9 Epidemiology of Pregnancy-Associated Breast Cancer

Anna L. V. Johansson and Hanne Stensheim

Abstract

Breast cancer diagnosed during pregnancy or lactation up to 1 year post-partum is often referred to as *pregnancy-associated breast cancer* (PABC), although the definition varies with length of post-partum period. The incidence rate has been reported to range from 17.5 to 39.9 per 100,000 births, but the rate is substantially lower during pregnancy (ranging from 3.0 to 7.7) than during the post-partum period (ranging from 13.8 to 32.2). The PABC incidence rate is increasing in many populations, and higher maternal age at birth is a likely explanation. Linkable population-based data on pregnancies and cancer are required to obtain reliable estimates of PABC incidence. In studies comparing outcomes in women with PABC to other young breast cancer patients, it is crucial to adjust for age, since the age distribution of PABC depends both on age at pregnancy and age at breast cancer. Large studies have shown similar prognosis for women with PABC compared to other young women with breast cancer, when accounting for differences in age, stage and other tumour characteristics.

Keywords

Age confounding · Exposure · Incidence · Pregnancy risk window · Prognosis

9.1 Definition of Pregnancy-Associated Breast Cancer Risk Windows

Pregnancy-associated breast cancer (PABC) is commonly defined as a breast cancer during pregnancy and up to 1 year postpartum. Some authors only include the pregnancy window, while others also include the second year post-partum or up to 5 or 10 years postpartum in the PABC risk window. The different pregnancy and postpartum risk windows reflect short- and long-term exposures and effects of pregnancy on breast cancer detection and management, e.g. mammographic density, masking, potential detection delays, diagnostic workup, treatment and survival. For most outcomes it is of relevance to separate effects in the different risk windows during pregnancy (first, second, third trimesters)

A. L. V. Johansson (✉)
Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
e-mail: anna.johansson@ki.se

H. Stensheim
Cancer Registry of Norway, Oslo, Norway
e-mail: hanne.stensheim@kreftregisteret.no

S. Alipour, R. Omranipour (eds.), *Diseases of the Breast during Pregnancy and Lactation*, Advances in Experimental Medicine and Biology 1252,
https://doi.org/10.1007/978-3-030-41596-9_9

and after delivery (0–6 months, 6–12 months, etc.). The pregnancy window is of particular interest for long-term follow-up of children exposed to cancer treatment in utero.

From an epidemiological point of view, it is important to realize that *pregnancy-association* is an exposure, and that PABC is a subgroup of young patients diagnosed with breast cancer, namely those cases diagnosed while exposed to pregnancy and lactation.

9.2 Incidence of Pregnancy-Associated Breast Cancer

Breast cancer, together with malignant melanoma and cervical cancer, are the most common malignancies diagnosed in pregnant or recently pregnant women [1–8]. Around 4% of women with breast cancer under age 45 are diagnosed during pregnancy or within the first year postpartum [2, 4, 9].

The incidence rate of PABC has been reported from several population-based studies (Table 9.1). There is a large variation in incidence across different populations and calendar periods. Reported estimates of PABC incidence rates range from 17.5 to 39.9 per 100,000 births; rates range from 3.0 to 7.7 during pregnancy, and from 13.8 to 32.2 during the first year postpartum [1, 3–7].

Hence, the risk pattern before and after delivery is strikingly different, with a lower incidence during pregnancy and an increasing incidence after delivery. This risk pattern was assessed in detail by Andersson et al. [1] who reported the relative risks of PABC as: 1st trimester: 0.05 (95% CI 0.02–0.11), 2nd trimester: 0.26 (0.18–0.36), 3rd trimester: 0.72 (0.59–0.87), 0–6 months postpartum: 0.59 (0.51–0.69), 6–12 months postpartum: 1.12 (1.01–1.24) and 12–24 months postpartum: 1.10 (1.03–1.18), compared to an age- and year-matched control population. This risk pattern could reflect a biologically lower risk during pregnancy, diagnostic delays or a healthy mother effect (reverse causation) during pregnancy [10].

Several studies have shown increasing incidence rates of PABC over calendar time [2–6]. The increasing incidence can to a large extent be explained by increasing maternal age and the ongoing trend of postponement of childbearing to ages where breast cancer is more common [2, 4, 5]. Other than age, risk factors of PABC are largely unknown.

There are several challenges when estimating PABC incidence rates. First, the estimates depend on which denominator has been utilized for calculating the incidence rate. Most commonly, PABC incidence is expressed as number of PABC cases per 100,000 deliveries or births, but also pregnancies (including elective and spontaneous abortions), live births, and person-time at risk have been used as denominator. The denominator should ideally capture the population at risk of PABC, namely pregnant (or recently pregnant) women. The total number of pregnant women may be difficult to ascertain in a population even with a birth registry, due to high rates of spontaneous abortion in the first trimester. Hence, births (deliveries) are a more stable measure of the pregnant population. Number of deliveries is also a good estimate of number of women at risk in the postpartum period, and using the same denominator before and after delivery makes the rates comparable.

Second, the incidence estimates may differ between studies due to the inclusion or exclusion of abortions (spontaneous or induced) and stillbirths in both the numerator and denominator of the incidence rate. Such hampered case ascertainment would lead to underestimation of PABC rates during pregnancy, in particular in early trimesters. Eibye et al. [4] reported that 81% of patients diagnosed with PABC in first trimester underwent elective abortion. However, in recent years the use of therapeutic abortion is likely to have decreased as more aggressive treatments are given during pregnancy.

Third, to obtain unbiased estimates of PABC incidence, population-based individual level data on both pregnancies and breast cancer is required. In many countries, population data is available in birth registries and in cancer registries. However, in order to classify a breast cancer as PABC these two registry databases must be linkable on an individual level, which may not be administratively possible in all countries.

Table 9.1 Population-based studies estimating incidence of pregnancy-associated breast cancer

First author, year	Country	Years covered by study	PABC definition	Proportion of PABC among all BC	Total PABC N (Py + 1y PP) N (Py) N (1y PP)	PABC incidence (per 100,000) Rate (Py + 1yPP) Rate (Py) Rate (1y PP)	Denominator in incidence	Incidence trend over calendar time
Cottreau, 2018 [3]	USA, 5 states	2001–2013	Py + 1 y	Not reported	208 56 152	26.8 7.2[a] 19.6[a]	775,709 births	Increasing trend
Parazzini, 2017 [6]	Lombardy, Italy	2002–2011	Py + 1 y	Not reported	479 93 386	39.9 7.7 32.2	1,200,263 Py	Not reported for PABC
Andersson, 2015 [1]	Sweden	1963–2007	Py + 1 y	Not reported	1486 139 1347	32.4[b] 3.0[b] 29.4[b]	4,580,005 live births	–
Eibye, 2013 [4]	Denmark	1997–2006	Py + 1 y	491/10963 = 4.4%	426 91 335[c]	17.5 3.7 13.8[c]	Induced abortions and live births	Increasing trend
Lee, 2012 [5]	New South Wales, Australia	1994–2008	Py + 1 y	Not reported	377 95 282	28.8 7.3 21.5	1,309,501 maternities (births)	Increasing trend
Smith, 2003 [7]	California	1991–1999	Py + 1 y	Not reported	935 266 669	19.3 5.4 13.8	4,846,505 births	–

BC breast cancer, *N* number, *PABC* pregnancy-associated breast cancer, *PP* postpartum, *Py* pregnancy, *y* year

[a]For Cottreau et al.: We have calculated the incidence for pregnancy window taking number of PABC divided by births at risk: 208/775,709 = 26.8, 56/775,709 = 7.2 and 152/775,709 = 19.6

[b]For Andersson et al.: Study used pregnancy+ 2 years PABC window, we have re-calculated numbers for pregnancy+ 1 year using numbers given in the tables in the article. We have also calculated incidence using the reported number of live deliveries (4,508,005). E.g. total incidence is calculated as 1486/4,508,005 = 32.4/100,000

[c]For Eibye et al.: Numbers and incidence 1 year postpartum was not reported in the article, but we have made calculations by taking total minus pregnancy window (426–91 = 335, and 17.5–3.7 = 13.8)

9.3 Age-Specific Incidence of Preganancy-Associated Breast Cancer and Maternal Age

Similar to the overall breast cancer incidence, the age-specific incidence rates of PABC increases over a woman's reproductive period and is highest above age 40 [2–4, 6]. However, the PABC incidence also depends on the age at childbirth (i.e. age at exposure). In most populations, the mean age at childbirth is below 30 years. Because the age distribution of PABC is the overlap between the age distributions of pregnancy (exposure) and of breast cancer (outcome), the absolute numbers of PABC are therefore highest in ages 30–34 years [2]. In this age group, pregnancy and breast cancer is most likely to co-occur. So, although the PABC incidence rate increases with age, the absolute numbers of PABC continuously decrease to zero at menopause after which women are no longer exposed to pregnancy and PABC does not occur.

In studies of PABC, women with PABC are often compared to other premenopausal women with breast cancer, often denoted "non-PABC". Non-PABC is usually defined as a breast cancer diagnosed in a nulliparous woman or in women more than 1 year after the latest childbirth. Women with non-PABC are thus similar to "premenopausal breast cancer" and will have an increasing age-distribution, since breast cancer becomes more common at higher ages. Hence, since the age of PABC women is shifted towards younger ages, while the age of non-PABC women is shifted towards higher ages, age at diagnosis is a very strong confounder in comparisons between PABC and non-PABC. Any comparison between PABC and non-PABC must therefore be thoroughly adjusted for differences in age at diagnosis to avoid age confounding. This can either be achieved via fine matching between PABC cases and non-PABC controls (e.g. 1-year age categories are often required) or via adjustments in the statistical analysis. Residual age confounding is a problem that many studies of PABC may have overlooked when using too broad age categories in the adjustment.

9.4 Prognosis of Pregnancy-Associated Breast Cancer

Several studies of varying sizes have assessed prognosis following breast cancer during pregnancy and lactation with somewhat conflicting results [8, 9, 11–20]. Two meta-analyses including both hospital-based and population-based studies found a worse prognosis in women with PABC compared to non-PABC, but the association was stronger in the postpartum period and weaker in women diagnosed during pregnancy [12, 16]. Women with PABC are more often diagnosed with advanced stage tumors and hormone receptor negative disease [8, 9, 11]. After adjustments for tumor stage and biology, the survival is similar between PABC and non-PABC, indicating that the worse prognosis reported in some studies can to a large extent be explained by adverse tumor characteristics [8, 9, 11].

Differences between studies include study setting (hospital-based, population-based), country, ages at diagnosis, calendar periods, treatments, postpartum windows, length of follow-up and study size. Population-based studies of prognosis following PABC often lack detailed information on clinical factors and treatment data, while institution-based materials often include those variables at high quality, but are at risk of selection bias. The poorer survival in cases diagnosed postpartum may partly be explained by delayed diagnosis, suboptimal treatment and lack of adjustment for several important clinical factors (see also Chap. 11).

References

1. Andersson TM, Johansson AL, Fredriksson I, Lambe M (2015) Cancer during pregnancy and the postpartum period: a population-based study. Cancer 121(12):2072–2077
2. Andersson TM, Johansson AL, Hsieh CC, Cnattingius S, Lambe M (2009) Increasing incidence of pregnancy-associated breast cancer in Sweden. Obstet Gynecol 114(3):568–572
3. Cottreau CM, Dashevsky I, Andrade SE, Li DK, Nekhlyudov L, Raebel MA et al (2018) Pregnancy-associated cancer: a US population-based study. J Women's Health 28(2):250–257

4. Eibye S, Kjær SK, Mellemkjær L (2013) Incidence of pregnancy-associated cancer in Denmark, 1977–2006. Obstet Gynecol 122(3):608–617
5. Lee YY, Roberts CL, Dobbins T, Stavrou E, Black K, Morris J et al (2012) Incidence and outcomes of pregnancy-associated cancer in Australia, 1994–2008: a population-based linkage study. BJOG 119(13):1572–1582
6. Parazzini F, Franchi M, Tavani A, Negri E, Peccatori FA (2017) Frequency of pregnancy related cancer: a population based linkage study in Lombardy, Italy. Int J Gynecol Cancer 27(3):613–619
7. Smith LH, Danielsen B, Allen ME, Cress R (2003) Cancer associated with obstetric delivery: results of linkage with the California cancer registry. Am J Obstet Gynecol 189(4):1128–1135
8. Stensheim H, Møller B, van Dijk T, Fosså SD (2009) Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol 27(1):45–51
9. Johansson AL, Andersson TM, Hsieh CC, Jirström K, Cnattingius S, Fredriksson I et al (2018) Tumor characteristics and prognosis in women with pregnancy-associated breast cancer. Int J Cancer 142(7):1343–1354
10. Sankila R, Heinävaara S, Hakulinen T (1994) Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect". Am J Obstet Gynecol 170(3):818–823
11. Amant F, von Minckwitz G, Han SN, Bontenbal M, Ring AE, Giermek J et al (2013) Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol 31(20):2532–2539
12. Azim HA Jr, Santoro L, Russell-Edu W, Pentheroudakis G, Pavlidis N, Peccatori FA (2012) Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. Cancer Treat Rev 38(7):834–842
13. Beadle BM, Woodward WA, Middleton LP, Tereffe W, Strom EA, Litton JK et al (2009) The impact of pregnancy on breast cancer outcomes in women≤ 35 years. Cancer 115(6):1174–1184
14. Bonnier P, Romain S, Dilhuydy JM, Bonichon F, Julien JP, Charpin C et al (1997) Influence of pregnancy on the outcome of breast cancer: a case-control study. Int J Cancer 72(5):720–727
15. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL (2002) The relation of reproductive factors to mortality from breast cancer. Cancer Epidemiol Biomark Prev 11(3):235–241
16. Hartman EK, Eslick GD (2016) The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat 160(2):347–360
17. Johansson AL, Andersson TM, Hsieh CC, Cnattingius S, Lambe M (2011) Increased mortality in women with breast cancer detected during pregnancy and different periods postpartum. Cancer Epidemiol Biomark Prev 20(9):1865–1872
18. Moreira WB, Brandão EC, Soares AN, Lucena CE, Antunes CM (2010) Prognosis for patients diagnosed with pregnancy-associated breast cancer: a paired case-control study. Sao Paulo Med J 128(3):119–124
19. Rodriguez AO, Chew H, Cress R, Xing G, McElvy S, Danielsen B et al (2008) Evidence of poorer survival in pregnancy-associated breast cancer. Obstet Gynecol 112(1):71–78
20. Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA (2004) Reproductive history and mortality after breast cancer diagnosis. Obstet Gynecol 104(1):146–154