

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

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ABSTRACT

Purpose

Most studies on postcancer reproduction are limited in patient numbers and lack of control group. We have computed 10-year first postdiagnosis cumulative reproduction rates (10-PDRs) and hazard ratios (HRs) avoiding these limitations.

Patients and Methods

Six thousand seventy-one patients with cancer age 15 to 45 years at diagnosis, treated from 1971 to 1997, and 30,355 controls from the general population, all born after 1950, were observed from the true (patients) or assigned (controls) date of diagnosis for a median of 10 years (range, 0 to 35). The primary focus of the study was the 10-PDR before and after 1988+ based on data from the Medical Birth Registry of Norway. Cox proportional hazards regression models were adjusted for age and calendar year at diagnosis, stratified by sex and prediagnosis parenthood.

Results

Across all cancer types, HRs of females were approximately 50% lower than those of the controls, the comparable percentage for male patients being approximately 30%, with some improvement after 1988+ for selected diagnoses. The highest 10-PDRs were observed in childless patients, with more favorable HRs in male than in female patients. In survivors with at least one child at diagnosis, the post-1988+ HRs improved significantly in patients with testicular and localized cervical cancer compared to pre-1988+ reproduction, with borderline improvement in localized ovarian cancer.

Conclusion

Postcancer reproduction is lower than that of the general population and influenced by sex, age at diagnosis, prediagnosis parenthood, and diagnostic period with more favorable rates in males than in females. Post-1988+ fertility-saving strategies may have improved the reproduction rates for select genital cancers.

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INTRODUCTION

The survival of patients with the most frequent malignancies during reproductive age has increased,¹ and so has the interest in their reproduction. Many authors have investigated reproduction after specific malignancies, such as Hodgkin's lymphoma,²⁻⁷ testicular cancer,⁸⁻⁹ breast cancer,¹⁰ or cancer of the female genital tract.¹¹⁻¹³ Others have evaluated congenital malformations or chromosomal aberrations in cancer survivors' offspring.^{14,15} The impact of prediagnosis parenthood on postdiagnosis reproduction has rarely been evaluated. In addition, most studies lack a control group.

Based on data from the Medical Birth Registry of Norway (MBRN), we have demonstrated that the first-time ever reproduction rate of 35-year-old male cancer survivors treated at the Norwegian Radium Hospital (NRH; Oslo, Norway) in the 1980s

and 1990s is similar to the rate of age-matched men from the general population, but lower in females.¹⁶ This study did not distinguish between pre- and postdiagnosis pregnancies. The influence of sex, age at diagnosis, and prediagnosis parenthood has also been shown in a preliminary report from our group,¹⁷ however, the results were not compared with a control group. Syse et al¹⁸ reported that postdiagnosis reproduction rates in Norwegian cancer survivors diagnosed between 1965 to 2001 were generally lower than in the general population. The results were based on census data, not taking into account abortions, miscarriages, or perinatal deaths.

In this study, we compare 10-year first postdiagnosis reproduction rates (10-PDRs) in patients with cancer treated at the NRH, with those of the general population, using reproduction data available at the MBRN. We anticipated that patients with cancer would display significantly lower

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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Table 1. Extent of the Disease and Treatment Strategies for the Most Frequent Malignancies in Young and Middle Age Cancer Patients Treated at the Norwegian Radium Hospital 1971-1997

Parameter	≤ 1980	≤ 1987	1980-1989	1988+	1990
Cancer cervicis uteri ²⁰					
Stage 1a		Conisation only exceptionally		Conisation routinely	
≥ Stage 1b		Wertheim op ²⁰ ± pelvic radiotherapy (46-50 Gy)		Wertheim op (stage Ib/Ila) combined with pelvic radiation therapy (46-50 Gy; ≥ stage IIb)	
Cancer ovarii					
Germ cell cancer ²⁰					
Stage I unilateral		Unilateral oophorectomy + L-field radiation therapy (40 Gy) or Doxorubicin ²¹		Unilateral oophorectomy + cisplatin-based chemotherapy ²³	
Stage I bilateral and stage II-IV		Bilateral oophorectomy + cyclophosphamide/VACAM ²⁴		Bilateral oophorectomy + cisplatin-based chemotherapy ± RSM ²⁵	
Epithelial cancer ¹⁹					
Stage 1a		Bilateral oophorectomy (unilateral oophorectomy only exceptionally)		Unilateral oophorectomy as a rule ± adjuvant cisplatin-based chemotherapy ²⁶	
≥ Stage 1b		Bilateral oophorectomy ± thiotepa/cyclophosphamide ± abdominal radiation/other		Bilateral oophorectomy + cisplatin-based chemotherapy ± resection of residual masses ²⁵	
Breast cancer					
General advice to avoid pregnancy for at least 2-3 years					
Stage I		Mastectomy ± regional lymph node/chest irradiation ²⁷		Mastectomy + tamoxifen (10 mg × 2 daily) for 2 years if grade 2 + 3 and hormone receptor positivity; adjuvant CMF × 9 if grade 3 ^{28,29}	
Stage II		Mastectomy + regional lymph node/chest irradiation ²⁷		Mastectomy + adjuvant CMF × 9 + regional lymph node/chest irradiation + 2 years antiandrogens (if hormone receptor positive) ^{28,29}	
Advanced		Mastectomy or involved field radiation therapy + medical treatment (hormones/chemotherapy) ovarian radiation		Mastectomy + tamoxifen 20 mg × 2 daily lifelong + chemotherapy (CMF, adriamycin) + involved radiation therapy field ^{28,29}	
Hodgkin's lymphoma					
Stage I/II		Mantle field or inverted Y-field irradiation (with testicular shielding/oophorectomy) ^{30,31}		ABVD (or variants) × 2-4 + mantle field/inverted Y-field radiation therapy ³²	
Stage III		MOPP × 8 or rarely total node irradiation ³³		ABVD × 8 (or variants) + radiation therapy to residual masses radiation therapy ^{32,34,35}	
Stage IV		MOPP × 8 ³³		Recurrence: high-dose chemotherapy with ABMT with or without whole-body irradiation ³⁶	
Cancer testis					
Seminoma					
Stage I/limited stage II		Radiation therapy L-field (40 Gy) with exceptional testicular shielding ³⁷		L-field radiation therapy (30-36 Gy) with routine testicular shielding ³⁸	
≥ Advanced stage II		Chemotherapy (cyclophosphamide/VACAM) + involved field irradiation ²⁴		Cisplatin-based chemotherapy ± involved field radiation or RSM ³⁹	
Non-seminoma					
Stage I/limited stage II	Radiation therapy (50 Gy) ⁴⁰		RPLND ± adjuvant cisplatin-based chemotherapy × 2-3 (if possible unilateral) ⁴¹		Surveillance or adjuvant chemotherapy × 2 ^{42,43}
≥ Advanced stage II	Chemotherapy (cyclophosphamide/VACAM) + large field radiation therapy ²⁴		Cisplatin-based chemotherapy × 4-6 ± RSM ^{44,45}		Cisplatin-based chemotherapy × 4-6 ± RSM (if possible nerve sparing) ^{44,45}

Abbreviations: L-field, para-aortic and ipsilateral pelvic target field; VACAM, Vincristine, Adriamycin, Cyclophosphamide, Actinomycin D, Methotrexate; RSM, resection of residual masses; CMF: cyclophosphamide, methotrexate, fluorouracil; ABVD, adriamycin, bleomycin, vinblastine, DTIC, XXX; MOPP, mustargen, oncovin, procarbazine, prednisone; ABMT, autologous bone marrow transplantation; RPLND, retroperitoneal lymph node dissection.

NOTE. Stages refer to International Federation of Gynecology and Obstetrics classification (gynecologic cancer), Royal Marsden classification (testicular cancer),⁴⁴ or are described in references 27-29 (breast cancer) and references 30-33 (Hodgkin's lymphoma).

rates, yet with some improvement after 1987 due to less intensive treatment of early-stage malignancies typical for young patients with cancer (Table 1).

PATIENTS AND METHODS

Each individual living in Norway is assigned a unique identification number at birth which enables merging of data from different registers. In this study, data from three databases provided information on patients with cancer and their controls.

NRH's Patient Registry

The NRH is a tertiary referral hospital for malignancies requiring radiation therapy and/or intensive chemotherapy. Patients with Hodgkin's lymphoma, testicular, cervical, or ovarian cancer from southern Norway are, however, referred for primary treatment. An electronic patient registry contains demographic and limited medical records on patients treated after 1970.

Cancer Registry of Norway

Since 1953 it has been mandatory to report all new cancer cases to this registry. For this study, the Cancer Registry of Norway provided information on the initial extent of the disease (except for malignant lymphoma/leukemia) and initial treatment, but not on relapse therapy.

MBRN

Starting in 1967 until 1998 this registry collected information on all pregnancies terminated in Norway after no fewer than 16 weeks of gestation. Since 1999 all pregnancies of at least 12 weeks duration have been registered. The records include demographic data on the newborn's parents and their reproductive history.

Data from the three registries were merged for identification of eligible patients with cancer, all born after 1950, age between 15 and 44 years at diagnosis of invasive cancer, and treated at the NRH between 1971 and 1997. Because these patients with cancer were at most 16 years old at the time the MBRN was established, we assumed that complete information on their pre- and postdiagnosis childbirths was available in this registry.

To create the comparison group (controls), each patient was sex- and birth year-matched with five randomly selected individuals from the Norwegian Population Registry, but with no record in the Cancer Registry of Norway at the time of study inclusion. Each patient and his/her controls were marked so that the six-member group remained identifiable for statistical analyses.

Statistical Analyses

Categorical variables were described with counts and proportions. Continuous variables were presented using medians and ranges.

To create a start of follow-up in the controls, each member of a control subunit was assigned the same data as the date of cancer diagnosis of his or her patient (this assigned date of diagnosis is here for simplicity reasons included into the term date of diagnosis). All individuals were followed from the date of diagnosis (true or assigned) to the date of their first postdiagnosis reproduction, date of death, emigration, or to December 31, 2005 (cutoff date of the study), whichever occurred first. Females were censored at the age of 50.

The first postdiagnosis reproduction was defined as any pregnancy taking place at least 8 months after the date of diagnosis thus avoiding precancer conceptions. It refers to the event of any postdiagnosis pregnancy independent of its duration or outcome (therapeutic or spontaneous abortion, stillborn, or living child) as recorded in the MBRN.

Comparisons between patients and the control group with regard to their PDR were analyzed with Cox proportional hazards regression and reported as hazard rate ratios (HR) with 95% CIs and cumulative rates. The analyses were adjusted for age at diagnosis and stratified by sex, prediagnosis parenthood, and diagnosis before and after 1988. Cumulative reproduction rates were calculated with the Breslow estimator. The main focus of the study was 10-PDR.

Investigation of the proportional hazards assumption¹⁹ warranted stratification by sex and prediagnosis parenthood. Therefore, separate models for

prediagnosis parity (none and \geq one child) and both sexes were fitted. 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 (for treatment details, see Table 1²⁰⁻⁴⁵) and anticipated changes in reproduction pattern.

The significance level was set to .05. All statistical analyses were performed with SPSS, version 13 (SPSS, Chicago, IL) and R statistical software.

RESULTS

Patients

A total of 6,071 patients (female, 55%; male, 45%) and 30,355 controls were identified. Approximately 60% of the patients were diagnosed in 1988 or later. They were 7 to 10 years older than those diagnosed earlier, and females were 2 to 5 years older than males. Overall, 60% of male and 56% of female patients had survived for more than 10 years.

About two thirds of the patients had localized or locoregionally confined cancer. More than 50% underwent radiation therapy, chemotherapy, or a combination of both, with or without surgery. The most frequent cancer types were testicular cancer (19%), malignant lymphoma/leukemia (17%), gynecologic (24%), and breast cancer (11%; Table 2).

Ninety-nine percent of the first postdiagnosis pregnancies fathered by patients or controls ended with a living child. In females, the comparable figure was 98% for both patients and controls. In vitro fertilization (IVF) was used for initiation of 6.3% of the first postdiagnosis pregnancies initiated by male patients compared with 1.2% for their controls. The comparable percentages in females were 2.0% and 1.6% (data not shown).

Prediagnosis Parenthood and Sex Differences

Of the 3,349 female patients with cancer, 444 (13%) initiated at least one postdiagnosis pregnancy; the comparable figures for male cancer patients was 819 of 2,722 (30%; Table 3).

Thirty-four percent of all female ($n = 1,126$) and 59% of all male patients ($n = 1,617$) were childless at diagnosis as compared with 36% ($n = 6,012$) and 62% ($n = 8,384$) of the controls, respectively.

Age/Extent of the Disease

Being diagnosed after the age of 35 years reduced female patients postdiagnosis reproduction from 20% to 0.5%; the comparable figures for male patients were 35% and 4%. Finally, the probability of postdiagnosis parenthood decreased with the extent of the disease, more so in females than in males (data not shown).

Postdiagnosis Reproduction

Patients versus controls. Postdiagnosis reproduction differed considerably between individuals who were childless at diagnosis and those who already had at least one child. In addition, different reproduction patterns emerged for childless individuals diagnosed pre- or post-1988+. In general, the reproduction rates of patients were always below those of their controls, with smaller differences among prediagnosis childless individuals and slightly decreasing in patients treated after 1988+ (Fig 1).

Sex differences. Childless female patients diagnosed pre-1988+ displayed a 10-PDR of 31% compared with 47% in their controls

Table 2. Patients' Characteristics

Table 2. Patients' Characteristics										
Parameter	Females Diagnosed				Males Diagnosed				Total	
	Pre-1988		Post-1988+		Pre-1988		Post-1988+			
	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	1,065	32	2,284	68	1,170	43	1,552	57	6,071	100
Median age at diagnosis, years	25		35		23		30		29	
Range	15-35		15-44		15-35		15-44		15-44	
Follow-up, years										
> 10	385	36	1,599	70	402	34	1,013	65	3,399	56
< 10	680	64	685	30	768	66	539	35	2,672	44
Total	1,065	100	2,284	100	1,170	100	1,552	100	6,071	100
Extent of the disease*										
Localized	692	65	1,073	47	670	57	716	46	3,151	52
Locoregional	219	20	495	22	318	27	475	31	1,507	25
Distant	105	10	298	13	163	14	220	14	786	13
Not known	49	5	418	18	19	2	141	9	627	10
Initial treatment										
Surgery only	474	44	865	38	437	38	413	27	2,193	36
Radiotherapy ± surgery	515	48	669	29	600	51	550	35	2,334	38
Chemotherapy ± surgery	10	1	246	11	14	1	257	17	527	9
Chemotherapy and radiation therapy ± surgery	30	3	481	21	34	3	270	17	815	13
Unknown	36	4	23	1	85	7	58	4	202	4
Most frequent cancer types										
Testicular†					485	43	654	57	1,139	100
Malignant lymphoma/leukemia	174	42	241	58	271	44	347	56		10 (male); 33 (female)
Hodgkin's, stage‡										
I, II	66		60		102		90		318	
III, IV	43		43		78		74		238	
Gynecologic	473	31	1,030	69					1,503	100
Cervical										
Total	286	31		9					934	100
Localized†§	234								763	
Ovarian										
Total	155	34		6					453	100
Localized²†§	85								234	
Corpus uteri										
Total	7	13	48	87					55	100
Localized‡	7		35						42	
Choriocarcinoma										
Total	25	41	36	59					61	100
Localized‡	19		22						41	
Breast cancer										
Total	102	16	536	84					638	100
Localized, stage I-III	84		355						439	
Other	316	34	615	66	414	43	554	57		18 (male); 99 (female)

*Total given column wise (100%).

†Indicates cancer types that are depicted in Figure 2.

‡As recorded in the hospital registry.

§As recorded in the cancer registry.

*Total given column wise (100%).

†Indicates cancer types that are depicted in Figure 2.

‡As recorded in the hospital registry.

§As recorded in the cancer registry.

($P < .001$; Fig 1A). After 1988+ the rates were 19% for patients compared with 29% for controls ($P < .001$). Reproduction for female patients who had children at diagnosis was even lower, both for those diagnosed before and after 1988+ (< 1988, 12% v 38%; 1988+, 4% v 10%). For male patients diagnosed pre-1988 and childless at diagnosis, the 10-PDR was 33% compared with 44% in their controls ($P < .001$; Fig 1B). When diagnosed after 1988+, the rates were 32% and 38% for patients and controls, respectively ($P = .014$). The 10-PDR of male patients who were fathers before the diagnosis

was 28% before 1988% and 17% thereafter (controls, 53% and 27%, respectively).

The results from Figure 1 are supplemented by hazard ratios (HRs; Table 4). Compared with controls, reproduction of patients was significantly reduced by approximately 50% in females and by 30% in males with only minimal improvement after 1988+. The most favorable HRs were always seen in prediagnosis childless patients. Interestingly, postdiagnosis reproduction in childless males with hematologic malignancy did not differ significantly from reproduction in controls.

Table 3. Prediagnosis Parenthood and Post-Diagnosis Reproduction

Prediagnosis Parity	No. of Children Born After Diagnosis								
	Female			Male			Overall		
	Total No.	≥ 1 Child		Total No.	≥ 1 Child		Total No.	Total ≥ 1 Child	
		No.	%		No.	%		No.	%
Patients									
Childless	1,126	287	26	1,617	556	34	2,743	843	31
≥ 1 child	2,223	157	7	1,105	263	24	3,328	420	13
Total	3,349	444	13	2,722	819	30	6,071	1,263	21
Controls									
Childless	6,012	2,861	48	8,384	4,537	54	14,396	7,398	51
≥ 1 child	10,733	2,471	32	5,226	2,092	40	15,959	4,563	29
Total	16,745	5,332	32	13,610	6,629	49	30,355	11,961	39

A similar finding emerged for prediagnosis childless females with breast cancer, though the HR computations are based on few child-births as reflected by large CIs.

Impact of Treatment Changes After 1988+

Significant improvement after 1988+ was observed in the subgroup of gynecologic cancer—both in women who were childless at diagnosis ($P = .048$) and those with at least one child at diagnosis ($P = .035$)—although post-treatment reproduction remained extremely low in these females (Fig 2). In addition, patients with testicular cancer who were fathers before their diagnosis (HR, 0.52) slightly increased their chances of having another child when diagnosed after 1988 (HR, 0.67; $P = .045$; Table 4).

After 1988+, the postdiagnosis reproduction increased significantly for patients with localized cervical and (Fig 2D) and testicular cancers (all stages, Fig 2F) with at least one prediagnosis child. Marginal improvement was observed for localized ovarian cancer (Fig 2B). For prediagnosis childless patients any after 1988+, improvement did not reach statistical significance. (For Hodgkin's lymphoma and breast cancer, see Appendix Fig A1 online only).

DISCUSSION

In this monoinstitutional study, we quantify 10-PDRs and show that the postdiagnosis reproduction in cancer survivors is reduced by approximately 50% in female patients and by approximately 30% in male patients compared with figures from the general population. We demonstrate that sex, treatment period (< 1988 v 1988+) and prediagnosis parenthood are associated with postdiagnosis reproduction, together with the type, extent, and treatment of the malignancy. For testicular and early cervical cancer the post-1988+ reproduction increased significantly compared to the preceding years in those with at least one prediagnosis child.

In general, the differences in 10-PDRs between cancer survivors and controls were smaller in prediagnosis childless individuals than in those with at least one child at diagnosis. This might reflect the former patients' desire to have at least one biologic offspring despite possible concerns for the mother's or infant's health.

Syse et al's study showed lower, although slightly increasing, reproduction in Norwegian cancer survivors compared with the general

population.¹⁸ Our results are consistent with the above mentioned report despite the differences between the two investigations. Syse et al's study covers the complete Norwegian population whereas our patients were treated at a single cancer center. Furthermore, 53% of our patients were diagnosed after 1990 when fertility-preserving treatments had been developed,⁴⁶⁻⁴⁸ compared with 26% of patients included in the study by Syse et al (A. Syse, personal communication, January 2008).

In childless individuals, the reproduction pattern changed after 1988+. This might reflect the fact that people who reached childbearing age during late 1980s and 1990s generally delayed parenthood compared with earlier decades. Therefore, we performed two separate analyses, for those diagnosed before and after 1988+, stratified by parity so that the original matching was broken. However, the median age at diagnosis was about the same for patients and controls for both parities and diagnostic periods (data not shown) and all analyses were adjusted for age at diagnosis. Moreover, except for testicular cancer, we have no reason to believe that a future cancer diagnosis would have influenced patients' prediagnosis reproduction. Thus, performing separate analyses based on parity did not introduce bias.

Overall, no clinically meaningful increase in reproduction was observed in patients diagnosed after 1988+, except for mothers with early-stage gynecologic cancer who benefited from the routine introduction of fertility-saving surgery. However, even in these cases the reproduction remained very low, perhaps also due to relatively high age at diagnosis. Post-1988+ improvement was also significant for testicular cancer survivors who had at least one child before their cancer diagnosis ($P = .013$). Interestingly, significant post-1988+ improvement was only observed in male and female patients with at least one child, thus known to be fertile before diagnosis and presumably having a partner.

In general, higher reproduction rates were observed in male compared with female patients. Males may have benefited slightly more from the post-1988 treatment changes which is in agreement with Magelssen et al's findings.¹⁶ Our results are furthermore consistent with observations made by Schover et al⁴⁹ that men who were childless prediagnosis and/or their partners highly prioritize postdiagnosis parenthood. Better medical options to preserve

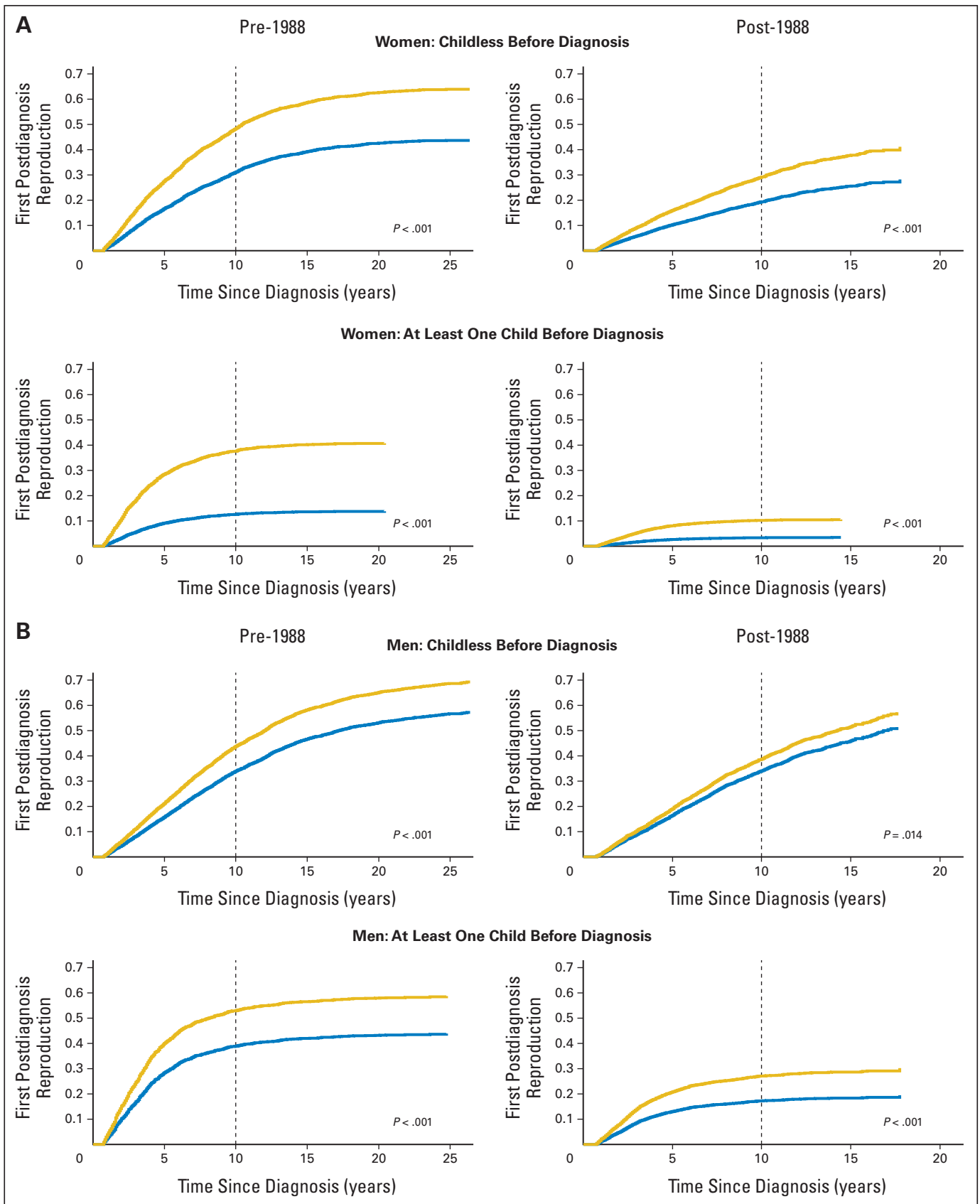


Fig 1. First-time postdiagnosis reproduction in male and female cancer survivors and their controls. 10-year first postdiagnosis reproduction rates depicted with a dotted line. Cox regression analysis was adjusted for age at diagnosis. Cases depicted in blue, controls in gold.

Table 4. HRs of First-Time Post-Diagnosis Reproduction

Parameter	All				Malignant Lymphoma/Leukemia				Testicular Cancer		Gynecologic Cancer		Breast Cancer	
	Female		Male		Female		Male		HR	95% CI	HR	95% CI	HR	95% CI
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI						
Diagnosed pre-1988														
No. of patients		1,065		1,170		174		271		485		473		102
All patients v controls	0.45	0.39 to 0.51	0.71	0.64 to 0.78	0.75	0.58 to 0.97	0.83	0.68 to 1.00	0.61	0.52 to 0.71	0.17	0.13 to 0.23	0.45	0.25 to 0.81
Childless	0.56	0.48 to 0.66	0.72	0.64 to 0.81	0.82	0.62 to 1.10	0.89	0.71 to 1.11	0.64	0.53 to 0.76	0.22	0.15 to 0.32	0.76	0.36 to 1.59
≥ 1 prior child	0.28	0.22 to 0.36	0.65	0.54 to 0.79	0.49	0.28 to 0.86	0.65	0.43 to 0.99	0.52	0.40 to 0.68	0.12	0.07 to 0.19	0.25	0.09 to 0.68
Diagnosed post-1988+														
No. of patients		2,284		1,552		241		347		654		1,030		536
All patients v controls	0.47	0.41 to 0.54	0.76	0.69 to 0.85	0.61	0.46 to 0.82	0.88	0.71 to 1.08	0.72	0.63 to 0.83	0.27	0.21 to 0.35	0.45	0.30 to 0.67
Childless	0.62	0.52 to 0.75	0.85	0.75 to 0.97	0.70	0.50 to 0.97	1.12	0.87 to 1.45	0.75	0.63 to 0.89	0.39	0.28 to 0.56	0.82	0.43 to 1.57
≥ 1 prior child	0.32	0.25 to 0.39	0.60	0.50 to 0.72	0.43	0.23 to 0.79	0.54	0.37 to 0.78	0.67	0.53 to 0.85	0.17	0.12 to 0.26	0.34	0.20 to 0.56

NOTE. Controls as the reference group.
Abbreviation: HR, hazard ratio.

postdiagnosis reproduction are available for males (sperm banking, IVF) than for female patients with cancer. Moreover, female patients are even more threatened by increasing age and advice to delay any post-treatment pregnancy. In addition, females might be reluctant to initiate such pregnancy as they may fear cancer recurrence and otherwise reduced health due to child bearing.⁴⁹ Other factors, not evaluated by us, such as differences in income and employment might have contributed to observed intersex differences.⁵⁰

We anticipated post-1988+ persistently low postdiagnosis reproduction in testicular cancer survivors, in particular in those childless at diagnosis. Treatment unrelated sub- and infertility due to the testicular dysgenesis syndrome⁵¹⁻⁵⁴ has been described in these patients as an important problem. Our findings thus indirectly confirm an inherent infertility problem in this group of patients. The post-1988+ improvement was greater in those who were already fathers, and thus proven fertile, than in the childless men. This latter group probably consisted of an unknown proportion of patients with treatment-unrelated infertility, which would not be influenced by fertility-saving treatment. Presently, it cannot be decided whether our promising figures for postdiagnosis reproduction in testicular cancer survivors are generally valid or reflect the NRH's attempts to preserve fertility in these patients. In contrast, our findings are in line with Bahadur et al's observations that patients with testicular cancer display a particularly low incidence of post-treatment azoospermia.⁵⁵

Reports on reproduction after different cancer types are mostly based on cancer survivors' responses to questionnaires,²⁻¹³ and/or related to defined therapies. Deceased or emigrated patients are usually not accounted for. Moreover, such clinical series are often restricted to survivors who attempted post-treatment parenthood, thus the reported postdiagnosis reproduction rates are considerably higher than in our study. Brydøy et al⁹ have reported an overall 15-year reproduction rate of 71% in patients with testicular cancer who attempted post-treatment fatherhood. In Kiserud et al's report,⁷ 63% of men and 75% of women who attempted postdiagnosis parenthood after Hodgkin's lymphoma were suc-

cessful. Even higher rates for males are reported when evaluation of postdiagnosis fertility was based on serum hormone levels⁶ or sperm counts.⁵⁴

The development of assisted reproduction techniques should not be overlooked as an explanation for our high postdiagnosis reproduction in male patients.^{56,57} We note that our male patients used IVF about 5 times more often than controls. In contrast, of 420 testicular cancer survivors with pretreatment cryopreservation, only 29 have ever used their deep frozen sperm cells resulting in pregnancies in 16 partners.⁵⁸ Similar low success rates have been published for those surviving Hodgkin's lymphoma.⁷

The improvement of selected cancer survivors' reproduction after 1988+ is encouraging and may indicate that our hospital's attempts to save fertility during the 1990s have been successful. However, the lack of improvement in survivors after Hodgkin's lymphoma was unexpected. Fertility-preserving anthracycline-based chemotherapy and avoidance of abdominal radiation have been routine in these patients since late 1980s and should theoretically have resulted in increased reproduction rates.^{32,42,45} In contrast, the increased median age of our patients diagnosed after 1987 might have reduced both the ability and the desire of Hodgkin's lymphoma survivors to become parents.

Our study has limitations connected to the use of large registries: detailed and individualized information about the extent of the disease at diagnosis and treatment is lacking, even in the hospital registry. We tried to compensate for this disadvantage by presenting time-related treatment strategies for the most frequent cancer types among fertile patients. In addition, we have no data on the patients' desire and/or attempts to become parents after their cancer. Considering generally improved cancer care during the last 25 years, increasing numbers of patients may have taken the risk to have children after their cancer, if biologically possible. Further, our definition of reproduction comprises living and stillborn postdiagnosis infants and, from 1999, abortions after the third month. However, the number of pregnancies not ending with a living child was minimal in our series.

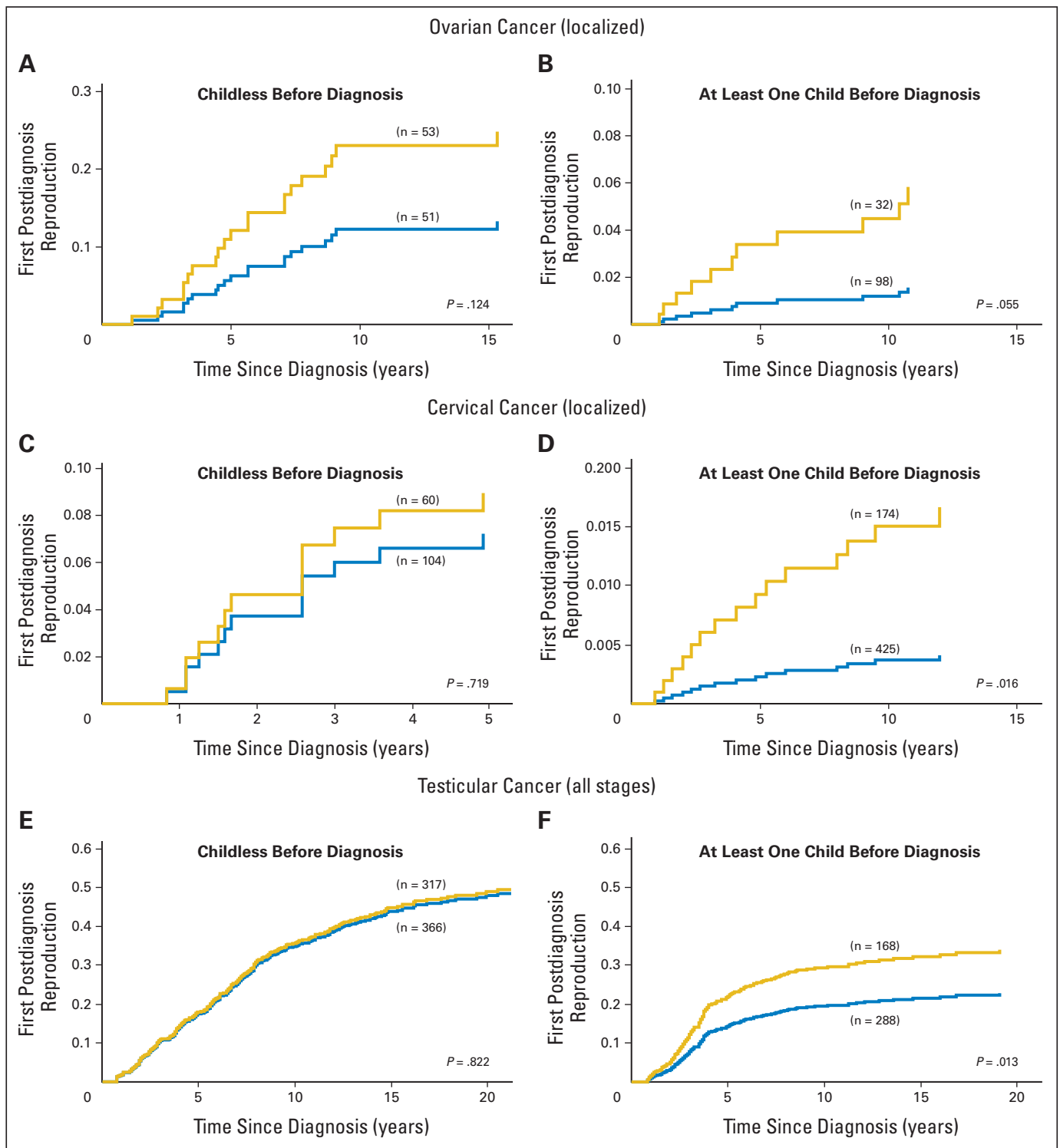


Fig 2. First-time postdiagnosis reproduction in cancer survivors diagnosed before 1988 and from 1988+. Patients diagnosed before 1988 in blue, diagnosed after 1987 in gold. Note the different scales of y-axes.

The large sample size is the main strength of our study together with the complete registration of first postdiagnosis reproduction. We suggest that our results can be used in counseling of today's cancer survivors because most of our patients were diagnosed after 1988+. Finally, the design is well balanced due to age

and sex matching with five controls, thus allowing for changes in reproduction of the general population.

In conclusion, compared with the general population postdiagnosis reproduction in cancer survivors is reduced by approximately 50% in females and by approximately 30% in males.

Fertility-preserving attempts after 1988+ have been successful for select diagnoses. However, there is much left to be done to improve postdiagnosis reproduction, in particular in women. This study demonstrates that postcancer fertility is influenced by sex, age at diagnosis, prediagnosis parity, and calendar year of diagnosis, as well as type and extent of the malignancy. Our monoinstitutional results need confirmation from population-based studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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