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Original Research

Cancer survival in women diagnosed with pregnancy-associated cancer: An overview using nationwide registry data in Sweden 1970–2018

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Abstract ***Background:*** Pregnancy-associated cancer (PAC) is increasing over time in many countries. We provide a comprehensive, population-based overview of cancer survival in women with PAC across five decades.
Methods: We performed a nationwide cohort study of 121,382 women diagnosed with cancer at age 15–49 between 1970 and 2018 using birth and cancer registers in Sweden. Pregnancy-

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Mortality;
Survival

associated cancer was defined as diagnosed during pregnancy and within one year of delivery, while non-PAC was outside this window. Cox regression estimated adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) comparing cancer mortality for PAC versus non-PAC.

Results: In total, 5079 women had a diagnosis of PAC. Cutaneous malignant melanoma, breast, cervical, thyroid and central nervous system (CNS) were the most common sites of PAC. A higher cancer mortality was observed in PAC versus non-PAC for breast (HR = 1.72, 95% CI 1.54–1.93) and uterine cancer (myometrium/unspecified) (8.62, 2.80–26.53), in which all PAC deaths were uterine sarcomas. Increased mortality was also observed in upper digestive tract cancer diagnosed during pregnancy and colon cancer diagnosed during first year after delivery. Contrary, the HR for CNS tumours was significantly decreased (0.71, 0.55–0.91). Survival after PAC improved for most sites over time, with survival after breast cancer during pregnancy in recent years being similar to that of non-pregnancy associated breast cancer.

Conclusion: For the majority of sites, PAC was not associated with poorer prognosis compared to non-PAC, a finding which was stable over time. The main exceptions were breast cancer and rarer cancers, such as uterine sarcoma.

1. Introduction

Cancer during pregnancy and breastfeeding is increasing in numbers worldwide, likely due to postponement of childbearing [1–3]. An estimated 80–140/100,000 deliveries are affected by pregnancy-associated cancer (PAC), which is commonly defined as cancer during pregnancy and up to one year postpartum [4]. The use of chemotherapy during pregnancy has increased over time, as safety has been shown for both mother and child [5,6]. However, reliable survival estimates are lacking for many cancer types.

Single- and multi-center survival studies of PAC often focus on the most common cancer types, e.g. breast and cervix, and many under-report cancer types often not treated by oncologists, e.g. cutaneous malignant melanoma (CMM). Population-based studies on PAC survival are needed to achieve sufficient power for rarer cancers and to reflect all patients in the population. Population-based data can also provide important time trends in PAC survival, which is a powerful tool to assess the impact of management and treatment changes over time for this special patient group.

Using nationwide cancer and birth registry data, we aimed to give an updated comprehensive overview of PAC survival. Specifically, we assessed time trends, survival by diagnostic windows before and after delivery and present estimates for understudied rarer cancer sites.

2. Methods

2.1. Study population

The Swedish Multigeneration Register (MGR) at Statistics Sweden includes Swedish residents born since 1932, with individual links to parents via the personal identification number assigned at birth or immigration. A cohort of women born from 1932 to 2003 was identified in the MGR, and childbirths to each woman until 2018 included via child–parental links.

The Swedish Cancer Register (SCR) records date of cancer diagnosis and codes for topography and morphology using the current version of the International Classification of Diseases for Oncology (ICD-O) and back-translates all years to the International Classification of Diseases (ICD) version 7 to enable comparisons over time. For this purpose, we used ICD-7 codes throughout the study period (Appendix Table A.1). Sarcoma was defined using the morphological code (Appendix Table A.2). Cancer sites were combined into groups with respect to the organ system, whereas some important subsites were investigated separately.

The MGR cohort of women was linked to the SCR to identify women with at least one recorded cancer diagnosis (ICD-7: 140–207) at ages 15–49 years between 1970 and 2018 (n = 122,057). Women with cancer diagnoses recorded before age 15 were excluded (n = 415). Among the remaining 121,642 women only the first cancer diagnosis recorded in ages 15–49 years was included in the analysis. The women were followed for death and emigration in the Cause of Death Register and the Total Population Register. We excluded 84 women with inconsistent migration history. We further excluded women with placental tumours (ICD-7 = 173; n = 176) which by definition only occur during pregnancy and therefore have no comparison group. The final analytical cohort included 121,382 women with cancer (Appendix Figure A.3).

2.2. Pregnancy-associated cancer (PAC)

Birthdates of liveborn children in the MGR determined whether the cancer was pregnancy-associated at time of diagnosis. A cancer diagnosed during pregnancy (0–9 months before birthdate of a child) and within 0–12

months after delivery (1st year postpartum) was defined as PAC. If two deliveries occurred in the diagnostic window, the delivery closest to the cancer diagnosis was used as index delivery. We further separated cancer during pregnancy and the first year postpartum into two entities because tumour progression seems to differ during pregnancy, lactation and weaning and the treatment-related difficulties in PAC are mainly restricted to treatment given during pregnancy. The pregnancy window was separated into trimesters using gestational age information from the Swedish Medical Birth Register available 1973–2017. Non-pregnancy-associated cancer (non-PAC) was defined as cancer diagnosed before pregnancy or >12 months after delivery, or cancer in nulliparous women. Furthermore, we assessed cancer in 12–24 months after delivery (2nd year postpartum), with non-PAC correspondingly defined as before pregnancy or >24 months after delivery, or cancer in nulliparous women.

2.3. Cause of death

Date and underlying cause of death was obtained from the Swedish Cause of Death Register. The primary endpoint was 'any cancer' death (malignant tumours according to ICD-7: 140–207; ICD-8: 140–209; ICD-9: 140–208; ICD-10: C00–C99) and not analysed specific to each site because of the complexity of ICD versions across time. The vast majority of deaths were site-specific as the cohort was young and with few second cancers.

2.4. Confounders

Confounders included number of children before cancer, maternal country of birth and education level at one year prior to cancer diagnosis (categorized as primary, secondary, tertiary <3 years or tertiary ≥3 years). Because of missing information (5.8%), education was only used in sensitivity analyses.

2.5. Statistical methods

Incidence rates were estimated as number of PACs per 100,000 deliveries per year. For survival, the start of follow-up was at date of cancer diagnosis, and the end of follow-up was at date of cancer death, date of other causes of death, date of first emigration after cancer, end of study (31 Dec 2018) or 10 years after cancer diagnosis, whichever came first. Cancer mortality rates were modelled using Cox regression yielding hazard ratios (HRs) with 95% confidence intervals (CIs) comparing PAC to non-PAC and with adjustment for age (1-year categories) and year (10-year categories) at diagnosis, country of birth (Nordic, non-Nordic) and parity before cancer (0, 1, 2, 3 or more children). Additional adjustment for education in women with known education status did not alter the results. Thus, education was excluded from the main analysis to retain more cases.

The PAC risk window was subdivided into finer windows before/after delivery to assess the timing of cancer and childbirth (1st, 2nd, 3rd trimesters, 0–3, 3–6, 6–12, 12–18 and 18–24 months postpartum). Interactions between PAC status and calendar period were tested using likelihood ratio tests. Age-standardized cancer survival proportions in the PAC group were estimated at 5 and 10 years using model-based predictions from a flexible parametric survival model [7]. All tests were two-sided and the significance level 5%. Stata version 16.0/IC was used for the analyses. Ethical approval was obtained from the Swedish Ethical Review Authority.

3. Results

Of 121,382 female patients diagnosed with cancer in ages 15–49 years during 1970–2018, 5079 (4.2%) were diagnosed during pregnancy and within first year postpartum, while 116,303 (95.8%) were diagnosed before pregnancy, >1 year after delivery or in nulliparous women (Appendix Table A.4). Women with PAC were younger and had fewer children than women with non-PAC. Median follow-up for death was 6.96 (PAC) and 6.97 years (non-PAC). The most common sites of PAC were the breast (n = 975), malignant melanoma of skin (n = 954), cervix (n = 704), brain and nervous system (n = 406), thyroid (n = 384) and lymphoid system (lymphoma) (n = 324) (Table 1, Appendix Fig. A.5). Pregnancy-associated cancer also occurred to some extent in other endocrine glands (n = 202), ovaries (n = 179), colon (n = 184), blood (leukemia) (n = 133) and remaining sites (n = 634). Rarer cancer types are presented in Appendix Table A.6. The incidence of PAC increased over time, with the incidence during pregnancy being about half of the incidence during the first- and second-year post-delivery (Fig. 1).

The majority of cancer sites showed no or non-significant differences in cancer mortality between PAC during pregnancy and within first year postpartum and non-PAC (Table 1). Increased cancer mortality was observed for breast (adjusted HR = 1.72, 95% CI: 1.54–1.93) and uterus (myometrium or unspecified) (8.62, 2.80–26.53) while the associations for the pancreas (1.72, 0.95–3.13), stomach (1.34, 0.90–2.00) and myeloma (1.46, 0.48–4.43) were non-significantly increased. Pregnancy-associated gynecological sarcomas were associated with increased cancer mortality (3.13, 1.06–9.25), and all PAC deaths occurred in women with uterine sarcoma (7.54, 2.16–26.30). Similar but attenuated effects were observed if pregnancy association was defined as within two years after delivery (Appendix Table A.7).

Compared to women with non-PAC, the cancer mortality was significantly increased in women

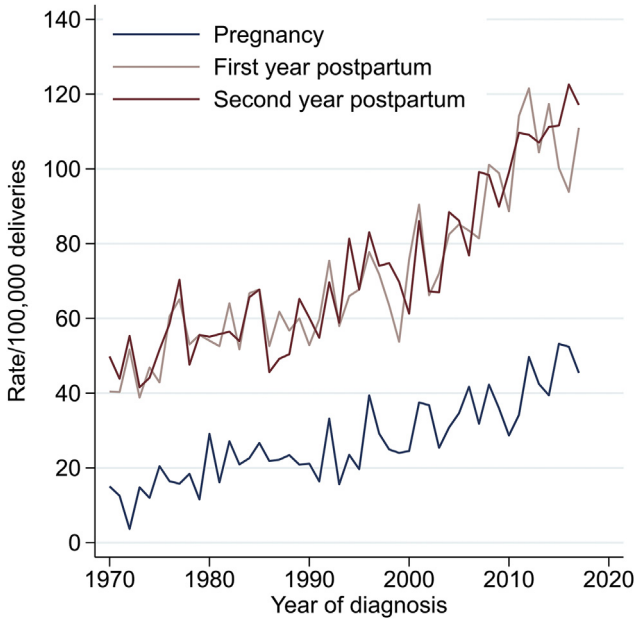

Fig. 1. Incidence of cancer during pregnancy, 1st year postpartum and 2nd year postpartum between 1970 and 2018.

diagnosed during pregnancy with cancers of the stomach (HR = 3.29, 95% CI: 1.42–7.61), pancreas (5.70, 1.97–16.47) and breast (1.80, 1.43–2.28) and during the first-year postpartum with cancers of the breast (1.76, 1.55–2.00), uterine myometrium (8.51, 2.76–26.22) and colon (1.42, 1.02–1.99) (Table 2). For diagnoses during the second-year postpartum, only breast cancer was significantly associated with increased mortality (1.27, 1.13–1.44). For CMM, cervical or ovarian cancers, no increased mortality was observed if diagnosed during pregnancy or up to two years after delivery. For the small number of women diagnosed with cancer of the respiratory tract during pregnancy, a non-significantly elevated HR was observed.

Further subdividing the PAC window into finer intervals during pregnancy trimesters and within two years postpartum, we observed an increased adjusted HR for breast cancer if diagnosed from the 2nd trimester until two years after delivery compared to non-PAC (Fig. 2, Appendix Table A.8). For cervical cancer, there was no association with increased mortality, although the HR was non-significantly elevated if diagnosed in the 3rd trimester and 6–12 months postpartum compared to non-PAC. For CMM, the HRs were non-significantly increased in women diagnosed in the 2nd and 3rd trimesters and 0–3 months after delivery, but also significantly increased 18–24 months after delivery. For central nervous system (CNS) tumours, there was no association with increased mortality during pregnancy and after delivery, although the HR was significantly decreased if diagnosed 0–3 months after delivery. The adjustments ensured that the comparison group (non-PAC) was similar to women with PAC in terms of age, year of diagnosis, previous parity and maternal country of birth.

3.1. Time trends

As a proxy for management and treatment changes over time, we evaluated time trends in survival of PAC. For PAC diagnosed during pregnancy and within first year postpartum, the 5- and 10-year age-standardized survival proportions improved over calendar period for breast cancer, cervical cancer, colon cancer, CMM, CNS cancer, lymphoma and leukemia, while only minor improvement was observed for ovarian cancer (Table 3). To assess whether the survival improvements over time in women with PAC were of similar magnitude to improvements in women with non-PAC, we assessed HRs comparing PAC to non-PAC over time. The adjusted hazard ratios indicated no differences between PAC and non-PAC over time, thus indicating similar survival improvements in both groups. However, for breast cancer diagnosed during pregnancy the hazard ratio decreased to non-significant over time but remained elevated if diagnosed within one year after delivery (Fig. 3, Appendix Table A.9).

4. Discussion

In this comprehensive population-based study covering nearly five decades of PAC, we found no worse cancer survival for women with PAC versus non-PAC for the majority of cancer types. The few, but important, exceptions were cancer of the breast and uterus (myometrium/UNS), where breast cancer represents a large proportion of PAC cases. We also found that neither CMM nor cervical cancer were associated with a poorer prognosis if diagnosed during or within a year of pregnancy. Upper digestive tract cancer during pregnancy was also associated with worse prognosis, as was colon cancer diagnosed during first year post-delivery. The CNS was the only site showing a significantly better prognosis for PAC than non-PAC.

In four selected tumour sites (breast, CMM, cervix and CNS) representing 60% of all PAC, survival after PAC improved over calendar periods. These improvements were of similar magnitude as in non-PAC, indicating that the overall estimates in Table 1 are valid throughout the study period and that treatment improvements have been beneficial for patients regardless of PAC status. For breast cancer diagnosed during pregnancy, survival has in recent years approached that of women with non-PAC, which is likely due to increasing use of standard breast cancer treatment also in pregnant patients [6].

Two major overview studies of maternal survival in PAC included up to ten cancer types; however, they did not report the rarer types presented in our study [3,8].

Several meta-analyses have investigated maternal prognosis in pregnancy-associated breast cancer and CMM, the two most common cancer types coinciding with pregnancy [9–13]. Additional larger studies have assessed cervical cancer [14–16], but fewer have investigated less common cancer types such as lymphoma, thyroid, colorectal and gastric cancer [3,17–19].

For breast cancer, we and others have shown that after adjustment for differences in stage, tumour biology and treatment, there was no difference in survival for women with breast cancer during pregnancy compared to non-pregnant women [20,21]. Neither have we found evidence of treatment delays for women with PAC of the breast [22]. Contrary to previous population-based studies on pregnancy-associated CMM [3,8,23], we found no significant overall survival disadvantage in the current analysis or in a previous publication [24]. Earlier studies have been stage-adjusted [8,23], while we were unable to adjust for stage or treatment. However, because effective systemic treatments have only been available in recent years, a decisive difference in treatment efficacy would have to be attributed to the surgical procedures.

In line with our findings, most recent studies have found no difference in survival for PAC and non-PAC of the cervix [8,15,16,25]. Sood *et al.* [26] reported a worse prognosis if diagnosed postpartum, while Eibye *et al.* [14] reported a higher mortality if diagnosed during pregnancy, also including pregnancies that ended in abortion. We did not have information on abortions, which may have introduced selection bias of estimates for early pregnancy. For rarer gynecological cancers, i.e. ovarian, endometrial, vaginal and vulvar cancer, the literature is scarce and prognosis appears to mainly depend on stage at diagnosis and tumor type rather than pregnancy [27–29]. Increased surveillance during pregnancy may also improve the chances of pre-symptomatic detection for gynecological cancers [29]. For vulvar

Table 1
Numbers of cases, cancer deaths and adjusted hazard ratios of PAC (during pregnancy combined with within 1st year postpartum) vs. non-PAC in women 15–49 years in Sweden 1970–2018.

Site	Cases			Deaths		PAC versus non-PAC
	Non-PAC	PAC	% PAC	Non-PAC	PAC	HR (95% CI)[a]
Head and neck	**1646**	**96**	**5.5**	**309**	**10**	**0.55 (0.29–1.08)**
Upper digestive tract	**2900**	**88**	**3.0**	**2231**	**66**	**1.33 (1.03–1.73)**
Stomach	1224	36	2.9	859	29	1.34 (0.90–2.00)
Liver and bile ducts	789	26	3.2	644	19	1.13 (0.68–1.88)
Pancreas	707	21	2.9	593	15	1.72 (0.95–3.13)
Lower digestive tract	**5876**	**249**	**4.1**	**1950**	**71**	**1.19 (0.92–1.53)**
Colon	3650	184	4.8	1199	49	1.25 (0.92–1.69)
Rectum	1933	51	2.6	657	19	1.16 (0.71–1.91)
Respiratory tract	**2722**	**39**	**1.4**	**2042**	**19**	**0.80 (0.50–1.29)**
Breast	**41,723**	**975**	**2.3**	**7914**	**340**	**1.72 (1.54–1.93)**
Gynecological	**19,191**	**929**	**4.6**	**4221**	**140**	**1.05 (0.88–1.25)**
Cervix uteri	9891	704	6.6	1547	92	1.06 (0.85–1.32)
Corpus uteri	2303	6	0.3	196	<5	4.58 (0.61–34.51)
Uterus (myometrium or UNS)	712	6	0.8	194	5	8.62 (2.80–26.53)
Ovary and tubes	5600	181	3.13	2110	37	0.98 (0.70–1.38)
Gynecological (other or UNS)	625	31	4.73	144	5	0.71 (0.27–1.90)
Urinary tract	**2040**	**72**	**3.4**	**487**	**10**	**0.88 (0.45–1.71)**
Cutaneous malignant melanoma (CMM)	**11,464**	**954**	**7.7**	**796**	**60**	**0.99 (0.75–1.31)**
Brain and nervous system	**7050**	**406**	**5.5**	**1591**	**73**	**0.74 (0.58–0.94)**
Central nervous system (CNS)	6659	379	5.4	1541	68	0.71 (0.55–0.91)
Endocrine glands	**9679**	**586**	**5.7**	**216**	**11**	**1.21 (0.64–2.30)**
Bone and soft tissue	**1577**	**103**	**6.1**	**440**	**25**	**0.81 (0.53–1.23)**
Lymphoma	**4818**	**324**	**6.3**	**956**	**52**	**1.17 (0.87–1.57)**
Non-Hodgkin lymphoma	2358	126	5.1	600	28	0.98 (0.66–1.46)
Hodgkin's disease	1844	173	8.6	154	14	1.16 (0.64–2.07)
Myeloma	421	10	2.3	168	6	1.46 (0.48–4.43)
Leukemia	**2617**	**133**	**4.8**	**1058**	**55**	**0.91 (0.69–1.21)**
Acute lymphoblastic leukemia (ALL)	389	19	4.7	194	10	0.77 (0.38–1.56)
Acute myeloid leukemia (AML)	1058	66	5.9	563	36	0.94 (0.65–1.35)
Sarcoma (any site)	**2424**	**121**	**4.8**	**745**	**35**	**0.95 (0.67–1.36)**
Gynecological sarcoma	629	10	1.6	186	5	3.13 (1.06–9.25)
Uterine sarcoma	546	6	1.1	157	5	7.54 (2.16–26.30)
Osteosarcoma	483	31	6.0	140	8	0.76 (0.34–1.72)
Soft tissue sarcoma	974	62	6.0	283	16	0.81 (0.47–1.39)

PAC, pregnancy-associated cancer.
[a] Hazard ratio (HR) adjusted for age and year at diagnosis, parity before cancer and maternal country of birth.

cancer, a review of 36 case reports indicated that pregnancy may instead delay diagnosis and thereby worsen prognosis [30].

Colorectal cancer (CRC) during pregnancy often has a more advanced stage at diagnosis than non-PAC, which could be due to CRC and pregnancy causing similar symptoms. However, pregnancy-associated CRC has not been associated with worse survival when adjusting for extent of disease [3,17]. Similar patterns have been observed for women with PAC in the stomach [18,31]. Gliomas are the most studied CNS tumours in pregnancy, and the overall findings from case series indicate no detrimental effect of pregnancy on survival [32]. Neither has pregnancy been associated with worse prognosis in women with hematological malignancies [8,33] or thyroid cancer [19,34]. For other endocrine tumours, we observed elevated yet non-significant point estimates for PAC compared to non-PAC, which has been reported previously [35]. Data on urinary tract cancers during pregnancy are sparse [36]. We found no increased mortality in urinary tract cancer either pre- or post-delivery. Case reports on lung cancer during pregnancy have indicated more late-stage disease and poorer prognosis [37]. We found a non-significantly increased mortality for women with lung cancer diagnosed during pregnancy but not if diagnosed post-delivery. In line with previous reports, we found no increased mortality in women with pregnancy-associated bone/soft-tissue sarcoma [38]. However, in women with gynecological sarcomas diagnosed after delivery we found a worse prognosis, to our knowledge not previously reported [39].

Although cancer during pregnancy and the postpartum period are often assessed in combination, these two entities are different in terms of biology, diagnostic difficulties and delays, and treatment. Hormonal and immunological changes during pregnancy could affect cancer progression across all malignancies, yet there may also be tumour type-specific effects. For breast cancer, the involution of the breast tissue after weaning has been suggested to promote tumour progression, which could explain the poorer prognosis for postpartum breast cancer [40]. The diagnostic patient and doctor delays due to misinterpreted cancer symptoms as

Table 2
Association between diagnostic windows of PAC (during pregnancy, 1st year and 2nd year postpartum) versus non-PAC and cancer mortality by selected sites and groups.

Site	Pregnancy			0–12 months post-partum			12–24 months post-partum		
	Cases	Deaths	HR (95% CI)[a]	Cases	Deaths	HR (95% CI)[a]	Cases	Deaths	HR (95% CI)[a]
Head and neck	24	<5	0.70 (0.22–2.29)	72	7	0.48 (0.22–1.05)	55	5	0.52 (0.21–1.29)
Upper digestive tract	15	14	3.08 (1.78–5.36)	73	52	1.13 (0.85–1.51)	62	39	0.78 (0.56–1.09)
Stomach	7	7	3.29 (1.42–7.61)	29	22	1.10 (0.70–1.72)	31	18	0.67 (0.41–1.08)
Liver and bile ducts	<5	<5	1.10 (0.33–3.71)	22	16	1.09 (0.63–1.88)	13	9	0.92 (0.45–1.85)
Pancreas	<5	<5	5.70 (1.97–16.47)	17	11	1.29 (0.63–2.62)	12	9	1.02 (0.48–2.15)
Lower digestive tract	70	16	0.91 (0.55–1.50)	179	55	1.30 (0.98–1.72)	144	40	1.04 (0.75–1.43)
Colon	54	10	0.85 (0.45–1.60)	130	39	1.42 (1.02–1.99)	96	27	1.18 (0.80–1.75)
Rectum	10	<5	1.43 (0.51–4.04)	41	15	1.11 (0.64–1.93)	43	13	0.92 (0.52–1.63)
Respiratory tract	8	5	1.74 (0.67–4.51)	31	14	0.67 (0.39–1.16)	41	24	0.85 (0.56–1.29)
Breast	234	74	1.80 (1.43–2.28)	741	266	1.76 (1.55–2.00)	1074	293	1.27 (1.13–1.44)
Gynecological	306	33	0.76 (0.53–1.07)	623	107	1.18 (0.97–1.44)	614	85	0.92 (0.74–1.14)
Cervix uteri	219	21	0.79 (0.51–1.22)	485	71	1.16 (0.91–1.49)	489	56	0.87 (0.66–1.14)
Uterus (myometrium or UNS)	0	0	N/A	6	5	8.51 (2.76–26.22)	9	<5	0.82 (0.19–3.52)
Ovary and tubes	74	11	0.77 (0.42–1.41)	107	26	1.11 (0.74–1.65)	106	25	1.04 (0.70–1.56)
Gynecological (other or UNS)	10	<5	0.37 (0.05–2.98)	21	<5	0.89 (0.29–2.72)	8	<5	1.22 (0.27–5.63)
Urinary tract	19	<5	0.78 (0.19–3.23)	53	8	0.91 (0.44–1.89)	53	8	0.93 (0.45–1.92)
Cutaneous malignant melanoma (CMM)	339	26	1.24 (0.83–1.87)	615	34	0.90 (0.63–1.28)	504	40	1.27 (0.91–1.76)
Brain and nervous system	63	8	0.52 (0.26–1.06)	343	65	0.75 (0.58–0.97)	290	59	0.82 (0.63–1.08)
CNS	62	8	0.52 (0.26–1.04)	317	60	0.72 (0.55–0.94)	272	58	0.84 (0.64–1.10)
Endocrine glands	144	<5	1.07 (0.26–4.39)	442	9	1.32 (0.66–2.65)	493	9	1.18 (0.59–2.36)
Bone and soft tissue	33	10	1.06 (0.55–2.03)	70	15	0.69 (0.40–1.18)	59	15	0.98 (0.57–1.69)
Lymphoma	73	7	0.67 (0.32–1.42)	251	45	1.30 (0.95–1.79)	193	25	0.83 (0.55–1.26)
Non-Hodgkin lymphoma	30	7	1.08 (0.50–2.34)	96	21	0.93 (0.59–1.46)	73	13	0.74 (0.42–1.30)
Hodgkin lymphoma	37	0	N/A	136	14	1.59 (0.88–2.88)	102	6	0.75 (0.32–1.77)
Myeloma	<5	0	N/A	9	6	1.54 (0.50–4.78)	14	<5	1.73 (0.51–5.87)
Leukemia	39	14	1.08 (0.63–1.86)	94	41	0.86 (0.62–1.19)	105	43	0.95 (0.69–1.32)
Acute lymphoblastic leukemia (ALL)	7	<5	0.54 (0.19–1.57)	12	6	1.00 (0.39–2.56)	14	8	0.86 (0.38–1.95)
Acute myeloid leukemia (AML)	17	8	1.13 (0.54–2.35)	49	28	0.86 (0.57–1.30)	51	20	0.69 (0.43–1.12)

CI, confidence interval; PAC, pregnancy-associated cancer.

[a] Hazard ratio (HR) of PAC versus non-PAC adjusted for age and year at diagnosis, parity before cancer and maternal country of birth. Non-PAC defined as cancer diagnosed before pregnancy or >2 year after delivery, or in nulliparous women.

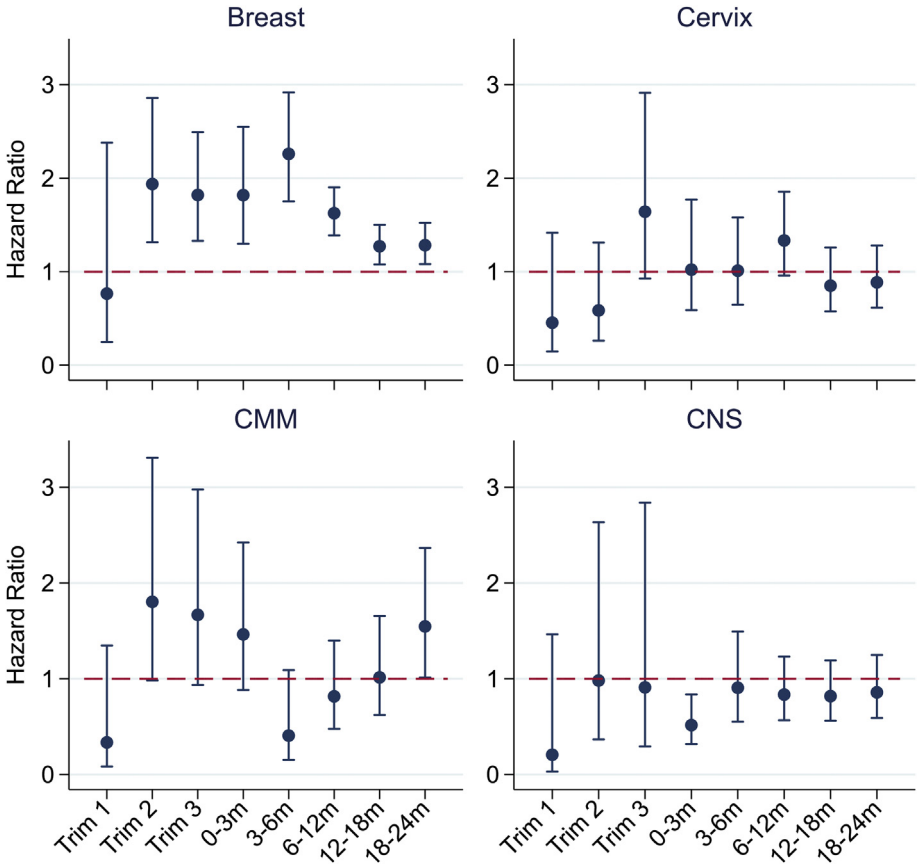

Fig. 2. **Association between diagnostic windows of PAC (during 1st, 2nd, 3rd trimesters, 0–3, 3–6, 6–12, 12–18 and 18–24 months postpartum) vs. non-PAC and cancer mortality for common sites.** Hazard ratios adjusted for age and year of diagnosis, parity before cancer and maternal country of birth. CMM, cutaneous malignant melanoma; CNS, central nervous system; PAC, pregnancy-associated cancer.

pregnancy-related may explain the advanced stage observed for some tumour types both during pregnancy and the postpartum period [22]. Certain diagnostic methods are more challenging to perform and interpret during pregnancy, while no such problems should be present for postpartum cancer with the exception of certain imaging methods of lactating breast tissue. Although treatment for cancer during pregnancy nowadays largely follow the guidelines for non-pregnant patients, some treatments are contraindicated during pregnancy, which is an important clinical difference compared to postpartum cancer.

This population-based overview is one of the largest studies to date of PAC and includes rarer sites, some of which have not been systematically assessed before. The possibility to link cancer registry data to complete birth data enabled survival estimation without the selection bias that hamper many other studies in this area. The long study period enabled consistent estimation of time trends and site comparisons. Importantly, this study includes comparisons to population-based non-PAC controls, with necessary thorough age-adjustment and adjustments for confounders.

The major limitation is the lack of clinical variables, such as the TNM stage, tumour biology and treatment, which we know matters, in particular, for breast cancer. The long study period undeniably reflects major changes in diagnostic procedures and treatments over time leading to varying case-mix. Despite the nationwide setting, power was limited for rarer PACs. The many comparisons in the study increased the likelihood of chance findings. Results for rarer sites should be interpreted with caution. We did not have information on spontaneous or induced abortions, or stillbirths. This may lead to selection bias for estimates regarding cancers in first and second trimesters, in particular, for cancers that require heavy treatment or have a very poor prognosis.

To conclude, in this comprehensive population-based study covering nearly fifty years, we found that survival for women with PAC was similar to that in non-PAC, a finding which was stable over time for the vast majority of cancer sites. Major exceptions were cancers of the breast and uterus (myometrium or unspecified). This study provides reassuring information for patients and clinicians and includes an important overview with novel information of previously unreported rarer cancer sites.

Table 3
Time trends in cancer survival proportions (age-standardized) and adjusted hazard ratios comparing PAC (during pregnancy combined with 1st year postpartum) vs. non-PAC at 5 and 10 years after diagnosis. Hazard ratios adjusted for age and year of diagnosis, parity prior to cancer and maternal birth country.

Site, year of cancer diagnosis	PAC				PAC versus non-PAC	PAC versus non-PAC
	Cases	Deaths 0-10 y	5-year Survival	10-year Survival	HR (95% CI) 0-5 y	HR (95% CI) 0-10 y
Breast						
1970–1979	95	58	48 (40– 57)	38 (30–48)	1.89 (1.40–2.56)	1.90 (1.45–2.48)
1980–1989	149	77	57 (50–65)	47 (39–55)	1.90 (1.47–2.45)	1.59 (1.26–2.01)
1990–1999	174	74	64 (58–71)	56 (49–63)	1.88 (1.45–2.44)	1.53 (1.21–1.94)
2000–2009	248	84	74 (69–79)	66 (61–72)	2.01 (1.54–2.62)	1.78 (1.42–2.22)
2010–2013	134	27	79 (74–84)		2.51 (1.68–3.74)	
p-value					p = 0.990	p = 0.593
Cervix uteri						
1970–1979	92	19	79 (72–87)	77 (68–85)	1.14 (0.70–1.87)	1.15 (0.72–1.83)
1980–1989	132	22	81 (76–87)	79 (73–86)	1.12 (0.71–1.75)	1.03 (0.66–1.59)
1990–1999	117	15	88 (82–93)	86 (80–92)	1.11 (0.64–1.90)	1.02 (0.60–1.71)
2000–2009	156	21	88 (84–93)	87 (82–92)	0.92 (0.54–1.56)	1.06 (0.68–1.66)
2010–2013	80	8	90 (86–94)		1.03 (0.50–2.12)	
p-value					p = 0.977	p = 0.985
Ovary and tubes						
1970–1979	42	11	70 (58–84)	67 (54–82)	1.47 (0.79–2.72)	1.20 (0.65–2.21)
1980–1989	42	6	75 (67–84)	73 (65–83)	0.59 (0.22–1.61)	0.68 (0.30–1.54)
1990–1999	37	7	78 (68–90)	76 (64–89)	0.94 (0.42–2.12)	0.83 (0.39–1.77)
2000–2009	36	11	74 (62–89)	71 (57–86)	1.54 (0.79–3.03)	1.35 (0.74–2.49)
2010–2013	13	<5	63 (55–72)		0.61 (0.08–4.40)	
p-value					p = 0.391	p = 0.488
Colon						
1970–1979	21	7	37 (26–52)	35 (24–51)	1.01 (0.47–2.19)	0.99 (0.45–2.14)
1980–1989	31	6	55 (45–68)	54 (43–68)	1.01 (0.44–2.30)	0.91 (0.40–2.08)
1990–1999	37	7	51 (43–61)	50 (41–60)	0.74 (0.32–1.68)	0.78 (0.36–1.67)
2000–2009	48	17	66 (55–79)	64 (53–77)	1.67 (0.97–2.87)	1.59 (0.95–2.64)
2010–2013	19	6	56 (46–68)		1.84 (0.79–4.26)	
p-value					p = 0.381	p = 0.219
CMM						
1970–1979	100	16	74 (70–78)	69 (63–76)	1.03 (0.54–1.93)	1.03 (0.61–1.75)
1980–1989	128	15	88 (85–92)	84 (78–89)	1.13 (0.59–2.18)	1.14 (0.67–1.94)
1990–1999	187	9	94 (92–96)	92 (89–95)	0.62 (0.23–1.69)	0.86 (0.43–1.69)
2000–2009	217	13	97 (95–99)	94 (91–97)	0.63 (0.28–1.45)	0.99 (0.56–1.76)
2010–2013	149	<5	97 (95–99)		0.83 (0.30–2.31)	
p-value					p = 0.368	p = 0.979
CNS						
1970–1979	55	25	38 (30–50)	30 (21–43)	1.03 (0.65–1.63)	1.05 (0.69–1.60)
1980–1989	61	12	77 (69–85)	72 (63–82)	0.43 (0.20–0.91)	0.53 (0.30–0.95)
1990–1999	87	14	82 (76–89)	78 (70–86)	0.71 (0.40–1.28)	0.60 (0.35–1.03)
2000–2009	89	12	90 (84–96)	86 (79–94)	0.62 (0.32–1.21)	0.60 (0.34–1.08)
2010–2013	39	<5	91 (86–96)		0.78 (0.25–2.48)	
p-value					p = 0.322	p = 0.174
Lymphoma						
1970–1979	47	16	50 (41–62)	45 (35–58)	1.15 (0.64–2.06)	1.11 (0.66–1.87)
1980–1989	50	13	70 (60–81)	65 (54–78)	1.58 (0.87–2.86)	1.26 (0.71–2.21)
1990–1999	60	12	77 (68–86)	72 (63–84)	1.39 (0.70–2.75)	1.37 (0.75–2.47)
2000–2009	84	7	93 (89–98)	92 (86–98)	0.77 (0.31–1.90)	0.83 (0.39–1.79)
2010–2013	35	<5	88 (83–93)		0.97 (0.23–4.05)	
p-value					p = 0.715	p = 0.754
Leukemia						
1970–1979	19	17	14 (7–30)	11 (4–27)	0.75 (0.43–1.30)	0.86 (0.52–1.42)
1980–1989	18	12	22 (14–37)	19 (11–34)	0.85 (0.47–1.53)	0.78 (0.43–1.42)
1990–1999	30	13	50 (38–66)	46 (33–63)	1.08 (0.61–1.91)	1.03 (0.58–1.83)
2000–2009	25	5	81 (68–96)	78 (64–95)	0.91 (0.37–2.24)	0.79 (0.32–1.95)
2010–2013	22	5	61 (52–71)		1.35 (0.54–3.41)	
p-value					p = 0.825	p = 0.918

CI, confidence interval; CMM, cutaneous malignant melanoma; CNS, central nervous system; PAC, pregnancy-associated cancer.

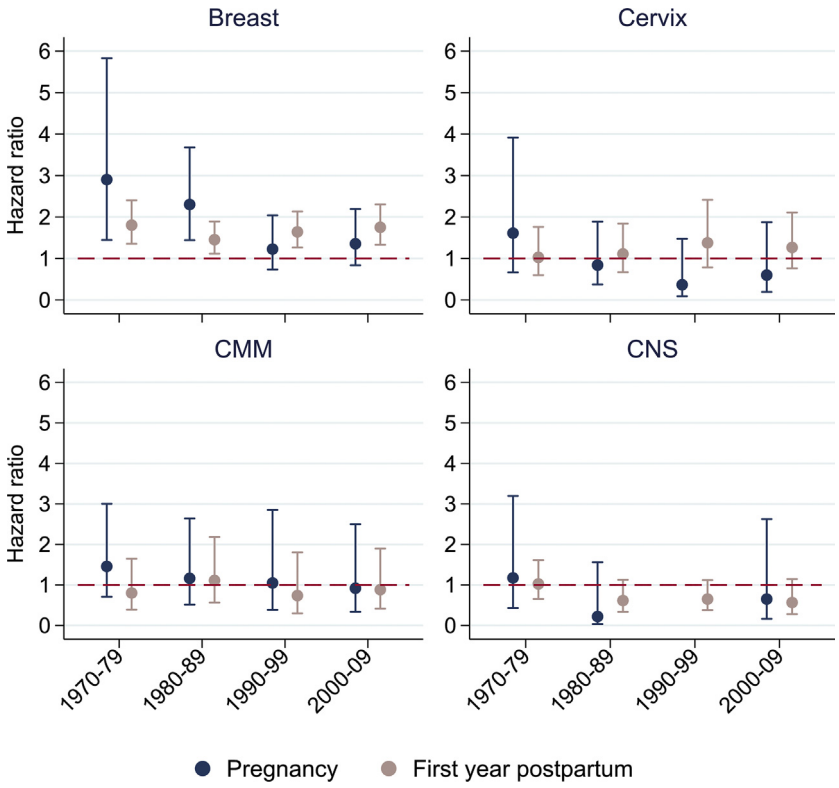

Fig. 3. **Associations between diagnostic windows of PAC (during pregnancy and 1st year postpartum) vs non-PAC and 10-year cancer mortality across calendar periods of cancer diagnosis.** Hazard ratios adjusted for age and year of diagnosis, parity before cancer and maternal birth country. There were no deaths among women diagnosed with CNS tumors during pregnancy 1990–99. CMM, cutaneous malignant melanoma; CNS, central nervous system; PAC, pregnancy-associated cancer.

CRediT author statement

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.07.008.

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