Increased mortality in women with breast cancer detected during pregnancy and different periods postpartum

Anna L.V. Johansson1*, Therese M-L. Andersson1, Chung-Cheng Hsieh2, Sven Cnattingius3, Mats Lambe1,4

1 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
2 Department of Cancer Biology, University of Massachusetts Medical School, Worcester, MA, USA
3 Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden
4 Regional Oncologic Center, Uppsala, Sweden

Running title: Mortality in women with pregnancy-associated breast cancer

Keywords: breast cancer, pregnancy, postpartum, mortality, survival

Financial support: This work was supported by grants from the Swedish Cancer Society (grant number 07-0526; Mats Lambe) and Susan G Komen for the Cure (grant number KG 100116; Mats Lambe).

* Corresponding author: Anna Johansson, Department of Medical Epidemiology and Biostatistics (MEB), Karolinska Institutet, P.O. Box 281, SE 17177 Stockholm, Sweden
Phone: +46-8-52486169, fax: +46-8-314975, email: anna.johansson@ki.se
Word count: 249 (abstract); 3,314 (body of text)
Total number of figures and tables: 4
Abstract

Background: Because of a continued trend towards postponed childbearing, the incidence of pregnancy-associated breast cancer (PABC) is likely to increase. This study investigated the mortality in women with PABC in relation to when the tumor was detected (during pregnancy, different postpartum periods) and by time since diagnosis, compared to women with non-PABC.

Methods: A population-based cohort study of 15,721 Swedish women diagnosed with breast cancer between ages 15 to 44 years, of whom 1,110 (7%) had a pregnancy-associated breast cancer (diagnosed during or within two years after pregnancy). Information on outcome and potential confounders was obtained from population-based health registers. Mortality rates and hazard ratios (HR) with 95% confidence intervals (CI) were estimated.

Results: Women with PABC had higher mortality compared to women with non-PABC diagnosed at the same age and calendar period. Among women with PABC, 46% died within 15 years after diagnosis, whereas 34% died among non-PABC patients. The mortality in both groups peaked at around two years after diagnosis, with the highest peak occurring in women diagnosed 4-6 months after delivery (HR=3.8, 95% CI 2.4-5.9). An increased mortality among women with PABC remained until 10 years after diagnosis.

Conclusions: Women with PABC had a poorer prognosis compared to women with breast cancer and no recent birth. The mortality increase was most pronounced in the subgroup of women diagnosed shortly after delivery.

Impact: An increased awareness among clinicians may help reduce the mortality in women with PABC, for example by avoiding undue delays in diagnosis and treatment.
Introduction

Pregnancy-associated breast cancer (PABC) commonly refers to a breast malignancy diagnosed during pregnancy or within one or two years following delivery (1). Because of a continued trend towards postponed childbearing, the incidence of pregnancy-associated breast cancer is likely to increase in many Western countries.

Pregnancy and breast cancer has often been viewed as an incurable combination. Several studies have found evidence of a diagnostic delays in pregnant women (2-7), which may explain why results from some, but not all, studies show that women with PABC have larger tumors and are more likely to have positive nodes, metastases and vascular invasion compared to non-pregnant women with breast cancer (2, 5, 8-10). A poor prognosis in PABC (4, 8-14) has previously primarily been attributed to diagnostic delays (7, 15). However, few studies have investigated whether the prognosis varies by time of diagnosis (during pregnancy and different postpartum time intervals). Some studies have distinguished between pregnant and lactating women (2, 4, 5, 10, 14), while most investigators have focused on cancers diagnosed after childbirth in one-year intervals following delivery (8, 9, 12, 13). In all these studies, ranging in size from 35 to 708 cases of PABC, proximity to pregnancy was associated with a worse prognosis. Another question of interest relates to whether mortality varies by time since diagnosis. Guinee et al. (10) found evidence of a mortality peak occurring two years after diagnosis in women with PABC.

In this large nation-wide Swedish study encompassing more than 1,100 cases of PABC, we used a detailed classification of PABC to assess all-cause mortality in relation to time of diagnosis (during pregnancy and in postpartum intervals) and also whether mortality varies over time from diagnosis.
Methods

We conducted a population-based study using data from the Swedish National Cancer Register. The study cohort was defined by women born 1948 and later with a breast cancer diagnosis between ages 15-44 years during 1963-2002. To determine if the diagnosis was pregnancy-associated (i.e. occurring during or within two years after pregnancy), information on dates of all births was retrieved from the Multi-Generation Register from 1961 and onwards. Information in the two registers was matched by means of record linkage using the national registration number (NRN), a unique identifier assigned to all Swedish residents(16).

We further linked the study cohort to the Swedish Cause of Death Register and the Population Register to obtain outcome and follow-up information (deaths, migrations). Information on educational level for each woman was obtained from the Education Register. Only first breast cancers (n=15,800) were included. We excluded 71 women with inconsistent migration history (immigration or emigration events not recorded in logical order) and 8 women diagnosed on the same day as they died. The final cohort for analyses encompassed 15,721 women with a breast cancer diagnosis between ages 15 to 44, of whom 1,110 (7%) had a pregnancy-associated breast cancer.

In the present study, pregnancy-associated breast cancers (PABC) were defined as malignancies diagnosed within 9 months before the delivery date (during pregnancy) or within two years after delivery. Breast cancers occurring outside this time window were referred to as non-PABC. For women with two childbirths within the time window (n=49), we chose the second pregnancy as the index birth related to the PABC.
Parity status was defined as number of births prior to diagnosis. For women experiencing PABC, the index birth was not counted in the parity variable.

Based on information in the Cause of Death Register, 91% of PABC cases and 90% of non-PABC cases who died had breast cancer listed as the underlying cause of death. For the purpose of the present study, all-cause mortality was chosen as the main outcome.

**Statistical analysis**

Person-time at risk was counted from date of breast cancer diagnosis until date of death or censoring. Censoring events were first emigration after diagnosis, end of study (2003-12-31) or 15 years after diagnosis, whichever came first.

We estimated crude mortality rates, defined as the number of events over total person-time at risk, with 95% confidence intervals (CI) based on the Poisson distribution. Mortality rates were calculated using days as time-unit and reported per 1000 person-years. The underlying timescale was time-since-breast cancer diagnosis. The mortality rates were modelled and adjusted for confounders using flexible parametric survival models(17, 18), which use a spline function for the baseline mortality rate. These models are proportional hazards models and provide hazard ratios (HR) with 95% confidence intervals (CI) as the measure of association between exposures and outcome. It is possible to estimate various fitted curves from the models, such as mortality rates and HRs over time.

In the modelling, we firstly investigated possible associations between mortality and the main exposure non-PABC (reference) and PABC. We also investigated associations between mortality and proximity of PABC diagnosis to delivery (categorized as breast cancer diagnosis during pregnancy (0-9 completed months prior to delivery), during months 1-3, 4-6, 7-12, 13-18 or 19-24 after delivery, or non-PABC (reference)). Models were
adjusted for age at breast cancer diagnosis (categorized as 15-29, 30-34, 35-39 or 40-44 years), calendar year at diagnosis (categorized as 1963-1974, 1975-1989 or 1990-2002) and educational level (≤9 years, 10-13 years, university undergraduate level or postgraduate level). We investigated parity prior to breast cancer (categorized as nulliparous, 1 childbirth or ≥2 childbirths), and the interaction between PABC and parity (categorized as PABC nulliparous, PABC parous, non-PABC nulliparous and non-PABC parous). All variables were categorized prior to the analysis. The significance level was 5% and tests were two-sided.

Secondly, we modelled the mortality rates for PABC and non-PABC allowing the HRs to vary over time since diagnosis. Within the flexible parametric modelling framework it is possible to allow exposures to have time-dependent effects (non-proportional hazards) by fitting separate spline functions for the different levels of the exposure. Differences between groups are still reported as hazard ratios, but now represent a function over time rather than a constant. The time-dependent HRs are reported at 2, 5 and 10 years after diagnosis. The baseline hazards were modelled using splines with 5 degrees of freedom (4 internal and 2 boundary knots), while the time-varying effects used splines with 3 degrees of freedom. A sensitivity analysis showed that our spline estimates were robust for different choices of knots.

Only women with complete information on all variables were included in the models (the only variable with missing values was education, 563 (4%) missing out of 15,721). The data was analysed using Stata Intercooled 11.0(19). The flexible parametric models were estimated using the Stata command stpm2(17).

The study was approved by the Research Ethics Committee at Karolinska Institutet.
Results

Mortality by age, calendar period and education

The mortality rate was higher in young (< 40 years at diagnosis) compared to older breast cancer patients (40-44 years at diagnosis) and was higher among patients diagnosed in the earlier periods (1963-1974 and 1975-1989) compared to the most recent period under study (1990-2002). The mortality rate increased with decreasing educational level (Table 1).

Mortality in women diagnosed during pregnancy and different time periods postpartum

Among 1,110 women with pregnancy-associated breast cancer (PABC), 515 (46%) died during fifteen years of follow-up, while among 14,611 women with non-PABC, 4,911 (34%) died (Table 1). The average time of observation was 7.5 years in women with PABC and 8.9 years in women with non-PABC. The crude mortality rate among PABC was 61.9 per 1000 person-years (95% CI 56.7-67.4) and 37.6 (95% CI 36.6-38.3) among non-PABC, indicating a much poorer prognosis among women diagnosed in connection with childbearing.

Compared to non-PABC, PABC was associated with a significantly increased mortality, both before (unadjusted HR 1.61, 95% CI 1.47-1.77) and after adjustment for age at diagnosis, calendar period and education (adjusted HR 1.51, 95% CI 1.36-1.68).

The PABC category was further subdivided by time between diagnosis and delivery. The poorest prognosis was observed in patients diagnosed during months 4-6 after delivery who had a more than two-fold increased mortality rate (adjusted HR 2.45, 95% CI 1.83-3.29) compared to non-PABC women. An almost doubled mortality rate was observed in women diagnosed during pregnancy (adjusted HR 1.85, 95% CI 1.34-2.56), while corresponding increases in mortality rates among women diagnosed during 1-3 and 13-24 months after delivery were around 30 percent.
Parity prior to breast cancer was not associated with the risk of death after adjustment for age, calendar period and education, and did not modify the effect of PABC on mortality, neither before nor after adjustment. Among non-PABC cases, mortality rates were similar in parous and nulliparous women (adjusted HR 0.95, 95% CI 0.88-1.03). Compared to nulliparous women with non-PABC, women with PABC and no history of earlier births had an adjusted HR of 1.30 (adjusted, 95% CI 1.05-1.62) while parous women with PABC had an adjusted HR of 1.51 (95% CI 1.33-1.72).

Mortality over time from diagnosis

The mortality rates varied with time from diagnosis, with a peak about two years after diagnosis both among PABC and non-PABC cases (Figure 1). The difference in mortality between PABC and non-PABC cases was most pronounced during the first five years of follow-up, and was not detectable after around eight years. The highest mortality rate was observed in women diagnosed during months 4-6 following delivery, with almost 250 deaths per 1000 person-years at two years of follow-up. Women diagnosed during months 1-3 after delivery had a peak rate of approximately 150 deaths per 1000 person-years (which occurred at around 18 months after diagnosis), while women diagnosed during months 7-24 after delivery had a peak rate just above 100 deaths per 1000 person-years. Among women with non-PABC, the peak mortality was around 50 deaths per 1000 person-years.

Figure 2 shows how the HRs for women with PABC compared to non-PABC (adjusted for age, calendar period and education) vary by time-since-diagnosis and by proximity of breast cancer to delivery. Among PABC diagnosed during pregnancy (panel A), the HR was two-fold increased during the first two years after diagnosis and decreased after approximately ten years to the same level as non-PABC. Among PABC diagnosed during
months 1-3 after delivery (panel B), the same pattern was observed. Among PABC diagnosed during months 4-6 after delivery (panel C), there was a four-fold peak in HR at two years following diagnosis. Much of the mortality increase was diminished after five years, but some difference still remained after 10 years, albeit close to non-significance. Among PABC diagnosed during months 7-12, 13-18 and 19-24 after delivery (panels D, E, and F, respectively), there were similar patterns with significantly increased mortality in the first five years, but HRs were lower compared to PABC diagnosed during months 4-6 after delivery. Among PABC diagnosed 13-18 and 19-24 months after delivery, there was also an indication of a protective effect beyond ten years after diagnosis. These groups were larger in numbers, as indicated by the narrower confidence bands.

To obtain point estimates from the curves, we extracted estimates of HRs and 95% CIs at two, five and ten years after diagnosis from the model adjusted for age, calendar period and education (Table 2). Compared to non-PABC, the mortality was almost doubled among PABC two years after diagnosis (HR 1.8, 95% CI 1.6-2.2). The mortality difference between PABC and non-PABC was reduced over time, and no difference was present after ten years (HR 1.0, 95% CI 0.8-1.3). When PABC was further subdivided by proximity of breast cancer diagnosis to delivery, the highest mortality was observed in women diagnosed during months 4-6 after delivery, who had an almost four-fold increased mortality rate compared to non-PABC at two years after diagnosis (HR 3.7, 95% CI 2.4-5.8). After ten years, the increased mortality was eliminated in all time windows of PABC, except in patients diagnosed during months 4-6 after delivery (HR 2.1, 95% CI 1.2-3.8).

The impact of PABC on mortality over follow-up time was the same among women with and without childbirths prior to breast cancer diagnosis (Table 2). Thus,
regardless of parity status, mortality rates were strongly driven by whether the breast cancer was pregnancy-associated or not.

Discussion

We found evidence of a higher mortality in women with PABC compared to women with non-PABC of the same age, educational level and calendar year of diagnosis. We observed a mortality peak around two years after diagnosis for both PABC and non PABC cases, when the largest difference in mortality between the two groups also occurred. A second important finding was that the elevated mortality among PABC women varied markedly with timing of diagnosis in relation to delivery. Compared to non-PABC patients, we observed nearly four times higher peak mortality in women diagnosed with a breast cancer 4-6 months postpartum. The second highest mortality rate was found in women diagnosed during pregnancy or within three months after birth. The mortality decreased with increasing time from the index delivery, and eight years following diagnosis there was no detectable mortality difference between PABC and non-PABC cases.

Strengths of the present study included the use of data from population-based registers that ensured virtually complete ascertainment of breast cancer cases, deliveries and deaths during four decades. This provided high statistical power and minimized selection and information bias. Data in the Swedish Multi-Generation Register allowed us to identify pregnancy-associated breast cancers, but we were unable to identify pregnancies that were electively terminated due to a breast cancer diagnosis. Also, PABC cases occurring after age 44 years were not included in the study, but more than 95% of Swedish women have completed their childbearing at age 40 years(27).
The analyses were adjusted for several known confounders, including age at diagnosis, calendar period at diagnosis and education. A major weakness of the present study was the lack of information in the Swedish National Cancer Register on prognostic factors, such as tumor characteristics (e.g. tumor size, lymph node status, hormone receptor status, stage, grade and lymph-vascular invasion) and treatment. Also, no information was available on breast feeding. From an international perspective, the frequency of breastfeeding in Sweden is high, with more than 90% of all infants being exclusively or partially breastfed at 2 months in the mid-1990s(28). We could not examine and control for confounding from physical activity, BMI or the use of oral contraceptives. However, these life style factors are unlikely to have varied between PABC and non-PABC cases. Finally, we had no information on family history of breast cancer.

There may be several explanations for a poorer prognosis in women with pregnancy-associated breast cancer, including delayed diagnosis, lower treatment intensity, stage and aggressiveness of the tumor, promotion by hormonal factors and a tumor promoting microenvironment.

Firstly, since changes in the breast tissue may be attributed to the pregnancy or lactation rather than a malignancy, patients with PABC may be more likely to experience diagnostic delays(7), leading to a more advanced stage at diagnosis. Our finding of a higher mortality among women diagnosed during and shortly after pregnancy indirectly supports this hypothesis. A recent review reported that the diagnostic delay may range from one to nine months(7). However, the increased mortality observed in women diagnosed up to two years after delivery is unlikely to be explained by diagnostic delays related directly to pregnancy. Secondly, there may be postponement of the initiation and the aggressiveness of treatment, because of conflicting interests between the cancer treatment and maintaining
the pregnancy. Such delay and lower treatment intensity are likely to be reflected in an increased mortality for breast cancers diagnosed during pregnancy, but not those diagnosed after delivery. Thirdly, a biological mechanism for a more aggressive potential of pregnancy-related tumors may be a selection and growth advantage of particularly malignant cells due to exposure to high levels of pregnancy hormones (20-22), primarily produced by the placenta. High placental weight - an indirect marker of pregnancy hormones - was recently associated with increased PABC mortality (23). This mechanism would give rise to increased mortality among all PABC cases, but primarily among those diagnosed close to delivery when hormone levels are high. Lastly, our finding of a particularly high mortality in women diagnosed with breast cancer during months 4-6 after delivery, when many women begin to wean the infant, may reflect a tumor promoting tissue micro-environment following involution of the breast, i.e. the regression of the mammary gland to its pre-pregnant state. According to this novel hypothesis, the involution process is inflammatory-like, i.e. with increased immune cell influx and breakdown of the stroma surrounding the gland and ducts, changes which have been postulated to enhance tumor growth and metastasis (24).

A peak in mortality at around two years after diagnosis is possibly reflecting tumors which do not respond to treatment. However, the maintained increased mortality for up to eight years after diagnosis in PABC cases is likely to reflect some other prolonged effect of pregnancy.

Childbearing has been associated with a transient increase in risk for breast cancer that is more pronounced after a first pregnancy (25, 26). However, similar to a previous study (12), we found no influence of previous parity on mortality among PABC women; an increased mortality among PABC women was present in both parous and nulliparous women.
Based on previous Swedish estimates of PABC incidence(29) and US birth statistics(30), we estimate that around 1,600 US women who gave birth in 2006 were diagnosed with pregnancy associated breast cancer. Applying the present mortality estimates, 480 of these women would be expected to die from their cancer within five years after diagnosis. If they would have experienced the same mortality rates as non-PABC cases, only 290 would succumb to the disease during the same time period.

While PABC accounts for a small proportion of the total breast cancer burden in women aged 15-44 years, it accounts for a relatively high proportion of all cases diagnosed in women aged 25-29 years, where at least one in five breast cancers coincide with pregnancy or lactation(3). A poor prognosis in women with PABC highlights the importance of optimizing management of this special group of young patients. An improved understanding of the underlying mechanisms for the high mortality in women diagnosed shortly after delivery may open up new venues for prevention and treatment.

In conclusion, we found evidence of an increased mortality among women with PABC which peaked around two years after diagnosis. Since the mortality increase was most pronounced in the subgroup of PABC women diagnosed shortly after delivery, these results give indirect support to the hypothesis that postpartum changes in the mammary gland microenvironment may enhance tumor growth and metastases. Thus, events following pregnancy may be more important than events during pregnancy. Our findings may also reflect a detrimental influence of diagnostic delays during pregnancy and lactation, as well as a promoting effect on breast cancer development from exposure to high levels of pregnancy hormones.

Grant Support
This work was supported by grants from the Swedish Cancer Society (grant number 07-0526; Mats Lambe) and Susan G Komen for the Cure (grant number KG 100116; Mats Lambe).
References


Table 1. Number of deaths, all-cause mortality rates and hazard ratios by PABC exposures in women diagnosed with breast cancer in Sweden 1963-2002.

<table>
<thead>
<tr>
<th>Age at breast cancer diagnosis</th>
<th>Breast cancers</th>
<th>Deaths</th>
<th>Mortality rate per 1000pyrs (95% CI)</th>
<th>Unadjusted aHR (95%CI)</th>
<th>Adjusted aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-29</td>
<td>656</td>
<td>270</td>
<td>49.0 (43.5-55.2)</td>
<td>1.45 (1.28-1.65)</td>
<td>1.12 (0.97-1.31)</td>
</tr>
<tr>
<td>30-34</td>
<td>1,977</td>
<td>822</td>
<td>50.2 (46.8-53.7)</td>
<td>1.47 (1.36-1.59)</td>
<td>1.30 (1.19-1.42)</td>
</tr>
<tr>
<td>35-39</td>
<td>4,612</td>
<td>1720</td>
<td>42.6 (40.6-44.7)</td>
<td>1.25 (1.18-1.33)</td>
<td>1.17 (1.10-1.25)</td>
</tr>
<tr>
<td>40-44</td>
<td>8,476</td>
<td>2614</td>
<td>34.1 (32.8-35.4)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year at breast cancer diagnosis</th>
<th>Breast cancers</th>
<th>Deaths</th>
<th>Mortality rate per 1000pyrs (95% CI)</th>
<th>Unadjusted aHR (95%CI)</th>
<th>Adjusted aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963-1974</td>
<td>2,811</td>
<td>1312</td>
<td>46.0 (43.5-48.5)</td>
<td>1.55 (1.44-1.68)</td>
<td>0.96 (0.88-1.04)</td>
</tr>
<tr>
<td>1975-1989</td>
<td>6,384</td>
<td>2666</td>
<td>38.4 (37.0-39.9)</td>
<td>1.30 (1.22-1.39)</td>
<td>1.10 (1.03-1.18)</td>
</tr>
<tr>
<td>1990-2002</td>
<td>6,526</td>
<td>1448</td>
<td>35.3 (33.5-37.1)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>Breast cancers</th>
<th>Deaths</th>
<th>Mortality rate per 1000pyrs (95% CI)</th>
<th>Unadjusted aHR (95%CI)</th>
<th>Adjusted aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤9 years</td>
<td>4,779</td>
<td>2193</td>
<td>49.0 (47.0-51.1)</td>
<td>1.48 (1.39-1.58)</td>
<td>1.53 (1.44-1.64)</td>
</tr>
<tr>
<td>10-13 years</td>
<td>6,130</td>
<td>1809</td>
<td>33.6 (32.1-35.2)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>University (undergraduate)</td>
<td>1,938</td>
<td>463</td>
<td>27.2 (24.8-29.8)</td>
<td>0.80 (0.72-0.89)</td>
<td>0.79 (0.71-0.88)</td>
</tr>
<tr>
<td>University (postgraduate)</td>
<td>2,311</td>
<td>452</td>
<td>20.8 (19.0-22.8)</td>
<td>0.62 (0.56-0.69)</td>
<td>0.62 (0.56-0.68)</td>
</tr>
<tr>
<td>Missing</td>
<td>563</td>
<td>509</td>
<td>299.0 (274.1-326.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PABC</th>
<th>Breast cancers</th>
<th>Deaths</th>
<th>Mortality rate per 1000pyrs (95% CI)</th>
<th>Unadjusted aHR (95%CI)</th>
<th>Adjusted aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PABC</td>
<td>14,611</td>
<td>4911</td>
<td>37.6 (36.6-38.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>PABC</td>
<td>1,110</td>
<td>515</td>
<td>61.9 (56.7-67.4)</td>
<td>1.61 (1.47-1.77)</td>
<td>1.51 (1.36-1.68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proximity of breast cancer to delivery</th>
<th>Breast cancers</th>
<th>Deaths</th>
<th>Mortality rate per 1000pyrs (95% CI)</th>
<th>Unadjusted aHR (95%CI)</th>
<th>Adjusted aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PABC</td>
<td>14,611</td>
<td>4911</td>
<td>37.6 (36.6-38.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>PABC during pregnancy</td>
<td>107</td>
<td>51</td>
<td>77.0 (58.5-101.3)</td>
<td>1.97 (1.50-2.60)</td>
<td>1.85 (1.34-2.56)</td>
</tr>
<tr>
<td>PABC during months 1-3 after birth</td>
<td>54</td>
<td>22</td>
<td>61.4 (40.5-93.3)</td>
<td>1.64 (1.08-2.50)</td>
<td>1.31 (0.80-2.15)</td>
</tr>
<tr>
<td>PABC during months 4-6 after birth</td>
<td>86</td>
<td>56</td>
<td>101.7 (78.2-132.1)</td>
<td>2.65 (2.03-3.45)</td>
<td>2.45 (1.83-3.29)</td>
</tr>
<tr>
<td>PABC during months 7-12 after birth</td>
<td>281</td>
<td>137</td>
<td>62.6 (53.0-74.0)</td>
<td>1.63 (1.38-1.93)</td>
<td>1.64 (1.37-1.97)</td>
</tr>
<tr>
<td>PABC during months 13-18 after birth</td>
<td>296</td>
<td>132</td>
<td>56.2 (47.4-66.7)</td>
<td>1.46 (1.23-1.74)</td>
<td>1.34 (1.11-1.62)</td>
</tr>
<tr>
<td>PABC during months 19-24 after birth</td>
<td>286</td>
<td>117</td>
<td>52.8 (44.0-63.2)</td>
<td>1.39 (1.15-1.66)</td>
<td>1.28 (1.04-1.57)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parity prior to breast cancer (PABC pregnancy not included in parity)</th>
<th>Breast cancers</th>
<th>Deaths</th>
<th>Mortality rate per 1000pyrs (95% CI)</th>
<th>Unadjusted aHR (95%CI)</th>
<th>Adjusted aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3,039</td>
<td>1063</td>
<td>41.1 (38.7-43.6)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>3,197</td>
<td>1214</td>
<td>42.7 (40.4-45.2)</td>
<td>1.05 (0.96-1.13)</td>
<td>1.03 (0.94-1.12)</td>
</tr>
<tr>
<td>2</td>
<td>9,485</td>
<td>3149</td>
<td>37.2 (35.9-38.5)</td>
<td>0.91 (0.85-0.97)</td>
<td>0.95 (0.88-1.03)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PABC x Parity prior to breast cancer</th>
<th>Breast cancers</th>
<th>Deaths</th>
<th>Mortality rate per 1000pyrs (95% CI)</th>
<th>Unadjusted aHR (95%CI)</th>
<th>Adjusted aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-PABC, nulliparous</td>
<td>2,743</td>
<td>942</td>
<td>39.6 (37.2-42.2)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-PABC, parous</td>
<td>3,969</td>
<td>3969</td>
<td>37.1 (36.0-38.3)</td>
<td>0.94 (0.88-1.01)</td>
<td>0.95 (0.88-1.03)</td>
</tr>
<tr>
<td>PABC, nulliparous</td>
<td>296</td>
<td>121</td>
<td>57.7 (48.3-69.0)</td>
<td>1.43 (1.18-1.73)</td>
<td>1.30 (1.05-1.62)</td>
</tr>
<tr>
<td>PABC, parous</td>
<td>814</td>
<td>394</td>
<td>63.3 (57.3-69.8)</td>
<td>1.57 (1.40-1.77)</td>
<td>1.51 (1.33-1.72)</td>
</tr>
</tbody>
</table>
a HRs from flexible parametric survival models, adjusting for time-since-diagnosis as underlying timescale and assuming proportional hazards. The models use n=15,721 observations, except for education (n=15,158).

b HRs from flexible parametric survival models, adjusting for follow-up time (underlying timescale) and confounders: age at breast cancer, calendar year at breast cancer and education. The shown estimates for confounders are from the model of PABC (yes/no). The models assume proportional hazards and use n=15,158 observations.

c Reference group.

PABC=pregnancy-associated breast cancer; pyrs = person-years; HR=hazard ratio; CI=confidence interval.
Table 2. Hazard ratios estimated at 2, 5 and 10 years after diagnosis by PABC exposures in women diagnosed with breast cancer in Sweden 1963-2002.

<table>
<thead>
<tr>
<th>PABC</th>
<th>2 years after</th>
<th>5 years after</th>
<th>10 years after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>diagnosis</td>
<td>diagnosis</td>
<td>diagnosis</td>
</tr>
<tr>
<td></td>
<td>HR(^a) (95%CI)</td>
<td>HR(^a) (95%CI)</td>
<td>HR(^a) (95%CI)</td>
</tr>
<tr>
<td>Non-PABC(^b)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>PABC</td>
<td>1.8 (1.6-2.2)</td>
<td>1.5 (1.3-1.8)</td>
<td>1.0 (0.8-1.3)</td>
</tr>
<tr>
<td><strong>Proximity of PABC to delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PABC(^b)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>PABC during pregnancy</td>
<td>2.1 (1.4-3.2)</td>
<td>2.0 (1.2-3.4)</td>
<td>1.1 (0.5-2.6)</td>
</tr>
<tr>
<td>PABC during months 1-3 after birth</td>
<td>2.1 (1.1-3.9)</td>
<td>0.7 (0.2-2.4)</td>
<td>N/A(^c) N/A</td>
</tr>
<tr>
<td>PABC during months 4-6 after birth</td>
<td>3.7 (2.4-5.8)</td>
<td>1.6 (0.9-3.1)</td>
<td>2.1 (1.2-3.8)</td>
</tr>
<tr>
<td>PABC during months 7-12 after birth</td>
<td>1.9 (1.5-2.6)</td>
<td>1.6 (1.2-2.2)</td>
<td>1.3 (0.9-2.0)</td>
</tr>
<tr>
<td>PABC during months 13-18 after birth</td>
<td>1.6 (1.2-2.1)</td>
<td>1.5 (1.1-2.1)</td>
<td>0.9 (0.5-1.4)</td>
</tr>
<tr>
<td>PABC during months 19-24 after birth</td>
<td>1.6 (1.2-2.1)</td>
<td>1.5 (1.1-2.0)</td>
<td>0.6 (0.4-1.1)</td>
</tr>
</tbody>
</table>

\(^a\) HRs from flexible parametric survival models (one separate model for each exposure, same model used at 2, 5, 10 years) assuming time-varying effects of the exposure (non-proportional hazards). The HRs are adjusted for follow-up time (underlying timescale), age at breast cancer, calendar year at breast cancer and education.

All three models use n=15,158 observations.

\(^b\) Reference group.

\(^c\) Values set to N/A for when there are no events at or beyond 10 years.

PABC=pregnancy-associated breast cancer; HR=hazard ratio; CI=confidence interval.
Figure legends

**Figure 1.** Mortality rates by time-since-diagnosis and by proximity of PABC diagnosis to delivery, estimated from an unadjusted flexible parametric survival model. The curves are only plotted until the last event time for each group.

**Figure 2.** Hazard ratios of PABC vs Non-PABC by time-since diagnosis and by proximity of PABC diagnosis to delivery (during pregnancy and during months after delivery). The hazard ratios (HR) adjusted for age at diagnosis, calendar time at diagnosis and education. The shaded areas represent 95% point-wise CIs around the curve. The straight line represents the reference group Non-PABC at HR=1.0. The curves are only plotted until the last event time for each group.
A. PABC during pregnancy

B. PABC during months 1-3

C. PABC during months 4-6

D. PABC during months 7-12

E. PABC during months 13-18

F. PABC during months 19-24
Mortality rate (per 1000 person−years)

Time−since−diagnosis (years)

- Non−PABC
- PABC overall
- PABC during pregnancy
- PABC during months 1−3 after delivery
- PABC during months 4−6 after delivery
- PABC during months 7−12 after delivery
- PABC during months 13−18 after delivery
- PABC during months 19−24 after delivery
Increased mortality in women with breast cancer detected during pregnancy and different periods postpartum


_Cancer Epidemiol Biomarkers Prev_ Published OnlineFirst July 12, 2011.

**Updated version**  Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-11-0515

**Author Manuscript**  Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

**E-mail alerts**  Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.