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ORIGINAL REPORT

Cause-Specific Survival for Women Diagnosed With Cancer During Pregnancy or Lactation: A Registry-Based Cohort Study

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ABSTRACT

Purpose
To assess if cancers diagnosed during pregnancy or lactation are associated with increased risk of cause-specific death.

Patients and Methods
In this population-based cohort study using data from the Cancer Registry and the Medical Birth Registry of Norway, 42,511 women, age 16 to 49 years and diagnosed with cancer from 1967 to 2002, were eligible. They were grouped as not pregnant (reference), pregnant, or lactating at diagnosis. Cause-specific survival for all sites combined, and for the most frequent malignancies, was investigated using a Cox proportional hazards model. An additional analysis with time-dependent covariates was performed for comparison of women with and without a postcancer pregnancy. The multivariate analyses were adjusted for age at diagnosis, extent of disease, and diagnostic periods.

Results
For all sites combined, no intergroup differences in cause-specific death were seen, with hazard ratio (HR) of 1.03 (95% CI, 0.86 to 1.22) and HR 1.02 (95% CI, 0.86 to 1.22) for the pregnant and lactating groups, respectively. Patients with breast (HR, 1.95; 95% CI, 1.36 to 2.78) and ovarian cancer (HR, 2.23; 95% CI, 1.05 to 4.73) diagnosed during lactation had an increased risk of cause-specific death. Diagnosis of malignant melanoma during pregnancy slightly increased this risk. For all sites combined, the risk of cause-specific death was significantly decreased for women who had postcancer pregnancies.

Conclusion
In general, the diagnosis of most cancer types during pregnancy or lactation does not increase the risk of cause-specific death. Breast and ovarian cancer diagnosed during lactation represents an exception. We confirmed the "healthy mother effect" for women with a postcancer pregnancy.

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INTRODUCTION

The question of how a pregnancy affects malignant disease has been raised for decades. Historically, elevated estrogen levels have been hypothesized to increase the biologic aggressiveness of cancer cells regarded as hormone dependent, such as breast and ovarian cancer, and also malignant melanoma.[1-4] Decreased survival for patients with breast cancer and malignant melanoma diagnosed during or shortly after a pregnancy has been reported, but results are contradictory.[2,5-16] Besides hormone changes, immunological suppression and increased vascularization during pregnancy might also imply adverse effects on tumor development.

Today, in industrialized countries women tend to postpone beginning a family. In Norway, more than 50% of all pregnancies occur in women 30 to 49 years old, compared with 24% in 1967,[17] and cancer incidence is also increasing in this age group.[18] A rising number of malignancies diagnosed during pregnancy or lactation is expected.[19]

In this study, we investigate the cause-specific survival of women diagnosed with a malignancy during pregnancy or lactation, as well as in women who had postcancer pregnancies. We report results for the most frequent malignancies in premenopausal women, which are breast, cervical, ovarian, and thyroid cancers, malignant melanoma, brain tumors, malignant lymphoma, and leukemia.[18] Our aim is to explore if pregnancy associated with cancer affects prognosis.

PATIENTS AND METHODS

Data Sources

With approval from the National Data Inspectorate and the Regional Committee for Medical Research Ethics

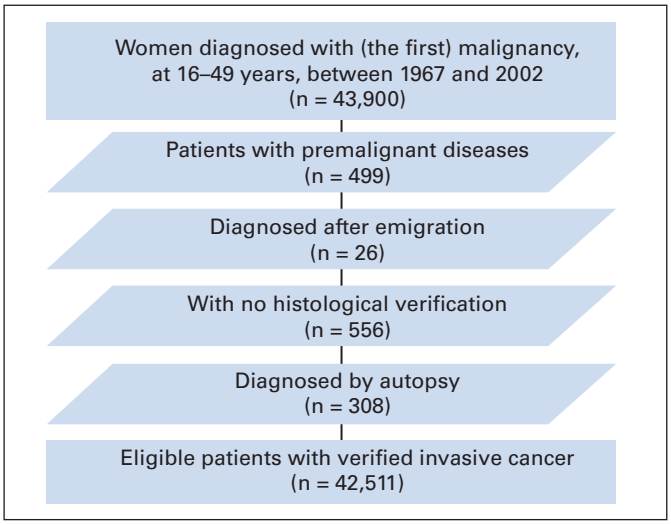

Fig 1. Flowchart showing number of eligible patients, and number of individuals excluded because of uncertainties about diagnostic factors.

data from two sources were linked by means of the 11-digit personal identification number given to all Norwegian citizens.

The Cancer Registry of Norway (CRN) has information on all new cancer cases, occurring in Norway since 1953, as all doctors are by law required to report these diagnoses. Cancer type, date of diagnosis, initial treatment, date of death or emigration, and cause of death is recorded. The initial extent of the disease at diagnosis is categorized as localized, regional, distant, or unknown.[18]

The death certificate information is incorporated in the CRN, originally provided from the Cause of Death Registry. In this study, only underlying cause of death was used.

The Medical Birth Registry of Norway (MBRN) was established in 1967 and has collected data on pregnancies of at least 16 weeks' duration (from 1999 all gestations from 12 weeks), compulsory reported by doctors and midwives. The MBRN provides information about maternal age, medical conditions before and during pregnancy, and medical parameters from the first examination of the newborn.[20] The date of delivery or other pregnancy termination is given as month and year. In most cases, the date of last menstruation and the pregnancy duration are recorded. If the date of last menstruation was missing, we used information about the infant's birth weight and "small/large for gestational age", which allowed estimation of the pregnancy onset. "Small/large for gestational age" refers to the infant's birth weight when born $\geq$ 37 weeks gestation, where small is $\leq$ 2,500 g and large is $\geq$ 4,500 g.

Patient Selection and File Construction

This is a retrospective, population-based cohort study based on linkage between CRN and MBRN. Eligible were women registered in the CRN with their first invasive malignancy diagnosed at age 16 to 49 years between 1967 and 2002. All malignant neoplasms according to International Classification of Disease, seventh revision (ICD-7) are included, except basal cell carcinomas. Current records from the MBRN were merged in. From both registries, updated information was available up to December 31, 2004.

Three diagnostic periods were defined: 1967 to 1984, 1985 to 1994, and 1995 to 2002. Age at diagnosis was grouped into 5-year intervals, except for the first age group, which included those diagnosed at age 16 to 24. We analyzed the most frequent cancer types for this age group, and all sites combined. Brain tumors are morphologically heterogeneous as benign tumors also are registered, and were therefore not analyzed as a separate group.

We performed two different analyses. The first explored cause-specific survival if the cancer was diagnosed during pregnancy or lactation. The second investigated cause-specific survival in women with postcancer pregnancies. For the first analysis, each woman was allocated to one of three groups.

Nonpregnant. Nulliparous or no pregnancies at or after diagnosis (reference group).

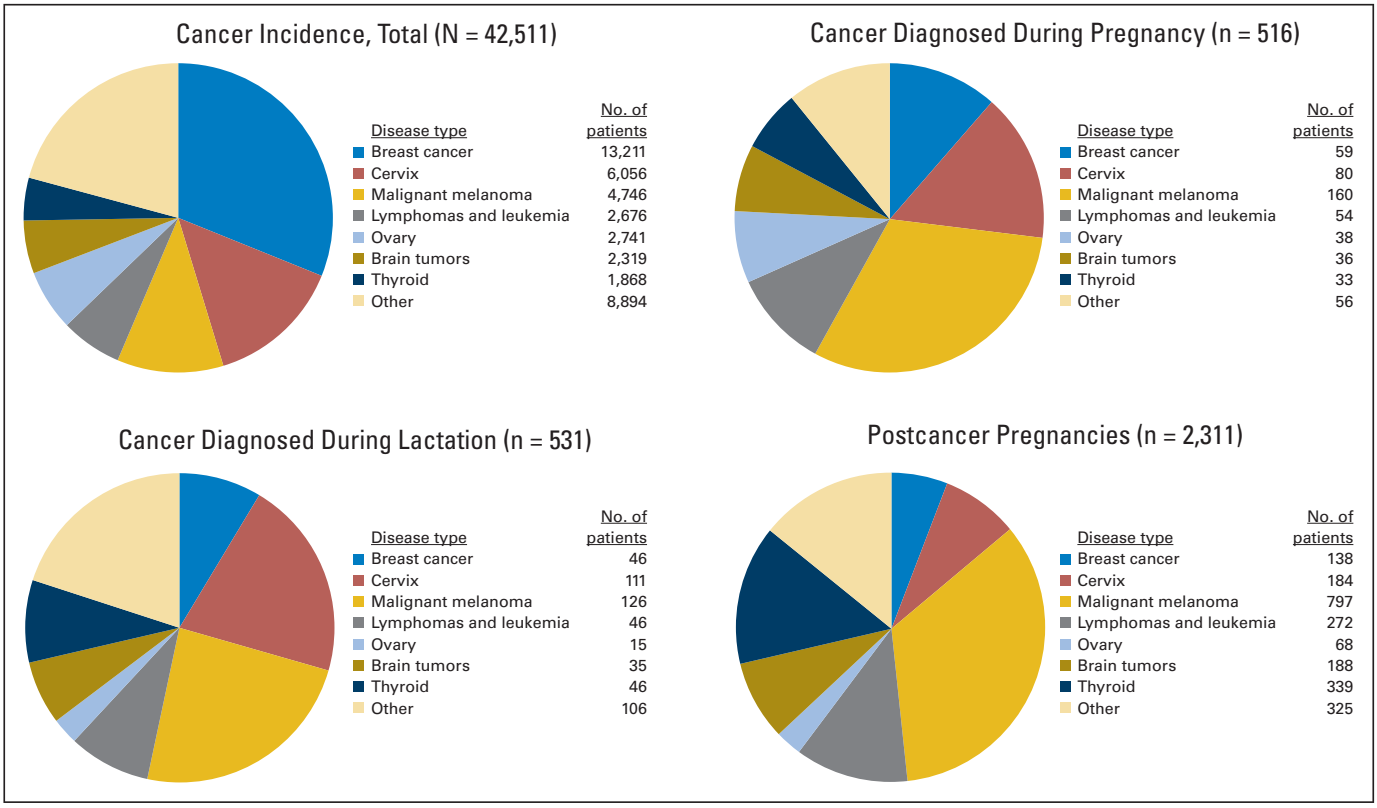

Fig 2. Cancer incidence overall, and in the different subgroups (pregnant, lactating, and postcancer pregnancy group).

Pregnant. Cancer diagnosed during pregnancy. Women with a malignancy diagnosed within the same month as their last menstruation until the date of delivery were included.

Lactating. Cancer diagnosed during the lactation period, defined as the period from the date of delivery of a living infant until 6 months postpartum. If the child was stillborn or died within 1 week, the lactation period was restricted to the first 2 months postpartum. Our definition of the lactation period refers to the postpartum hormone changes more than the actual breastfeeding duration.[21] None in the lactating group had pregnancies shorter than 25 weeks.

If a woman fulfilled the criteria for more than one group, the pregnant group was given preference compared with the lactating group, and the lactating group over the not pregnant group.

For the second analysis, we introduced a time-dependent variable. All patients started out as not pregnant patients (reference group, defined as in the first analysis), and the women who had any pregnancy starting after the date of diagnosis, changed to the postcancer pregnancy group at the date of delivery.

Statistics

We used the Cox proportional hazards model for the first analysis to compare cause-specific survival in the three groups. The women were followed from date of diagnosis until date of death, date of emigration, age of 60, or until December 31, 2004, whichever occurred first.

For the second analysis, we used a time-dependent Cox model. The women who finally constituted the postcancer pregnancy group contributed time at risk in the reference group until the date of the first delivery after cancer, from which date the follow-up started. Follow-up for both groups in the second analysis ended as described for the first analysis.

In addition to univariate hazard ratios (HRs), we controlled for potential confounders by adjusting for age at diagnosis, initial extent of disease, and diagnostic periods in a multivariate model. Hazard ratios and 95% CIs were calculated for both crude and adjusted analyses. *P* value of less than .05 was considered statistically significant. Trends in proportional changes per year of incidence of cancer diagnosed during pregnancy or lactation were tested by a loglinear model with calendar year as a continuous variable. SPSS version 15.0 (SPSS, Chicago, IL) was used for all analyses.

RESULTS

Among the 42,511 eligible women (Fig 1) included in the first analysis, 41,464 were not pregnant, 516 were pregnant, and 531 were lactating (Fig 2, Table 1). In the second analysis, the reference group included 40,200 women and the postcancer pregnancy group consisted of 2,311 at end of follow-up (Fig 2, Table 2).

Figure 2 displays the frequency of the different cancer types observed in the whole study population and in the different subgroups. Although breast cancer was the most frequent diagnosis in the age group studied, malignant melanoma and cervical cancer were the

Table 1. Descriptive Data for the Subgroups Not Pregnant, Pregnant, and Lactating When Diagnosed With Cancer (first analysis)

	Total		Cause-Specific Death		OAS 60		Diagnosed and Deceased						Median (years)		Extent of Disease (%)			
							1967-1984		1985-1994		1995-2004							
Cancer Type	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Age	Follow-Up	Localized	Regional	Distant	Unknown
All sites																		
Not pregnant	41,464	97.5	12,965	31	14,355	35	17,202	38	12,799	32	11,463	21	42	9.0	53	18	11	18
Pregnant	516	1.2	133	26	144	28	179	35	185	26	152	15	29	9.9	63	10	8	19
Lactating	531	1.2	135	25	149	28	218	38	153	18	160	16	30	9.8	65	13	9	13
Malignant melanoma																		
Not pregnant	4,460	93.9	551	12	646	15	1,546	18	1,641	11	1,273	7	39	11.9	89	2	2	7
Pregnant	160	3.4	25	16	29	18	57	30	56	7	47	9	29	11.9	89	1	2	9
Lactating	126	2.7	15	12	19	15	44	25	49	6	33	3	30	13.8	91	3	1	5
Cervical cancer																		
Not pregnant	5,865	96.9	1,237	21	1,477	26	3,074	23	1,557	22	1,234	15	39	11.9	82	12	3	3
Pregnant	80	1.3	14	18	14	18	22	9	33	30	25	8	30	10.8	80	13	6	1
Lactating	111	1.8	15	14	17	15	41	20	34	12	36	8	31	11.5	87	7	3	4
Breast cancer																		
Not pregnant	13,106	99.2	4,065	31	4,410	34	5,082	39	4,083	36	3,941	16	44	8.8	35	31	3	31
Pregnant	59	0.4	26	44	28	48	15	73	23	44	21	24	34	4.9	24	31	12	34
Lactating	46	0.3	31	67	32	70	17	94	15	47	14	57	34	3.0	20	40	17	24
Lymphoma and leukemia																		
Not pregnant	2,576	96.1	1,145	44	1,260	49	1027	62	827	42	722	23	38	6.1	14	0	6	80
Pregnant	54	2.1	26	48	29	54	27	56	15	60	12	17	26.5	5.1	11	0	13	76
Lactating	46	1.8	16	35	19	41	18	39	14	43	14	21	28	7.6	15	0	11	74
Thyroid cancer																		
Not pregnant	1,789	95.8	40	2	77	4	790	3	565	2	434	1	37	14.4	69	26	2	3
Pregnant	33	1.8	1	3	1	3	11	0	15	7	7	0	27	15.8	58	40	0	3
Lactating	46	2.4	0	0	2	4	21	0	8	0	17	0	29	16.3	54	41	0	4
Ovarian cancer																		
Not pregnant	2,688	98.0	1,250	47	1,351	50	1,265	52	818	47	605	35	43	5.7	38	5	54	3
Pregnant	38	1.4	4	11	4	11	15	13	14	7	9	11	28	13.5	61	8	24	8
Lactating	15	0.6	7	47	7	47	9	56	4	50	2	0	31	5.9	60	7	33	0

NOTE. OAS 60 refers to overall survival at the age of 60, if not restricted by date (December 31, 2004). OAS 60 is given as number of deceased patients by all causes and percentage related to total number per group.

Table 2. Time-Dependent Survival (second analysis) for Women Nulliparous or Only With Precancer Pregnancies (before) Compared With Women With Postcancer Pregnancies (after)

	Univariate Analysis															
		Cause-Specific Death		OAS 60		Median (years)		Diagnosed and Deceased						Multivariate Analysis for Cause-Specific Death			
								1967-1984		1985-1994		1995-2004					
Cancer Site	Total No.	No.	%	No.	%	Age	Follow-Up	No.	%	No.	%	No.	%	Crude HR	95% CI	HR	95% CI
All sites																	
Before	40,200	13,105	33	14,479	36	42	8.6	16,764	39	12,217	34	11,219	21	1.00 (ref)		1.00 (ref)	
After	2,311	128	6	169	7	26	15.2	835	9	920	4	556	2	0.34*	0.29 to 0.41	0.49*	0.41 to 0.59
Malignant melanoma																	
Before	3,949	550	14	646	16	40	11.4	1,375	21	1,416	12	1,158	8	1.00 (ref)		1.00 (ref)	
After	797	41	5	48	6	26	15.4	272	9	330	4	195	2	0.63*	0.46 to 0.88	0.86	0.60 to 1.22
Cervical cancer																	
Before	5,872	1,264	22	1,502	27	39	11.8	3,094	23	1,542	23	1,236	15	1.00 (ref)		1.00 (ref)	
After	184	2	1	6	3	28	12.3	43	2	82	1	59	0	0.12*	0.03 to 0.48	0.22*	0.06 to 0.89
Breast cancer																	
Before	13,073	4,092	31	4,438	34	44	8.8	5,071	39	4,053	37	3,949	16	1.00 (ref)		1.00 (ref)	
After	138	30	22	32	23	30	12.7	43	35	68	18	27	11	0.95	0.66 to 1.36	0.70	0.48 to 1.02
Lymphoma and leukemia																	
Before	2,404	1,173	49	2,404	53	39	5.0	965	67	751	48	688	25	1.00 (ref)		1.00 (ref)	
After	272	14	5	272	12	23	15.5	107	11	105	1	60	2	0.20*	0.12 to 0.35	0.25*	0.14 to 0.43
Thyroid cancer																	
Before	1,529	39	3	74	5	39	13.8	672	4	461	2	396	1	1.00 (ref)		1.00 (ref)	
After	339	2	1	6	2	26	17.7	150	0	127	1	62	2	0.57	0.13 to 2.44	1.67	0.32 to 8.82
Ovarian cancer																	
Before	2,673	1,259	47	1,360	51	43	5.5	1,272	52	804	48	597	35	1.00 (ref)		1.00 (ref)	
After	68	2	3	2	3	26	13.6	17	12	32	0	19	0	0.13*	0.03 to 0.53	0.75	0.18 to 3.04

NOTE. Univariate analyses are presented as crude HR. Multivariate analyses are adjusted for age, diagnostic period, and initial extent of disease.
Abbreviations: HR, hazard ratio; ref, reference.
*Indicates significant HRs; $P < .05$.

most common malignancies during pregnancy or lactation. The incidence of cancer diagnosed during pregnancy or lactation have slightly increased during the study period, annually 2.5% (95% CI, 1.7 to 3.3) and 1.6% (95% CI, 1.0 to 2.4), respectively (Fig 3). In general, about 1 in 2,000 pregnancies is complicated by cancer.

For all sites combined, the median follow-up was 9.0 years (range, 0 to 38 years), with similar figures for the pregnant and lactating subgroups (Table 3). For the postcancer pregnancy group, median observation time from diagnosis was 15.2 years (Table 2), and median time until first postcancer delivery 3.5 years (not shown).

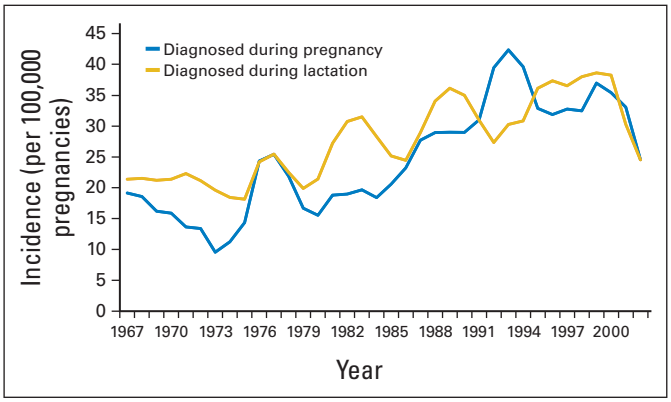

Fig 3. Annual incidence of cancer diagnosed during pregnancy or lactation, using 3-year moving averages, showed as proportions per year per 100,000 pregnancies. Mean annual proportions in the period studied for pregnant women were 24.5/100,000 pregnancies and for lactating women 27.7/100,000 pregnancies.

In general, there were no intergroup differences in extent of disease at diagnosis. Exceptionally, 57% of the women with breast cancer during lactation had advanced disease (regional or metastatic disease) compared with 34% among the not pregnant. The highest percentages of cause-specific death were observed among lactating women diagnosed with breast or ovarian cancer, 67% and 47%, respectively, and patients with lymphoma and leukemia diagnosed during pregnancy (48%; Table 1).

For all sites combined, with adjustment for age, extent of disease, and diagnostic period, the hazard ratios for cause-specific death were not significantly different in pregnant or lactating women compared with the not pregnant group (Table 3).

For pregnant women diagnosed with malignant melanoma, an elevated risk of cause-specific death was seen (HR, 1.52; 95% CI, 1.01 to 2.31; $P = .047$). No increased risk was found for those with the same diagnosis during lactation. The main primary tumor sites for pregnant women with malignant melanoma were head, neck, and trunk, constituting 54%, which was significantly different from the corresponding figure in not pregnant women (41%, analysis not shown) in whom leg melanomas were most frequent.

The risk of cause-specific death was significantly increased if breast or ovarian cancer was diagnosed during lactation (HR, 1.95; 95% CI, 1.36 to 2.78; $P < .001$ and HR, 2.23; 95% CI, 1.05 to 4.73; $P = .036$, respectively). No statistically significant intergroup differences were

Table 3. Cause-Specific Survival for the Subgroups Not Pregnant, Pregnant, And Lactating When Diagnosed With Cancer (first analysis)

Cancer Site	Cause-Specific Death			
	Crude HR	95% CI	HR	95% CI
All sites				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	0.79*	0.66 to 0.93	1.03	0.86 to 1.22
Lactating	0.76*	0.64 to 0.90	1.02	0.86 to 1.22
Malignant melanoma				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.23	0.83 to 1.84	1.52*	1.01 to 2.31
Lactating	0.92	0.55 to 1.53	1.10	0.65 to 1.85
Cervical cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	0.86	0.51 to 1.46	0.89	0.52 to 1.53
Lactating	0.61	0.37 to 1.02	0.94	0.56 to 1.57
Breast cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.77*	1.20 to 2.60	1.23	0.83 to 1.81
Lactating	3.44*	2.40 to 4.92	1.95*	1.36 to 2.78
Lymphoma and leukemia				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.09	0.74 to 1.61	1.15	0.77 to 1.70
Lactating	0.72	0.44 to 1.18	0.89	0.54 to 1.46
Thyroid cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.34	0.18 to 9.71	4.58	0.59 to 35.87
Lactating	0.00	0.00 to ∞	0.00	0.00 to ∞
Ovarian cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	0.17*	0.06 to 0.46	0.46	0.17 to 1.23
Lactating	0.93	0.44 to 1.95	2.23	1.05 to 4.73

NOTE. Univariate analyses are presented as crude HR. Multivariate analyses (right column) are adjusted for age, diagnostic period and initial extent of disease.
Abbreviations: HR, hazard ratio; ref, reference.
*Indicates significant HRs; $P < .05$.

observed for pregnant or lactating women for the other diagnoses in the adjusted multivariate analyses (Table 3).

For all sites combined, women with a postcancer pregnancy had a significantly lower risk of cause-specific death than the reference group (HR, 0.49; 95% CI, 0.41 to 0.59). Compared with women without a subsequent pregnancy, women with postcancer pregnancies and a diagnosis of cervical cancer, lymphoma, or leukemia, had approximately 80% lower risk of cause-specific death (Table 2).

DISCUSSION

For all sites combined, no increased risk of cause-specific death was observed in 1,047 women with their first cancer diagnosed during pregnancy or lactation. However, in the subgroups of lactating women diagnosed with breast or ovarian cancer, the HRs were doubled. For pregnant women diagnosed with malignant melanoma, the risk of cause-specific death was slightly elevated. For all sites combined and for patients with cervical cancer and lymphoma and leukemia with a postcancer pregnancy, a significantly reduced risk of cause-specific death was found. This is described as "the healthy mother effect", implying a self-selection among women who have undergone cancer treatment, whether they choose to get pregnant afterward or not.[22]

The most frequent malignancy diagnosed during pregnancy in our population was malignant melanoma. This is consistent with a Swedish study, but different from most other reports.[6,11,12,23] Compared with several studies with observation of only 5 years, our long follow-up (median time, 11.9 years) is considered advantageous, as malignant melanoma frequently have a long natural history. If diagnosed during pregnancy, we found a slightly raised risk of cause-specific death (HR, 1.52; $P = .047$). The elevated HR for pregnant women is possibly related to delayed diagnosis. Both pregnant women and their doctors may underestimate the possible risk of a darkening mole, as hyperpigmentation during pregnancy is common. Marked changes of a nevus during pregnancy should be suspected as a malignant development and warrants diagnostic excision.[3,6,24] Myths have persisted from 1951 about worse survival for pregnant women diagnosed with malignant melanoma.[1,3,6] Based on a small, uncontrolled study where only 10 women were pregnant at diagnosis, the authors suggested hormone factors to be related to unfavorable outcome. Contradictory results have later been published. A recent study from Sweden similar to ours did not find an increased risk of death in women diagnosed during pregnancy.[6] Some researchers mention a more advanced stage at diagnosis, as a greater Breslow thickness, or a poorer prognostic site distribution in pregnant women as reasons for worse survival.[7] We did not find any intergroup difference in stage. However, the extent of the disease is described in coarse terms by the registry. As the risk of cause-specific death in the pregnant group differed from that in the reference group, we added available information about stage, and did a subanalysis comparing tumor thickness in the pregnant group with two nonpregnant controls for each case matched for age and time period. For 55% of the pregnant group in which the Breslow thickness was available, we found no difference in tumor thickness compared with not pregnant patients (data not shown). As the intergroup differences of cause-specific survival were observed to be relatively small, and particularly no increased death risk was observed among lactating women, pregnancy-related hormone factors seem unlikely to be the main explanation of our slightly elevated HRs in the pregnant group. The prognostically negative site localization[25] for the pregnant group (larger proportions with head, neck, and trunk melanomas) could partly explain the poorer outcome for this subgroup. When adjustment for localization, the HR was reduced from 1.52 to 1.45 (95% CI, 0.96 to 2.21) for the pregnant women (analysis not shown). Our results are, in our opinion, not differing from the view developed in recent decades, doubting that malignant melanoma diagnosed during pregnancy is adversely influenced by pregnancy-induced hormone levels.[6,7]

Unlike most other cancer types, cervical cancer is relatively easily detected during pregnancy. Our results for pregnant or lactating women confirm previous observations of no differences in survival if adjusted for stage, age, and period.[8,26,27] However, there might still be some delay of diagnosis in the later part of the pregnancy, as the number of patients diagnosed during the first 6 months postpartum is greater than during pregnancy (Table 1). Patients with cervical cancer with postcancer pregnancies had a decreased risk of cause-specific death. Obviously, these patients had low-stage primary tumors, and underwent fertility-preserving treatment.

In this study, we found worse outcome for lactating women with breast cancer, even when adjusted for age and extent of disease. In pregnant and lactating women, patient and doctor delay probably represents one explanation, as changes or lumps in the breast during

pregnancy or lactation may be regarded as normal. Mammograms are also difficult to interpret in these patients. Some previous studies explained the poorer outcome of pregnant women as due to faster estrogen-mediated progression of the malignancy.[28] Our findings support this assumption only partly, as we observed increased death risk only if the breast cancer was diagnosed during lactation. Conversely, the tumor cells have been exposed to increased estrogen levels throughout the whole pregnancy. If there truly were a hormone link, our pregnant group should also have displayed a significantly increased HR. The influence of the extent of the disease cannot satisfactorily be assessed by our coarse categorizations. The imperfect stage categorization and the lacking information about hormone receptor status, implies that there could be residual confounding factors associated with these variables. The HR declines from 3.44 to 1.95 shown by the uni- and multivariate analyses (Table 3). The confounding effect thus leads us to believe that the extent of the disease, probably related to diagnostic delay, plays an important role. More advanced stages among women diagnosed during pregnancy, or shortly thereafter have also been reported in previous studies.[2,4,10] Unrecognized hormone factors, or physiological or immunological changes could partly explain the raised risk of death, but the available data could not identify a particular reason. Even after adjustment for number of previous pregnancies, there were no differences in survival among those who had no, one, two, or three or more pregnancies before the cancer diagnosis (data not shown).

For lymphoma and leukemia diagnosed during pregnancy and lactation, there seems to be no difference in survival compared with the not pregnant group. Our results confirm the case reports published earlier,[29,30] although the impact of histological subtype and stage could not be studied in detail because such information were lacking. Delay in treatment and even diagnostic delay may influence the prognosis for certain leukemia's and non-Hodgkin's lymphomas, while in Hodgkin's disease patients, treatment may be safely postponed until after delivery in selected cases.

The percentage of women who became pregnant after cancer was highest among those who were diagnosed with thyroid cancer (Table 2). Like other studies published on thyroid cancer, we observed no significant difference in survival for pregnant or lactating women, when compared with not pregnant patients.[31,32]

For women with ovarian cancer, we found poorer survival if the malignancy was detected during lactation, although admittedly this was only in 15 women. The pregnant women seemed to have reduced risk of cause-specific death. Physical examination and ultrasound investigation during pregnancy might imply early diagnosis of an ovarian tumor, likewise with incidentally detected tumors during caesarean delivery. As shown in other studies, a greater proportion (60%) was diagnosed with only local disease in the pregnant and lactating group, in contrast to approximately 40% in the not pregnant group.[33-35] Approximately 5% to 10% of all patients with ovarian cancer are hereditarily predisposed, which is associated with tumor development about 10 years earlier.[36] Lacking information about genetic factors, we do not know the status of *BRCA1/BRCA 2* mutations of the 15 patients with ovarian cancer in the lactating group.

This is a nationwide, registry-based study, covering the most frequent cancer diagnoses for women in their childbearing period. Most articles on this topic only investigate one cancer type, and the vast majority is single institution reports, which may include selection bias. Contrary to several other studies using Kaplan-Meier statistics or standard Cox regression, we used time-dependent Cox regression analyses, which is of pivotal importance when analyzing the postcancer pregnancy group. We would otherwise introduce bias toward too high survival for those with a subsequent pregnancy.[37,38]

Some limitations of our study have to be mentioned. For the period studied, there are no serum tumor markers, hormone receptor status or other newer prognostic factors registered and the extent of the disease is registered only in coarse terms. The underlying cause of death may imply uncertainty, including positive and negative misclassification. However, the HR for overall survival as an end point did not differ substantially from our cause-specific survival results (analyses not shown). The CRN provides data about initial treatment (usually first 4 months postdiagnosis), but because cancer treatment often lasts longer, this information is not complete enough to be incorporated in our analyses. Neither is there any information on relapse therapy.

In conclusion, a new cancer diagnosis during pregnancy or lactation does not, in general, increase the risk of cause-specific death compared with cancers diagnosed in not pregnant or nonlactating women.

Exceptions are a diagnosis of breast cancer or ovarian cancer during lactation and malignant melanoma detected during pregnancy. Detection of these malignancies requires particular awareness by health care professionals. We confirmed the "healthy mother effect" seen in women pregnant after a cancer diagnosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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