antegrade ejaculation and post-treatment fatherhood (Brydøy, et al., 2005).

Compared to the situation before 1979 and taking into account the fertility-saving treatments of TC introduced in Norway in the 1980s (Tandstad, et al., 2009; Jacobsen, et al., 1999), TC survivors' improved post-diagnosis reproduction rates should be evident in patients diagnosed from the end of the 1980s onwards.

Hodgkin's lymphoma

The mean age at diagnosis for HL in males is 30 years, and about 50% of the patients have at least one child before the start of anti-cancer treatment (Fossa, et al., 2004; Viviani, et al., 1985). The MOPP combination, the standard treatment therapy up to approximately 1987, was followed by permanent infertility in more than 90% of male HL- survivors. After introduction of the ABVD treatment as standard treatment and omission of alkylating agent-based therapies, serum hormone analyses indicate that spermatogenesis recovers in approximately 80% of male HL patients (van der Kaaij, et al., 2007). BEACOPP chemotherapy (Diehl, et al., 2006), for high risk HL patients (approximately 10 patients per year in Norway) was introduced in Norway in 2000 and leads to persistent infertility in 90% of the patients (Sieniawski, et al., 2008).

Females

Hodgkin's lymphoma

The introduction of ABVD chemotherapy and avoidance of pelvic radiotherapy have increased the chances of post-treatment motherhood in approximately 80% of female HLSs who attempted pregnancy (Kiserud, et al., 2007; Hodgson, et al., 2007). However even woman who regain menstrual cycles after treatment are at risk for developing premature ovarian failure POF after 15–20 years of observation (Haukvik, et al., 2006). Patients diagnosed after the age of 30 years are at particular high risk of POF is for patients diagnosed after the age of 30 years. Eight courses of BEACOPP chemotherapy is followed by permanent infertility in almost all females (Behringer, et al., 2005).

Breast cancer

Approximately 10% of breast cancer diagnoses occur in woman younger than 45 years. For most of them, the question of future post-diagnosis motherhood is not relevant because they have completed their families. On the other hand, many women in industrialized countries now delay motherhood to an age of 30 to 35 years. Because of adjuvant cytostatic treatment and several years of hormone therapy, the 10-year cumulative rate of post-diagnosis pregnancies is low, although childbirth has been reported after adjuvant chemotherapy, even when combined with tamoxifen.

Gynecologic cancer

Approximately 40% of women who have cervical cancer and 9% of those who have ovarian cancer are younger than 45 years of age. Because their treatment often consists of dissections of the reproductive organs or high-dose pelvic radiotherapy post-treatment reproduction rates are very low. Some improvement has to be expected after the introduction of fertility-saving surgery (Sjøborg, et al., 2007; Boss, et al., 2005). Cisplatin-based chemotherapy of ovarian germ cell cancer (Gershenson, et al., 2007) and treatment with Methotrexate for choriocarcinoma (Goto, et al., 2004) are followed by recovery of the ovarian function in almost all patients. Overview of the cytotoxic drugs and their effect on gonadotoxicity is listed in Table 3 (modified after Lee and Schover (Lee, et al., 2006)**.**

Table 3: Cytotoxic drugs and gonadotoxicity

Single drug	**Combination drugs**
Low risk • vincristine • vinblastine • dactinomycin (actinomycin D) • bleomycin • methotrexate • mercaptopurine	**Low risk** • ABOD (adriamycin, bleomycin, vincristine, dacarbazine) • ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) .
M**edium risk** • cisplatin • carboplatin • doxorubicin • etoposid	**Medium risk** • BEP (cisplatin, etoposid, bleomycin) • CHOP (cyclophosphamide, adriamycin, vincristine, prednison) • CVB (cisplatin, vinblastin, bleomycin) • BEP (bleomycin, etoposid, cisplatin)
High risk • cyclophosphamide • mechlorethamine • ifosfamide • busulfan • chlorambucil • procarbazine	**High risk** • MOPP(mechlorethamine, vincristine, procarbazine, prednisolon) • CAOS (cyclophosphamid, adriamycin, vincristine, actinomycin D) • BEACOPP (cyclophosphamid, adriamycin, vincristine, etoposide, procarbazine, bleomicin, prednisone)

II. The present project

Proportion of cure

In spite of the experience of increasing survival rates in cancer patients, not all 5-year survivors are "cured". Both patients and health administrators are, however, interested in what proportion of patients with a malignant diagnosis can be cured—meaning that their survival is similar to that of the general population. Bearing these questions in mind, in 2007 the Cancer Registry of Norway (CRN) decided to analyze the data using a published statistical model that estimates both the proportion of cured patients and median survival time of fatal cases. Despite being available in the literature for a long time, cure models have seldom been applied and systematically tested across all major cancer sites.

Age and socio-economic status as prognostic factors for men with testicular cancer

Published literature on TC did not consider age, race and SES combined with medical data in one multivariate analysis, despite the fact that clinical experience indicated the prognostic significance of these factors. Therefore we decided to assess the relation between age and SES and survival also taking into account demographic variables, histology and EOD using data from a large database.

Post-diagnosis reproduction

As of 2007 only a few large studies had reported post-diagnosis reproduction rates in patients with adult-onset cancer. Further, in most cases the published observations on post-diagnosis fertility and reproduction reflected mono-institutional experience among patients with selected malignancies, and usually without a control group from the general population.

In 2006 Fosså et al published a preliminary report on post-diagnosis reproduction among patients treated at the NRH by linkage of the clinical database of the NRH (established in 1971) with the CRN and the MBRN. This study demonstrated that male cancer patients had lower post-treatment reproduction rates than observed in the general population (Magelsen, et al., 2006). The highest proportions of patients with at least one pregnancy after their cancer diagnosis were observed among patients with malignant lymphoma, testicular cancer, malignant melanoma and choriocarcinoma (respectively 18 %, 20 %, 16 % and 50 %), whereas the comparable figures for

breast and cervical cancer were low (respectively 2 % and 1 %). Increasing age and pre-treatment parenthood decreased the reproduction rates. This preliminary publication on patients treated at the NRH did not relate post-diagnosis reproduction to treatment and its changes and reported only results of univariate analyses. Having these raw data available, we wanted to analyse them using more advanced analytical and statistical methods. Subsequently, we became aware of the selection bias related to the patients treated at the NRH.

We thus wanted to further explore post-diagnosis reproduction in an unselected group of patients identifiable in CRN. New detailed analyses should be restricted to post-diagnosis reproduction rates in men and women, for whom the complete history of reproduction was known.

Ethical concerns

The estimation of proportion of statistically cured patients was regarded as a part of the routine tasks to be performed at the CRN (Paper I). According to the Norwegian laws valid in 2006, the Data Inspectorate and the Ethical Committee approved the linkage between the registries used to identify patients used in Paper III and Paper IV, whereas no ethical concerns were raised for the use of the publically accessible SEER database (Paper II).

III. Aims of this thesis

The principal objective of this thesis is to illustrate whether and under what conditions clinically valuable information retrieved from large population-based and hospital–based registries can be used to investigate prognostic factors that impact on survival and post-diagnosis reproduction rates of cancer patients.

Our hypothesis is that it would be possible to identify patients with a favourable outcome and those with an impaired outcome (in terms of survival and post-diagnosis fertility) based on data accessible in large population-based and hospital-based registries. We aimed specifically at answering the following questions:

1. Can a proportion of statistically cured patients be estimated for a wide range of cancer diagnoses? Can such estimates of statistical cure and median survival time of fatal cases be meaningfully interpreted in the context of improved cancer care over time?
   Our hypothesis is that the cure model can be used to estimate a proportion of cured cancer patients together with a median survival time of fatal cases and to calculate changes in these estimates over time. In addition, we expected to be able to show that survival times of fatal cases have increased in line with anticipated improvement in palliative care.

2. What is the impact of increased age and low socio-economic status in a population-based sample of testicular cancer patients? In a population-based series of testicular patients, we expected high age and low socio-economic status to be associated with increased TC specific mortality.

3. What is the rate of post-diagnosis reproduction in adult-onset cancer patients compared to the general population and what factors influence this rate? We hypothesized that the post-diagnosis reproduction rates in cancer patients would be significantly lower than in comparable individuals from the general population. We expected several factors such as gender, type and extent of cancer, pre-diagnosis parity and calendar period of diagnosis to influence the rates of reproduction. In addition, we hypothesized that the impact of the above mentioned factors would differ among the different cancer sites.

IV. Patients, methods and results

1 Paper I: Proportion Cured Models Applied to 23 Cancer Sites in Norway

1.1 Identification of study population

National incidence and follow-up data on Norwegian cancer patients was extracted from the Cancer Registry of Norway. The 23 most-frequently recorded cancers for the diagnostic period 1963–2007 were selected for the analysis and follow-up on matching vital status was obtained from the Deaths Registry at *Statistics Norway*. Following some necessary eliminations, 627 346 cases were included in the analyses, 97.7% of the total.

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1.2 Statistical methods

There is a methodological difference between being clinically and statistically cured. The concept of *statistical cure* is applicable at a group level and is distinct from *medical cure* at an individual level. Medical curability is commonly determined on the basis of lack of specific symptoms of the individual, and it is achieved when all cancerous cells in the body have been persistently eradicated (Lambert, 2007). Medical cure cannot usually be studied using population based cancer registry data. However, it may be possible to calculate a proportion of statistically cured cancer survivors who as a group, exhibit the same mortality as observed in the general population.

The cure proportion was estimated using the mixture cure proportion model. This model, when applied to population-based cancer survival data, serves to provide estimates of the proportion of statistically-cured individuals, that is, a group of cancer patients who, after a certain time period, are observed to have little or no excess mortality relative to the general population. In addition, cure model provides an estimate of a median survival time of fatal cases (cancer patients who are bound to die of their cancer).

Temporal trends between 1963–2002 in the proportion of cured patients, and the median survival of fatal cases, were estimated applying the complete approach as suggested by (Brenner, et al., 2004), whereby all diagnosed cases over the period regardless of the length of their follow-up

were used in the estimations. The main focus here was on estimating changes in trends for patients diagnosed at different five-year time periods; hence period of diagnosis was modeled as a categorical variable with the 5-year periods as the categories.

The changes in proportion cured and median survival of uncured cases between the first period (1963–1967) and the last period (1998–2002) were quantified as the absolute difference between the estimates of both cure proportion and median survival with the corresponding 95% confidence intervals.

The most up-to-date estimates of the proportion of cured patients and the median survival of fatal cases were modeled using period approach with a 3-year observation window (2005–2007) and a 15-year follow-up, thus accruing sufficient case numbers to ensure the estimates were reasonably up-to-date while retaining an acceptable degree of precision. Using this method the follow-up was set to 15 years but there were no constraints on the model concerning the time at which a statistical cure will have to be reached.

1.3 Results

The cure models fitted well for cancers of the mouth and pharynx, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung and trachea, ovary, kidney, bladder, CNS, non-Hodgkin lymphoma and leukaemia. The up-to-date proportion of cured patients was highest for those with bladder cancer and CNS tumours (67% and 64%, respectively). It was not possible to fit the cure proportion for eight of the 23 selected neoplasms (breast, prostate, cervical, endometrial, testicular, thyroid, Hodgkin lymphoma and melanoma of the skin). In addition, changes in proportion cured patients and in median survival of fatal cases between the diagnostic period 1963–1967 and the period 1998–2002 were calculated.

The largest changes in the cured proportion were observed for patients with bladder cancer (73.4 % for males and 68.9% for females) and CNS tumours (52.1% for males and 71.3 for females). Median survival time for patients with uncured colon cancer increased from 0.42 to 0.61 years, for rectal cancer from 0.56 to 0.73 years and for ovarian cancer from 0.73 to 1.36 years between the above defined diagnostic periods.

2 Paper II: Adverse prognostic factors for testicular cancer-specific survival: a population-based study of 27,948 U.S. patients

2.1 Identification of study population

Men were included in this study if they were registered in the SEER database (http://seer.gov/data; Nov 2008 Submission) with a histologically confirmed invasive germ cell TC as a first primary malignancy at age 15 years or older between January 1, 1978 and December 31, 2006. Based on age at TC diagnosis, patients were categorized into two groups: "younger": age: 15-39 years (corresponding to peak incidence rates for TC) and "older" age: 40+ years. Extent of the disease (EOD) was dichotomized into "localized" and "metastatic" disease. Three calendar year periods after 1977 were identified: Period 1: 1978–1987; Period 2: 1988–1997; and Period 3: 1998–2006.

In addition, socio-economic, demographic and medical information were retrieved from the SEER database. Data concerning the use of initial post-orchiectomy radiotherapy were available for all patients and since 1998, also information regarding RPLND. No data were available with regard to type and dose of chemotherapy nor date of treatment or relapse. Vital status for each patient was determined through December 31, 2006, including date and cause of death. Each individual patient was assigned an educational class (EDUC class) by county of residence at TC diagnosis according to results of the U.S. Census (1980, 1990 or 2000), whichever was closest to the patient's year of TC diagnosis. The EDUC class was viewed to represent the level of SES (Hoffman, paper II, nr.10 ref). In this study, EDUC was categorized based on tertiles of the distribution of "county educational class".

2.2 Statistical methods

The primary outcome was TC-specific mortality. The cumulative incidence functions and disease-specific hazard ratios were estimated using competing risks survival analysis techniques (Fine, et al., 1999). TC specific mortality was the main event of interest and death of other causes as the competing event.

Follow-up was defined as time from diagnosis to date of death or study cutoff date (December 31, 2006), whichever occurred first. In addition, for selected analyses, follow-up was right-censored at ten years after TC diagnosis since (1) the proportional hazards assumption is more

tenable for limited time periods and (2) most TC-specific deaths occurred within the first decade after diagnosis. 10-year TC-specific mortality rates were estimated together with 95% confidence intervals.

Multivariable competing risk Cox models were fitted separately for seminoma and for non-seminoma patients. The proportional hazards assumption was tested using the scaled Schoenfeld residuals and with visual inspection of the log minus log plots. Predictors included age at diagnosis (<40 years vs 40+ years), race (non-Hispanic whites *vs* others), and marital status (married *vs* unmarried), EOD (localized *vs* metastatic), calendar year of diagnosis (<1988 *vs* 1988+). Socio-economic status was coded as an ordinal variable, whereby 1 (highest SES) was the reference, and 3 was the lowest. Seminoma patients were also categorized based on whether or not they were treated with radiotherapy. A separate Cox regression analysis restricted to the latest calendar year period (1998–2006) was analyzed with the same variables (except for radiotherapy and year of TC diagnosis) to explore the influence of RPLND on TC-specific mortality in non-seminoma patients. Patients missing any of the above predictors were excluded from the multivariable analyses.

2.3.Results

The study cohort comprised 27,948 TC patients (57% seminoma, 43% non-seminoma); 74% of them were categorized as "younger" (age <40) and 26% as "older" (age 40+). Ninety-three percent of the patients were white. Compared with younger patients, diagnostic age 40+ was associated with increased TC-specific mortality (seminoma: HR=2·00, 95%CI: [1.54 to 2.61], non-seminoma: HR=2·09, 95%CI: [1.72 to 2.55]), and most evident in metastatic disease (HR=8.62, 95%CI: [6.38 to 11.65], and HR=6.35, 95%CI: [5.23 to 7.70], respectively). Unmarried men had 2-to 3-fold excess mortality compared to married men, respectively. Among non-seminoma patients, the mortality was significantly higher with low levels of SES and for non-white race. For seminoma, the effect of race and SES was not significant. Diagnosis after 1987 resulted in reduced mortality compared to earlier calendar years (HR=0·58, 95%CI: [0.42 to 0.80], and HR=0·74, 95%CI: [0.63 to 0.88], respectively). Lack of RPLND was associated with a 7-fold increase in death in non-seminoma patients ($p<0.001$).

3 Paper III: Reproduction Rates After Cancer Treatment: Experience From the Norwegian Radium Hospital

3.1 Identification of study population

Three Norwegian registries (The NRH`s patient registry, MBRN and CRN)_were merged for identification of eligible cancer patients ("Cases"), all born after 1950, aged between 15–44 years at diagnosis of invasive cancer and treated at the NRH between 1971–1997.
To create the comparison group ("Controls"), each Case was gender and birth-year matched with five randomly selected individuals from the Norwegian Population Registry, alive and with no record in the CRN at the time of diagnosis for the case.

3.2 Study design and statistical methods

The first post-diagnosis reproduction (PDR) was the primary endpoint of all analyses and was here defined as any pregnancy terminated at least 8 months after the date of diagnosis. PDR refers to the event of any post-diagnosis childbirth independent of the pregnancy's duration or outcome (therapeutic or spontaneous abortion, stillbirth or living child) as recorded in the MBRN.

Each individual of the Control subunit was assigned the same date as the date of cancer diagnosis of his or her Case (for simplicity included in the term "Date of diagnosis"). Each patient and his/her Controls were identifiable so that it was possible to fit a model stratified by matched set. All individuals were followed from the date of diagnosis to the date of their first post-diagnosis reproduction, date of death, emigration or to June 30th, 2004 (cut-off date of the study), whatever occurred first. Females were censored at the age of 50.

Comparisons between patients and the Control group with regard to their post-diagnosis reproduction (PDR) were analysed with Cox proportional hazards regression and reported as hazard rate ratios (HR) with 95% confidence intervals (CI) and cumulative rates. The analyses were adjusted for age at diagnosis and by gender, pre-diagnosis parenthood and diagnosis before and after 1988. The probability of initiating a pregnancy with death treated as censored was calculated with the Breslow estimator. Since the proportional hazards assumption did not hold,

separate models were fitted for each gender and pre-diagnosis parenthood (none and ≥1 child). In addition, all analyses were performed separately for those diagnosed before 1988 ('pre-1988') and after 1987 ('post-1988+', 1988 included) due to significant treatment alternations and anticipated changes in reproduction pattern.

3.3.Results

A total of 6.071 Cases (females: 55 %, males: 45%) and 30.355 Controls were identified. About 60% of the Cases were diagnosed after 1987. Compared to Controls, reproduction among Cases was significantly reduced both for females and males. The overall HRs were HR=0.45, 95%CI [0.39 to 0.51] and HR=0.71, 95%CI [0.64 to 0.78] for females and males respectively. The most favourable HRs were always seen in pre-diagnosis childless patients. Fertility-preserving attempts after 1988+ have been successful for selected diagnoses, such as ovarian, cervical and testicular cancer patients with at least one child prior to the diagnosis. For pre-diagnosis childless Cases fertility improvement after 1987 did not reach statistical significance.

4 Paper IV: Reproduction after Cancer: a Population-based matched cohort study

4.1 Identification of study population

After necessary exclusions, all men and women registered in the CRN from 1967 to 2004 were included, with the first histologically verified malignancy at age 16 to 45 years and born after 1950. All invasive malignant neoplasms and all intracerebral tumours were included, except basal cell carcinomas.

For the tumour-specific analyses some restrictions were made regarding stage due to the manner this variable is recorded in the CRN. Only stage I patients were considered for analyses of cervical cancer. In some of the sub-analyses, ovarian cancer was categorised into epithelial stage I and germ cell or sex-cord tumours of local or locoregional stage. The level of education achieved at the time of cancer diagnosis (or assigned diagnosis for controls) was supplied from SSB.

4.2 Statistical methods

To create matched sets comprising of a case and five gender- and age-matched controls, the same approach was applied as described in Paper III. Follow-up was defined as the time from the actual or assigned date of diagnosis to the date of the first post-cancer birth, date of death or emigration, age 46 or December 31, 2006, whichever occurred first. Cox proportional hazards models were fitted to compute overall reproduction hazards rates for both male and female cancer survivors compared to the age- and gender-matched controls. Proportional hazards assumptions were checked by visual inspection of log-log plots. The models were fitted separately for each gender and selected diagnoses and stratified by matched set (a patient and his/her corresponding five controls).

The hazard rates (HR) with 95% confidence intervals (95% CI) were adjusted for age at diagnosis through the matching. Further, adjustments for pre-cancer parity and educational level at diagnosis were made in all analyses. In addition, we performed sub-analyses for selected diagnoses where we stratified by diagnostic periods (based on changes in treatment strategies

during the study period), and by extent of disease and pre-cancer parity. Cumulative reproduction curves were derived using a competing risk approach.

4.3 Results

In total, 27,556 cancer patients were analysed (11.451 males and 16.105 females).

Compared to their controls, male cancer survivors' reproduction was significantly reduced by 26% (HR=0.74, 95%CI [0.71 to 0.78]), the comparable figure for females being 39% (HR=0.61, 95%CI [0.58 to 0.64]). Post-diagnosis fertility rates did not differ between patients and their controls for malignant melanoma and thyroid cancer, and the lowest rates were seen for acute leukemia, cervical and breast cancer patients.

Increased reproduction rates during the study period were detected for selected malignancies: ovarian cancer HR=0.19, 95%CI[0.11 to 0.32] and HR=0.67, 95%CI[0.49 to 0.90]) between diagnostic periods 1967-1987 and 1988-2004, respectively; for TC survivors HR=0.61, 95%CI[0.43 to 0.86] and HR=0.76, 95%CI[0.70 to 0.83], between 1967-1979 and 1989-2004, respectively and finally for male HL survivors HR=0.68, 95%CI[0.53 to 0.87] and HR=0.87, 95%CI[0.73 to 1.04], between 1967-1987 and 1988-2004, respectively. Pre-diagnosis parity did not influence male survivors' reproduction, whereas females had higher reproduction rates when childless at diagnosis.

V. Discussion

As the principal author of this thesis is a statistician, the medical aspects will not be the main focus of this section, whereas the statistical methods will be discussed in more depth.

1 Clinical aspects

1.1 Paper I

Proportion cure models can be used to estimate the proportion of cured cancer patients, median survival time of fatal cases and changes in these two estimates over time. We believe that these changes mainly reflect changes and hopefully improvement in cancer care. As opposed to medical curability which is very hard to define, the concept of statistical cure is easy to explain and possibly intuitive to understand. Patients that are considered statistically cured have the same level of relative survival as seen in the general population. However, the absolute estimates of the cure proportion are speculative, particularly for cancer sites where medical curability is not anticipated.

The statistical model described in Paper I demonstrates a good concordance between the statistical and clinically anticipated curability for 15 of 23 initially selected cancer types.

Preliminary evidence suggests that the cure models perform best when mortality is neither very low nor high, as confirmed in our study. Of note, compared with the non-cancer population, some patients with selected cancer types may be at an increased risk of death for a long time after 5 years, reaching the general population's level of mortality after 7–8 years when they are "statistically cured"(for example colon and bladder cancer survivors). For other groups of cancer patients, statistical cure could not be estimated with a follow-up of 15 years (breast cancer) in agreement with the clinical experience of the continuous risk of late recurrences for this cancer type. However, the cure model did not fit for eight cancer types which are known to have high 5- and 10-year survival rates such as testicular and thyroid cancer and malignant lymphoma. In these cancer patients the level of mortality is low and similar to that in the general population. Statistical cure could not be estimated for patients with cancer of the mouth and pharynx, a group of patients who can be cured medically. These patients have a very high risk of second cancer and a high mortality due to other, non-malignant co-morbidities, such as

cardiovascular disorders. Thus this patient group can never be considered statistically cured as their mortality is always higher than mortality of the general population.

Compared to the period 1963–1967 and the period 1998–2002, we document an increase of the proportion of statistically cured patients, in particular those with bladder cancer and CNS tumours. We believe that these positive changes mainly reflect improvement in cancer care in correspondence with the decreased mortality rates for selected cancer sites as HL, TC and BC (Cancer of Norway, 2008).

Our data on bladder cancer should, however be viewed cautiously as they may be related to changes in administrative routines in the CRN. From early in the 1970s non-invasive bladder tumours were no longer separated from invasive tumours. Both tumour types were included into the ICD-7 code 181. An obvious consequence of this change in registration routines was a seemingly reduced mortality in patients with bladder cancer.

What is the clinical interpretation of our estimates of statistical cure? The results from our cure model provide us with information about certain patient groups; given their diagnosis there is a certain proportion of patients that will survive their cancer and will from a certain time point have the same level of mortality as seen in the general population. In oncological practice most clinicians will appreciate the possibility to communicate with their patients about this aspect.

In addition, using the cure model, we are able to estimate median survival time of fatal cases. The increase of time to death for patients with "fatal cancer" is valuable for clinicians as it proves in a population-based sample the efficacy of life-prolonging palliative therapeutic tasks increasingly used during the last 3 decades. However, some limitations of the cure model have to be considered. As the model is based on relative survival, no information is provided about the causes of death. This model, as applied in Paper I, does not separate the results according to known prognostic factors as extent of the disease and age. Further, we can only speculate whether any increase of the cured proportion is due to an improved treatment or if it is related to earlier diagnosis for example as a result of screening.

Finally, in our view, the interpretation of the results derived from the cure model require a close co-operation between statisticians and clinicians who understands the clinical course of the disease and have detailed knowledge about the treatment and diagnostic procedures and its changes.

1.2 Paper II

TC-specific mortality is doubled among patients diagnosed with either seminoma or non-seminoma after age 40, even when initial EOD is taken into account. Among men with non-seminoma, non-white race and decreasing SES also significantly increases TC-specific mortality. Most oncologists consider germ cell TC as a disease of young men, aged less than 40 years. Though this is true, one important finding of our study is that 26% of patients are older than 40 years, some of them even in their 70s and 80s. In the oldest patients pathologists and clinicians should, however, be aware of the possibility of misclassification, as malignant lymphoma is a frequent cause of a testicular tumour in higher age (Koukourakis, et al., 2010).

There is a higher risk of "older" patients with TC to die of their malignancy. One may question whether an age of 40 years as used in the present study is the most appropriate cut-off age. We chose this age with the background in the well-known clinical recommendation to avoid bleomycin in men above the age 40 years, in spite of the recognition that this drug is an essential component of cisplatin-based chemotherapy (Horwich, et al., 2006; Simpson, et al., 1998; O'Sulivan, et al., 2003). As no information is available in the SEER registry about chemotherapy it cannot be decided how much the eventual omittance of bleomycin represented a cause of inferior TC-specific survival in our "older" patients. Most probable the shown age-related risk of TC–related death is due to overall less intensive treatment.

Our education variable "EDUC" reflects primarily the level of education within the patients' county of residence. Preferably one should have used the individual patients' education level at the time of diagnosis. This information was not available in the SEER registries. The use of "EDUC" class as a surrogate of an individual's SES thus requires the acceptance of two assumptions: 1.The educational level of a geographical area (a county) reflects the area's SES. 2. The county's SES is a surrogate for an individual's SES. The first assumption has been verified by Paasche-Orlow (Paasche-Orlow, et al., 2005), and has also been the basis of Hoffman et al. study (Hoffman, et al., 2008), who showed that seminoma patients from US areas with low levels of education at a decreased level were offered radiotherapy compared to those from geographical areas with higher education. The second association has been demonstrated for cancer patients in general by (Kravdal, 2006) for Norwegian patients and, for TC patients by Power et al. (Power, et al., 2001) Also Boyle`s (Boyle, 2003) observations from Eastern

Germany and a recent report from Estonia (Aareleid, et al., 2010) indicate reduced survival in TC patients living in areas with considerable socio-economic problems.

The observation that mortality decreased with increasing calendar-year periods of diagnosis is encouraging. Power et al showed a similar development: in Wales the association between SES and the survival was reduced when comparing patients diagnosed between1971–1975 and those diagnosed between 1986–1990. This observation and our results are most probably associated with better availability of modern treatment of TC, even for patients of low SES. Improvement of TC specific survival in the most recent calendar years also reflects improved knowledge among clinicians how to apply new cytostatic drug combinations optimally and how to avoid toxicity, the later aim of particular relevance for "older" patients. The omittance of RPLND had a stronger negative effect in non-seminoma patients compared to the patients with seminoma. However, these observations should be cautiously interpreted due to the fact that only initial treatment was recorded. There is a non-quantifiable risk that post-chemotherapy surgery is insufficiently recorded.

Admittedly the shown survival differences in Paper II are small. They are greater among patients with non-seminoma than in those with seminoma. These differences between the two major histological types are associated with inherent differences of tumour biology as for example expressed by different stage distribution at diagnosis, different radiation sensitivity and different risk of post-diagnosis metastatic property. This again is associated with a higher level of treatment complexity in non-seminoma versus seminoma patients requiring more economic resources and a higher level of competence of the medical team taking care of patients with non-seminoma.

1.3 Paper III and IV

In Paper III, post-diagnosis reproduction of patients referred to a tertiary cancer centre is below that of the general population and influenced by gender, type of malignancy, pre-diagnosis parity and diagnostic period, with more favourable rates in males than in females. Improved reproduction rates were observed post 1988+ for patients with selected genital cancers and males with Hodgkin's lymphoma.

The results from Paper IV based on unselected patients from CRN show similar results as in Paper III with post-diagnosis reproduction rates which are lower in cancer survivors than in the

general population. Exceptions are patients with thyroid cancer and malignant melanoma for whom the reproduction rates were similar to those of the general population. Improvement in post-diagnosis reproduction rates in the last decade of the previous century are at least partly related to attempts of fertility preserving treatment.

Cure is the primary aim of all treatment in young cancer patients, but oncologists have increasingly become aware of survivorship issues (Ganz, 2009; Aziz, 2006), post-diagnosis reproduction being one of them. For example at the NRH about 70% of the TC patients (Magelssen, et al., 2005) opted for pre-treatment semen cryopreservation, in agreement with Schover et al`s experience (Schover, 2009). Brydøy et al (Brydøy, et al., 2009) described that 39.% of ≥5 year TC survivors attempted post-diagnosis fatherhood, the comparable figure being 45% among male and 50% among female HL patients (Kiserud, et al., 2007).

At the outset of this thesis we were interested not only in post-diagnosis reproduction of cancer patients but also in cancer patients' overall ability after their treatment to initiate a pregnancy. Therefore we included miscarriages and stillbirths into Paper III. Our figures for early abortions might, however represent underestimations, both for patients and their controls. We therefore decided not to include the number of abortions in Paper IV. Other reasons for falsely high estimates of male post-diagnosis reproduction may be that the recorded father was not the biological father, in particular as donor inseminations are not recorded. Further, some mothers might have chosen not to reveal the fathers identity.

During the work with Paper III and IV, two other population-based studies have been published, one from Norway and one from Finland. Syse et al`s (Syse, et al., 2007) followed patients with adult-onset cancer identified by the CRN up to 2001. The included patients were born from 1935 to 1984 and they were followed to December 2001. The endpoint was post-cancer reproduction as recorded in the Norwegian Population registry which does not record miscarriages, abortions or stillbirths. Syse et al demonstrated that the post-cancer reproduction rates for both genders were reduced by approximately 25% compared to the general population. These authors also showed that post-diagnosis reproduction increased among patients diagnosed during the last 2 decades of their study period. The reasons for the difference between Syse et al's and our reproduction rates published in Paper IV have been intensely discussed. The following explanations seem reasonable and plausible. The selection of cases and their controls differ: Syse

et al's studied individuals born from 1935 to 1984, whereas all of our cases and controls were born after 1950.

Post-diagnosis reproduction of cancer patients, who had died before 1965 has thus not been included in Syse' et al's report. In contrast, we had information on complete reproduction history in all individuals included in our study, assuming that no pregnancy was initiated before the age of 16 for any of these individuals. Our comparison group consisted of five age- and gender-matched individuals selected at random from the general population whereas Syse et al used data from the entire general population. Using five controls instead of the whole population might have caused a loss in efficiency, however this loss is considered very small and negligible. Further, Syse et al included childhood cancer survivors whereas our sample consisted only of adult-onset cancer patients.

Finally, the inclusion of older birth cohorts in Syse et al's study reflects to a larger degree an 'old-fashioned' treatment of cancer patients compared to the treatment being given to patients included in Paper IV. We assume that most of the patients with advanced disease that were treated during the 50ties to 70ties when effective chemotherapy was rarely available, would most likely have died before they had a possibility to initiate a pregnancy. On the other hand patients who had survived could have become parents after end of cancer treatment of their (most likely) localized disease. In contrast, in the 80ties and 90ties of the last century effective chemotherapy and combination treatment strategies have been developed and young cancer patients with advanced disease were more likely to survive but at the expense of impaired fertility. We thus speculate that a larger proportion of cancer survivors with a more advanced disease and a more intensive treatment could lead to lower overall post-diagnosis reproduction rates. We therefore conclude that the differences between Syse et al's and our report are mainly related to the differences in the two study cohorts.

In the second study from Finland (Madanat, et al., 2008), the authors evaluated the post-diagnosis reproduction in cancer patients aged 0–34 years at diagnosis. Similar to the report by Syse et al., the Finnish study was based on information from the Finnish Population Registry Center. Siblings were used as controls. The post-diagnosis reproduction rate for at least one child was reduced by 54% in females and by 43% in males.

The overall low post-diagnosis reproduction rates in the Finnish study are in agreement with our results. Also the Finnish started their observation time 9 months after the malignant diagnosis,

which we consider appropriate. As in our Paper IV female cancer patients' post-diagnosis reproduction was found below that of males. But again, the selection of patients differs from our studies, as childhood cancer patients were included in the Finnish report.

We refrain from direct comparison of the results from Paper III and IV due to the different patient selection and some differences in the statistical methods. However, the different findings of the effect of pre-diagnosis parity in male cancer patients need to be commented on; in Paper III, pre-diagnosis childless men had a higher post-diagnosis reproduction rates compared to those with at least one child prior to the malignant diagnosis. Such a difference was not observed in Paper IV. It might be that childless young men with cancer diagnosis and strong desire of post-diagnosis fatherhood have selectively been referred to the NRH where fertility-saving treatment including semen cryopreservation generally were introduced 2–3 years before these tasks became standard in the country elsewhere.

Due to selection bias as to the wish of post-diagnosis parenthood, it is neither justified to compare the results between mono-institutional studies or compare results from different institutions with population-based studies. This refers, in particular, to studies which are restricted to patients who attempted post-diagnosis reproduction (Brydøy, et al., 2005; Kiserud, et al., 2007; Behringer, et al., 2005) versus population-based studies.

Paper III and IV contain information valuable in the pre-treatment communication between clinicians and new patients with adult-onset cancer. Specifically, our results enable clinicians to estimate the chance of post-diagnosis parenthood for selected diagnoses, though recognizing that the majority of our estimates of PDRs document treatment applied during the last three decades of the 20th century. The figures for post-diagnosis reproduction shown in Paper III and IV may thus be lower than those achievable today after the introduction of new techniques for fertility-saving (cryopreservation of ovarian tissue, testicular sperm cell extraction (Shufaro, et al., 2010; Salihu, et al., 2003). In addition, treatments of adult-onset cancers are in continuous development affecting a cancer patient's post-diagnosis reproduction. The more frequent use of the surveillance policy in non-metastatic TC patients will also lead to increased production in these patients (Pagliaro, 2010). On the other hand, more intensive treatment in other malignancies will reduce the chances of post-diagnosis reproduction as for example the introduction of new chemotherapy regimens in Hodgkin`s lymphoma (Evens, et al., 2008) or the 5 years application of anti-estrogens in breast cancer patients. (Zervoudis, et al., 2010; Muss, 2001)

2 Statistical considerations

2.1 Matching

Matching is a design feature where a subject of interest, here called an index case, is assigned a number of subjects that are equal, or similar, to the index subject with respect to matching variables. Typical matching variables are sex, age, year of birth, social class and area of residence.

The simplest form of matched data is paired data, where one individual is matched to the index case, and the difference between the index cases and their matched controls is assed with a paired t-test instead of comparing the individual outcomes for index subjects and controls. In this way one can adjust for systematic difference between individuals. Generally, with other types of outcomes and more subjects matched to the index case one may often apply simple analytical methods that take care of systematic differences due to the matching variables.

One should distinguish between matched cohort studies, used in Paper III and IV, and matched case-control studies. In a matched case-control study the index cases are the individuals who experience the outcome of interest (response) of the study, typically a disease, and the matched controls are disease free individuals that are equal (similar) to the cases on the matching variables. Specially designed methods are required to analyze matched case-control data.

In a matched cohort study, on the other hand, the index cases are individuals exposed to a certain risk factor and the matched subjects are individuals without this exposure that are similar to the index subject with respect to the matching background variables. The outcome in a matched cohort study could be some future event. In the matched cohort we thus achieve balance between the exposure variable and the matching variables.

In Paper III and IV the exposure variable is a cancer diagnosis and the matched subjects are thus individuals without cancer (at the time of diagnosis of their index case). The outcome of interest is a future reproduction, or more specifically, time to reproduction. The aim is not to study what caused the cancer, but rather how cancer effected reproduction, and the cancer diagnosis is the main exposure variable of the study, whereas the matching variables are considered as covariates.

When designing our studies for Paper III and IV, we had two possibilities: we could match our index cases with a given number of cancer free individuals or we could have conducted a full cohort study involving all individuals in the Norwegian population. However, the chosen time-

scale for both of our studies was time from cancer diagnosis. For subjects free of cancer this time-scale would not apply without assigning a 'time of diagnosis' and this assignment was made possible with matching on year of birth and start of follow-up from the date of cancer diagnosis of the index case.

Still, a study using the complete Norwegian population could have been possible, matching all available cancer free individuals to the cancer survivors (index cases) on year of birth and being alive at time of diagnosis of the index subject. However, it was considered that a study with five subject matched to each index case was statistically sufficiently efficient. The data sets then became much smaller than what the complete population data would have been and were much easier to deal with computationally.

Reproduction is strongly age and birth cohort dependent. An analysis that ignores these factors may be flawed. With our design, based on a cancer case (index case) matched to five cancer free individuals, it was possible to analyse the data with Cox-regression stratified on matched sets as was done in Paper IV. Such analyses are based on very flexible simultaneous modeling of age and year of birth.

However, in many instances it is sufficient to only include main effects of these variables, as was done in Paper III. Under a more specific model, for instance including the matching variable in a regression, a valid and sometimes more efficient analysis of the association between the main exposure and the outcome is possible. One needs to bear in mind that the choice of the model always depends on the actual data and alternative models might still give a good fit but it might be more difficult to model the matching variables correctly. On the other hand, dissolving the matched set or changing their size might lead to a more flexible modelling of the covariates. When analysing data for Paper III, we have investigated several scenarios concerning the size of matched set. We have fitted Cox models stratified by the matched set, stratified by a larger set constructed of all patients and controls born in the same year and during the same five-year period. Finally, also a model where matching was ignored and where one adjusted for age as a covariate was fitted. As can be seen from Table 4, the differences between HR and the corresponding CI estimated using stratification by matched set and adjusting for age as a covariate are very small. So the final analysis performed on data in Paper III models age at diagnosis as a continuous variable and all models are fitted separately for males and females.

Table 4: Cox regression adjusted for age at diagnosis vs Cox regression stratified by matched set

	Total number of cancer patients		Reproduction after cancer, HR [95% CI] Cox regression adjusted for age at diagnosis		Reproduction after cancer, SHR [95% CI] Cox regression stratified by matched set	
	M	F	M	F	M	F
	4238	6940				
Breast cancer		**4,061**		**0.36 [0.30 to 0.43]**		**0.35 [0.29 to 0.42]]**
Cervical cancer stage I		**1,970**		**0.35 [0.30 to 0.40]**		**0.33 [0.29 to 0.39]**
Ovarian cancer stage I		**402**		**0.48 [0.38 to 0.62]**		**0.50 [0.38 to 0.64]**
Testicular cancer	**3,511**		**0.75 [0.70 to 0.79]**		**0.74 [0.69 to 0.79]**	
Hodgkin's lymphoma	**727**	**507**	**0.90 [0.78 to 1.02]**	**0.70 [0.59 to 0.83]**	**0.88 [0.76 to 1.00]**	**0.66 [0.56 to 0.79]**

2.2 Representativeness

In epidemiology, representativeness is a major concern for consideration of external validity: How well does the study sample represent the population of interest?

In cancer patients, the majority of studies on late effects as reproduction and survival are based on data that goes far back in time. One evaluates treatments and social situations which may no longer be valid in cancer patients today. This limitation with regard to generalisability of our results to a current cancer patients' population must always be kept in mind. On the other hand, our conclusions drawn from older data might still lead to a better understanding of biological phenomena as recovery of spermatogenesis after chemotherapy or of the role of SES for survival of cancer patients.

Further, the results from Paper II reflect the American situation, where differences as to race, SES and availability of health care service most certainly differ from the situation in Europe and in the Nordic countries.

Therefore, the conclusions drawn from Paper II may be limited to countries with a similar social structure and availability of heath care service as it is in the USA. On the other hand, our results

clearly show that both age and SES are important factors that impact on survival, although they are not often considered in analyses performed by medical professional.

The question regarding generalisability is also of interest for patients of Paper III; Table 5a and 5b clearly shows that between 1971 and 1997, only 1/3 of the country patients during the study period have been treated at the NRH and that there are great differences in the proportions of treated patients depending on the actual cancer diagnosis. For example, large proportions of patients with malignant melanoma, thyroid and breast cancer were not referred to the NRH as their treatment can be applied at the community hospitals. On the other hand, patients with Hodgkin's lymphoma and gynecological cancers have been preferably treated at the NRH. Patients from Paper III are thus representative for patients seen at the NRH, which is the leading Oncological Center in Norway and is supposed to provide the most up-to-date treatment at any time available for patients in need of chemotherapy or radiotherapy including fertility-saving treatment modalities. We believe that our observations thus reflect the results as to post-diagnosis reproduction which can be achieved among all patients referred to a large academic oncological unit in Europe. However, they may not be completely representative for a population of unselected cancer patients identifiable in national cancer registries.

The results in Paper IV are representative for all patients with adult onset cancer. They reflect the post-diagnosis reproduction rates achievable in Scandinavian countries with a public healthcare service covering most of all expenses related to cancer treatment. This cohort also comprises cancer diagnoses usually not treated at NRH or only limitedly seen at a tertiary referral oncological center.

Also the representativeness of the control groups in Paper III and IV has to be considered. The only criteria for the matching performed were age, gender and being cancer-free at the date of diagnosis for the relevant case. Place of residence, education and partnership are also important factors for reproduction but were not available for analyses. As education and partnership are associated with reproduction, as shown by Kravdal (Kravdal, et al., 2008) for a Norwegian cohort, these variables should have been taken into account and adjusted for as covariates in the analyses. In this connection it is of interest that Syse et al found an increased divorce rate (Syse, et al., 2007) among men with a TC diagnosis. On the other hand, Kravdal reported only a minimal effect of education on cancer survivors. For subgroups of patients the educational level seems to be associated with post-diagnosis reproduction, as shown in Paper IV.

Patients treated at NRH and elsewhere in Norway between 1971 and 1997, aged 16 to 45 at diagnosis

Table 5a: Males

Cancer diagnosis	Not treated at NRH	Treated at NRH	Total
Hodgkin's lymphoma	167 (34%)	320 (66%)	487
Testicular cancer	1154 (54%)	1000 (46%)	2154
Malignant melanoma	779 (84%)	152 (16%)	931
Colon ca.	177 (89%)	21 (11%)	198
Thyroidea	109 (72%)	43 (28%)	152
Other	2086 (68%)	960 (31%)	3046
Total	**4477 (64%)**	**2499 (36%)**	**6976**

Table 5b: Females

Cancer diagnosis	Not treated at NRH	Treated at NRH	Total
Hodgkin's lymphoma	116 (36%)	202 (63%)	318
Malignant melanoma	1453 (89%)	171 (10%)	1624
Cervix, stadium I	336 (35%)	635 (65%)	971
Ovarian, localised	107 (39%)	164(60%)	271
Breast ca.	1390 (72%)	551 (28%)	1941
Colon ca.	184 (84%)	35 (16%)	219
Thyroidea	489 (81%)	114 (19%)	603
Other	2065 (63%)	1233 (37%)	3298
Total	**6140 (66%)**	**3105 (34%)**	**9245**

Cause specific survival versus competing risk models

Introduction

Standard survival data measure the time span from some time origin until the occurrence of an event of interest. If several types of events occur, a model describing progression to each of these competing risks may be needed. The interest in competing risk modelling goes as far back as the 18th century, when Bernoulli studied the possible consequences of eradication of smallpox on mortality rates. The problem of estimation of failure probabilities after elimination (or modification) of one of the competing risks has been of great importance and a subject of much debate since the 1970s and many new perspectives, models and methods to analyze such models have been developed over the last two decades.

Typically, one type of event is the event of interest; however, other competing event types might prevent the event of interest from occurring (Figure 6). In Paper II and IV the main event is post-diagnosis reproduction and the competing event is death. In Paper II the event of interest is the cause-specific TC mortality and the other type is death of all other causes.

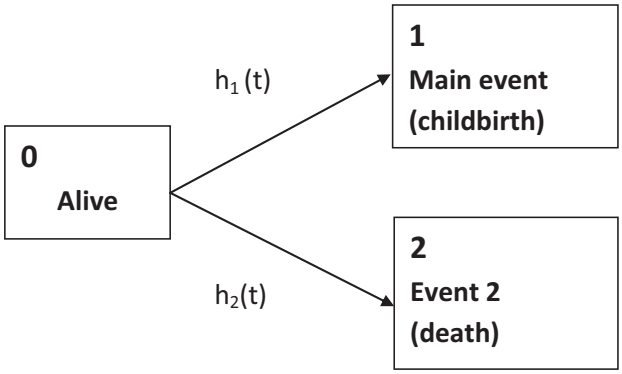

Figure 6: The competing risk model for two competing events where $h_j(t)$ is the hazard for transition to state j.

Caution is needed for analyses of the event of interest occurring in the presence of these so-called competing risks. Treating the competing events as censored observations may be difficult to interpret. For instance the Kaplan-Meier estimate (KM) that treats the competing risk as censoring, could be interpreted as the survival function if the competing risk could have been eradicated. Furthermore, this would require that the event of interest and the competing risk were independent, which is a dubious and unverifiable assumption. The Cox proportional hazards

model can still be used, based on the stochastic process scheme in Figure 6, but the interpretation of the results would be different from the interpretation when there are no competing events.

One may argue that a more sensible function to estimate, than 1-KM, is the cumulative incidence function (CumInc) i.e. the probability that the event of interest has occurred before time t when this event can be prevented from occurring by the competing risk. Figure 7 illustrate a situation with one competing risk (death) and one main event of interest (child birth) for selected diagnoses (data from Paper IV). When depicting the CumInc for both events (the main event of childbirth and the competing event of death) we want to emphasize that both events are modelled simultaneously.

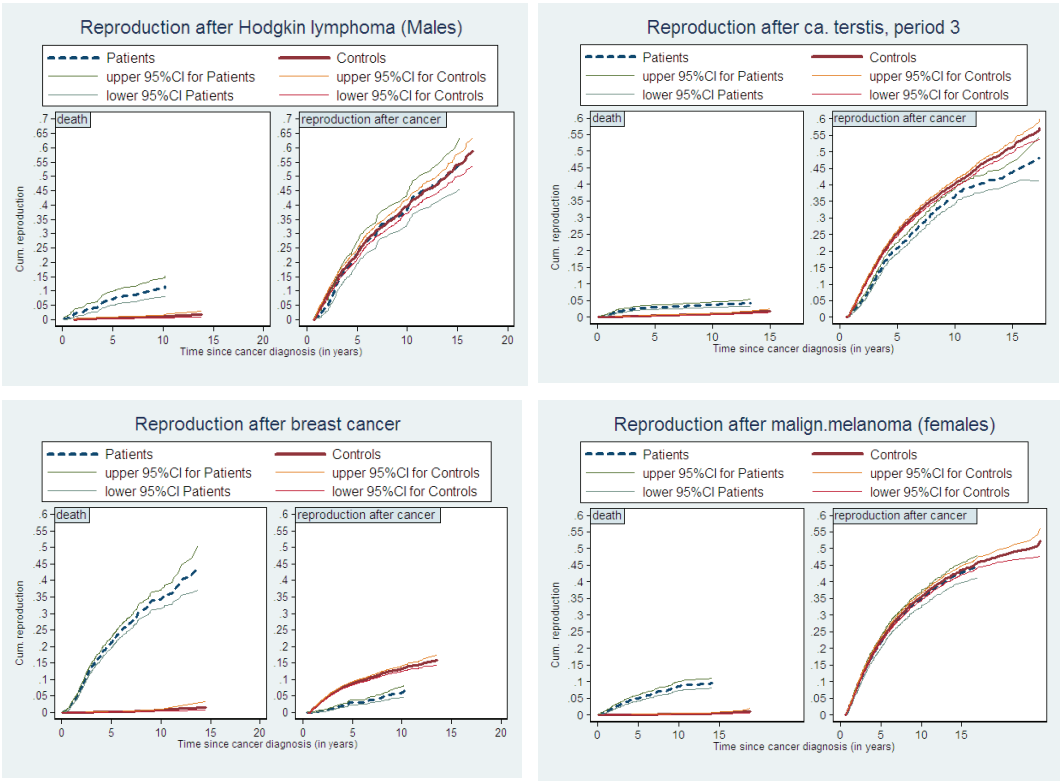

Figure 7: Cumulative incidence functions depicted for the main event (child-birth) and the competing risk event (death).

Right censoring and the independence assumption

The independence between the event and censoring distribution is often assumed without further consideration, but it might easily be violated. There are several reasons for right censoring:

- *End of study.* We only have information on the individuals enrolled in a study until a certain point in time. Therefore, some individuals are not followed up long enough for the event of interest to occur. This type of censoring is often called administrative censoring.
- *Loss to follow-up:* an individual previously enrolled in a study has left the study, possibly due to migration or study fatigue. He or she might experience the event of interest, but we do not have any information about it.
- *Competing risk:* another event has occurred which prevents occurrence of the event of interest.

When censoring is due to ending of study, we can in general safely assume the assumption of independence is fulfilled and the censoring is not informative. However, in the other two situations (loss to follow-up and competing risk), one should be cautious.

For example some patients enrolled in a study might get healthy during the follow-up and lose their interest in the study. Censoring such individuals would cause a downward bias of the estimated survival curve, which means that the probability of the event of interest will be overestimated. An opposite situation might also occur; some individuals are too ill to continue participation in the study and are censored at the time they decide to drop out. Here, such censoring will cause an upward bias and the probability of the event of interest will be underestimated.

Censoring due to a competing risk is even more problematic. When only the first event can be observed it is not possible to address the question of whether the times to the two events are independent. Thus estimates under the independence assumption cannot be interpreted are difficult to explain.

An explanation in terms of the stochastic process scheme in Figure 6 is however possible. The cumulative hazard $H_1(t)$ is the integral of the hazard $h_1(t)$ for transition to state 1. In presence of censoring due to end of study this may be estimated by the Nelson-Aalen (NAa) estimator. The KM estimate will then be approximately equal to exp(-NAa) and have interpretation $\exp(-H_1(t))$, but admittedly it is difficult to explain what this means in simple language. It is, however, possible to show that 1-KM will be larger than the estimate of CumInc under presence of independent censoring (due to end of the study).

Figure 8 depicts both the CumInc and 1-KM estimates for breast cancer (left) and testicular cancer. There are still many women who do not survive their breast cancer, especially those diagnosed at a young age so the difference between CumInc and 1-KM is very large. The treatment of testicular cancer has been very successful after new therapies have been introduced in the 1980s so the number of deaths as a competing risk is much smaller for these diagnoses and the difference between the two estimates is much smaller.

Some authors argue that in the presence of competing risk, 1-KM should never be used, even if the number of competing risk events is relatively small and the two estimates (1-KM and CumInc) are likely to be very similar (Crowley, et al., 2006). In addition, it is important to bear in mind that the discrepancy between 1-KM and CumInc is dependent on the timing and frequency of the failures from a competing risk; the earlier they appear and the more frequent they are, the larger will be the difference between 1-Km and CumInc. Two situations are illustrated in Figure 8: many patients diagnosed with breast cancer die of their cancer so there are many competing events (deaths). In contrast, a great majority of TC cancer patients survive so there only a few deaths competing with the main event (post-diagnosis reproduction). Therefore it is important when analysing and presenting results from an analysis involving competing risk to describe probabilities of failure not only from the event of interest, but also from failures from a competing risk event(s).

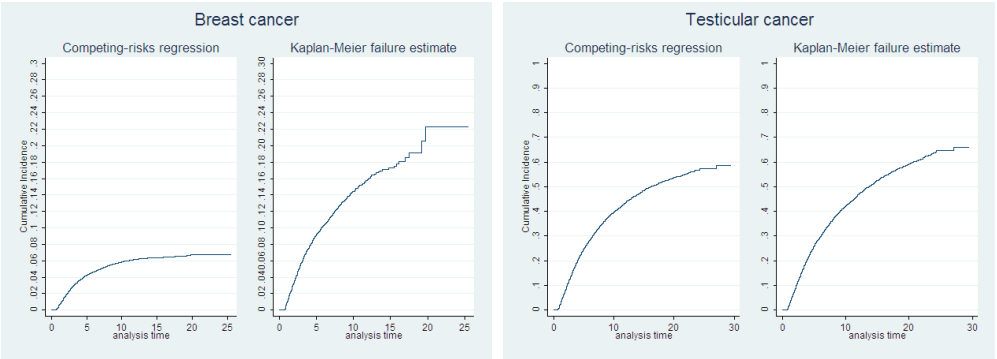

Figure 8: Differences between cumulative incidence (CumInc) and 1-Kaplan-Meier estimates

2.2.1 Comparisons between different modelling approaches

Cox regression and competing risk regression

As explained above, a great deal of caution has to be used when depicting the CumInc function in the presence of competing risk. However, the HR estimates computed using Cox regression and Competing risk regression (Fine, et al., 1999) are very similar for our data used in Paper III and Paper IV as illustrated in Table 6 (data from Paper IV). For breast, cervical, ovarian and testicular cancer both the point estimates of HR and SHR and their corresponding 95% CI were almost identical. For Hodgkin's lymphoma, the estimates were very similar for females but slightly different for males. However, the difference is small and negligible.

Still, one has to keep in mind that the two approaches are theoretically different. The more traditional approach would be to apply Cox regression treating the competing risk as censoring. In this case one analyses the cause-specific hazard $h_1(t)$. Using the other method, one models hazard derived from treating the CumInc as an (improper) cumulative distribution function with a proportional hazards model.

	Total number		Reproduction after cancer, HR [95% CI] Cox regression stratified by matched set		Reproduction after cancer, SHR [95% CI] Competing risk regression (Fine & Gray)	
	M	F	M	F	M	F
Breast cancer		**4,061**		**0.33 [0.27 to 0.39]**		**0.31 [0.26 to 0.38]**
Cervical cancer stage I		**1,970**		**0.34 [0.29 to 0.40]**		**0.33 [0.28 to 0.38]**
Ovarian cancer stage I		**402**		**0.43 [0.33 to 0.56]**		**0.44 [0.34 to 0.57]**
Testicular cancer	**3,511**		**0.68 [0.63 to 0.72]**		**0.67 [0.62 to 0.71]**	
Hodgkin's lymphoma	**727**	**507**	**0.79 [0.69 to 0.92]**	**0.61 [0.51 to 0.73]**	**0.74 [0.65 to 0.85]**	**0.62 [0.53 to 0.72]**

Table 6: Differences between Cox regression and Competing risk regression. Both models adjusted for age (continuous), parity (3 categories) and educations at diagnosis (3 levels)

2.2.2 Summary and concluding remarks

Modelling the effect of covariates on cause-specific hazards may lead to different conclusions than modelling their effect on sub-distribution hazards and cumulative incidence functions. However, the standard Cox model can be used to model the effect of covariates on the cause-specific hazards of the different endpoints (here childbirth or death). Applying the Cox model, there is a great advantage of being able to use well-developed theory and statistical software. Cause-specific hazards obtained from a Cox model can be translated into cumulative incidence curves where such curves are estimated as the sum of all the unconditional probabilities of experiencing event from a chosen cause. Unfortunately, there is a problem with such an approach–proportionality is lost and the effect of a selected covariate on the cumulative incidence curves can no longer be expressed simply as a number. So to determine the effect of a covariate on the cumulative incidence of an event of interest, it is important to consider the competing risk(s)—both baseline and the covariate effect. Still, results from the Cox model do not answer to the question of what the effect of some covariate would have been on the cause-specific hazard if the competing risks were absent, unless they are independent.

2.3 Proportion cure models

Definitions

Relative survival, R(t) is defined as the ration between the observed, S(t) and expected survival, $S^*(t)$:

$$R(t)= S(t)/ S^*(t)$$

so the relative survival model can be written as follows $S(t)= S^*(t)\, R(t)$.

Statistical cure can be modelled using two approaches: the mixture and non-mixture model. The first one is the most popular and commonly used one, possibly because it is intuitive and easy to understand.

When modelling cure using the mixture model we define an asymptote at the cure fraction, π, for the relative survival function R(t) (Lambert, et al., 2007; Lambert, et al., 2007):

$$S(t) = S^*(t)(\pi + (1 - \pi)Su(t))$$

π is the proportion cured (the cure fraction), $(1 - \pi)$ is the proportion 'uncured' (or those 'bound to die' fatal cases) and Su(t) is the survival function for the uncured individuals.

Median survival of the uncured is defined as follows:

$$Su(median) = 1/2$$

In order to fit the model one needs to choose a parametric distribution for S(t). The most popular choice is a Weibull distribution with two tuning parameters, λ (for scale) and γ (shape), which often provides a good fit.

If the relative survival curve does not reach a plateau, then the estimate of cure is based on extrapolation beyond the time range of the data. In theory, cure occurs when time approaches infinity. For practical purposes cure is assumed to be reached when the relative survival function of the 'uncured' group is below a stated amount, 1% in this study. Estimation of the cure model parameters is obtained using maximum likelihood on the individual level data. The estimation procedure is similar to that of De Angelis (de Angelis, et al., 1999) but extended to model both parameters in the Weibull distribution (Lambert, et al., 2007).

The motivation behind non-mixture cure proportion model (Lambert, et al., 2007) is that after end of cancer treatment, it is assumed that a cancer survivor still has N_i cancer cells that might cause metastases. The distribution of N_i can be modelled with a Poisson distribution with mean θ so the cure fraction is defined as a probability of θ equal to zero. When it is not the case, we can define time Z_j of the jth metastatatic cell needed to produce a new tumour. The times Z_j follow a distribution:

$$F_z = 1 - S_z(t).$$

Now the overall survival can be written as:

$$S(t) = \pi^{Fz(t)}$$

Alternatively, the non-mixture model can be rewritten so that it resembles the mixture model:

$$S(t) = S^*(t)(\pi + (1 - \pi)(\frac{\pi\, Fz(t) - \pi}{1 - \pi}))$$

Comparisons between mixture versus non-mixture models

There is a wide range of distribution to choose from when modeling the cure proportion, the most commonly used are Weibull, lognormal and Gamma distribution. Both the cure fraction π and the parameters in the distributions may vary by covariates. Sposto (Sposto, 2002) described three link functions when modelling the covariates X (age in categories and sex):

- The identity link: $\pi_i=\beta'X$
  This is relatively easy to interpret but may have boundary problems for low and high cure fractions.
- The logistic link $\log(\pi_i/(1-\pi_i) =\beta'X$
  Covariates are expressed as (log) odds ratios, similar to those in logistic regression.
- The log(-log) link $\log(-\log(\pi_i)) =\beta'X$
  This link is useful for the non-mixture model.

To study the differences between mixture and non-mixture models and the effect of different link functions defined above, we fitted both mixture and non-mixture models with Weibull, lognormal and Gamma distribution and identity, logistic and log-log link. All 23 selected cancer sites were modeled using these 18 models. The details are listed in the Appendix.

There were very small differences between estimates derived with mixture and non-mixture models both with regards to proportion cured and median time of fatal cases. Overall, the non-mixture model estimates were slightly lower compared to those from the mixture model concerning proportion cured and marginally higher when estimating median time of fatal cases. The models converged most often when using the logistic link regardless of the choice of distribution and for both mixture and non-mixture models.

Given the type of model and the choice of distribution, the differences between estimates of proportion cure and the median survival of fatal cases computed using different link functions are negligible. However, the number of cancer sites when a convergence was achieved depended on the choice of link function.

For the Weibull distribution, the estimates were almost identical for mixture and non-mixture models. The model always converged with non-mixture model and logistic link. Using the identity link, the convergence was not achieved for cancer sites where medical cure is either not expected or questionable. With lognormal distribution, convergence was achieved for almost all sites using the logistic link. The estimates of proportion cured were the lowest of all three distributions, more so with the non-mixture model. When the model was fitted with the Gamma distribution, the non-mixture model gave slightly lower estimates for all sites when both models converged. For liver and pancreas the mixture model did not converge for all link function but

the non-mixture model always converged. Regarding prostrate, testis, kidney, thyroid and Non-Hodgkin, none of the models converged for any choice of the link function.

According to the literature (Lambert, 2007), in most cases it does not matter if one uses the mixture or non-mixture models when the aim was to estimate the cure proportion and median survival of uncured cases. Our comparison of different distributions and link functions confirmed this finding. However, the mixture models are easier to explain and provide estimates of the survival function of the fatal cases. On the other hand, the non-mixture models have slightly better fit when measured with Akaike information criterion (AIC). Additionally, there are documented fewer convergence problems with the non-mixture model. In our study the number of non-convergences was the same for the mixture and non-mixture model with the exception of Gamma distribution. With this distribution the mixture model had the most convergence problems, especially when fitted with the log-log link.

I. Conclusions

We have demonstrated in this Thesis that large population-based and hospital-based registries are a useful source of information when the aim is to elucidate clinical questions so our principal hypothesis was thus confirmed. However, a close collaboration between the responsible statistician and a medical professional is recommended to ensure a correct choice of a statistical approach and a valid interpretation of the results.

1. We have demonstrated that proportion cured models can be applied to an unselected and large range of cancer types and that the model fit and results are almost unaffected by the choice of model (mixture or non-mixture) and the link function. However, the model cannot be used for cancer types where the chances of medical curability are very high and the anticipated proportion cured over 90%. In addition, the model cannot be applied to cancer sites where a medical cure is not anticipated and very late relapses might occur.

2. In addition to the well known role of extent of the disease, age over 40 is independently associated with increased TC specific mortality. For non-seminoma patients, high SES also plays an important role in decreasing TC mortality. Overall, race, calendar period of diagnosis and marital status are independent factors that influenced TC mortality rates.

3. Post-diagnosis reproduction rates in cancer patients are lower than the rates of the general population and more so in females compared to males. Regardless of the patient selection, the rates are influenced by the type of the malignancy and parity. An improvement in fertility rates is evident along with the introduction of fertility-saving tasks for selected cancer types.

VII. Further projects

Childhood cancer survivors are a growing survivor group for which fertility is an important issue. Given a relatively small size of this group, one needs to have an access to large registries and long-follow up to be able to investigate post-diagnosis fertility for childhood cancer survivors. Further research has to be aimed to elucidate post-diagnosis reproduction – both using the information available in large registries but also using information obtained from surveys so that also a patient's wish and interest in starting a family can be considered.

Another much debated issue is sub-fertility of testicular cancer patients before their diagnosis. There have been several studies linking testicular dysgenesis syndrome and sub-fertility but there is also growing evidence that a large proportion of TC patients does not have lower pre-diagnosis fertility (Kim, et al., 2010; Akre, et al., 2009). This issue is currently being investigated in Norwegian cancer patients and a preliminary report by Oldenburg and Cvancarova has been presented at 7th Copenhagen Workshop on CIS Testis and Germ Cell Cancer. Our group will continue working on this project since more research is needed to investigate this issue in depth.
As we indicated in Paper II, SES has an impact on survival of good prognosis TC patients from the USA. The role of SES for cancer patients in general should be examined in more detail also in countries with well developed and organised health care service as in Europe and especially in Scandinavia using SES available on an individual level.

Appendix :

The mixture model with various link functions

a) Proportion cured

	Weibull			Lognormal			Gamma		
	identity	logit	log-log	identity	logit	log-log	identity	logit	log-log
mouth,pharynx	0,428404	0,428404	0,428404	0,35149	0,35149	0,351492	0,180004	0,180004	nc
oesophagus	0,120127	0,120127	0,120127	0,091727	0,091727	0,091727	0,108318	0,108318	0,108318
stomach	0,227016	0,227016	0,227016	0,182081	0,182081	0,182081	0,194376	0,194376	0,194376
colon	0,574275	0,574275	0,574275	0,481947	0,481947	0,481949	0,575464	0,575464	0,575464
rectum	0,601867	0,601867	0,601867	0,519637	0,519637	0,519637	0,605338	0,605338	0,605338
liver	0,103683	0,103683	0,103683	0,073499	0,073499	0,073499	nc	nc	nc
gallbladder	0,171404	0,171404	0,171404	0,132919	0,132919	0,132919	0,16071	0,16071	0,16071
pancreas	0,068124	0,068124	0,068124	0,040648	0,040648	0,040648	nc	nc	nc
lung,trachea	0,127766	0,127766	0,127766	0,070585	0,070585	0,070585	0,092231	0,092231	0,092231
melanoma of the skin	nc	0,817115	0,817115	0,79855	0,79855	nc	nc	0,8102	nc
breast	nc	0,646845	0,646845	0,07164	0,07164	nc	nc	0,639846	nc
cervix	nc	0,676449	0,676449	0,537809	0,537809	0,537809	0,579477	0,579477	0,579471
corpus uteri	nc	0,849872	0,84987	nc	0,788961	nc	nc	0,855863	nc
ovary	0,384932	0,384932	0,384932	0,278425	0,278425	0,278425	0,391911	0,391911	0,391911
prostate	nc	nc	nc	nc	nc	nc	nc	nc	nc
testis	nc	0,976682	0,000107	0,944376	0,944376	0,944374	nc	nc	nc
kidney	0,502796	0,502796	0,502798	0,383038	0,383038	0,38304	-27	0	nc
bladder	0,702463	0,702463	0,702463	0,617175	0,617175	0,617175	0,512393	0,512393	0,512536
CNS	0,70513	0,70513	0,70513	0,633853	0,633853	0,633853	0,579164	0,579164	0,579166
thyroidea	nc	0,933386	0,933386	nc	0,927641	nc	nc	nc	nc
Hodgkin lymphoma	nc	0	0,000001	nc	0,000001	nc	-111,3	0,265558	0,006219
non-Hodgkin lymphoma	nc	0,418254	0,418266	-0,107	0	nc	nc	nc	nc
leukaemia	0,533963	0,533963	0,533963	0,40733	0,40733	0,40733	0,461	0,499753	0,499755

nc=not converged

b) Median survival of the uncured

	Weibull			Lognormal			Gamma		
	identity	logit	log-log	identity	logit	log-log	identity	logit	log-log
mouth,pharynx	3,053644	3,053644	3,053644	3,63118	3,63118	3,631155	6,737938	6,737938	nc
oesophagus	0,665003	0,665003	0,665003	0,612028	0,612028	0,612028	0,636204	0,636204	0,636204
stomach	0,643296	0,643296	0,643296	0,615886	0,615886	0,615886	0,617498	0,617498	0,617498
colon	1,363927	1,363927	1,363927	1,945712	1,945712	1,945696	1,364072	1,364072	1,364072
rectum	2,115203	2,115203	2,115203	2,77566	2,77566	2,775659	2,11252	2,11252	2,112518
liver	0,402671	0,402671	0,402671	0,35222	0,35222	0,35222	nc	nc	nc
gallbladder	0,735856	0,735856	0,735856	0,670455	0,670455	0,670455	0,702857	0,702857	0,702857
pancreas	0,396828	0,396828	0,396828	0,360412	0,360412	0,360412	nc	nc	nc
lung,trachea	0,600881	0,600881	0,600881	0,589414	0,589414	0,589414	0,585648	0,585648	0,585648
melanoma of the skin	nc	2,849196	2,849196	3,14818	3,14818	nc	nc	2,893647	nc
breast	nc	10,738593	10,738584	63,963192	63,963192	nc	nc	11,038505	nc
cervix	nc	4,473705	4,473706	10,1	11,088599	11,088557	7,8	8,34162	8,341966
corpus uteri	nc	1,917749	1,917782	nc	3,503657	nc	nc	1,879487	nc
ovary	2,361046	2,361046	2,361046	2,974104	2,974104	2,974104	2,4	2,370179	2,370178
prostate	nc	nc	nc	nc	nc	nc	nc	nc	nc
testis	nc	0,780183	4381,38794	2,8	7,304973	7,305525	nc	nc	nc
kidney	2,666696	2,666696	2,666687	4,3	4,367831	4,367794	103,7	28,528497	nc
bladder	1,962403	1,962403	1,962403	3,3	3,305425	3,305421	6,976121	6,976121	6,969131
CNS	0,95708	0,95708	0,95708	1,473496	1,473496	1,473496	2,08846	2,08846	2,088434
thyroidea	nc	1,776942	1,776947	nc	1,816073	nc	nc	nc	nc
Hodgkin lymphoma	nc	82,992044	83,014125	nc	295,437417	nc	166,5	37,989427	57,97409
non-Hodgkin lymphoma	nc	5,090391	5,090137	43,1	30,149195	nc	nc	nc	nc
leukaemia	1,819377	1,819377	1,819377	3,28178	3,28178	3,281776	2,036444	2,036444	2,03643

The non-mixture model with various link functions

a) Proportion cured

	Weibull			Lognormal			Gamma		
	identity	logit	log-log	identity	logit	log-log	identity	logit	log-log
mouth,pharynx	0,419156	0,41915609	0,41916	0,336525	0,33652	0,336521	0,115838	0,115676	0,115526
oesophagus	0,111516	0,11151638	0,11152	0,068935	0,068935	0,068935	0,104779	0,104779	0,104779
stomach	0,216171	0,21617082	0,21617	0,162265	0,162265	0,162265	0,188206	0,188206	0,188206
colon	0,571878	0,57187851	0,57188	0,458479	0,458481	0,458481	0,578594	0,578594	0,578594
rectum	0,599906	0,59990532	0,59990	0,500119	0,500119	0,500119	0,60696	0,60696	0,60696
liver	0,087495	0,08749471	0,08749	0,05363	0,05363	0,05363	0,06121	0,06121	0,06121
gallbladder	0,16558	0,16558037	0,16558	0,104486	0,104485	0,104485	0,165555	0,165555	0,165555
pancreas	0,057207	0,05720659	0,05721	0,025313	0,025313	0,025313	0,030765	0,030765	0,030765
lung,trachea	0,107963	0,10796274	0,10796	0,040979	0,040979	0,040979	0,078728	0,078728	0,078728
melanoma of the skin	nc	0,8165351	0,81654	nc	0,797127	nc	nc	0,810261	nc
breast	nc	0,63540815	0,63541	0,074801	0,074673		nc	0,631099	nc
cervix	nc	0,67112226	0,67112	0,524216	0,524217	0,524219	0,574386	0,57437	0,57437
corpus uteri	nc	0,84931843	0,84932	nc	0,784877	nc	nc	0,855974	nc
ovary	0,380157	0,38015744	0,38016	0,224222	0,224218	0,224218	0,391427	0,391427	0,391427
prostate	nc	0,37416166	nc	nc	0	nc	nc	nc	nc
testis	nc	0,9766802	nc	0,945533	0,945556	0,945561	nc	nc	nc
kidney	0,49321	0,49321332	0,49321	0,37399	0,373989	0,373992	nc	nc	nc
bladder	0,69889	0,69889035	0,69889	0,607561	0,607545	0,607548	0,476746	0,476753	0,476738
CNS	0,696544	0,69654406	0,69654	0,62646	0,62646	0,62646	nc	0,575499	0,575499
thyroidea	nc	0,93336598	0,93337	nc	0,927492	nc	nc	nc	nc
Hodgkin lymphoma	nc	nc	nc	nc	nc	nc	nc	0,298249	0
non-Hodgkin lymphoma	0,384373	0,38437179	0,38437	0,033548	0,033548	0,033551	nc	0,488723	nc
leukaemia	0,529786	0,5297844	0,52978	0,3743	0,374309	0,374299	0,501292	0,501291	0,50129

b) Median survival of the uncured

	Weibull			Lognormal			Gamma		
	identity	logit	log-log	identity	logit	log-log	identity	logit	log-log
mouth,pharynx	3,062668	3,0626679	3,0626687	3,770366	3,77046	3,770452	989,274923	996,748945	1001,897179
oesophagus	0,652184	0,65218388	0,65218387	0,637183	0,637183	0,637183	0,64208	0,64208	0,64208
stomach	0,633846	0,6338458	0,63384578	0,637384	0,637384	0,637383	0,624005	0,624005	0,624004
colon	1,359052	1,3590521	1,359052	2,206933	2,206915	2,206915	1,359323	1,359322	1,359323
rectum	2,11477	2,1147722	2,1147741	3,029498	3,029497	3,029497	2,105233	2,105233	2,105233
liver	0,39125	0,39125022	0,39125022	0,36503	0,36503	0,36503	0,363403	0,363403	0,363403
gallbladder	0,714211	0,71421057	0,71421057	0,716504	0,716505	0,716505	0,714153	0,714153	0,714153
pancreas	0,383592	0,38359179	0,38359177	0,367554	0,367554	0,367554	0,367553	0,367552	0,367553
lung,trachea	0,600688	0,60068759	0,6006875	0,631385	0,631385	0,631385	0,60081	0,600811	0,60081
melanoma of the skin	nc	2,8518642	2,8518646	nc	3,188128	nc	nc	2,891884	nc
breast	nc	11,223048	11,223021	62,598966	62,61384	nc	nc	11,413796	nc
cervix	nc	4,5920168	4,5919963	12,091079	12,091002	12,090817	8,579422	8,580338	8,580319
corpus uteri	nc	1,9249699	1,9249856	nc	3,659544	nc	nc	1,878482	nc
ovary	2,368752	2,3687519	2,3687519	3,575946	3,576026	3,576023	2,357279	2,357277	2,357279
prostate	nc	17,654233	nc	nc	35,024655	nc	nc	nc	nc
testis	nc	0,77974761	4387,5564	nc	6,829952	6,827945	nc	nc	nc
kidney	2,724993	2,7249464	2,724942	4,529215	4,529233	4,529169	nc	nc	nc
bladder	1,988867	1,9888618	1,9888652	3,52667	3,527062	3,526998	39,517535	39,508521	39,517546
CNS	1,014548	1,014549	1,0145497	1,528132	1,528138	1,528138	nc	4,619422	4,619422
thyroidea	nc	1.7705695	.:1,770572	nc	1,822188	nc	nc	nc	nc
Hodgkin lymphoma	nc	83,114922	nc	nc	nc	nc	nc	42,961868	83,014038
non-Hodgkin lymphoma	5,87058	5.8706044	2 5,8705559	25,992784	25,99407	25,993852	nc	3,91533	nc
leukaemia	1,821683	1,8216953	1,821696	3,942703	3,942492	3,942727	2,02315	2,023161	2,023166

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Paper I

PROPORTION CURED MODELS APPLIED TO 23 CANCER SITES IN NORWAY

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Abstract

Background *Statistical cure* is reached when a group of patients has the same mortality as cancer-free individuals, and cure models predict the cured proportion and the median survival of fatal cases. Cure models have seldom been applied and tested systematically across all major cancer sites.

Methods Incidence and follow-up data on 23 cancers recorded at the Cancer Registry of Norway 1963-2007 were obtained. Mixture cure models were fitted to obtain trends and up-to-date estimates assuming cured and uncured groups exist.

Results The model fitted for cancers of the mouth and pharynx, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung and trachea, ovary, kidney, bladder, central nervous system, non-Hodgkin lymphoma and leukemia. The proportion of cured patients increased 1963-2002 for both sexes, with the largest changes seen for leukemia (in % units), males given first (46.4 and 46.7) and CNS (35.9, 42.0). Median survival time for the uncured cases increased for colon (0.42 years and 0.61years), and rectal cancer (0.56 years, 0.75 years), and there was a three- fold increase in median survival time (from 0.73 years to 1.36 years) for patients with fatal ovarian cancers. Cancers of bladder and CNS had the highest up-to-date proportion cured (67.4% and 64.0 %, respectively), pancreas and liver were amongst the worst (5.7% and 9.9%, respectively).

Conclusion

Cure models are useful when monitoring progress in cancer care, but must be applied and interpreted with caution. The absolute estimates of the cure proportion are speculative, particularly for cancer sites where cure is not medically anticipated.

Introduction

Increasingly, cancer patients as a group – at least those diagnosed with treatable cancers in higher-resource settings – survive their initial diagnosis and remain tumor-free for longer periods than has been observed previous decades (1) This favorable trend in cancer care has warranted the development of novel statistical tools to monitor the effectiveness of early-detection strategies and the quality of clinical care and cancer management, including procedures to estimate the *proportion of cured patients* alongside the *median survival of fatal cases* using so-called *cure* models (2;3) . From the offset, the inherent differences between the concepts of clinical versus statistical cure need to be understood. *Statistical cure* is applicable to observations examined at the group level, and is distinct from *medical cure* of the individual, as commonly determined in a clinical setting on the basis of lack of specific symptoms of the patients, achieved, for example, when all cancerous cells in the body have been persistently eradicated (4). The models, when applied to population-based cancer survival data, serve to provide estimates of the proportion of statistically-cured individuals, that is, a group of cancer patients whom, after a certain time period, are observed to have little or no excess mortality relative to the general population.

Such models have been applied to aid clinical interpretation of survival trends for specific cancer sites in one or more population. A recent EUROCARE study presented estimates of the cured proportion for a limited number of cancer forms (breast, lung, prostate, colon and rectum, stomach and all sites combined) for a subset of European cancer patients diagnosed from 1988 to 1999 (5). Lambert et al have reported the long-term survival trends among colorectal cancer patients in Finland, in terms of the proportion cured and median survival of fatal cases (6) while trends in the proportion of childhood cancer patients with leukemia has been studied in British children diagnosed between 1971 and 2000 (7).

There has however been a paucity of work examining the systematic application of cure models to long-term survival and trends across the major cancer types. The objective of this study is therefore to perform such an analysis, providing national estimates of the cured proportion and median survival of fatal cases for patients with the 23 most common cancer sites diagnosed in Norway over the period 1963 to 2007. We aimed to illustrate both the major temporal trends in the two estimates as well as provide up-to-date estimates of the cured proportion and the median

survival of patients who eventually die. A secondary aim was to assess the general applicability of these models in the context of statistical and clinical cure of specific cancers.

Material and methods

Data sources

National incidence and follow-up data was extracted from the population-based Cancer Registry of Norway. The reporting of neoplasms and certain precancerous lesions to the Cancer Registry of Norway has been compulsory following a directive from the Ministry of Health and Social Affairs in 1951, further strengthened by the Health Registry Act in 2002 that included statutory regulations and the requirement that relevant institutions report new cases to the Registry. A recent evaluation suggests that multiple source reporting and effective trace-back has meant that the Registry has retained a high level of overall completeness for many years (8). In terms of validity, the Registry's effective use of reports from pathology laboratories, clinical records and death certificates has been shown to provide reasonable and comparable accuracy, with only a small fraction of cancer registrations obtained solely from death certificate sources (DCO) (8). A review of registrations 2001–5 showed that three-quarters of the main cancer sites had a DCO proportion of less than 1%. However, for certain sites, including pancreatic and liver cancer, the percentages were higher, ranging from 3 to 4%.

Survival data

Incidence data on the 23 most frequently recorded cancers for the diagnostic period 1963–2007 were obtained together with follow-up on matching vital status from the National population Registry. Except for precancerous diagnoses for bladder cancer and central nervous system (CNS) and endocrine organs, only invasive malignant cancer diagnoses were included. Patients with previous cancer diagnoses were therefore included given it has been shown that exclusion of such patients - usually diagnosed with tumor associated with inferior prognoses - may give higher estimates of survival by their inclusion (9). Beginning with a total of 642,219 registered diagnoses of the 23 cancers under investigation: 7142 DCO cases were excluded (1.1%) alongside 5350 cases diagnosed at autopsy (0.8%). We removed a further 268 cases for which a survival time could not be estimated as event dates were missing, and 2,113 cases (0.3%) with either an erroneous event date (survival time < 0) and or zero survival time (survival time $= 0$).

Following these eliminations, 627,346 cases were included in the analyses described below, 97.7% of the number extracted prior to exclusions.

Statistical methods

Relative survival (10; 11; 12) is computed as the ratio of observed (all causes) and expected survival and provides a measure of excess mortality (compared to the general population) associated with diagnosis of the disease:

$$R(t)=S(t)/S^{*}(t),$$

where $R(t)$ is relative survival, $S(t)$ is observed and $S^{*}(t)$ is expected survival.

To provide recent estimates of long-term (1- to 15-year) survival proportions of Norwegian cancer patients, we used the period approach of Brenner et al (13; 14; 15; 16).

The cure proportion is estimated using the mixture cure proportion model (17; 18; 19):

$$S(t) = S^{*}(t)(\pi + (1 - \pi)S_{u}(t))$$

where $S^{*}(t)$ is the expected survival, π is the proportion cured (the cure fraction), $(1 - \pi)$ is the proportion 'uncured' (or those 'bound to die' fatal cases) and $S_{u}(t)$ is the survival function for the uncured individuals. $S_{u}(t)$ was modeled with a Weibull distribution with two parameters λ and γ:

$$S_{u}(t) =\exp(-\lambda t^{\gamma})$$

If the relative survival curve does not reach a plateau then the estimate of cure is based on extrapolation beyond the time range of the data and becomes sensitive to the choice of parametric distribution. In theory, cure occurs when time approaches infinity, but in practice the cure proportion is estimated where the relative survival curve is seen to plateau, usually between six and ten years post diagnosis. Estimation of the cure model parameters is obtained using maximum likelihood on the individual level data. The estimation procedure is similar to that of De Angelis (2) but extended to model both parameters in the Weibull distribution (4).

Temporal trends between 1963–2002 in the proportion of cured patients, and the median survival of fatal cases, were estimated applying the complete approach as suggested by Brenner at al. (14), whereby all diagnosed cases over the period irrespective of the length of their follow-up were used in the estimations. The main focus here was on estimating changes in trends for patients diagnosed at different five-year time periods, hence period of diagnosis was modeled as a categorical variable with the 5-year periods as the categories.

The changes in proportion cured and median survival of uncured cases between the first period (1963-1967) and the last period (1998-2002) were quantified using the absolute difference between the estimates of both cure proportion and median survival. 95% confidence intervals for these differences were constructed using the delta method.
The most up-to-date estimates of the proportion of cured patients and the median survival of fatal cases were modeled using the period approach with a 3-year observation window (2005-2007) and a 15-year follow-up, thus accruing sufficient case numbers to ensure the estimates were reasonably up-to-date while retaining an acceptable degree of precision. Using this method the follow up was set to 15years but there were no constraints on the model concerning the time at which a statistical cure will have to be reached. Age at diagnosis (in categories) and sex were modeled as covariates.

All computations were conducted using the statistical software Stata (20). The mixture cure proportion models (4) were fitted with the *strsmix* command (version 1.0.2).

Results

Model fitting

The cure models fitted well for cancers of the mouth and pharynx, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung and trachea, ovary, kidney, bladder, CNS, non-Hodgkin lymphoma and leukaemia. When we compared the up-to-date estimates of long term relative survival and the proportion cured derived from the mixture model, both estimates were very similar for all 15 cancer sites where convergence was reached except for Non-Hodgkin lymphoma and mouth and pharynx. For those two sites the plateau was not reached within 15 years after the cancer diagnosis (at least empirically, by means of visual inspection of the relative survival plots). It was not possible to fit the cure proportion for eight of the 23 selected neoplasms (breast, prostate, cervical, endometrial, testicular, thyroid, Hodgkin lymphoma and melanoma of the skin).

Trends in the proportion cured and median survival

The proportion of cured patients significantly increased from 1963 to 2002 for both male and female patients where the model provided a reasonable fit, with cancers of mouth and pharynx among men the only exception (Table 1: IA,IB and IIA,IIB). The temporal trends are depicted

graphically in Figure 1. The largest increases in the cured proportion were seen for leukemia (46.4 and 46.7, males and females, respectively), CNS (35.4 and 42.0), Non-Hodgkin lymphoma (35.4 and 27.7), bladder (28.6 and 30.3), and rectum (30.2 and 31.1), all differences given in % units.

The median survival time for fatal cases has increased significantly for male patients diagnosed with cancers of the stomach, rectum, colon, CNS, Non-Hodgkin lymphoma and leukemia. For females, the median survival of fatal cases increased significantly for cancers of colon, rectum, ovary, CNS, Non-Hodgkin lymphoma and leukemia.

The estimates of the proportion cured for the latest period (1998-2002) tended to be higher for females than males, although only for cancers of the lung and CNS were the differences statistically significant. Overall, the highest absolute differences in median survival of fatal cases between the period 1963-1967 and 1998-2002 was seen for cancers of rectum (0.56 years and 0.75 years, males and females, respectively), leukemia (0.65 years and 0.68 years) colon (0.42 years and 0.61 years,), CNS(0.44 years and 0.31 years) and Non-Hodgkin lymphoma (0.40 years and 1.23 years).

While the proportion cured has remained unchanged for patients diagnosed with ovary cancer, there has been about a three-fold increase in the median survival time of fatal cases (from 0.73 years to 1.36 years) from 1963 to 2002. The prognosis for patients with gallbladder and lung cancers has slightly improved in terms of a higher proportion cured. However, median survival of fatal cases has remained unchanged for both malignancies. (Table 1: IA,IB and IIA,IIB).

Up-to-date estimates of proportion cured and median survival

A summary of the estimates of proportion cured and median survival of fatal cases with follow up 2005-2007 is depicted graphically in Figure 2 and listed in Table 1. The highest proportion cured was reached by the survivors of cancers of bladder and CNS where more than two thirds were considered statistically cured: 67.4% [62.7% to 72.1%] and 64.0 % [59.9% to 69.2%], respectively (square brackets indicate 95%CI). More than half of the patients were considered cured following diagnoses of colon and rectal cancer, with the proportion cured being 55.1 % [53.0% to 57.3%] and 57.7 % [54.9% to 60.9%], respectively. The poorest survival was observed

for cancers of pancreas and the liver, the cured proportion being only 5.7% [4.1% -7.3%] for the former neoplasm.
The median survival time of fatal cases was longer than one year for eight (mouth and pharynx, colon, rectum, ovary, kidney, bladder, CNS and leukemia) of the 15 sites analyzed. The longest median survival of fatal cases was estimated for mouth and pharynx (3.05 [2.31 to 4.04], ovary (2.36 [2.09 to 2.67], rectum (2.11 [1.90 to 2.36] and bladder (2.19 [1.43 -2.70]).

Discussion

In this study, we have systematically attempted to fit cure models to 23 cancers and were able to derive estimates of cure for 15, and report a general increase in the proportion of cured patients in Norway from 1963-1967 to 1998-2002 patients diagnosed with each of these neoplasms. Over half of the patients diagnosed with cancers of the colon, rectum, bladder, CNS and leukemia may considered (statistically) cured of their cancer, while the median survival for those who eventually die from cancers – including cancers of the mouth and pharynx, colon, rectum, ovary, kidney, bladder, CNS and leukemia – are greater than one year.
These conclusions are derived from statistical models that are based on concepts of statistical cure. For a number of common cancers, the relative survival function will reach a plateau at some point after diagnosis, with the corresponding level an indication of the proportion of survivors whom, as a group, no longer exhibit any excess mortality compared to the general, cancer-free population (at a given age and sex) (21; 22; 23). Statistical cure refers to a population of patients rather than to individual patients; selected long-term survivors may still die from their cancer even though they were considered (as part of a group) statistically cured. A critical assumption on applying these mixture models is therefore that there exists a cured and an uncured group – comprising of fatal cases or in other words, those bound to die – defined at the time of diagnosis. Where the cure model reached convergence and the estimates could be derived, particular caution must be applied in their interpretation. The absolute estimates of the cured proportions are speculative, particularly for those sites where statistical cure is not clearly indicated, e.g. where long term relative survival fails to reach a plateau (melanoma of the skin, female breast cancer, and prostate cancer).

We did not find any major differences between the estimates regardless of the choice of model (mixture and non-mixture), distribution and the link function. According to the literature (4), in most cases it does not matter if one uses the mixture or non-mixture models when the aim was to estimate the cure proportion and median survival of uncured cases. Our comparison of different distributions and link functions confirmed this finding.

It should be noted that we did not embark on any age standardization procedure, and it is possible therefore that the estimates might vary more were the models fitted with several covariates. However, the aim of this study was to compare the proportion cured estimates across different cancer sites and diagnostic periods; therefore the use of models based on unadjusted survival estimates was justified.

There are 15 candidate sites in our study for which patients may potentially exhibit properties pertaining to both statistical and clinical cure, and the underlying reasons for such changes are likely to be multiple. Improvement in treatment and introduction of new therapies together with an increase in diagnostic intensity contribute to a higher proportion of cured patients, but also to increases in the median survival of fatal cases. Colorectal cancers are increasingly diagnosed earlier than previously due to a raised awareness among the general population and improved multimodal treatment (24). New chemotherapy for treatment of childhood and adult-onset leukemia was introduced in the 1970s and has led to improved survival (25;26). However, not all the rises in the cured proportion may represent genuine improvements in cancer care, but may be artifacts related to changing registration practices as for example for bladder cancer. From early in the 80ies the Cancer Registry of Norway coded pre-invasive bladder lesions together with invasive tumors, so this change in coding rather than altered treatment is reflected in changes in survival rates. There has been little improvement in treatment of bladder cancer so the high degree of change in proportion of cured patients is more likely explained by change in coding practices.

The mixture cure model did not converge when estimating the proportion cured for 8 cancers, namely breast, prostate, cervix, endometrium, testis, thyroid, as well as Hodgkin lymphoma and melanoma of the skin. For a number of these cancer forms, it is reasonable to assume that statistical cure could not be estimated as medical cure is not established in some of these patients even several decades after diagnosis (including melanoma of the skin, female breast cancer, and

prostate cancer). Theories concerning cures for breast cancer vary from the concept that no patients are cured (27;28), to the idea that the hazard to patients who have survived eight years is no greater than that for the general population (29).

A selection effect may have also played a role. Testicular cancer is now one of the cancers with the highest proportion of survivors. However, those who survive might be on average of better general health than observed in the general population so that the relative survival of testicular cancer patients does not reach a plateau but rather continues to increase even after long-term follow-up. For several malignancies, such as childhood cancers, Hodgkin's lymphoma and testicular cancer, long-term survivors are at risk to develop life-threatening adverse induced by the cancer treatment many years after initial treatment and hence relative survival of these patients never reaches a plateau but continues to decline (30;31;32).

For certain sites, there is an absence of statistical cure in this study, yet clinical evidence of patient cure. In such circumstances, there may statistical grounds as to why there is a lack of convergence of the proportion cure models for certain cancer sites. It is possible that the underlying Weibull distribution may not be sufficiently flexible to capture the shape of the long term survival curves. However, it should be possible to fit the model even though the assumption of existence of a cured and uncured fraction is violated. Another explanation could relate to the use of general life tables that insufficiently represent the demographics of the patient groups. It is known that cervical cancers are more common among women of lower social classes. When computing relative survival we used life tables constructed from the data on the whole population which might have caused underestimation of the relative survival of these patients and in turn caused problems in estimation of the proportion cured.

Overall, the estimates of proportion cure for the latest period 1998-2002 were higher for females compared to males. This is in agreement with a number of previously-published articles: Micheli et al, for instance, suggest that female sex hormone may have a role in women's superior ability to cope with cancer using the EUROCARE-4 data (33). However, these findings are speculative and have to be confirmed in future studies.

Most cure models have been applied to specific cancer sites. A recent study demonstrated the effect of year of diagnosis and stage on cancer of colon using data from three French registries (21). Lam and colleagues applied several variants of cure models on breast cancer data with focus was on the statistical properties of the models, rather than the clinical interpretation of the

results (34). Yu and colleagues analyzed US data on Hodgkin disease and Sposto et al compared cure and Cox regression models using examples based on Hodgkin and non-Hodgkin lymphoma as well as acute lymphocytic leukemia (35). Mixture survival models have been applied to colon cancer data collected in Finland 1953-1992 and Weston et al has described the long-term survival following diagnoses of Ewing's sarcoma, quantifying the cure in young patients (37). Proportion cured models are useful when monitoring progress in cancer care; however they must be applied and interpreted with caution. The existence of a cured and an uncured group of patients is a necessary but rather strong assumption underlying the mixture model. The absolute estimates of the cure proportion are speculative, particularly for cancer sites where a cure is not clearly indicated. Our results provide neither direct relationships between the changes in patient care, nor any information regarding the extent that there has been improved survival at the individual level. However, the methods may result in a better quantification of the lives of cancer patients beyond their initial diagnosis and aid understanding as to the reasons for increasing survival for certain cancers, among them improvements in therapy and management and better palliative care.

Conflict of interest statement

None declared.

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Table 2: Up-to-date estimates of proportion cured and median survival for those uncured (based on patients with follow-up time 2005-2007)

Cancer site	No of patients	Proportion cured	95% CI	Median of fatal cases	95%CI
Mouth. pharynx	2627	39.1	31.9 to 46.4	3.05	2.31 to 4.04
Oesophagus	942	11.2	7.9 to 14.6	0.66	0.58 to 0.76
Stomach	2660	21.4	18.4 to 24.4	0.64	0.57 to 0.73
Colon	10938	55.1	53.0 to 57.3	1.33	1.22 to 1.46
Rectum	5873	57.7	54.9 to 60.5	2.11	1.90 to 2.36
Liver	562	9.9	5.4 to 14.3	0.40	0.30 to 0.53
Gallbladder	645	16.2	11.0 to 21.3	0.74	0.60 to 0.90
Pancreas	2913	5.7	4.1 to 7.3	0.40	0.36 to 0.44
Lung. trachea	11395	11.7	10.6 to 12.9	0.60	0.57 to 0.63
Ovary	2153	35.0	31.4 to 38.6	2.36	2.09 to 2.67
Kidney	2705	46.6	37.6 to 55.7	2.67	1.64 to 4.34
Bladder	6021	67.4	62.7 to 72.1	2.19	1.43 to 2.70
CNS	4663	64.0	58.9 to 69.2	1.96	1.77 to 2.18
Non-Hodgkin lymphoma	3829	39.7	28.9 to 50.5	5.09	4.58 to 5.60
Leukaemia	2520	51.1	45.8 to 56.3	1.82	1.32 to 2.51

Table 1: Trends in proportion cured and median survival of fatal cases

I: Males

A) proportion cured

	1963-1967		1998-2002			
Cancer site	**Proportion cured**	**95%CI**	**Proportion cured**	**95%CI**	**Difference (% units)**	**95%CI**
Mouth and pharynx	60.6	55.4 to 65.8	52.7	48.7 to 56.7	-7.9	-1.4 to -1.3
Oesophagus	4.7	1.8 to 7.6	8.2	5.5 to 10.9	3.5	-0.5 to 7.5
Stomach	11.6	10.3 to 12.8	19.2	16.6 to 21.7	7.6	4.8 to 10.4
Colon	31.3	27.9 to 34.6	51.7	49.1 to 54.3	20.4	16.2 to 24.6
Rectum	22.5	18.5 to 26.5	52.7	49.4 to 55.9	30.2	25.1 to 35.3
Liver	4.6	0.6 to 8.7	6.6	3.2 to 9.9	2.0	-3.3 to 7.3
Gallbladder	2.1	0.0 to 5.7	16.7	10.6 to 22.7	14.6	7.6 to 21.6
Pancreas	2.5	1.3 to 3.7	3.4	2.2 to 4.7	0.9	-0.9 to 2.7
Lung, trachea	7.6	6.2 to 8.9	9.5	8.6 to 10.4	1.9	0.3 to 3.5
Kidney	26.4	21.5 to 31.4	52.4	48.5 to 56.4	26.0	19.6 to 32.4
Bladder	44.8	40.1 to 49.5	73.4	70.5 to 76.2	28.6	23.1 to 34.1
CNS	16.2	13.1 to 19.3	52.1	29.4 to 54.8	35.9	31.8 to 40.0
Non-Hodgkin lymphoma	19.6	15.1 to 24.1	55.0	51.0 to 59.0	35.4	29.4 to 41.4
Leukaemia	2.5	0.5 to 4.5	48.9	42.2 to 55.6	46.4	39.3 to 53.4

B) median survival time of fatal cases

	1963-1967		1998-2002			
Cancer site	**Median time (years)**	**95%CI**	**Median time (years)**	**95%CI**	**Difference (% units)**	**95%CI**
Mouth and pharynx	1.34	1.10 to 1.64	1.52	1.32 to 1.75	0.18	-0.06 to 0.42
Oesophagus	0.47	0.41 to 0.53	0.56	0.50 to 0.63	0.09	-0.09 to 0.27
Stomach	0.45	0.43 to 0.48	0.63	0.57 to 0.69	0.18	0.07 to 0.29
Colon	0.66	0.57 to 0.75	1.08	0.96 to 1.22	0.42	0.23 to 0.61
Rectum	1.04	0.91 to 1.20	1.60	1.41 to 1.83	0.56	0.38 to 0.74
Liver	0.12	0.09 to 0.15	0.31	0.26 to 0.38	0.19	-0.15 to 0.53
Gallbladder	0.35	0.25 to 0.49	0.46	0.36 to 0.61	0.11	-0.31 to 0.53
Pancreas	0.24	0.22 to 0.27	0.32	0.30 to 0.35	0.08	-0.03 to 0.19
Lung, trachea	0.43	0.40 to 0.46	0.47	0.45 to 0.49	0.04	-0.04 to 0.12
Kidney	0.90	0.75 to 1.09	0.93	0.77 to 1.12	0.03	-0.23 to 0.29
Bladder	1.55	1.29 to 1.85	1.66	1.38 to 1.99	0.11	-0.15 to 0.37
CNS	0.44	0.38 to 0.51	0.88	0.80 to 0.97	0.44	0.26 to 0.61
Non-Hodgkin lymphoma	0.83	0.69 to 1.00	1.23	1.00 to 1.49	0.40	0.12 to 0.68
Leukaemia	0.62	0.53 to 0.72	1.27	0.88 to 1.83	0.65	0.25 to 1.05

II: Females

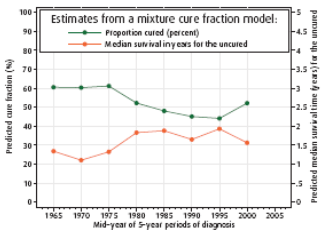
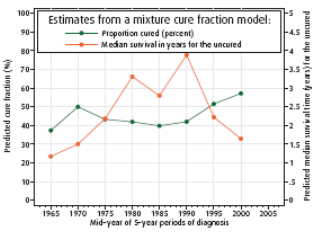
A) *proportion cured*

Cancer site	1963-1967 Proportion cured	95%CI	1998-2002 Proportion cured	95%CI	Difference (% units)	95%CI
Mouth and pharynx	37.2	27.8 to 46.7	57.7	52.1 to 63.4	20.5	9.4 to 31.6
Oesophagus	8.7	2.9 to 14.5	9.5	4.7 to 14.3	0.8	-6.7 to 8.3
Stomach	10.8	9.3 to 12.4	23.4	20.4 to 27.3	12.6	8.4 to 16.8
Colon	33.7	30.8 to 36.5	55.1	52.9 to 57.4	21.4	17.8 to 25.0
Rectum	27.3	23.1 to 31.4	58.4	54.6 to 62.2	31.1	25.5 to 36.7
Liver	5.6	0.0 to 11.9	10.3	5.3 to 15.3	4.7	-3.3 to 12.7
Gallbladder	5.7	2.4 to 9.0	13.1	8.3 to 17.8	7.4	1.7 to 13.1
Pancreas	2.1	0.7 to 3.4	4.0	2.7 to 5.4	1.9	0.0 to 3.8
Lung, trachea	9.6	6.4 to 12.9	13.4	12.1 to 14.7	3.8	0.2 to 7.3
Ovary	29.5	26.7 to 32.2	33.8	29.5 to 38.1	4.3	0.8 to 9.4
Kidney	31.5	24.6 to 38.3	55.5	50.8 to 60.1	24.0	15.8 to 32.2
Bladder	38.6	33.3 to 43.9	68.9	65.2 to 72.5	30.3	23.9 to 36.7
CNS	29.3	25.3 to 33.3	71.3	69.1 to 73.6	42.0	37.4 to 46.6
Non_Hodgkin lymphoma	27.7	22.5 to 32.8	55.4	48.5 to 62.2	27.7	19.2 to 36.2
Leukaemia	4.3	1.9 to 6.6	51.0	44.1 to 57.9	46.7	39.4 to 54.0

B) *median time of fatal cases*

Cancer site	1963-1967 Median time (years)	95%CI	1998-2002 Median time (years)	95%CI	Difference (% units)	95%CI
Mouth and pharynx	1.18	0.85 to 1.63	1.61	1.31 to 1.98	0.43	-1.25 to 2.11
Oesophagus	0.54	0.43 to 0.68	0.63	0.53 to 0.75	0.09	-0.19 to 0.37
Stomach	0.46	0.43 to 0.49	0.59	0.52 to 0.66	0.13	0.0 to 0.27
Colon	0.66	0.59 to 0.74	1.27	1.15 to 1.40	0.61	0.46 to 0.76
Rectum	1.14	0.98 to 1.31	1.89	1.59 to 2.24	0.75	0.52 to 0.98
Liver	0.21	0.14 to 0.33	0.35	0.27 to 0.45	0.14	-0.34 to 0.62
Gallbladder	0.23	0.19 to 0.28	0.48	0.39 to 0.59	0.25	-0.03 to 0.53
Pancreas	0.27	0.24 to 0.30	0.35	0.31 to 0.37	0.08	-0.09 to 0.25
Lung, trachea	0.46	0.40 to 0.53	0.53	0.50 to 0.56	0.07	-0.08 to 0.22
Ovary	0.73	0.66 to 0.81	2.09	1.82 to 2.41	1.36	1.19 to 1.53
Kidney	0.94	0.69 to 1.27	0.80	0.64 to 0.99	-0.14	-0.52 to 0.24
Bladder	0.76	0.63 to 0.92	0.88	0.72 to 1.08	0.12	-0.15 to 0.39
CNS	0.41	0.34 to 0.49	0.72	0.63 to 0.82	0.31	0.08 to 0.54
Non-Hodgkin lymphoma	0.74	0.60 to 0.89	1.97	1.38 to 2.81	1.23	0.82 to 1.64
Leukaemia	0.59	0.50 to 0.70	1.27	0.87 to 1.84	0.68	0.27 to 1.09

Figure 1: **Up-to-date estimates of proportion cured and median survival of fatal cases** (all patients combined)

Males	Females
Mouth, pharynx	
	
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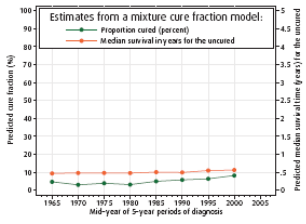	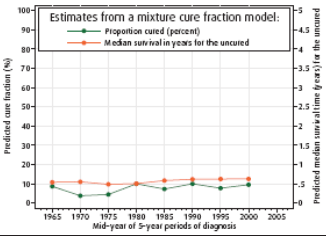
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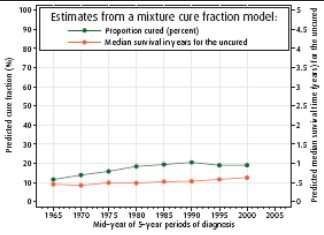	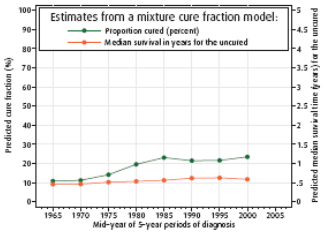
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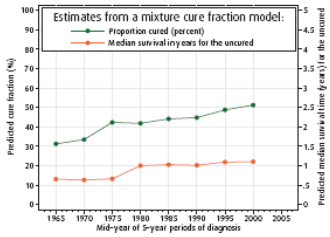
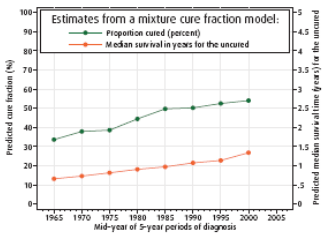
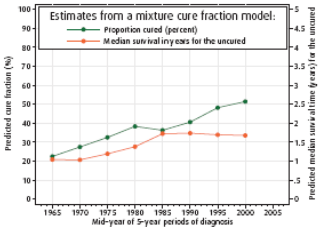
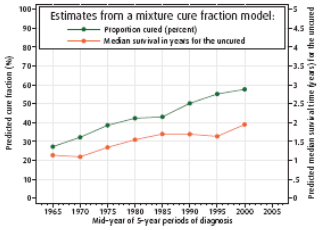
	

Males	Females
Rectum	
	
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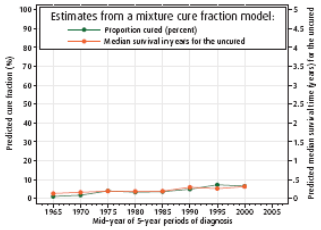	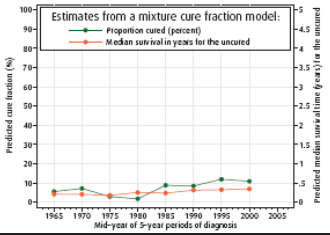
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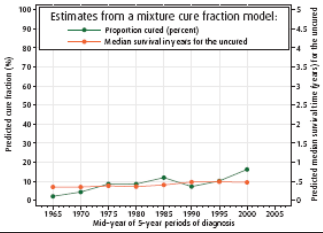	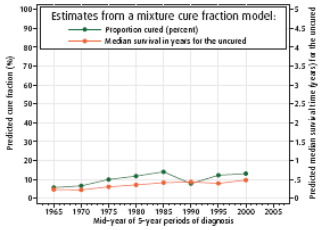
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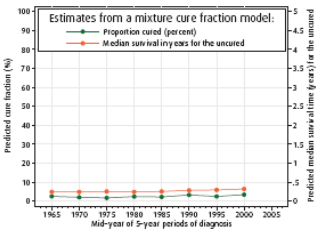	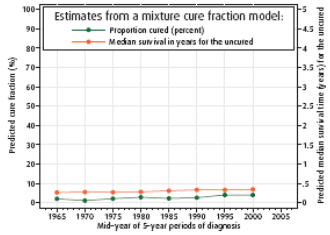

Males	Females
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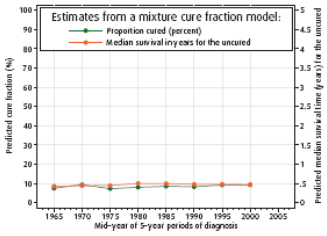	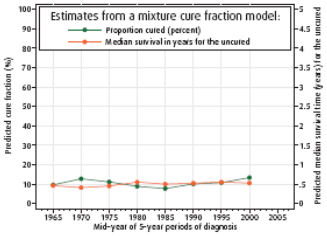
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	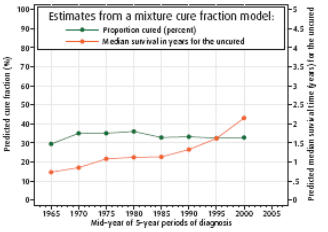
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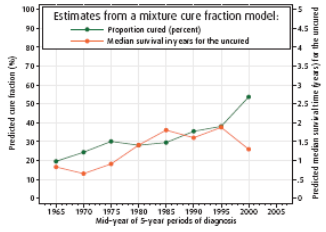	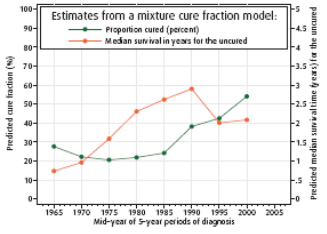
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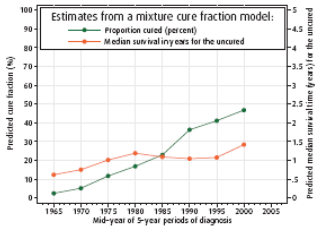
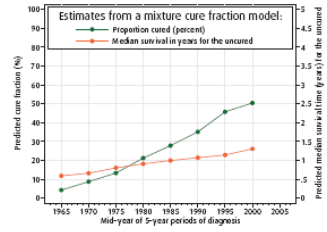
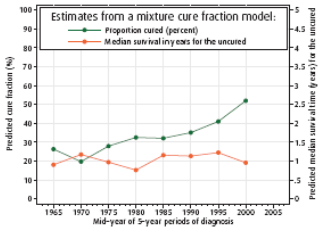
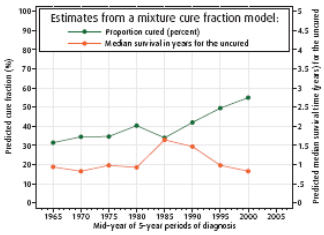
	

Males	Females
Kidney	
	
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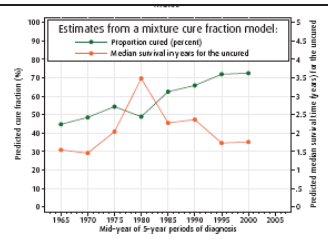	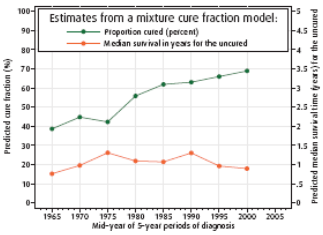
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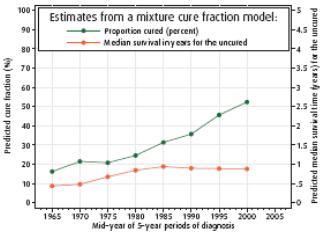
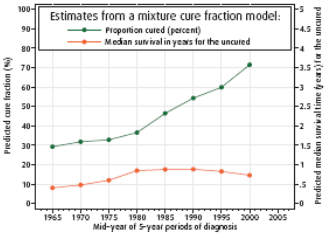
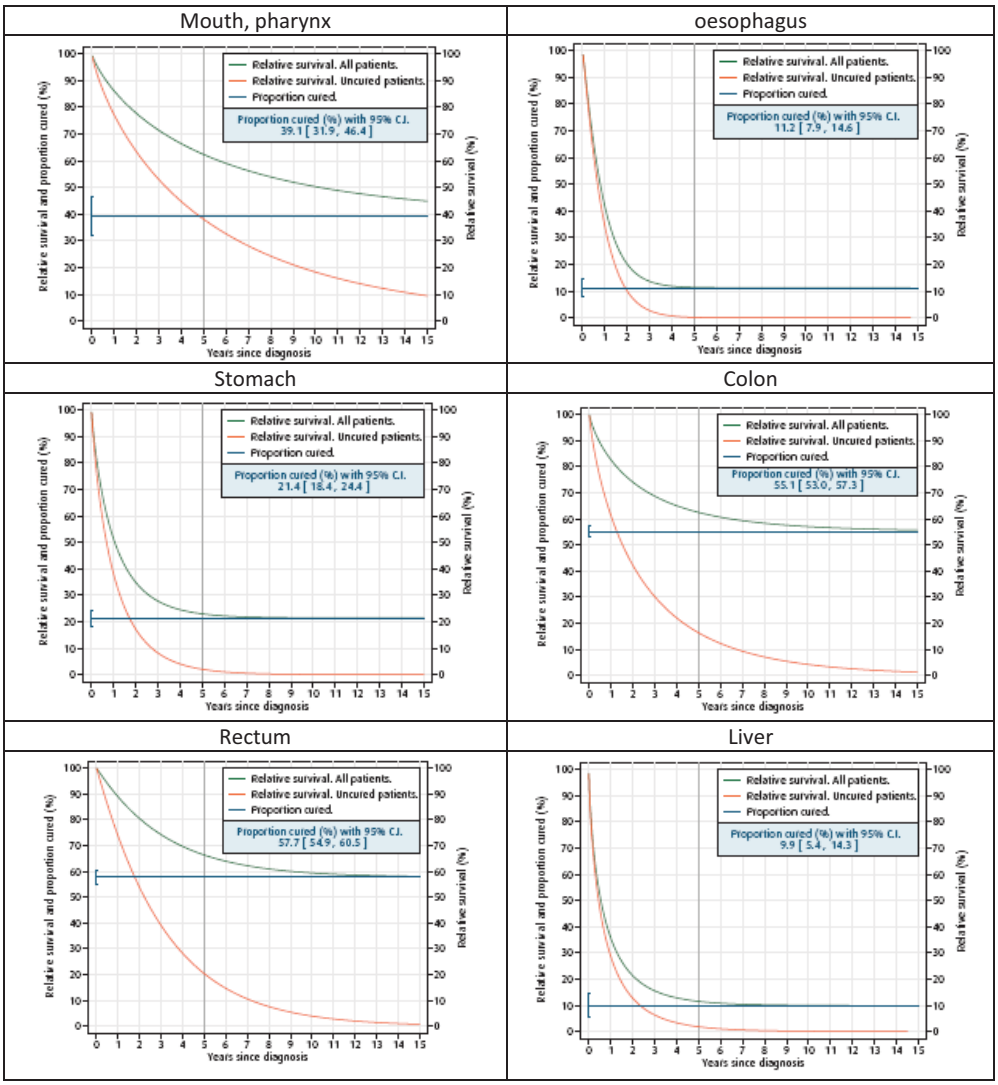
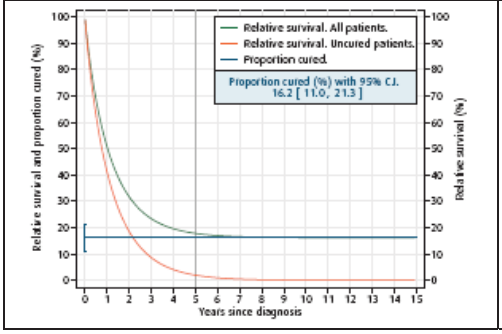
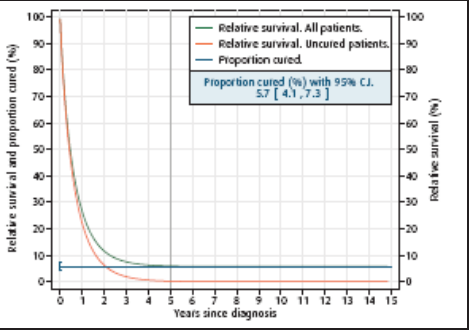
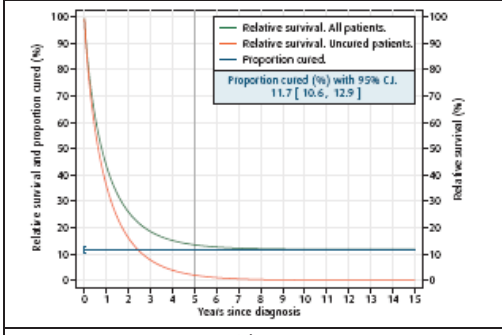
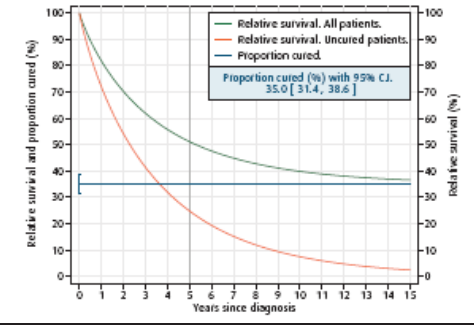
	

Figure 2: **The estimated proportion cured and median survival time for fatal cases for patients diagnosed 1965-2005**



Gallbladder	Pancreas
	

Lung, trachea	Ovary
	
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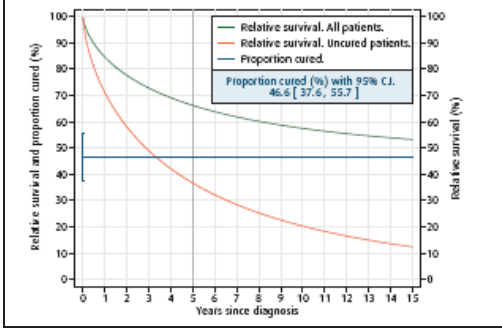	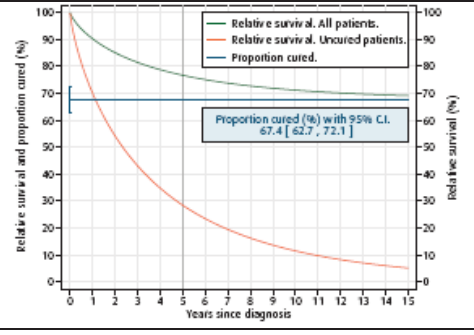

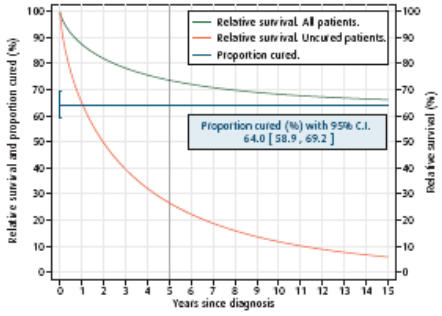

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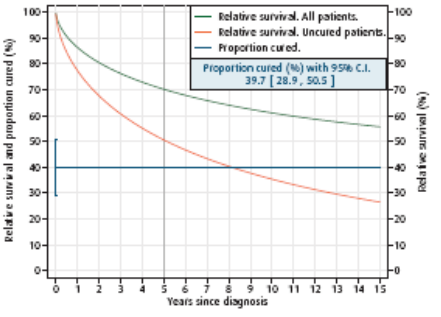

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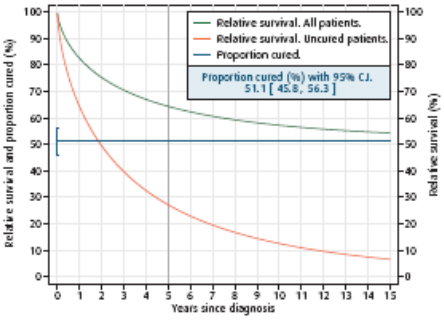

Leukaemia

Paper II

Paper III

Paper IV

REPRODUCTION AFTER ADULT CANCER:

A POPULATION-BASED MATCHED COHORT STUDY

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ABSTRACT

Background: Despite fertility-preserving initiatives, we expect post-cancer reproduction rates to be lower than general population rates.

Methods: Using data from the Cancer Registry and the Medical Birth Registry of Norway, we analyzed post-cancer reproduction rates for the most frequent cancer types in 11,451 male and 16,105 female survivors, compared to five matched controls from the general population. All were born after 1950, diagnosed from 1967-2004 at age 16-45, and with observation time from date of diagnosis (assigned date for controls), until pregnancy, death, age 46, or December 31, 2006. Cox regression models were used to estimate reproduction rates, adjusted for educational level, parity, and diagnostic period.

Results: Overall, cancer survivors had lower reproduction rates than the controls, but higher among males than females (HR=0.74 [95% confidence interval (CI) 0.71–0.78] and HR=0.61 [95% CI 0.58–0.64], respectively). However, malignant melanoma and thyroid cancer survivors did not differ from the controls, whereas the lowest hazard rates for pregnancies after cancer were seen after acute leukemia, cervical, and breast cancer. Increased reproduction rates during the study period were detected for ovarian cancer (HR=0.2 [95% CI 0.1–0.3] to HR=0.7 [95% CI 0.5–0.9]), testicular cancer (HR=0.6 [95% CI 0.4–0.9] to HR=0.8 [95% CI 0.7–0.8]) and Hodgkin lymphoma diagnosed in men (HR=0.7 [95% CI 0.5–0.9] to HR=0.9 [95% CI 0.7–1.0]).

Conclusions: Compared to controls, post-diagnostic reproduction rates were reduced in cancer survivors, but higher in males than females. Fertility-preserving attempts have succeeded in patients with ovarian and testicular cancer and males with Hodgkin lymphoma.

Reproduction after adult cancer: A population-based matched cohort study

With improvement in prognosis and longevity after cancer, fertility and parenthood are important quality-of-life issues for cancer survivors and several fertility-preserving initiatives have been launched (1-4). Examples are introduction of gonadal preserving treatment (5), as for Hodgkin lymphoma (6-9) and testicular and gynecological cancers of low stage (5;10;11). Gonadal shielding during radiotherapy, cryopreservation of embryos and sperm cells has further enabled post-cancer reproduction. However, more intensive chemotherapeutic treatment has been initiated for other malignancies, such as breast cancer and acute leukemia, with possibly negative influences on post-cancer fertility.

Most studies on reproduction after adult onset cancer are monocentric, uncontrolled, or limited to one cancer type (12-17). Surveys have revealed that the majority of young adults are both desiring to have children after cancer, and are concerned about the treatment-related complications (1;9;18-20). Among the few population-based studies that are performed (21;22), a Finnish study reported a 50% lower probability of parenting a first child after cancer for nulliparous individuals compared to sibling controls, but only slightly lower probabilities of parenting a second child (22). A Norwegian study, including childhood and adulthood cancer survivors, found an approximately 25% reduction in first-time birth rates among cancer survivors compared to the general population, without stratification for treatment (21).

In the present nationwide study we explored gender-specific reproduction rates after adult onset cancer for all cancer types combined and separately for the most frequent cancer types. We hypothesized that the probability of post-cancer parenthood, compared to the general population,

would be lower for the cancer patients, but higher in male than in female survivors. We expected to find differences in post-cancer reproduction rates related to prediagnostic parity, initial extent of disease, as well as altered treatment strategies during the last four decades (12).

Methods

Data sources

The Cancer Registry of Norway (CRN) has information on all cancer cases diagnosed in Norway from 1953 onwards, as all doctors are required by law to report these diagnoses. Mandatory reporting ensures a high level of completeness (23). Cancer type, date of diagnosis, extent or stage of disease at diagnosis, and initial treatment in broad terms are recorded. Not included were type of chemotherapy, radiotherapy doses or target field, nor date of recurrence or relapse treatment. Within the CRN, the extent of disease of solid tumors is classified as localized, regional spread, distant spread, or unknown. Tumors of the uterine cervix are staged I-IV, according to FIGO (Fédération Internationale de Gynécologie et d'Obstétrique(24)). Breast tumor stage I-IV refers to localized tumors (I), regional lymph node metastases (II), direct tumor extension to the chest wall or skin (III), or distant metastases (IV), respectively. Brain tumors, meaning all benign and malignant intracerebral tumors, both benign and malignant, and non-solid tumors are not classified by stage or extent (25;26).

The Medical Birth Registry of Norway (MBRN) was established in 1967, and collects data on pregnancies lasting a minimum of 16 weeks (and from 1999 all gestations with a duration of 12 weeks or longer), which are compulsorily reported by all doctors and midwives. The MBRN provides demographic data of the parents, and information on the pregnancy, like date of the last menstruation and gestational duration and whether the pregnancy was initiated by

assisted reproductive technology (ART). Date of birth or pregnancy termination is registered, together with measurements of the newborn like weight, length, and vital status. (27;28). Adoptions are not registered.

Statistics Norway contains individual level information on all citizens, and provided information on educational level at the time of diagnosis, vital status as to December 31, 2006, and the corresponding date for emigration or death (29).

Patient Selection and File Construction

With approval from the National Data Inspectorate and the Regional Committee for Medical Research Ethics, data from the three above sources were linked by means of the personal identification number given to all Norwegian inhabitants since 1964.

From the CRN, all cancer patients registered with their first verified malignancy in the age group 16 to 45 years were selected. To obtain the complete reproductive history in each individual, we restricted our study to cancer patients who were 16 years or younger in 1967, when the MBRN was established. Accordingly, only those diagnosed in the period from 1967 to 2004 were included. . All malignant neoplasms according to the International Classification of Disease version 7 (ICD-7; 140-207) were included, except basal cell carcinomas. In total, 27,556 cancer patients were finally eligible for analyses (Figure 1).

The most common cancer types among young adult females in Norway are malignant melanoma, brain tumors, lymphomas, leukemia, breast, cervical, ovarian, and thyroid cancer (25;26). For young adult males, testicular cancer, malignant melanoma, lymphomas, leukemia and brain tumors, are the most frequent malignancies (25). For the tumor-specific analyses of these cancers, some restrictions were made regarding stage. Only stage I patients were

considered for analyses of cervical and ovarian cancer, since the treatment of stage II-IV patients in general means hysterectomy which results in post-treatment infertility, with exception of germ cell ovarian cancer, for which all locoregional tumors were included. Analyses of ovarian cancer tumors were restricted to invasive only (borderline tumors excluded). Because of prognostic and therapeutic differences, subanalyses of the effect of ovarian cancer were stratified according to epithelial stage I and germ cell or sex-cord tumors.

To circumvent the lack of treatment information at an individual level, reproduction rates were analyzed according to the general treatment guidelines throughout the periods studied. A table covering the main changes during the study period was developed, to allow for a stratification of the different treatment-related periods (Table 1). The impact of different treatment modalities on fertility are published elsewhere (2;4;30).

A comparison group from the general population, for simplicity also called the controls, consisted of five age- and-gender-matched individuals per patient, selected from the Office of the National Registrar. Like for the cancer survivor cohort, information on pregnancy history (for both genders) was provided from the MBRN, and educational status and dates of death or emigration from SSB. All controls had to be alive and living in Norway at the time of diagnosis of the matched patient, and none of the controls had been diagnosed with cancer before the time of being matched. For the comparison group, an assigned "date of diagnosis" was defined using the date of diagnosis for the matched patient. Likewise, the expressions "post-cancer pregnancy" and "post-cancer parenthood" were used both for male and female cancer survivors and controls.

As a measure of the ability to conceive after cancer, the main outcome was the first post-cancer pregnancy, independent of duration and outcome, including registered stillbirths and abortions. We defined pregnancies after cancer as gestations with the last menstruation dating

coincidently with or later than the date of diagnosis, using the date of birth as the event point in time. When the date of last menstruation was missing (N=4,666 (7.1%)), the time span between the date of diagnosis and the date of birth together with the pregnancy duration were used to categorize the pregnancy as initiated before or after the cancer diagnosis. Educational level was included as a proxy of socio-economic status, categorized based on total duration, low (≤9 years), medium (10-14 years), high (≥15 years) or unknown.

Statistical analyses

Data were described with median and range for continuous data and counts and proportions for categorical data. The observation time was defined as the interval from the actual or assigned date of diagnosis to the date of the first post-cancer birth, date of death or emigration, attained age 46 or December 31, 2006, whichever occurred first.

Cox proportional hazards models were fitted to compute post-cancer reproduction hazards rates for the cancer survivors compared to the controls. Proportional hazards assumptions were checked by visual inspection of log-log plots. The models were fitted separately for each gender and for selected diagnoses, and stratified by matched sets (a survivor and his/her corresponding five controls).

The hazard rates (HR) with 95% confidence intervals (95% CI) were adjusted for prediagnostic parity and educational level at diagnosis. In addition, subanalyses were performed for selected diagnoses, stratifying on diagnostic period, (Table 1), extent of disease, and prediagnostic parity.

Cumulative reproduction curves were derived using a competing risk approach. For several of the cancer diagnoses included, the prognosis is quite poor and death as a competing

event was thus incorporated into the analyses. The occurrence of one type of event may influence or fundamentally alter the probability of occurrence of the main event, requiring consideration of the competing events when depicting the cumulative incidences (31). However, when computing the hazard ratios for post-cancer childbirth, it is still possible to fit a proportional hazards model and treat the competing event as censored. Resulting hazard rates convey the information about the mechanisms associated with the specific outcome.

P-values <0.05 were considered statistically significant, and all the tests were two-sided. Descriptive statistics and Cox-analyses were performed using SPSS and competing risk analyses using Stata.

Results

Among the 11,451 male cancer survivors, 23% initiated at least one pregnancy after cancer, compared to 32% among the males in the age-matched comparison group ($p<0.001$, Table 2). For female cancer survivors (N=16,105), 13% achieved a post-cancer pregnancy, in comparison with 22% among the controls ($p<0.001$). Median age at diagnosis for all cancer types combined was 36 years for females and 32 years for males, and median observation time 6.2 and 6.5 years, respectively. When the father was a cancer survivor, 6% of the first post-cancer pregnancies were initiated by ART (male comparison group 2%, $p<0.001$). However, the proportions of female patients and controls using ART were about the same (2%). In total, 7,670 post-cancer pregnancies were registered, resulting in 7,594 liveborn children among the cancer survivors (Table 2).

The largest proportions of individuals with at least one post-cancer pregnancy were found in both genders with thyroid cancer, Hodgkin lymphoma or malignant melanoma, and for the gender-specific malignancies testicular and ovarian germ cell or sex-cord cancer (Table 3).

The hazard rates of post-cancer pregnancies were in general below 1 for the cancer survivors. Exceptions were malignant melanoma and thyroid cancer survivors, whose reproduction rates were similar to those of controls. Male survivors had higher hazard rate ratios for post-cancer parenthood than females (HR=0.74 vs. 0.61). Female survivors of leukemia, breast, or cervical cancer had the lowest probability of a post-cancer pregnancy with HRs lower than 0.4 (Table 3).

Comparing the different treatment periods with each other, the biggest difference were seen for patients with epithelial ovarian cancer stage I, with HR of post-cancer pregnancies increasing from HR=0.06 to HR=0.61 (Table 4). For survivors of ovarian germ cell or sex-cord tumors the hazard rates almost doubled. Also for males with Hodgkin lymphoma and testicular cancer, increasing rates were observed from the first to second period whereas for female Hodgkin lymphoma survivors, the rates did not change.

Figure 2 depicts stratification by extent of disease and number of children prior to diagnosis. For all female survivors, the hazard rate of a post-cancer pregnancy was lower for patients with at least one child at diagnosis compared to those who were childless at diagnosis (HR=0.52 vs. HR= 0.73), whereas no similar difference was observed for overall male cancer patients (HR=0.74 vs. HR=0.75, for prediagnostic parity ≥1 and 0, respectively). Female survivors initiated pregnancies after a diagnosis of metastatic cancer only exceptionally (HR=0.2), whereas men had twice as high probability to parent a child even after advanced disease, regardless pre-diagnostic parity (Figure 2).

Competing risk curves depict the difference in crude cumulative reproduction between cancer patients and their comparison group (Figure 3). Except for males diagnosed with Hodgkin lymphoma the last treatment period, the plot shows continuous subfecundity for the cancer survivors, from the time of diagnosis and the 15 years of observation. Even if some of the curves show a steeper gradient some years after diagnosis, no real catch-up effect was seen, compared to the curves depicting controls.

Discussion

Reproduction rates after cancer for 27,556 patients diagnosed from 1967 to 2004 were for all cancer types combined lower than for the comparison group. The hazard ratios of post-cancer pregnancies were higher among males than among females, male cancer survivors had a 26% reduction and the corresponding figure was 39% among females, with a median observation time of more than 6 years. Exceptions were malignant melanoma and thyroid cancer where both genders experienced similar rates as those of controls. The hazard ratios for pregnancies among cancer survivors have increased during the study period for several malignancies, corresponding to changes in treatment, in particular for females diagnosed with ovarian cancer stage I and for male survivors of Hodgkin lymphoma and testicular cancer.

Among the limitations of our study, is lack of information about partner status at diagnosis, the attempts of achieving parenthood after cancer and whether ART was used due to the patient's or the partner's subfertility. For female cancer survivors without a partner at diagnosis, we know from other studies that they tend to stay single to a larger degree than male survivors (32). Not available in the registry files or only occasionally reported were detailed prognostic markers (like hormonal receptor status for breast cancer) and data on induced

abortions or early miscarriages. We are aware that there is a slight underestimation of parity for men as there are about 2% of children born for whom their fathers are not reported to the MBRN (33). On the other hand, both for the cancer survivors and the general population, there are a small number of males registered with fatherhood after cancer, where the child actually has a different biological father.

As expected, females had lower probabilities than males to initiate a pregnancy after cancer. In general, females with at least one child before cancer had lower reproduction rates than females childless at diagnosis. This difference was not seen among males with similar parity. The distress related to a pregnancy and perhaps the fair of recurrence during eventually offspring's childhood contributes to this observation as female cancer survivors may prevent to conceive if they do not feel well enough. The desire to have a(nother) child might also change during the process of being diagnosed and treated for a malignancy (34). Fertility-preserving treatment for women is currently limited compared to the situation for male patients, since men have been offered semen cryopreservation for more than 30 years (35). No real similar opportunities are offered female patients, even if cryopreservation of embryos has been offered for many years. It might not always be possible since it requires a partner, a hormonal stimulation, and results in a treatment postponement. Cryopreservation of ovarian tissue or oocytes has occasionally helped females to achieve post-cancer parenthood, but is still considered experimental. In vitro fertilization was significantly more frequently used by male compared to female cancer survivors, reflecting the possibility of sperm cryopreservation, even though the proportion of Norwegian cancer survivors using the preserved sperm is modest (9).

Breast cancer survivors had the lowest rates of post-cancer motherhood (Table 3 and 4, (15;16). This might be explained by ovariotoxic treatment with ovarian ablation before 1980

(ovarian irradiation or oophorectomy), gradually substituted with tamoxifen for estrogen receptor positive (ER+) tumors during the 1980s (36;37). Since the 1990s, more intensive chemotherapy, also for lower stages, and prolonged endocrine therapy, has lead to a considerable risk of premature ovarian failure (POF), especially taken the high median age at diagnosis (39 years) into account (38-40)(Table 1). It is believed that modern chemotherapy (FEC) works partly through reversible ovarian ablation in young women with ER+ tumors, but presumably less in younger women (41). It remains to prove if ovarian ablation through long-term antiestrogen therapy (more than 5 years) is prognostic beneficial, and thereby further may challenge the task of fertility-preservation after breast cancer (42). With an increasing maternal age at first pregnancy (26) and a prolonged endocrine treatment, it is likely that the wish to have a child after cancer might partly be the reason for early discontinuation of hormonal therapy in younger women, as recently reported (43). The above explanations for low rates of post-cancer parenthood are in contrast to Madanat et al's interpretation expressing a fear of a hormonally driven risk of recurrence associated with a subsequent pregnancy (22). We have recently published a study demonstrating that women with subsequent pregnancies had no impaired survival, in line with similar studies, presumably caused by a selection mechanism known as "the healthy mother effect"(15;16;26;44).

For low risk ovarian cancer stage I, action was taken during the 1980s to preserve fertility in young females with a wish to conceive (5;45;46). Our data show the success of such attempts. For germ cell ovarian cancer, the treatment has generally been fertility-preserving during the entire study period as ipsilateral oophorectomy has commonly been performed. However, some of these are phenotypic women but with chromosomal abnormalities and inherited infecundity and they will thus not benefit from fertility-preserving treatment (5;46).

No change in reproduction rates over time were seen for cervical cancer patients. Subanalyses thus demonstrated that 159 of 190 females with cervical cancer and subsequent pregnancies were stage IA1, for whom conization has been the standard treatment since the 1970s if no high risk factors were present (Table 1 and S1, the second available online) (5;46).

The prognosis for testicular cancer has improved dramatically during the period studied, which also is reflected in increasing rates of post-cancer parenthood over the study period. The decrease in the reproduction rates for patients diagnosed during the 1980s might be caused by the introduction of retroperitoneal lymph node dissections (RPLND) which at least in the first years, caused nerve damage in 90% and thereby dry ejaculation (47). During the late 1980s the extensive bilateral intervention were replaced by nervesparing RPLND, and surveillance for stage I nonseminoma testicular cancer patients (19). Among testicular patients childless at diagnosis a subgroup of men with inherent fertility problems would probably have lifelong difficulties to initiate a pregnancy, due to subfertility linked to the diagnosis (48;49). However, most testicular cancer survivors have a relatively low incidence of post-treatment azoospermia, and experience recovery of spermatogenesis during a few years (50). An overall 15-year reproduction rate of 71% among former testicular cancer patients attempting to achieve parenthood after cancer was reported from a national survey based study, which is consistent with our findings (19). Further, we saw a weak negative association between stage of disease and post-diagnostic parenthood, also described earlier (48). Overall, prediagnostic parity was not a predictor of subsequent fatherhood after testicular cancer, and this is in contrast to the findings of Cvancarova et al (12).

Malignant melanoma had similar reproduction rates as the control group. A localized malignant melanoma will in most cases only require surgical removal, and presumably does not

interfere with family planning in the way more invasive malignancies might do. However, the counseling of the female patients about future pregnancies might have varied for malignant melanoma in particular and for cancer in general. Doctors have for decades been concerned about an increased risk of cancer recurrence caused by the hormonal changes during pregnancy. In recent years several studies have failed in verifying such a risk (26;51;52). Compared to hospital-based studies, our reproduction rates for malignant melanoma in both gender are much higher, which underscores the selection-problem including less low stage patients materials from oncological units (53;54).

A pregnancy after treatment for thyroid cancer is regarded safe today, and the good prognosis is likely to support a former cancer patient's choice of having a family, expressed by the similar reproduction rates as the controls. Both for males and females receiving radioiodine therapy, a transient period of gonadotoxicity is reported, but with recovery within a year. Women might be at risk for a slightly lower age at menopause at least when treated at age 40 or older (55;56).

We have included brain tumors in our study since the incidence among young adults is quite high, even though the group is very heterogeneous. Disturbances of the hypothalamic-pituitary axis are common sequelae of head tumor treatment, caused by cranial surgery and in particular radiotherapy. Normal reproductive cycles can be recreated with administration of exogenous hormones (57;58). The severe prognosis of glioblastoma and other highly malignant cranial tumors might influence the fecundity itself.

Regarding Hodgkin lymphoma in males, we found an improvement over time, and higher reproductive ability than in females with Hodgkin lymphoma (21). In accordance with our

results, a survey-based study by Kiserud reported that 63% of female and 75% of male Hodgkin lymphoma survivors succeeded among those who attempted post-cancer parenthood (9). Male patients more than females seem to have benefitted from the treatment change to ABVD (Table 1), at least based on our post-treatment reproduction rates. There might, however, be other reasons than POF explaining the gender difference, and based on the data available, we are not able to measure the portion of females experiencing ovarian failure some time after treatment.

Unlike Hodgkin lymphoma patients, those with Non-Hodgkin have not been offered less gonadotoxic treatment in recent years, rather more intensive treatment for some of the subgroups. However, with improved diagnostics and higher cure rates, fertility preservation is crucial. Since Non-Hodgkin's lymphoma survivors make up a heterogeneous group with correspondingly different treatment regimes, the reported estimates vary widely: Pregnancy rates vary from 27 to 64% post-treatment and from 6 to 44% of the female patients may develop POF. Similarly, the estimates of males with impaired spermatogenesis vary from 17 to 100% (59-61). Monocentric or smaller materials might also have an age-distribution which influences the outcomes and make comparisons less appropriate.

Acute leukemia is an example of a malignancy where both the severity of the disease and the treatment heavily influence on post-cancer reproduction, despite the low median age at diagnosis. The alkylating agents used or the high total dose of combined chemotherapeutic agents and eventually craniospinal or total body irradiation represents a serious fertility threat. Pretreatment options to preserve fertility, at least for women, are often limited, since the treatment has to be initiated immediately after diagnosis (62). Ovarian tissue cryopreservation might not be safe for patients with leukemia, since the graft could be contaminated with malignant cells and a possible risk of recurrence exists during transplantation (63). The literature

on post-treatment reproduction in adult leukemia patients is scarce, as most studies focus on fertility and parenthood after childhood acute leukemia. A Japanese survey-based study revealed that only 3.8% of adult long-term survivors of either gender became parents subsequently (64).

This is a large controlled nationwide study including the reproductive history of 27,556 adult cancer patients. We were able to use registry information covering the whole Norwegian population diagnosed with cancer for the relevant age groups (16-45 years) and during a period of almost 40 years. It could have been argued that observation only until age 46 for males was too short, but only 3% (27) of men are fathering children after that age in our cohort. This linkage also allowed us to compare different cancer types with each other. Post-diagnostic parenthood is for several cancer types a quite seldom event, and large numbers of patients are required to compute statistically trustworthy estimates. Comparing our results with other population-based studies, even with some differences in study design, we found in general similar results. However, the most recent therapeutic improvements might not be reflected in studies published some years ago, and treatment-related factors are seldom considered in registry-based cohorts (21;22). Several quite large cohorts have been reported on from hospital-based studies, but these studies might have a selection-problem, which may in part explain why the estimates differ substantially (9;12;13;53).

Compared to controls, post-diagnostic reproduction rates were reduced in cancer survivors, but higher in males than females. Fertility-preserving attempts have succeeded in patients with ovarian and testicular cancer and males with Hodgkin lymphoma. To further improve the young adult cancer patients' chances of subsequent parenthood, multidisciplinary counseling to provide the best options of cancer treatment and future fertility should be offered.

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Figure and tables

Figure 1

Cancer patients eligible for the study

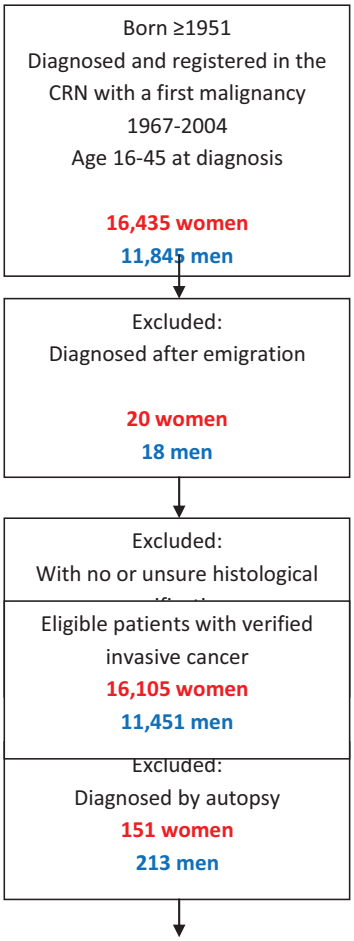
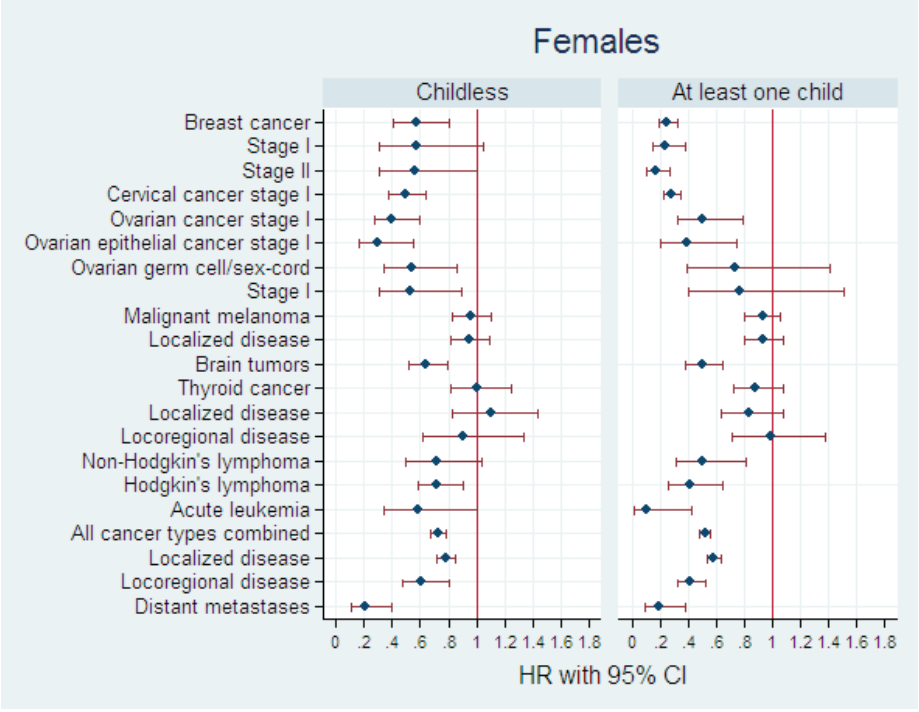


Figure 2
Parity and extent of the disease at diagnosis.

Forest plot depicting hazard rates for post-cancer pregnancies when stratified on prediagnostic parity and stage or extent of disease (when relevant). The analyses are adjusted for age and educational level at diagnosis. Only the stages where at least ten patients were registered with a pregnancy after cancer have been included. For malignant melanoma in males, 11 became fathers post-cancer among those with locoregional disease and childless at diagnosis, HR 1.17 [0.42 to 3.22]. Broad confidence intervals reflect the small number of events in some groups.



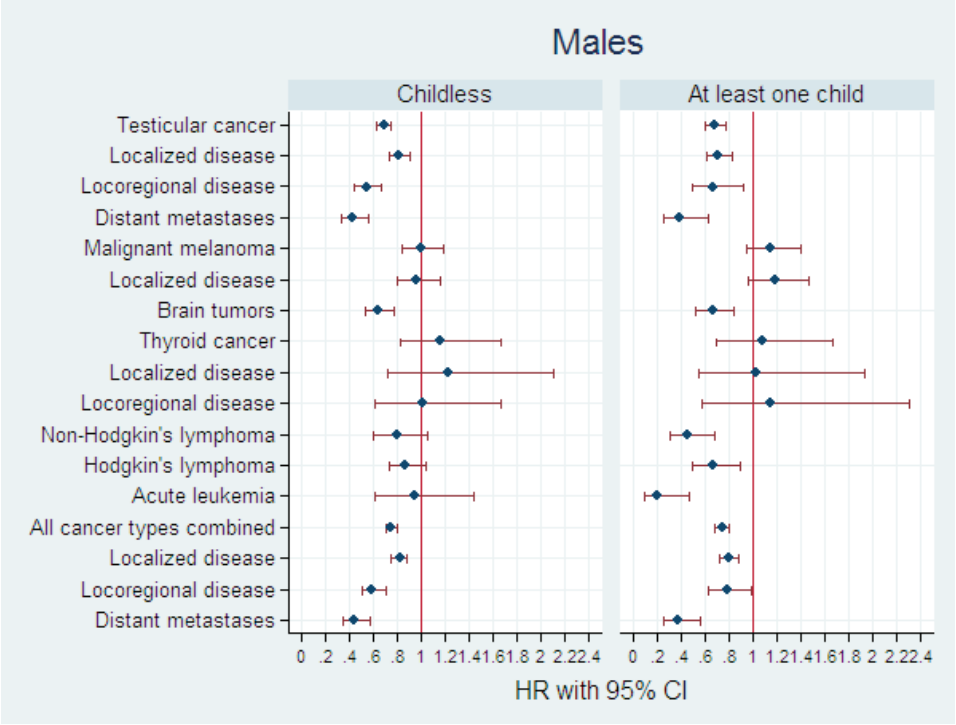

Males
Childless
At least one child
Testicular cancer
Localized disease
Locoregional disease
Distant metastases
Malignant melanoma
Localized disease
Brain tumors
Thyroid cancer
Localized disease
Locoregional disease
Non-Hodgkin's lymphoma
Hodgkin's lymphoma
Acute leukemia
All cancer types combined
Localized disease
Locoregional disease
Distant metastases
0 .2 .4 .6 .8 1 1.21.41.61.8 2 2.22.4
0 .2 .4 .6 .8 1 1.21.41.61.8 2 2.22.4
HR with 95% CI

Figure 3

Competing risk plot. Controls depicted with solid red lines, and patients in dotted blue lines. Confidence intervals (95%) with thin solid lines.

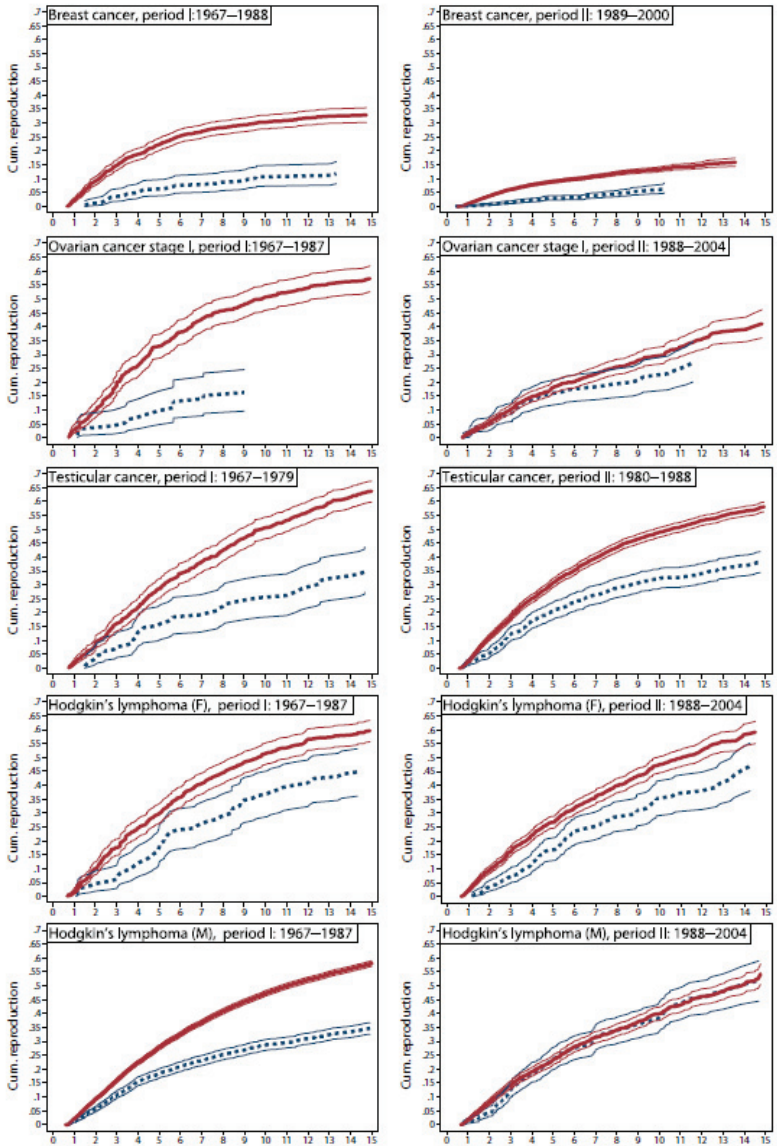


Table 1

Major treatment strategies during the period studied. Only primary treatment for in general non-metastatic disease is given in the table. All years given in the table signaling changing treatment routines are approximately, since there might have been regional differences in implementation. Abbreviations are explained below.

Diagnosis	Time periods	Treatment strategies
Breast cancer	1967-1988	Mastectomy ± RT. Eventually CT, from 1982 adjuvant perioperative CT* (65;66). Anti-hormonal treatment: Ovarian RT or oophorectomy independent of hormonal receptor status to all premenopausal women. From 1982 tamoxifen 2 years if T ≥ 5 cm + ≥4 positive nodules. Oophorectomy/ovarian RT for premenopausal women (35).
	1989-2000	Mastectomy ± RT or lumpectomy + RT. Adjuvant CT: Perioperative CT*. If N+ and <age 50: Prolonged CT 3-6 months† (67). From 1993 nine CMF if N+ disease (68). Anti-hormonal treatment: ER+/ER-unknown: Tamoxifen 2 years if T≥ 5 cm /N+ (67), from 1994 if T≥ 2 cm (69), and from 1999 duration 5 years (70). Eventually LH-RH analog for premenopausal women.
	2001-2004	Mastectomy ± RT or lumpectomy + RT. Adjuvant CT: Six FEC if T ≥ 2 cm + histological grade ≥ II (71). Anti-hormonal treatment: ER+/ER-unknown: Tamoxifen x 5 years if T≥ 2 cm/N+ (71).
Cervical cancer stage I	1967-1987	Hysterectomy + pelvic RT in general. Stage Ia1 (microinvasive): Conization from 1970s (44). Stage Ia2: Individually based conization for selected young women wishing to prevent fertility (44).
	1988-2004	Hysterectomy and pelvic lymphadenectomy ± pelvic RT in general. Stage Ia: Conization or radical trachelectomy (cervical amputation, ad modum Dargent) ± pelvic lymphadenectomy for selected patients (10;11;72;73) Stage Ib1: From 1992 radical trachelectomy + pelvic lymphadenectomy for selected patients with T<2cm
Ovarian cancer stage I		See subgroups below
–epithelial	1967-1987	Stage Ia: Unilateral oophorectomy + chemotherapy (44)
ovarian cancer stage I		Stage Ib: Bilateral oophorectomy + CT ± pelvic irradiation (44)
	1988-2004	Stage Ia: Unilateral oophorectomy and no CT (5).
–germ cell/ sex-cord ovarian cancer	1967-1987	Unilateral oophorectomy for selected patients ± RT of ipsilateral pelvic and periaortic lymph nodes' area (43). If advanced, combination CT (platinum-based), from 1984 BEP (not for stroma-cell-tumors)(43;74)
	1988-2004	Unilateral oophorectomy and pelvic lymph adenectomy (staging) in general. CT (BEPx3) if remaining tumor mass after surgery (5).
Testicular cancer	1967-1979	Orchiectomy. Stage I-II: RT 50 Gy (dog-leg/hockey-stick-field). Stage III-IV: CT with alkylating agents and infradiaphragmatic RT or surgical removal of residual masses (46;75).
	1980-1988	Orchiectomy. Cisplatin-based CT (CVB, later BEP) in case of metastases and diagnostic bilateral RPLND stage I-II, post-CT for stage III-IV, unilateral RPLND from mid 1980s. Infra-diaphragmatic RT (19;45;46;75;76).
	1989-2004	Orchiectomy. Stage I: Surveillance. Stage II-IV: Cisplatin-based CT (mostly BEP). Nervesparing RPLND if metastatic disease. (75;76).
Malignant melanoma	1967-2004	No substantial change in treatment routines during the period. Local disease: Surgery only. For metastatic disease DTIC, from 2000 adjuvant interferon (clinical study).
Brain tumors	1967-2004	No substantial change in treatment routines during the period. Treatment depending on morphologic type, in general surgery, RT (total brain or involved field), eventually surveillance.
Thyroid cancer	1967-2004	No substantial change in treatment routines during the period. Surgery, radioactive iodine (131-I) and eventual supplementation of thyroid hormones afterwards.
Acute leukemia	1971-1982	ALL: COAP Total treatment period about 3.5 years. (77) AML: TRAP/PRAP or other combinations including cytarabine and daunorubicin. (77).
	1983-2004	ALL: Hammersmith. Allogenic hematopoietic cell transplantation more frequent from the 90s for high-risk patients (78).

		AML: Anthracycline- and cytarabine-based induction regimens. Intensive post-remission therapy; bone marrow transplant or high-dose cytarabine. Allogenic bone marrow stem cell transplantation more frequent from the 90s (79).
Hodgkin lymphoma	1967-1979	Stage I-II: RT only (mantle field or inverted Y-field), from 1980 four ChlVPP or ABVD for high-risk patients. RT only for low-risk patients (9;80). Stage III-IV: Eight MVPP/ChlVPP. RT if bulky tumor or residual mass. Total nodal irradiation to some patients with advanced disease (81).
	1980-2004	Stage I-II and high-risk: Two-four EBVP before RT. Low-risk RT only. Stage III-IV: Eight ABVD (or ABOD/ChlVPP) and RT if bulky tumor or residual mass (82)
Non-Hodgkin lymphoma	1967-1974	No systematically guidelines, in most cases some CT (CHOD) and eventually RT.
	1975-2004	CHOP or COP ±RT (± rituximab) ± HMAS depending on the type of NHL (82;83).

Abbreviations:

ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine
ALL: Acute lymphatic leukemia
AML: Acute myelogenous leukemia
BEP: Bleomycin, etopocid, cisplatin
ChlVPP: Chlorambucile, vinblastine, procarbazine, prednisone
CHOD: Cyclophosphamide, doxorubicin, vincristine, dexamethasone
CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone
CMF: Cyclophosphamide, methotrexate, 5-FU
COAP: Cyclophosphamide, vincristine, cytarabine, prednisone
COP: Cyclophosphamide, vincristine, prednisone
CT: Chemotherapy
CVB: Cisplatin, vinblastine, bleomycin
EBVP: Epirubicin, bleomycin, vinblastine, prednisone
FEC: 5-FU, epirubicine, cyclophosphamide
Hammersmith: Cyclophosphamide, doxorubicin, methotrexate, vincristine
MVPP: Mustine, vinblastine, procarbazine, prednisone
POF: Premature ovarian failure (premature menopause)
4 RPLND: Retroperitoneal lymph node dissection
RT: Radiotherapy
TRAP/PRAP: Tioguanin/merkaptopurin, daunorubicin, cytarabine, prednisone
T = tumor

* Perioperative CT: Day 1 cyclophosphamide, 5-FU, vincristine, day 7 cyclophosphamide, methotrexate, vincristine
†Cyclophosphamide, 5-FU, methotrexate

Table 2

Cohort characteristics of all cancer patients and their age- and gender-matched controls

	Male patients	Male controls	Female patients	Female controls
Total number	11,451	57,200	16,105	80,500
Median age at diagnosis *	32 years	32 years	36 years	36 years
Median observation time	6.2 years (0-29.8)	8.2 years (0-29.9)	5.0 years (0-29.8)	6.5 years (0-29.8)
Deceased	2,651 (23%)	530 (0.9%)	3,098 (19%)	266 (0.3%)
Individuals with at least one post cancer pregnancy	2,618 (23%)	18,292 (32%)	2,157 (13%)	17,279 (22%)
Total number of pregnancies after diagnosis	4,273	31,636	3,407	27,019
Total number of liveborn children after diagnosis	4,238 (99.2%)	31,488 (99.5%)	3,356 (98.5%)	26,712 (98.9%)
Use of ART† (total number)	263 (6%)	608 (2%)	81 (2%)	606 (2%)
Educational level, low (≤9 years)‡	3,244 (28%)	15,130(26%)	4,592 (29%)	21,022 (26%)
Educational level, medium (10-14 years)	5,293 (46%)	24,709 (43%)	6,918 (43%)	33,286 (41%)
Educational level, high (≥15 years)	2,553 (22%)	12,026 (21%)	4,134 (26%)	20,839 (26%)

Footnote:

*Range 16-45 years

†ART= assisted reproductive technologies, including in vitro fertilization

‡Educational level unknown not included in the table, 4%, 10%, 2% and 7%, respectively.

Table 3

Characteristics of the study population for each of the most frequent cancer types.
Post-diagnosis parenthood frequencies are displayed in absolute numbers and as a percentage of the total of pregnancy cases. Hazard rates (HRs) in comparison to the control population. Bold=significantly different from the comparison group.

	Total number		Median age (years)*		Median obs. time (years)†		Total no. of patients with post-cancer pregnancies (%)		Deceased, number, (%)		Reproduction after cancer, HR [95% CI]‡	
	M	F	M	F	M	F	M	F	M	F	M	F
Breast cancer		4,061		39		3.6		124 (3)		828 (20)		**0.33 [0.27 to 0.39]**
Cervical cancer stage I		1,970		33		8.2		190 (10)		143 (7)		**0.34 [0.29 to 0.40]**
Ovarian cancer stage I		402		32		8.7		70 (17)		22 (6)		**0.43 [0.33 to 0.56]**
- epithelial stage I		255		34		7.5		28 (11)		17 (7)		**0.32 [0.22 to 0.49]**
- germ cell/ sex-cord §		137		26		11.2		41 (30)		4 (3)		**0.57 [0.40 to 0.81]**
Testicular cancer	3,511		29		9.8		1,081(31)		174 (5)		**0.68 [0.63 to 0.72]**	
Malignant melanoma	1,453	2,495	34	32	6.5	8.2	410 (28)	716 (29)	223 (15)	168 (7)	1.03 [0.92 to 1.16]	0.93 [0.85 to 1.01]
Brain tumors	1,374	1,274	31	32	4.9	5.2	252 (18)	208 (16)	460 (34)	301 (24)	**0.70 [0.61 to 0.81]**	**0.59 [0.51 to 0.69]**
Thyroid cancer	241	947	32	31	10.2	9.2	97 (40)	315 (33)	10 (4)	6 (1)	1.11 [0.86 to 1.44]	0.95 [0.83 to 1.08]
Non-Hodgkin lymphoma	729	468	34	34	5.4	4.4	109 (15)	75 16)	230 (32)	118 (25)	**0.61 [0.49 to 0.76]**	**0.67 [0.51 to 0.88]**
Hodgkin lymphoma	727	507	26	25	10.8	8.9	264 (36)	162 32)	84 (12)	54 (11)	**0.79 [0.69 to 0.92]**	**0.61 [0.51 to 0.73]**
Acute leukemia	362	273	27	28	2.6	1.9	42 (12)	23 (8)	214 (59)	162 (59)	**0.57 [0.40 to 0.80]**	**0.35 [0.22 to 0.56]**
All cancer types combined	11,451	16,105	32	36	6.2	5.0	2,618 (23)	2,164 (13)	2,651 (23)	3,098 (19)	**0.74 [0.71 to 0.78]**	**0.61 [0.58 to 0.64]**

Footnote:

*Median age at diagnosis
†Median observation time: From date of diagnosis until death, emigration, age 46, or date 31 Dec, 2006.
‡HRs adjusted for the number of children prior to diagnosis and educational level at diagnosis.
§Germ cell and sex-cord ovarian tumors; localized and locoregional stages included.

Table 4

Reproduction rates for the most frequent cancer types. Hazard rates for post-cancer parenthood for the most frequent cancer types, separated into different periods to assess the impact of major changes in treatment on reproduction rates. The HRs for the matched comparison group for each cancer type is set to 1.0. Malignant melanomas, thyroid cancers and brain tumors are excluded since no major changes in treatment has occurred during the period studied. (See table 1 for major treatment changes during the period studied). Bold=significantly different from the comparison group.

	Time periods	Male patients, no. (%)*	Male patients, HR [95% CI]	Female patients, no. (%)*	Female patients, HR [95% CI]
Breast cancer	1967-1988			268 (12)	**0.35 [0.24 to 0.51]**
	1989-2000			2,563 (3)	**0.35 [0.27 to 0.44]**
	2001-2004			1,230 (1)	**0.22 [0.13 to 0.38]**
Cervical cancer stage I	1967-1987			364 (15)	**0.31 [0.23 to 0.42]**
	1988-2004			1,606 (8)	**0.35 [0.29 to 0.42]**
Ovarian cancer stage I	1967-1987			92 (16)	**0.19 [0.11 to 0.32]**
	1988-2004			310 (18)	**0.67 [0.49 to 0.90]**
- epithelial stage I	1967-1987			54 (6)	**0.06 [0.02 to 0.19]**
	1988-2004			201 (12)	**0.61 [0.39 to 0.95]**
- germ cell/ sex-cord	1967-1987			37 (32)	**0.38 [0.20 to 0.71]**
	1988-2004			100 (29)	0.74 [0.48 to 1.13]
Testicular cancer	1967-1979	131 (38)	**0.61 [0.43 to 0.86]**		
	1980-1988	662 (41)	**0.51 [0.45 to 0.59]**		
	1989-2004	2,718 (28)	**0.76 [0.70 to 0.83]**		
Non-Hodgkin lymphoma	1967-1974	8 (50)	0.85 [0.09 to 8.12]	6 (33)	0.41 [0.07 to 2.55]
	1975-2004	721 (15)	**0.60 [0.48 to 0.75]**	462 (16)	**0.67 [0.51 to 0.87]**
Hodgkin lymphoma	1967-1987	204 (47)	**0.68 [0.53 to 0.87]**	131 (45)	**0.68 [0.50 to 0.92]**
	1988-2004	523 (32)	0.87 [0.73 to 1.04]	376 (27)	**0.57 [0.46 to 0.71]**
Acute leukemia	1967-1982	65 (8)	0.84 [0.27 to 2.68]	43 (9)	**0.24 [0.08 to 0.74]**
	1983-2004	297 (13)	**0.55 [0.38 to 0.80]**	230 (8)	**0.37 [0.23 to 0.62]**

Footnote:

*Total number diagnosed in each period and percentage of individuals with at least one post-cancer pregnancy.