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Pregnancy after adolescent and adult cancer: a population-based matched cohort study

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Despite fertility-preserving initiatives, postcancer reproduction is expected to be lower than that of the general population. Using data from the Cancer Registry and the Medical Birth Registry of Norway, postcancer pregnancy rates were analyzed in 27,556 survivors and compared to those from a matched comparison group ("controls") from the general population. All were born after 1950, diagnosed from 1967 to 2004 at age of 16–45, and had an observation time from the date of diagnosis (assigned date for controls), until pregnancy, death, age 46, or December 31, 2006. Cox regression was used to estimate pregnancy rates, after adjusting for educational level, parity and diagnostic period. Overall, cancer survivors had a lower pregnancy rate than the controls, but the rate for survivors was higher in males than in females [hazard rate (HR) = 0.74 (95% confidence interval (CI) 0.71–0.78) and HR = 0.61 (95% CI 0.58–0.64), respectively]. However, the rates did not differ between controls and survivors of malignant melanoma or thyroid cancer. By contrast, the lowest HRs for pregnancy occurred in survivors of leukemia, cervical or breast cancer. Increased pregnancy 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)]. In summary, fertility-preserving attempts have succeeded in patients with ovarian or testicular cancer and in males with Hodgkin lymphoma. Male survivors initiated pregnancies in a higher degree than female survivors.

With improvements 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.[1,2] Examples include introduction of gonadal-preserving treatment, such as those used in the treatment of Hodgkin lymphoma[3,4] and testicular and gynecological cancers of low stage.[5–7] Gonadal shielding during radiotherapy and cryopreservation of embryos and sperm cells have further improved postcancer reproduction. However, more intensive chemotherapeutic treatment has been introduced for other malignancies such as breast cancer and acute leukemia, with possibly negative effects on postcancer fertility. Parental age at first birth has increased in most populations, a trend that may also influence fertility after cancer and the total number of children among cancer survivors.

Most studies on reproduction after cancer diagnosed in adolescence or adulthood are monocentric, uncontrolled, or limited to one cancer type.[8–11] Surveys show that most young adults wish to have children after cancer and are concerned about the treatment-related complications.[4,12,13] Among the few published population-based studies, 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 probability of parenting a second child.[14] A Norwegian study of childhood and adulthood cancer survivors found a 25% reduction in first-time birth rates among cancer survivors compared to the general population, but the data were not stratified according to treatment.[15]

The aim of the present nationwide study was to investigate sex-specific pregnancy rates after cancer diagnosed in adolescence or adulthood for all cancer types combined and separately for the most frequent cancer types. We hypothesized that the probability of a postcancer pregnancy would be lower in cancer survivors than in the general population but would be higher in male than in female survivors. We expected that the differences in postcancer pregnancy rates would be related

Key words: fertility, parenthood, pregnancy, cancer survivor, population-based

Abbreviations: ART: assisted reproductive technology; CI: confidence interval; CRN: Cancer Registry of Norway; ER+: estrogen receptor positive; HR: hazard rate; ICD: International Classification of Disease; MBRN: Medical Birth Registry of Norway; Premature ovarian failure (premature menopause) (POF): premature ovarian failure; Retroperitoneal lymph node dissection (RPLND): retroperitoneal lymph node dissection

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to prediagnostic parity, initial extent of disease and altered treatment strategies during the past four decades.[8]

Material and Methods

Data sources

The Cancer Registry of Norway (CRN) collects information on all cancer cases diagnosed in Norway since 1953 because all doctors are required by law to report these diagnoses. Mandatory reporting ensures a high level of completeness.[16] Cancer type, date of diagnosis, extent or stage of disease at diagnosis and initial treatment in broad terms are recorded. Not included are the type of chemotherapy, radiotherapy doses or target field and 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 the Fédération Internationale de Gynécologie et d'Obstétrique. Breast tumor stages are classified as localized tumors (I), regional lymph node metastases (II), direct tumor extension to the chest wall or skin (III) or distant metastases (IV). Brain tumors include all benign and malignant intracerebral tumors, but nonsolid tumors are not classified by stage or extent.[17,18]

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; these are reported compulsorily by all doctors and midwives. The MBRN provides demographic data about the parents and information about the pregnancy such as the date of the last menstruation, gestational duration and whether the pregnancy was initiated by assisted reproductive technology (ART). The date of birth or pregnancy termination is registered together with measurements of the newborn such as weight, length and vital status.[19] Adoptions are not registered.

Statistics Norway compiles individual-level information on all citizens and provided information such as the educational level at the time of diagnosis, date of emigration and vital status as of December 31, 2006.[20]

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-mentioned sources were linked using 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 16–45 years were selected, giving a total of 16,435 women and 11,845 men. After excluding those diagnosed by autopsy, with no histological verification, or who emigrated before diagnosis, the records of 27,556 cancer patients were eligible for analysis. To obtain the complete reproductive history for each person, 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 of 1967–2004 were included. All malignant neoplasms according to the International Classification of Disease version 7 (ICD-7; 140–207) were included, except for basal cell carcinomas.

The most common cancer types among young adult females in Norway are malignant melanoma, brain tumor, lymphoma, leukemia, and breast, cervical, ovarian and thyroid cancer.[17,18] For young adult males, the most frequent malignancies are testicular cancer, malignant melanoma, lymphoma, leukemia and brain tumor.[17] For the tumor-specific analysis of these cancers, we imposed some restrictions on stage. Only stage I patients were considered for analysis of cervical and ovarian cancer because the treatment of stage II–IV patients usually involves hysterectomy, which results in posttreatment infertility. The exception was for patients with germ cell ovarian cancer, for whom all locoregional tumors were included. Analysis of ovarian cancer tumors was restricted to invasive tumors, and borderline tumors were excluded. Because of prognostic and therapeutic differences, subanalysis of the effect of ovarian cancer was stratified according to epithelial stage I and germ cell or sex-cord tumors.

To circumvent the lack of treatment information at an individual level, pregnancy 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 stratification of the different treatment-related periods (Table 1). The impacts of different treatment modalities on fertility are published elsewhere.[1,2]

A comparison group from the general population, for simplicity called the "controls," comprised five age- and sex-matched individuals per patient who were selected from the data compiled by Office of the National Registrar. As for the cancer–survivor cohort, information on pregnancy history (for both sexes) was obtained from the MBRN, and educational status and date of death or emigration were provided by Statistics Norway. All controls had to be alive and living in Norway at the time of diagnosis of the matched patient; none of the controls had been diagnosed with cancer before age of 46 years. For the controls, an assigned "date of diagnosis" was defined using the date of diagnosis for the matched patient. Similarly, the expression "postcancer pregnancy" was 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 postcancer pregnancy. All registered gestations were included, regardless of duration and outcome; including stillbirths and abortions. We defined pregnancy after cancer as a gestation with the last menstruation dating coincident with or later than the date of diagnosis. When the date of last menstruation was missing [N = 4,666 (7.1%)], the pregnancy duration was used to categorize the pregnancy as initiated before or after the cancer diagnosis. Educational level was included as a proxy of socioeconomic status and was categorized according to the total duration of education as low ($\leq$9 years), medium (10–14 years), high ($\geq$15 years) or unknown.

Table 1. Major treatment strategies during the study period

Diagnosis	Time periods	Treatment strategies
Breast cancer	1967–1988	Mastectomy ± RT. Eventually CT, from 1982 adjuvant perioperative CT (Ref. 21).[1,2]
		Antihormonal treatment: ovarian RT or oophorectomy independent of hormonal receptor status to all premenopausal women.
		From 1982, tamoxifen 2 years if $T \geq 5$ cm + ≥4 positive nodules. Oophorectomy/ovarian RT for premenopausal women (Ref. 22).
	1989–2000	Mastectomy ± RT or lumpectomy + RT.
		Adjuvant CT: perioperative CT.[1] If $N+$ and <age 50: prolonged CT 3–6 months.[2] From 1993 nine CMF if $N+$ disease.[3]
		Antihormonal treatment: ER+/ER-unknown: tamoxifen 2 years if $T \geq 5$ cm /$N+$, from 1994 if $T \geq 2$ cm, and from 1999 duration 5 years. Eventually LH–RH analog for premenopausal women.[2]
	2001–2004	Mastectomy ± RT or lumpectomy + RT.
		Adjuvant CT: six FEC if $T \geq 2$ cm + histological grade ≥ II.[2]
		Antihormonal treatment: ER+/ER-unknown: tamoxifen × 5 years if $T \geq 2$ cm/N+.[2]
Cervical cancer stage I	1967–1987	Hysterectomy + pelvic RT in general.
		Stage Ia1 (microinvasive): conization from 1970s (Ref. 23).
		Stage Ia2: individually based conization for selected young women wishing to prevent fertility (Ref. 23).
	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 (Ref. 7).
		Stage Ib1: From 1992 radical trachelectomy + pelvic lymphadenectomy for selected patients with $T < 2$ cm.
Ovarian cancer (see subgroups below)		
Epithelial ovarian cancer stage I	1967–1987	Stage Ia: unilateral oophorectomy + chemotherapy (Ref. 23).
		Stage Ib: bilateral oophorectomy + CT ± pelvic irradiation (Ref. 23).
	1988–2004	Stage Ia: unilateral oophorectomy and no CT (Ref. 6).
Germ cell/sex-cord ovarian cancer	1967–1987	Unilateral oophorectomy for selected patients ± RT of ipsilateral pelvic and periaortic lymph nodes' area (Ref. 24).
		If advanced, combination CT (platinum-based), from 1984 BEP (not for stroma-cell tumors) (Ref. 24).
	1988–2004	Unilateral oophorectomy and pelvic lymph adenectomy (staging) in general. CT (BEP × 3) if remaining tumor mass after surgery (Ref. 6).
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 (Refs. 25,26).
	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. Infradiaphragmatic RT (Refs. 13,25–27).
	1989–2004	Orchiectomy. Stage I: surveillance. Stage II–IV: cisplatin-based CT (mostly BEP). Nervesparing RPLND if metastatic disease (Refs. 26,27).
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 afterward.

Table 1. Major treatment strategies during the study period (Continued)

Diagnosis	Time periods	Treatment strategies
Acute leukemia	1971–1982	ALL: COAP. Total treatment period about 3.5 years (Ref. 28).
		AML: TRAP/PRAP or other combinations including cytarabine and daunorubicin (Ref. 28).
	1983–2004	ALL: Hammersmith. Allogenic hematopoietic cell transplantation more frequent from the 90s for high-risk patients.[2]
		AML: Anthracycline- and cytarabine-based induction regimens. Intensive postremission therapy; bone marrow transplant or high-dose cytarabine. Allogenic bone marrow stem cell transplantation more frequent from the 90s.[2]
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 (Ref. 4).
		Stage III–IV: Eight MVPP/ChlVPP. RT if bulky tumor or residual mass. Total nodal irradiation to some patients with advanced disease (Ref. 4).
	1980–2004	Stage I–II and high-risk: Two-four EBVP before RT. Low-risk RT only (Ref. 4).
		Stage III–IV: Eight ABVD (or ABOD/ChlVPP) and RT if bulky tumor or residual mass (Refs. 4,29).
Non-Hodgkin lymphoma	1967–1974	No systematic guidelines, in most cases some CT (CHOD) and eventually RT.
	1975–2004	CHOP or COP ± RT (± rituximab) ± HMAS depending on the type of NHL (Ref. 29).

Only primary treatment for in general nonmetastatic disease is given in the table. All years given in the table signaling changing treatment routines are approximate, as there might have been regional differences in implementation.
[1]Perioperative CT: Day 1 cyclophosphamide, 5-FU, vincristine, day 7 cyclophosphamide, methotrexate, vincristine.
[2]Based on national programmes of action for the respective periods.
[3]Cyclophosphamide, 5-FU, methotrexate.
Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; ALL: acute lymphatic leukemia; AML: acute myelogenous leukemia; BEP: bleomycin, etopocid, cisplatin; ChlVPP: chlorambucil, 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, epirubicin, cyclophosphamide; Hammersmith: cyclophosphamide, doxorubicin, methotrexate, vincristine; MVPP: mustine, vinblastine, procarbazine, prednisone; POF: premature ovarian failure (premature menopause); RPLND: retroperitoneal lymph node dissection; RT: radiotherapy; TRAP/PRAP: thioguanine/mercaptopurine, daunorubicin, cytarabine, prednisone; and T = tumor.

Statistical analysis

The data are described as 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 postcancer birth, death or emigration, or when the person attained age of 46 years or December 31, 2006, whichever occurred first.

Cox proportional hazards models were fitted to compute postcancer pregnancy hazard rates (HRs) for the cancer survivors compared to the controls. Assumptions of proportional hazards were checked by visual inspection of log–log plots. The models were fitted separately for each sex and for selected diagnoses and were stratified by matched sets (a survivor and his/her five corresponding controls).

The HRs and 95% confidence intervals (95% CIs) were adjusted for prediagnostic parity and educational level at diagnosis. Subanalysis was also performed for selected diagnoses after stratifying by 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 analysis. 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 incidence.[30] However, when computing the HRs for postcancer childbirth, it remains possible to fit a proportional hazards model and to treat the competing event as censored. The resulting HRs conveys information about the mechanisms associated with the specific outcome.

p values <0.05 were considered significant, and all tests were two sided. Descriptive statistics and Cox analyses were performed using the SPSS 18.0 software (SPSS, Chicago, IL), and competing-risk analysis was performed using the statistical package Stata 11.1 (StataCorp LP, College Station, TX).

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 postcancer pregnancy compared to 22% among the controls ($p < 0.001$). The median ages at diagnosis for all cancer types combined were 36 years for females and 32 years for males, and the median observation times were 6.2 and 6.5 years, respectively. When the father was a cancer survivor, 6% of the first postcancer pregnancies were initiated by

Table 2. Cohort characteristics of all cancer patients and their age- and sex-matched controls

	Male patients	Male controls	Female patients	Female controls
Total number	11,451	57,200	16,105	80,500
Median age at diagnosis[1] (years)	32	32	36	36
Median observation time (years)	6.2 (0–29.8)	8.2 (0–29.9)	5.0 (0–29.8)	6.5 (0–29.8)
Deceased	2,651 (23%)	530 (0.9%)	3,098 (19%)	266 (0.3%)
Individuals with at least one postcancer 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 live-born children after diagnosis	4,238 (99.2%)	31,488 (99.5%)	3,356 (98.5%)	26,712 (98.9%)
Use of ART[2] (total number)	263 (6%)	608 (2%)	81 (2%)	606 (2%)
Abortions registered (ratio of liveborn children)[3]			5 (0.0015)	48 (0.0018)
Educational level, low ($\leq$9 years)[4]	3,244 (28%)	15,130 (26%)	4,592 (29%)	21,022 (26%)
Educational level, medium (10–14 years)	5,293 (46%)	24,709 (43%)	6,918 (43%)	33,286 (41%)
Educational level, high ($\geq$15 years)	2,553 (22%)	12,026 (21%)	4,134 (26%)	20,839 (26%)

[1]Range 16–45 years.
[2]ART = assisted reproductive technologies, including *in vitro* fertilization.
[3]Induced abortions are registered since 1999 by MBRN, after a gestational length of at least 12 weeks. No numbers are reported for the male population in our cohort.
[4]Educational level unknown not included in the table, 4%, 10%, 2% and 7%, respectively.

ART (male controls 2%, $p < 0.001$). However, the percentages of female patients and controls using ART were about the same (2%). In total, 7,680 postcancer pregnancies were registered, resulting in 7,594 live-born children among the cancer survivors (Table 2).

The largest percentages of individuals with at least one postcancer pregnancy occurred in male and female survivors of thyroid cancer, Hodgkin lymphoma, or malignant melanoma or in survivors of the sex-specific malignancies testicular and ovarian germ cell or sex-cord cancer (Table 3).

The HRs of postcancer pregnancy were predominantly <1 for the cancer survivors. Male survivors had higher HRs for a postcancer pregnancy than did females (HR = 0.74 *vs.* 0.61). Similar results were found in the youngest subgroup of the study population (aged 16–25 years at diagnosis); the HRs were 0.70 (95% CI 0.65–0.75) for males and 0.67 for females (95% CI 0.63–0.73) (data not shown). Malignant melanoma and thyroid cancer survivors were exceptions and their pregnancy rates were similar to those of controls. Female survivors of leukemia or breast or cervical cancer had the lowest probability of a postcancer pregnancy, with HRs <0.4 (Table 3).

We analyzed the data according to different treatment periods. The largest differences were for patients with epithelial ovarian cancer stage I, whose HR of postcancer pregnancy increased from 0.06 to 0.61 (Table 4). For survivors of ovarian germ cell or sex-cord tumors, the HRs almost doubled. For male survivors of Hodgkin lymphoma or testicular cancer, the HRs increased from the first to second period, whereas the HRs did not change for female Hodgkin lymphoma survivors.

Figure 1 depicts the stratification by extent of disease and number of children before the diagnosis. For all female survivors, the HR of a postcancer pregnancy was lower for survivors with at least one child at diagnosis compared to those who were childless at diagnosis (HR = 0.52 *vs.* 0.73); no similar difference was observed in male cancer survivors (HR = 0.74 *vs.* 0.75, for prediagnostic parity $\geq$1 and 0, respectively). Female survivors initiated pregnancy after a diagnosis of metastatic cancer rarely compared to the controls (HR = 0.2); by contrast, the probability of initiating pregnancy was twice as high in male survivors after advanced disease regardless of prediagnostic parity (Fig. 1).

Competing-risk curves depict the difference in crude cumulative reproduction rates between cancer survivors and their controls (Fig. 2). Except for males diagnosed with Hodgkin lymphoma in the last treatment period, the plot shows continuous subfecundity for the cancer survivors, from the time of diagnosis and during the 15 years of observation. Even though some of the curves show a steeper gradient some years after diagnosis, no real catch-up effect was seen when compared to the curves depicting the controls.

Discussion

In the 27,556 patients diagnosed from 1967 to 2004, the pregnancy rates after all types of cancer combined were lower than those in the comparison group. The HRs of postcancer pregnancies were higher in males than in females. Compared to the controls, male cancer survivors had a 26% lower rate and female survivors had a 39% lower rate during a median observation time of >6 years. Exceptions were malignant melanoma and thyroid cancer, where male and female survivors had rates similar to those of the controls. The HRs for pregnancies among cancer survivors increased during the study period for several types of malignancies, and these changes corresponded to changes in treatment, in particular for women diagnosed with ovarian cancer stage I and for male survivors of Hodgkin lymphoma and testicular cancer.

Table 3. Characteristics of the study population for each of the most frequent cancer types

	Total number		Median age (years)[1]		Median observation time (years)[2]		Total number of patients with postcancer pregnancy (%)		Deceased, number (%)		Pregnancy after cancer, HR (95% CI)[3]	
	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 [0.27–0.39]
Cervical cancer stage I		1,970		33		8.2		190 (10)		143 (7)		0.34 [0.29–0.40]
Ovarian cancer stage I		402		32		8.7		70 (17)		22 (6)		0.43 [0.33–0.56]
Epithelial stage I		255		34		7.5		28 (11)		17 (7)		0.32 [0.22–0.49]
Germ cell/sex-cord[4]		137		26		11.2		41 (30)		4 (3)		0.57 [0.40–0.81]
Testicular cancer	3,511		29		9.8		1,081 (31)		174 (5)		0.68 [0.63–0.72]	
Malignant melanoma	1,453	2,495	34	32	6.5	8.2	410 (28)	716 (29)	223 (15)	168 (7)	1.03 [0.92–1.16]	0.93 [0.85–1.01]
Brain tumors	1,374	1,274	31	32	4.9	5.2	252 (18)	208 (16)	460 (34)	301 (24)	0.70 [0.61–0.81]	0.59 [0.51–0.69]
Thyroid cancer	241	947	32	31	10.2	9.2	97 (40)	315 (33)	10 (4)	6 (1)	1.11 [0.86–1.44]	0.95 [0.83–1.08]
Non-Hodgkin lymphoma	729	468	34	34	5.4	4.4	109 (15)	75 (16)	230 (32)	118 (25)	0.61 [0.49–0.76]	0.67 [0.51–0.88]
Hodgkin lymphoma	727	507	26	25	10.8	8.9	264 (36)	162 (32)	84 (12)	54 (11)	0.79 [0.69–0.92]	0.61 [0.51–0.73]
Acute leukemia	362	273	27	28	2.6	1.9	42 (12)	23 (8)	214 (59)	162 (59)	0.57 [0.40–0.80]	0.35 [0.22–0.56]
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 [0.71–0.78]	0.61 [0.58–0.64]

Postcancer pregnancies are displayed in absolute numbers and as a percentage of the total of pregnancy cases. Hazard rates (HRs) in comparison to the control population.
[1]Median age at diagnosis.
[2]Median observation time: From date of diagnosis until death, emigration, age 46, or date December 31, 2006.
[3]HRs adjusted for the number of children prior to diagnosis, diagnostic period and educational level at diagnosis.
[4]Germ cell and sex-cord ovarian tumors; localized and locoregional stages all included.

Table 4. Pregnancy rates for the most frequent cancer types

	Time periods	Male patients, number (%)[1]	Male patients, HR [95% CI]	Female patients, number (%)[1]	Female patients, HR [95% CI]
Breast cancer	1967–1988			268 (12)	0.35 [0.24–0.51]
	1989–2000			2,563 (3)	0.35 [0.27–0.44]
	2001–2004			1,230 (1)	0.22 [0.13–0.38]
Cervical cancer stage I	1967–1987			364 (15)	0.31 [0.23–0.42]
	1988–2004			1,606 (8)	0.35 [0.29–0.42]
Ovarian cancer stage I	1967–1987			92 (16)	0.19 [0.11–0.32]
	1988–2004			310 (18)	0.67 [0.49–0.90]
Epithelial stage I	1967–1987			54 (6)	0.06 [0.02–0.19]
	1988–2004			201 (12)	0.61 [0.39–0.95]
Germ cell/sex cord	1967–1987			37 (32)	0.38 [0.20–0.71]
	1988–2004			100 (29)	0.74 [0.48–1.13]
Testicular cancer	1967–1979	131 (38)	0.61 [0.43–0.86]		
	1980–1988	662 (41)	0.51 [0.45–0.59]		
	1989–2004	2,718 (28)	0.76 [0.70–0.83]		
Non-Hodgkin lymphoma	1967–1974	8 (50)	0.85 [0.09–8.12]	6 (33)	0.41 [0.07–2.55]
	1975–2004	721 (15)	0.60 [0.48–0.75]	462 (16)	0.67 [0.51–0.87]
Hodgkin lymphoma	1967–1987	204 (47)	0.68 [0.53–0.87]	131 (45)	0.68 [0.50–0.92]
	1988–2004	523 (32)	0.87 [0.73–1.04]	376 (27)	0.57 [0.46–0.71]
Acute leukemia	1967–1982	65 (8)	0.84 [0.27–2.68]	43 (9)	0.24 [0.08–0.74]
	1983–2004	297 (13)	0.55 [0.38–0.80]	230 (8)	0.37 [0.23–0.62]

Hazard rates for postcancer pregnancies for the most frequent cancer types, separated into different periods to assess the impact of major changes in treatment on pregnancy rates. The HR for the matched comparison group for each cancer type is set to 1.0. Malignant melanomas, thyroid cancers and brain tumors are excluded as no major changes in treatment has occurred during the study period. (See Table 1 for major treatment changes during the period studied).
[1]Total number diagnosed in each period and percentage of individuals with at least one postcancer pregnancy.

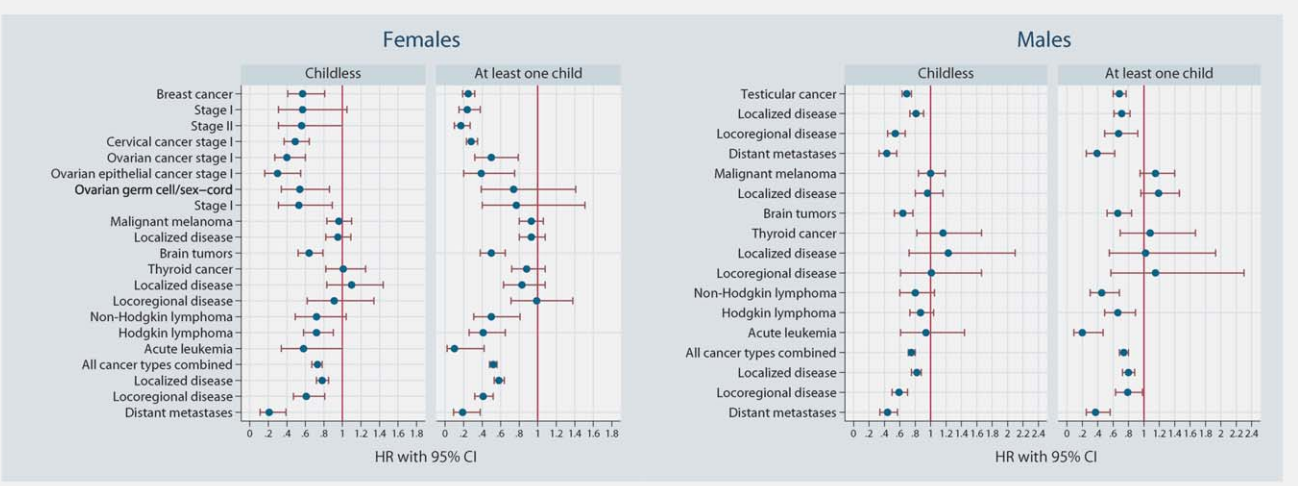

Figure 1. Parity and extent of the disease at diagnosis. Forest plot depicting hazard rates for postcancer pregnancies when stratified on prediagnostic parity and stage or extent of disease (when relevant). The analyses are adjusted for age and educational level at diagnosis. Only the stages where at least 10 patients were registered with a pregnancy after cancer have been included. For malignant melanoma in males, 11 became fathers postcancer among those with locoregional disease and childless at diagnosis, HR 1.17 [0.42–3.22]. Broad confidence intervals reflect the small number of events in some groups. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

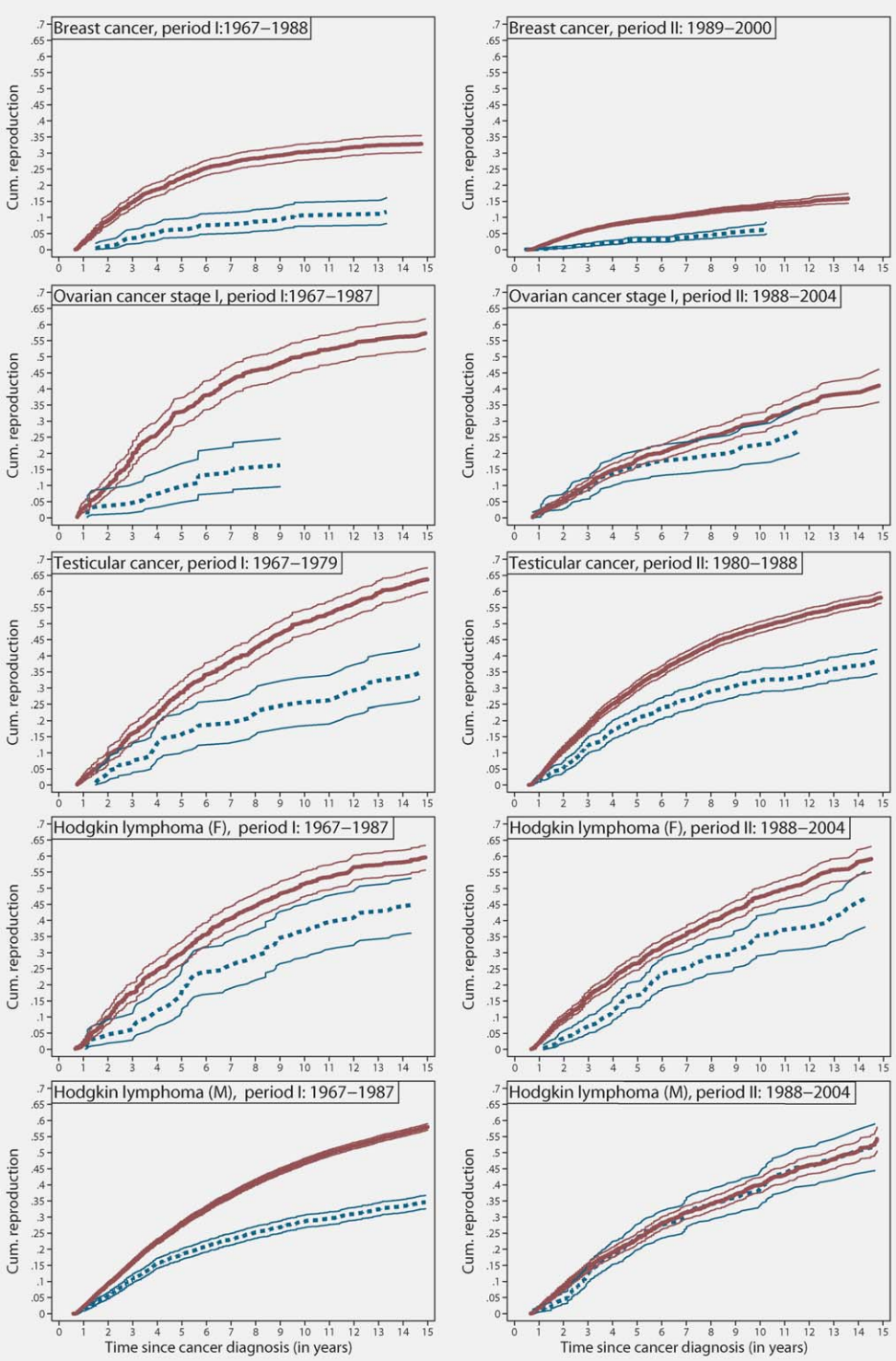

Figure 2. Cumulative pregnancy rates after cancer. Competing risk plot with controls depicted with solid red lines, and patients in dotted blue lines. Confidence intervals (95%) with thin solid lines. M = males and F = females.

Limitations of our study include the lack of information about partner status at diagnosis, attempts to initiate a pregnancy after cancer and whether ART was used because of the patient's or partner's subfertility. From other studies, we know that female cancer survivors without a partner at diagnosis are more likely to remain single than are male survivors.[31] Other information that was not available in the registry files or was reported only occasionally was detailed

prognostic markers such as hormonal receptor status for breast cancer and data on induced abortion or early miscarriage. There is a slight underestimation of parity for men because the father of 1–2% of newborn children is not reported to the MBRN.[19] On the other hand, both for cancer survivors and the general population, a small number of males are registered as fathers, although the child had a different biological father.

As expected, female survivors had a lower probability of initiating a pregnancy than did male survivors after cancer. In general, female survivors with at least one child before diagnosis had lower pregnancy rates than did female survivors who were childless at diagnosis. This difference was not seen in male survivors with similar parity. The distress related to a pregnancy and perhaps the fear of recurrence during the eventual offspring's childhood may contribute to this lower rate because female cancer survivors may prevent conception if they do not feel well enough to initiate pregnancy. The desire to have another child might also change during the process of being diagnosed and treated for a malignancy.[32] Even for the youngest proportion of our cohort (age 16–25 years at diagnosis), the probability of a pregnancy after cancer was similar to that for the whole cohort. Fertility-preserving treatment for women is currently limited compared to the situation for male patients because semen cryopreservation has been available for >30 years.[33] No similar practical opportunities are offered to female patients, even if cryopreservation of embryos has been available for many years. This technique might not always be possible because it requires a partner and hormonal stimulation and can delay treatment. Cryopreservation of ovarian tissue or oocytes has occasionally helped women achieve a postcancer pregnancy, but this method remains considered experimental. *In vitro* fertilization was used significantly more frequently by male than by female cancer survivors, reflecting the possibility of sperm cryopreservation, even though the proportion of Norwegian cancer survivors using preserved sperm is modest.[4]

Breast cancer survivors had the lowest rates of postcancer motherhood (Tables 3 and 4).[10,11] This might be explained by the use of ovariotoxic treatment including ovarian ablation before 1980 (ovarian irradiation or oophorectomy), which was substituted gradually with tamoxifen for estrogen receptor-positive (ER+) tumors during the 1980s.[22] Since 1990s, more intensive chemotherapy, applied at earlier stages, and prolonged endocrine therapy have lead to a considerable risk of premature ovarian failure (POF), especially when considering the high median age at diagnosis (39 years) (Table 1).[34] It is believed that modern chemotherapy [fluorouracil, epirubicin and cyclophosphamide (FEC)] works partly through reversible ovarian ablation in women with ER+ tumors, but is presumably less effective in younger women.[35] It remains to be proven whether ovarian ablation through long-term antiestrogen therapy (>5 years) is prognostically beneficial; if so, this treatment may further challenge preserving fertility after ER+ breast cancer.[36] With an increasing maternal age at first pregnancy[18] and prolonged endocrine treatment, it is likely that the wish to have a child after cancer might influence the decision for early discontinuation of hormonal therapy in younger women, as reported recently.[37] The above explanations for low rates of postcancer pregnancy contrast with the interpretation of Madanat et al.[14] that female survivors fear a hormonally driven recurrence associated with a subsequent pregnancy. Consistent with similar studies, our group have recently published data showing that women with subsequent pregnancy do not have impaired survival, presumably because of a selection mechanism known as "the healthy mother effect."[10,11,18]

For women with low-risk ovarian cancer stage I, action was taken during the 1980s to preserve fertility in young women wishing to conceive later.[6,23,24] 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 because ipsilateral oophorectomy was performed routinely. However, some of these are phenotypic women but with chromosomal abnormalities and inherited infecundity, and they will not benefit from fertility-preserving treatment.[6,23]

Pregnancy rates did not change with time in cervical cancer survivors. Subanalysis demonstrated that 159 of 190 female survivors of cervical cancer with subsequent pregnancies were stage IA1 disease, for which conization has been the standard treatment since the 1970s if no high risk factors were present (Tables 1 and Supporting Information Table S1).[6,23]

The prognosis for testicular cancer improved markedly during the period studied and this is also reflected in the increasing rate of postcancer pregnancy during the study period. The decrease in the pregnancy rates for patients diagnosed during the 1980s might be explained 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.[25] In the late 1980s, extensive bilateral intervention was replaced by nerve-sparing RPLND and surveillance for patients with stage I nonseminoma testicular cancer.[13] A subgroup of men with testicular cancer who were childless at diagnosis and who had inherent fertility problems would probably have lifelong difficulties in initiating a pregnancy caused by subfertility linked to the disease.[25,38] However, most testicular cancer survivors have a relatively low incidence of post-treatment azoospermia, and experience recovery of spermatogenesis within a few years.[13,24] An overall 15-year reproduction rate of 71% in former testicular cancer patients attempting to achieve a pregnancy after cancer was reported from a national survey-based study, which is consistent with our findings.[13] We found a weak negative association between the disease stage and number of postdiagnostic pregnancies, which has also been described earlier.[25] Overall, prediagnostic parity was not a predictor of subsequent fatherhood after testicular cancer (Fig. 1), a finding that contrasts with those of Cvancarova *et al.*[8]

Survivors of malignant melanoma had similar pregnancy rates as the control group. In most patients, a localized malignant melanoma requires only surgical removal and presumably does not interfere with family planning in the way more invasive malignancies might. However, the counseling of female patients about future pregnancy might have varied for these patients, as in all cancer patients. Doctors have long been concerned about an increased risk of cancer recurrence caused by the hormonal changes during pregnancy, although several recent studies have failed in verifying such a risk.[18,39] The pregnancy rates for male and female survivors of malignant melanoma in this population-based material are much higher than those of hospital-based studies; this discrepancy underscores possible selection problems, including fewer low-stage patients in samples from oncology units.[40]

A pregnancy after treatment for thyroid cancer is regarded as safe today, and the good prognosis is likely to support a former cancer patient's choice to start a family, which is reflected in the similar pregnancy rates as in the controls. Both males and females receiving radioiodine therapy might have a transient period of gonadotoxicity, but they usually recover within a year. Women might be at risk for a slightly lower age at menopause at least when treated at age of 40 years or older.[41,42]

We included patients with brain tumors in our study because the incidence among young adults is high, even though the group is heterogeneous. Disturbances of the hypothalamic–pituitary axis are common sequelae of head tumor treatment, especially cranial surgery and in particular radiotherapy. Normal reproductive cycles can be recreated with administration of exogenous hormones.[43,44] The severe prognosis of glioblastoma and other highly malignant cranial tumors might influence fecundity directly.

In male survivors of Hodgkin lymphoma, we found an improvement with time and greater reproductive ability than in females with this disease (Table 4 and Fig. 2).[15] Similar to these results, a survey-based study by Kiserud *et al.*[4] reported that 63% of female and 75% of male Hodgkin lymphoma survivors succeeded among those who attempted a postcancer pregnancy. Our data (Table 4) suggest that male survivors seem to have benefitted more than females from the change to Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) treatment (Table 1). Using the data available, we cannot measure the percentage of female survivors who experience ovarian failure within a few years after treatment. There might, however, be reasons in addition to POF explaining the sex difference.

Non-Hodgkin lymphoma is a heterogeneous disease, and at least some of the subtypes are treated more intensively in recent years. With improved diagnostics and higher cure rates, fertility preservation is crucial. In this material, a 39% and 33% reduction in postcancer pregnancy rates were seen in female and male survivors, respectively (Table 3). Few studies have focused on postcancer pregnancy rates in survivors of adult non-Hodgkin lymphoma. A hospital-based study of 36 female survivors with a median age of 28 years (range 17–40 years) at diagnosis showed a 50% postcancer pregnancy rate and that 6% developed POF.[45] A Finnish population-based study reported a 50% probability of postcancer parenthood for both female and male survivors compared to their siblings.[14]

Acute leukemia is an example of a malignancy where both the severity of the disease and the treatment strongly influence postcancer fecundity 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 represent a serious threat to the fertility. Pretreatment options to preserve fertility, especially for women, are limited, because the treatment has to be initiated immediately after diagnosis.[46] Ovarian tissue cryopreservation might not be safe for patients with leukemia, because the graft could be contaminated with malignant cells, which pose a possible risk of recurrence during transplantation.[47] The literature on post-treatment fecundity in adult leukemia patients is scarce, and most studies focus on fertility and parenthood after childhood acute leukemia. A Japanese survey-based study showed that only 3.8% of adult long-term survivors of either sex became parents.[48]

This is a large controlled nationwide study including the reproductive history of 27,556 adolescent and adult cancer patients. We were able to use registry information covering the entire Norwegian population diagnosed with cancer for the relevant age groups (16–45 years) and during a period of almost 40 years. It could be argued that observation only until age 46 years for males is too short, but only 3%[19] of men father children after that age in the cohort. This linkage also allowed us to compare postcancer pregnancy rates between different cancer types. For several cancer types, postdiagnostic pregnancy is a rare event, and many patients are required to compute statistically trustworthy estimates. Comparing our results with the few population-based studies published, with some differences in study design, we found generally similar results. However, the most recent therapeutic improvements might not be reflected in studies published some years ago.[14,15] Several large cohorts have been included in hospital-based studies, but these studies might have a selection problem regarding stage, which may in part explain why the estimates differ substantially.[4,8,9,40]

Post-diagnostic pregnancy rates were markedly lower in cancer survivors compared to controls but were higher in male survivors than in female survivors. Fertility-preserving attempts have succeeded in patients with ovarian and testicular cancer and males with Hodgkin lymphoma. To improve further the young adult cancer patient's chances of subsequent parenthood, multidisciplinary counseling should focus on the best options for cancer treatment and the effects on future fertility.

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