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Recent childbirth is an adverse prognostic factor in breast cancer and melanoma, but not in Hodgkin lymphoma ☆

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Abstract **Background:** The relationship between gestation, childbirth and cancer prognosis is unknown for most cancers (e.g. Hodgkin lymphoma), whereas a body of evidence exists for melanoma and breast cancer.
Methods: The national cancer registration and hospital discharge data for women in England (1998–2007) were linked, and the records for Hodgkin lymphoma, melanoma and breast cancer were indexed as to whether women had delivered a child in separate time periods prior to their cancer diagnosis. Survival analyses were conducted in order to characterise prognosis in relation to childbirth, with statistical adjustment for age and (where possible) stage.
Findings: For melanoma and breast cancer, survival was strongly reduced in women who gave birth in the year prior to cancer diagnosis. The age-adjusted hazard ratios (HR) with 95% confidence intervals (CI) were 2.06 (1.42–3.01) for melanoma and 1.84 (1.64–2.06) for breast cancer. The associations were only slightly attenuated by further adjustment for tumour stage. For breast cancer, the excess death rate in women with a recent childbirth peaked at 2 years and remained elevated for 6 to 8 years. Previous childbirth had no overall effect on the outcome of Hodgkin lymphoma.

Interpretation: Melanoma and breast cancer prognosis are adversely affected by recent gestation and childbirth in a way that is not due to stage of the cancer, but rather to inherent biological properties of the tumours. Possible biological mechanisms include immunosuppression (melanoma), the hormonal milieu in gestation and a tumour promoting microenvironment post-partum (breast cancer).

1. Introduction

Two of the authors of this paper care for patients with haematological malignancies. They had observed advanced or fatal cases in women diagnosed with Hodgkin lymphoma within a few years after childbirth, and hypothesised that recent childbirth is associated with poor prognosis.

We explored this hypothesis using a linked dataset of English cancer registrations and hospital discharge records. To compare with two other malignancies for which studies of the same hypotheses have been done, we analysed the association between recent childbirth and survival after cancer diagnosis in women with melanoma of the skin or breast cancer, two of the most common cancers in women of childbearing age.

Hodgkin lymphoma is the most common lymphoma in women of childbearing age.[1] Several studies have examined the occurrence of Hodgkin lymphoma in relation to childbirth and parity.[2,3] The results are consistent with a moderately protective effect of parity on Hodgkin lymphoma risk, but a similar association was seen in males as well as in females, and may be attributable to confounding by socio-economic factors. The survival of Hodgkin lymphoma diagnosed during pregnancy has been reported to be similar to non-pregnant women,[4] but the evidence base on prognosis is limited. One study found higher survival with increasing parity.[2] The magnitude of the mortality reduction was similar in women and men. A large study from Norway found no difference in cause-specific survival from lymphoma and leukaemia in patients diagnosed in pregnancy or while lactating.[5]

The incidence of melanoma of the skin has no consistent association with a woman's parity.[6,7] The influence of reproductive history on prognosis remains unclear. Case studies have described patients with rapidly growing melanoma during pregnancy, but recent reviews have concluded that melanoma prognosis does not appear to be affected by pregnancy.[8,9] Large, population-based studies on progression and prognosis in melanoma in relation to pregnancy and childbirth have shown inconsistent results[5,10–12] and the general consensus is that pregnancy or recent childbirth does not affect the prognosis in clinically localised melanoma of the skin.[8,10–12] An open question remains about the prognosis in non-localised melanoma, and to the independent and joint effects of reproductive history and tumour characteristics such as anatomic location, thickness and stage of disease.[13]

Breast cancer incidence has strong associations with reproductive characteristics of the woman. Childbirth conveys a long-term reduction in the incidence of the most common types of breast cancer[14] despite a transient, short-term increase in incidence.[15] Pregnancy-associated breast cancers, defined as cancers diagnosed during pregnancy or in the year following childbirth, are known to have an adverse prognosis,[16–20] but there is uncertainty about the biological basis and the pathological correlates of this association.[21]

2. Materials and methods

2.1. Patient data

From the cancer registration dataset for the England population, we extracted records for women aged 10–54 years, diagnosed in 1998–2007 with Hodgkin lymphoma (3603 cases), melanoma of the skin (16,528) and breast cancer (110,943).

In the linked hospitals' admission data we extracted episodes relating to an obstetric event (ICD10 codes O00 to O99 or OPCS4 surgery codes starting with Q or R) or relating to reproduction (Z codes between Z30 and Z39) in the diagnosis and operation fields of the hospital discharge dataset. These were further examined to identify those which related to labour, delivery, postpartum care and/or childbirth.

Each cancer registration record was then indexed to indicate whether childbirth had or had not happened in different time-windows prior to the time of cancer diagnosis: childbirth within 1 year before the diagnosis (0–1), in the second full year before diagnosis (1–2), etc., up to the 5th year before diagnosis. All recorded childbirths for each woman were used and these indices were analysed separately. We used Cox's proportional hazard regression to estimate the hazard ratio for having (versus not having) given birth in each interval. The regression analyses were adjusted for age. Follow-up was to the end of 2008, giving a maximum duration of follow-up of 11 years (1998–2008).

2.2. Analysis

In order to visualise the main results for breast cancer, we plotted Kaplan–Meier survival functions for

two groups of women: those who had given birth in the year before their breast cancer diagnosis and those who had not.

To give an appreciation of the age-specificity and persistence of the effect of recent childbirth in breast cancer, we modelled the absolute hazard of death as a function of age and time since breast cancer diagnosis, using flexible parametric survival models. The baseline hazards were modelled using splines with four degrees of freedom (three interval and two boundary knots); while the time varying effects of log (age) and time since diagnosis used splines with three degrees of freedom. The estimated hazards were plotted for three values of age at diagnosis (25, 35 and 45 years) for the interval of follow-up from breast cancer diagnosis and up to 10 years thereafter.

We attempted to assign a tumour-node-metastasis (TNM) stage to all breast cancer cases on the basis of available stage data and data on tumour size, affected lymph nodes and metastasis. Using all the available data, 87.5% of breast cancers had a valid assigned TNM. The assigned TNM stage for breast cancer was used to pursue a stage-adjusted Cox proportional hazards regression analysis, and stratified, stage-specific Kaplan–Meier survival analysis.

Similarly, we used available data for melanoma to assign a TNM stage in 72% of the cases, and we repeated the Cox proportional regression analysis with adjustment for stage. We were not able to extract data on disease stage or prognostic indices in Hodgkin lymphoma.

3. Results

3.1. Hodgkin lymphoma

Table 1 shows the results of the Cox proportional hazard analysis. For women with Hodgkin lymphoma there were 3603 women in the analysis of childbirth in the recent year before cancer diagnosis, of which 138 had given birth. Among the latter, ten died within the course of follow-up. The hazard ratio of 0.96 (95% confidence interval 0.51–1.82) indicate that childbirth within 1 year before Hodgkin lymphoma diagnosis had no statistically significant or clinically relevant association with the subsequent prognosis.

For childbirth in the two proceeding intervals before Hodgkin lymphoma diagnosis there was a marginally higher than expected death rate associated with childbirth in the interval 1–2 years before cancer diagnosis (1.42; 0.75–2.70), and a lower than expected death rate with childbirth in the interval 2–3 years before cancer diagnosis (0.15; 0.02–1.05). In total, 32 deaths occurred and the expected value was 32.3.

3.2. Melanoma

For melanoma of the skin there was a two-fold death rate for women who had given birth within 1 year before the cancer diagnosis (2.06; 1.42–3.01) (Table 2), but no significant association with childbirth more distant from the time of diagnosis. We reviewed the clinical information in the cancer registry for the 29 women who gave birth in the year prior to the diagnosis and who died during the course of follow-up. Of these, 16 women had stage 1 or 2 when diagnosed, six had stage 3 or 4, and seven could not be staged. Twenty-five deaths were due to melanoma and four deaths were from another or an unknown cause. Their median survival time was 722 days (quartile range: 468–1336 days).

With adjustment for TNM stage, the hazard ratio estimate of 2.06 (1.42–3.01) for women with childbirth in the year prior to the melanoma changed to 1.92 (1.32–2.79).

Table 1
Hazard ratios for death in female Hodgkin's lymphoma patients in relation to childbirth in different periods before the cancer diagnosis.

Period before cancer diagnosis (years)	Total number of women	Number with childbirth	Deaths in women with childbirth	Hazard ratio, age-adjusted	95% confidence interval	
0 to 1	3603	138	10	0.96	0.51	1.82
1 to 2	3246	105	10	1.42	0.75	2.70
2 to 3	2894	81	1	0.15	0.02	1.05
3 to 4	2534	68	5	1.09	0.44	2.66
4 to 5	2183	54	6	1.69	0.74	3.88

Table 2
Hazard ratios for death in female melanoma patients in relation to childbirth in different periods before the cancer diagnosis.

Period before cancer diagnosis (years)	Total number of women	Number with childbirth	Deaths in women with childbirth	Hazard ratio, age-adjusted	95% confidence interval	
0 to 1	16,528	306	29	2.06	1.42	3.01
1 to 2	15,229	267	15	1.22	0.73	2.05
2 to 3	13,923	225	11	1.14	0.62	2.08
3 to 4	12,458	229	13	1.33	0.76	2.32
4 to 5	10,829	201	9	1.18	0.61	2.30

Note: the estimate of 2.06 changed to 1.92 (1.32–2.79) with adjustment for stage.

Table 3
Hazard ratios for death in female breast cancer patients in relation to childbirth in different periods before the cancer diagnosis.

Period before cancer diagnosis (years)	Total number of women	Number with childbirth	Deaths in women with childbirth	Hazard ratio, age-adjusted	95% confidence interval	
0 to 1	110,943	1014	316	1.84	1.64	2.06
1 to 2	100,062	1068	204	1.09	0.95	1.26
2 to 3	88,800	1143	219	1.26	1.10	1.45
3 to 4	77,502	1162	209	1.38	1.20	1.59
4 to 5	66,278	1120	153	1.16	0.99	1.36

Note: the estimate of 1.84 changed to 1.68 (1.50–1.88) with adjustment for stage.
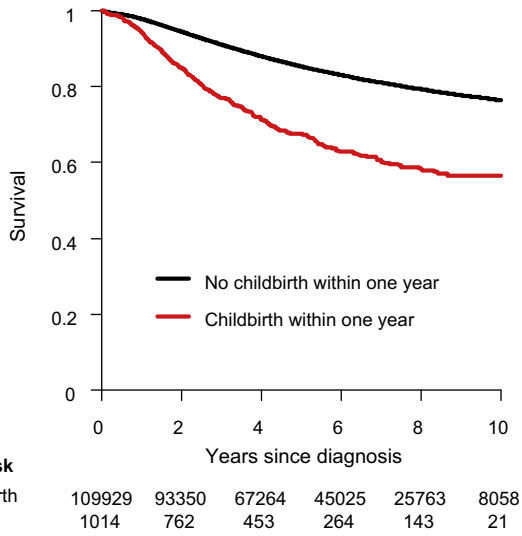

Fig. 1. Kaplan–Meier survival functions for women with breast cancer who had (red) a childbirth in the year prior to diagnosis, or who had no birth in that interval (black).

3.3. Breast cancer

For breast cancer there was a substantial and statistically significant excess death rate in women who had given birth within 1 year before the diagnosis with breast cancer (hazard ratio 1.84; 1.64–2.06) (Table 3). Smaller, but statistically significant increases in the death rate were seen for women who had delivered in the periods from 1 to 4 years before cancer diagnosis. For delivery in the most distant period before diagnosis (4 to 5 years before cancer diagnosis), the survival effect had waned to 1.16 (0.99–1.36).

We repeated this analysis in the subset of women in the narrower age-range 25–34 years and found similar results.

The Kaplan–Meier plot (Fig. 1) shows the cumulative effect of childbirth in the recent year before diagnosis of breast cancer. The effect on survival was evident from less than 1 year after diagnosis and the difference built up gradually up to three to 4 years after diagnosis.
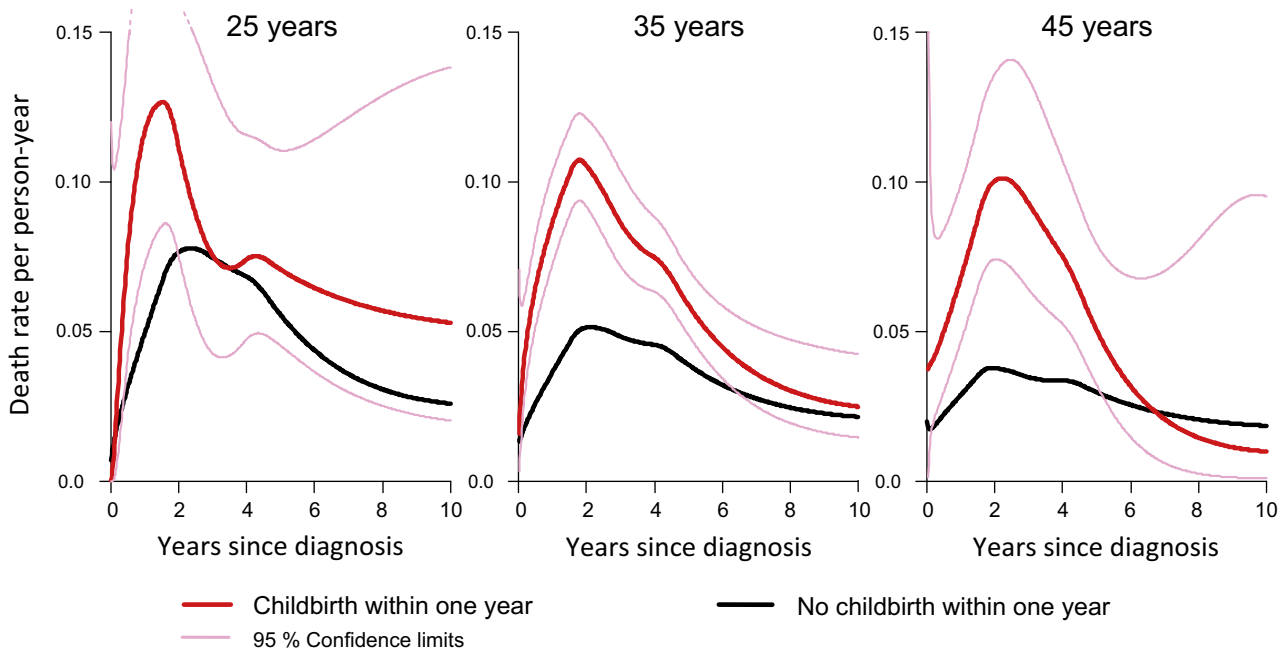

Fig. 2. Estimates of the absolute hazard of death (rate of death per person-year) from a flexible parametric survival model for women with breast cancer who had (red) a childbirth in the year prior to diagnosis, or who had no birth in that interval (black). The model includes age and estimates are plotted for three fixed values of age. Ninety-five percent confidence intervals are indicated for women with a recent childbirth.

The modelled hazard of death (Fig. 2) shows that the absolute hazard of death in breast cancer patients was slightly higher in young women, both in those who gave birth in the recent year and in those who did not. Within each age-specific analysis, there was a gradual increase up to a doubling of the hazard of death associated with recent childbirth around 2 years after cancer diagnosis. In the analysis fixed at 25 years of age, the two hazard functions tended to separate again from 4 to 10 years into follow-up, but judging from the 95% confidence intervals, that difference was not statistically significant. In the older age groups, the hazards decreased gradually from about 1 year and onwards and at 6 to 8 years after diagnosis there was no longer any important difference between women who gave birth in the year before their breast cancer diagnosis and women who did not.

Table 4 shows the distribution of TNM stage in women with and without childbirth in the year before breast cancer diagnosis. The proportions of women where a stage could be assigned were similar (84% versus 87%). Among women where a stage could be assigned, the stage distribution was unfavourable in women with recent childbirth: stage 1: 21% versus 35%; stage 2 or higher: 79% versus 65%.

With adjustment for TNM stage, the hazard ratio estimate of 1.84 (1.64–2.06) for women with childbirth in the year prior to breast cancer diagnosis did not change much. The stage-adjusted estimate was 1.68 (1.50–1.88).

Fig. 3 shows the Kaplan–Meier survival functions separately for TNM stages 1–4 and for the unstaged cases. Regardless of stage, the survival was worse in women with recent childbirth before breast cancer diagnosis.
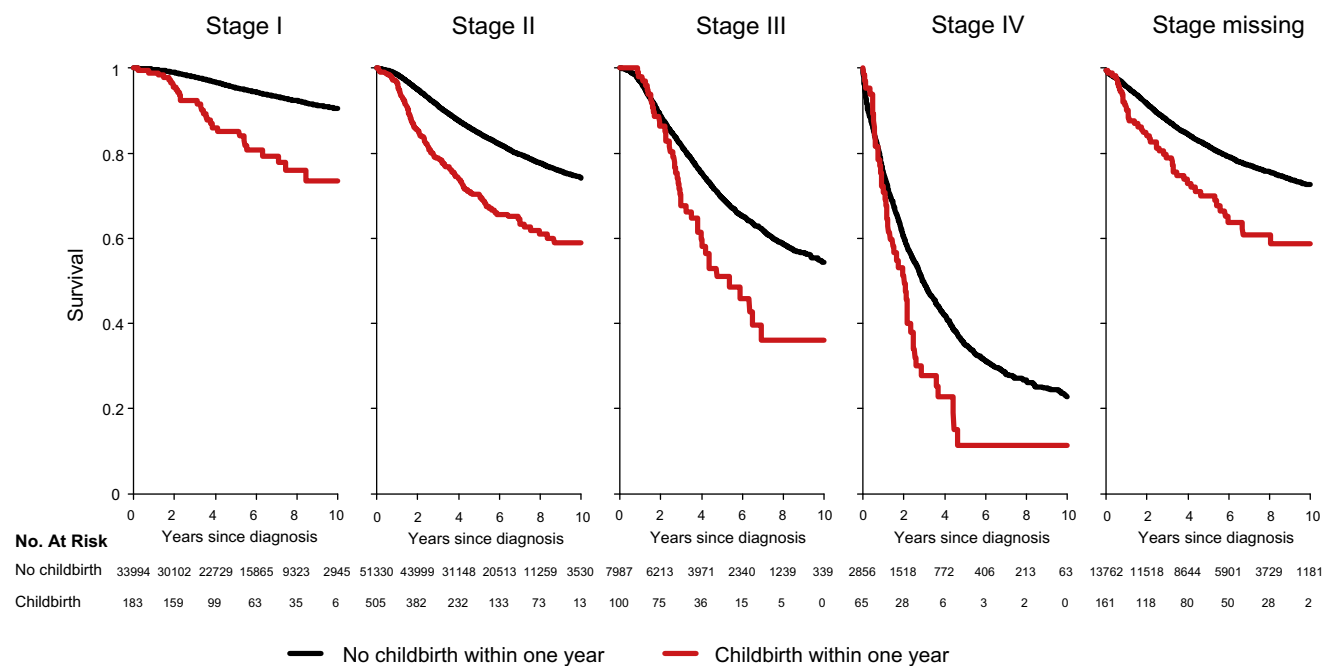

Fig. 3. Kaplan–Meier survival functions, stratified by stage, for women with breast cancer who had (red) a childbirth in the year prior to diagnosis, or who had no birth in that interval (black).

Table 4
Distribution of imputed tumour-node-metastasis (TNM) stage in 1014 women with childbirth in the year before breast cancer diagnosis and 109,929 women without a childbirth in this interval.

TNM stage	With childbirth in (0 to 1) year interval			Without childbirth in (0 to 1) year interval		
	N	%	% excl NA	N	%	% excl NA
1	183	18	21	33,994	31	35
2	505	50	59	51,330	47	54
3	100	10	12	7987	7	8
4	65	6	8	2856	3	3
NA	161	16	–	13,762	13	–
Total	1014	100	100	109,929	100	100

4. Discussion

4.1. Definition of pregnancy-associated cancer

We considered as a pregnancy-associated cancer case only women who had a recent childbirth (within 1 to 5 years) when they were diagnosed with cancer due to several reasons: Firstly, our only means of identifying women with pregnancy-associated cancer was a linkage to information about a completed pregnancy and childbirth taking place in a hospital. No national data allow for pregnancies to be assigned to cancer registration records. Secondly, the inclusion of pregnancy-associated cancer defined by pregnancy and not by childbirth would lead to the inclusion of pregnancies that were subsequently terminated. Thirdly, the treatment for cancer patients may differ if the patient is pregnant and any difference in survival could be due to differences in treatments rather than the physiology associated with pregnancy and childbirth. With this definition of pregnancy-associated cancer, our results do not apply to clinical questions of management of cancer during pregnancy, or to implications of a pregnancy in a person who had cancer in the past.

4.2. Interpretation of the data on Hodgkin lymphoma

Our results suggest that recent childbirth does not influence survival from Hodgkin lymphoma. Despite the large study population, the number of women with Hodgkin lymphoma and a recent childbirth was small, and the number of deaths among those women was only 32, implying high statistical uncertainty. In the analysis of childbirth in the year before Hodgkin lymphoma diagnosis (i.e. the interval where strong signals were detected for melanoma and breast cancer), the estimate of 0.96 implies no association, but the 95% confidence interval of 0.51–1.82 is consistent with a range of estimates.

4.3. Interpretation of the data on melanoma

We found a large and statistically significant excess mortality in melanoma patients diagnosed within a year after childbirth. Most of these women had stage 1 or 2 melanoma, the median survival was more than 2 years, and the cause of death registered was malignant melanoma. After adjustment for stage an almost two-fold increased mortality rate remained.

This result counters the prevailing assessment of no or little association between pregnancy, childbirth and melanoma prognosis but several reports have observed an adverse stage-distribution in pregnancy associated melanoma.[22,23]

It can be debated whether stage should be adjusted for in the analysis of pregnancy-associated melanoma and survival. Some authors (e.g. Ref.[11]) consider that such adjustment is natural and necessary, others (e.g. Refs.[24,25]) emphasise the stage-adjusted and the unadjusted analysis address two different questions of causation, both of which are clinically relevant. The unadjusted analysis allows for stage to be a mechanism whereby pregnancy and childbirth adversely affects survival. A delay in diagnosis or a more aggressive type of melanoma could both contribute to this association. The stage-adjusted analysis aims to eliminate the intermediate effect of advanced stage and addresses more directly the question of the stage-independent malignant potential of the cancer. Our results suggest that the increased mortality of melanoma patients with a recent childbirth is mainly due to a stage-independent casual pathway.

There is no evident biological mechanism. One possibility is that pregnancy is associated with immune suppression and an immunosuppressed state permits some melanomas with high malignant potential to progress and come to clinical diagnosis in the short term following a childbirth. Consistent with this hypothesis, several studies have shown increased case-fatality in melanoma in immunosuppressed patients, regardless of the stage of the melanoma.[26,27]

4.4. Interpretation of the data on breast cancer

Pregnancy and childbirth provokes a transient wave of excess occurrence of breast cancer, and this excess is largest in older, uniparous women and maximal immediately after the childbirth, where after it decreases over the following 10–15 years.[15] Many studies have established that these pregnancy-associated breast cancers have a relatively poor prognosis.[16–21,25]

The stage-stratified and stage-adjusted analyses of our data show that in this population the adverse prognosis of pregnancy-associated breast cancer is largely independent of stage, and manifest also in localised and otherwise good-prognosis cancers. The implication is that the breast carcinogenic processes facilitated by the pregnancy lead to inherently more aggressive forms of breast cancer.

In addition to stage-independent phenomena, the stage distribution gives indication of a less favourable stage distribution in pregnancy-associated breast cancers. Firstly, breast cancer that occurs in the post-partum period and during lactation may be diagnosed with delay, for example if the cancer masquerades as mastitis.[28] Secondly, more advanced stage-distribution may be secondary to the more aggressive, and plausibly faster growing, biological phenotype. We are not able to assess the relative contributions of diagnostic delay and biological aggressiveness to the adverse stage-distribution. There are probably combined reasons for the more advanced stage distribution in pregnancy-associated breast cancers, where biological mechanisms, delay of diagnosis due to delay of seeking medical consultation

and/or suboptimal diagnostic procedures may be contributing factors. Results consistent with these were recently published from Sweden.[25]

The excess mortality manifests very shortly, if not immediately, after breast cancer diagnosis and rise to a maximum around 2 years after diagnosis. Further, whereas the adverse prognosis is strongest in women with childbirth within 1 year prior to the breast cancer diagnosis, there is also an indication of less strong mortality increase in women with longer duration (up to 4 to 5 years) between childbirth and breast cancer diagnosis. The excess mortality decays thereafter, and 6 to 8 years after diagnosis, there is no longer any excess risk of breast cancer death.

4.5. Limitations of the study

We lack stage information in women with Hodgkin lymphoma. Our classification of melanoma and breast cancer stage was retrospective and based on incomplete data in the cancer registry. The accuracy of this stage information is lower than stage data assigned prospectively in a standardised way. The routine cancer registration data do not permit classification of histopathological type of breast cancer. Such information may have given information about the biological nature of pregnancy associated breast cancers in terms of e.g. basal type characteristics or triple-negativity.

4.6. Implications for population health and clinical practice in oncology

In many developed countries, there has been a trend towards postponement of reproduction and childbirth. The incidence rates of most cancers increase with age, and postponement of childbirth therefore leads to an increase in the rate of pregnancy-associated cancers.[29]

Carers of patients with melanoma or breast cancer should be aware of the increased risk of death in women who are diagnosed within a few years after having a child, including those patients who had small and localised cancers, normally associated with very good prognosis. This knowledge may have implications for guidelines for follow-up for women with a recent childbirth. Women with breast cancer and a recent childbirth may be assured that the excess risk of death is a transient phenomenon which wanes over the course of 6 to 8 years after the breast cancer diagnosis.

Conflict of interest statement

None declared.

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