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EPIDEMIOLOGY

The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis

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Abstract
Objective Previous meta-analyses have examined the prognosis of women with pregnancy-associated breast cancer (PABC) as well as pregnancy that follows breast cancer diagnosis. Since then, many additional studies have been performed. We conducted an updated meta-analysis to examine the prognosis for women who become pregnant before, during and after a diagnosis of breast cancer. We also performed analyses on the various subgroups within PABC such as pregnancy and postpartum cases, as well as on time periods postpartum.
Methods We identified studies that reported on overall (OS) and disease-free survival (DFS) in patients diagnosed with breast cancer during pregnancy or up to 5 years postpartum from four electronic databases. We also identified studies that reported on OS and DFS where pregnancy up to 5 years occurred after a breast cancer diagnosis.
Results 41 studies met our inclusion criteria (cases = 4929; controls = 61,041) for pregnancy occurring during or before breast cancer diagnosis. There was an overall increased risk of death amongst patients compared to non-pregnant controls [HR 1.57; 95 % CI 1.35–1.82]. Subgroup analysis indicated poor survival outcomes for those diagnosed either during pregnancy or postpartum (PABC) [HR 1.46; 95 % CI 1.17–1.82] as well as those diagnosed during pregnancy alone [HR 1.47; 95 % CI 1.04–2.08]. Those diagnosed postpartum had the poorest overall survival [HR 1.79; 95 % CI 1.39–2.29]. Similarly, patients with PABC had decreased DFS compared to controls [HR 1.51; 95 % CI 1.22–1.88]. Those diagnosed postpartum were the most at risk of disease progression or relapse [HR 1.86; 95 % CI 1.17–2.93]. 19 studies met our inclusion criteria (cases = 1829; controls = 21,907) for pregnancy following breast cancer diagnosis. Such women had a significantly reduced risk of death compared to those who did not become pregnant [pHR 0.63; 95 % CI 0.51–0.79]. A subgroup analysis to account for the "healthy mother effect" generated similar results [pHR 0.65; 95 % CI 0.52–0.81].
Conclusion Pregnancy that occurs before or concurrently with a diagnosis of breast cancer is more likely to result in death and decreased disease-free survival. On the other hand, pregnancy occurring after a breast cancer diagnosis reduces the risk of death.

Keywords Breast cancer · Pregnancy-associated breast cancer · PABC · Pregnancy · Postpartum · Gestation · Meta-analysis

Introduction

The diagnosis of breast cancer for the expectant mother is certainly devastating. At a time when a woman and her family are preparing to celebrate the joy of new life, to be faced with the real possibility of death is a substantial emotional challenge. Such a situation also signifies a complex medical conundrum. The practitioner must provide best care to the mother whilst at the same time ensuring the care of the foetus is not compromised.

Pregnancy-associated breast cancer (PABC) is generally defined in the literature as breast cancer diagnosed during

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pregnancy or the first year postpartum. Some studies, however, have extended this definition to up to 5 years following delivery [1–3]. Whether or not such an extended definition is warranted remains unclear and will be explored in this analysis.

Breast cancer is one of the most common malignancies encountered during pregnancy. Approximately 0.2–3.8 % of all breast cancers are pregnancy related [4], whilst 10 % of breast cancers in women <40 years of age occur during pregnancy [5]. The incidence of PABC in Western countries is estimated to be 1 in 3000 to 1 in 10,000 pregnancies [6], and as women increasingly delay childbearing to older maternal ages, it is likely this incidence will rise.

The treatment of PABC requires the careful balancing of interests between the mother and foetus. Standard treatment includes surgery as well as neoadjuvant and adjuvant chemotherapy from the second trimester. Exposure during the second and third trimesters has not been associated with teratogenic effects [7–9]. Most cases during pregnancy are treated with a combination chemotherapy regimen such a FAC (5-fluorouracil, doxorubicin and cyclophosphamide); however, recent studies have also demonstrated successful outcomes with taxanes [10, 11]. Radiotherapy is contraindicated and should be delayed until after delivery.

The rarity of cases and the impracticability of conducting randomised controlled studies in this setting have limited reports on prognosis to retrospective studies with generally small cohorts. Studies that address the impact of pregnancy on the prognosis of such cases have had inconsistent results. Whilst some studies suggest outcomes for women are similar to non-pregnant patients with breast cancer [5, 12–17], others have demonstrated that pregnancy in itself is an adverse prognostic factor for survival [18–23]. A meta-analysis of 30 studies conducted by Azim et al. in 2012 concluded that PABC is associated with poorer prognosis, particularly when diagnosed postpartum [24]. Amant et al. [11] conducted the largest study to date on the prognosis of breast cancer diagnosed during pregnancy and did not find a significant difference in disease-free survival (DFS) or overall survival (OS) between 311 pregnant women with breast cancer and those of 865 non-pregnant controls matched for known prognostic factors such as stage, age, hormonal receptors and type of treatment.

A further challenge to the practitioner are women who have previously been diagnosed and treated for breast cancer and who subsequently desire to become pregnant. Such women are likely to wonder whether a future pregnancy could adversely affect their prognosis and how long they should wait to conceive following cessation of their treatment. A meta-analysis of 14 studies by Azim et al. in 2011 found that pregnancy following breast cancer was safe and in fact those who became pregnant after a diagnosis of breast cancer had improved survival outcomes compared to those who did not become pregnant [25].

It is debatable whether these favourable results are due to a selection bias rather than the actual protective effect of pregnancy. The "healthy mother effect" [26] suggests that women who have had more favourable outcomes are more likely to conceive than those who have had a recurrence after diagnosis and hence the improved outcome observed is really a reflection of selecting women who have not relapsed. In order to account for this bias, some studies have matched cases and controls according to nodal status, ER status, disease-free interval and treatment [27].

In the last 5 years, important studies have been performed in this area, significantly adding to the body of literature and understanding in the field. Since Azim's 2012 meta-analysis [24], there have been an additional 14 studies that have examined pregnancy occurring before or concurrently with breast cancer diagnosis, whilst there have been an additional 5 studies examining pregnancy after diagnosis. Studies unique to these meta-analyses appear in bold in Tables 1 and 2. Azim's 2012 meta-analysis defined PABC as during pregnancy or up to 1 year postpartum [24]. This study adopted a broader definition of PABC whereby cases were defined as those during pregnancy or up to 5 years postpartum. We also performed sub-analyses where cases were defined up to 2 years postpartum and up to 1 year postpartum to determine whether the extended time period postpartum provided by some studies is meaningful. It has been hypothesised that the poor prognosis seen in cases diagnosed postpartum may be responsible for the overall increased risk seen in PABC. As such we performed sub-analyses based on studies that only reported on postpartum cases, as well as those that only reported on cases during pregnancy. This study therefore aims to provide an updated and comprehensive meta-analysis on the mortality and morbidity of woman diagnosed with breast cancer before, during and after pregnancy.

Methods

Study protocol

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [28]. A systematic search of the databases MEDLINE, EMBASE, PubMed and Google (first 20 pages) through to 31 August 2016 was conducted to identify relevant articles. The search used the terms 'pregnant' or 'gestation' and 'breast' and 'cancer' or 'neoplasia' or 'carcinoma', which were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant

Table 1 Study characteristics (pregnancy before/during diagnosis) ($n = 41$)

First author	Year	Country	Study type	Cases (PABC)	Control	PABC definition	Mean age	Follow-up (years)	Outcomes measured
Mausner [64]	1969	America	Retro. CCS	73	647	Pregnancy + <6 months postpartum	35	5	OS*
Wallgren [36]	1977	Sweden	Retro. CCS	15	58	Pregnancy + <1 year postpartum	<30	5	OS*
Nugent [5]	1985	America	Retro. CCS	19	155	Pregnancy	32	5	OS*
Tretli [20]	1988	Norway	Retro. CCS	35	40	Pregnancy + postpartum (unspecified)	33	4	OS+
Greene [12]	1988	America	Retro. CCS	8	36	Pregnancy	33	7.5	OS*
Zemlicks [65]	1992	Canada	Retro. CCS	118	269	Pregnancy + postpartum (unspecified)	<50	5	DFS
Guinee [19]	1994	America	Retro. CCS	66	139	Pregnancy + <1 year postpartum	28	5	OS
Von Schoultz [1]	1995	Sweden	Retro. cohort	173	1740	Pregnant + <5 year postpartum	<50	7	DFS
Ezzat [13]	1996	Saudi Arabia	Retro. CCS	28	84	Pregnancy	<45	7	OS, DFS
Anderson [66]	1996	America	Retro. CCS	22	205	Pregnancy + <1 year postpartum	<30	10	OS, DFS+
Bonnier [67]	1997	France	Retro. CCS	154	308	Pregnancy + <6 months postpartum	33.9	5	OS, DFS
Ibrahim [14]	2000	Saudi Arabia	Retro. CCS	72	216	Pregnancy	34	4	OS*, DFS*
Daling [68]	2002	America	Retro. CCS	83	309	<2 years postpartum (only postpartum)	<45	5	OS
Aziz [37]	2003	Pakistan	Retro. CCS	24	48	Pregnancy + <1 year postpartum	32	7	OS*
Siegelmann-Danieli [38]	2003	Israel	Retro. CCS	22	192	Pregnancy + <1 year postpartum	33	5	OS*, DFS*
Bladstrom [18]	2003	Sweden	Retro. CCS	94	14,599	Pregnancy	34	5	OS
Whiteman [69]	2004	America	Retro. CCS	59	355	<1 year postpartum (only postpartum)	<54	15	OS
Rodriguez [70]	2008	America	Retro. CCS	797	4177	Pregnancy + <1 year postpartum	<55	13	OS
Mathelin [22]	2008	France	Retro. CCS	40	61	Pregnancy + <1 year postpartum	33.8	10	OS, DFS
Stensheim [16]	2009	Norway	Retro. CCS	105	13,106	Pregnancy + <6 months postpartum	34	5	OS
Beadle [15]	2009	America	Retro. cohort	104	548	Pregnancy + <1 year postpartum	33	10	OS*, DFS*
Halaska [17]	2009	Czech Rep./ Greece	Retro. CCS	32	32	Pregnancy + <1 year postpartum	33.7	10	OS*, DFS+
Largillier [56]	2009	France	Retro. cohort	105	788	Pregnancy + <1 year postpartum	32	10	OS, DFS
Moreira [71]	2010	Brazil	Retro. CCS	87	252	Pregnancy + <1 year postpartum	35	10	OS
Johansson 1 [23]	2011	Sweden	Retro. CCS	1110	14,611	Pregnancy + <2 years postpartum	<45	15	OS
Murphy [39]	2012	America	Retro. CCS	99	186	Pregnancy + <1 year postpartum	35	18	OS
Azim [21]	2012	Italy	Retro. CCS	65	130	Pregnancy	36	4	OS, DFS
Amant [11]	2012	Belgium	Retro. cohort	311	865	Pregnancy	33	5	OS, DFS
Ali [72]	2012	America	Retro. CCS	40	40	Pregnancy + <1 years postpartum	33	10	OS*, DFS*
Litton [35]	2013	America	Prospect. CCS	75	150	Pregnancy	<45	5	OS, DFS
Valentini [40]	2013	America	Retro. CCS	75	269	Pregnancy + <1 year postpartum	32.5	15	OS, DFS*
Dimitrakakis [47]	2013	Greece	Retro. CCS	39	39	Pregnancy + <1 year postpartum	34.3	5	OS, DFS*
Callihan 1 [2]	2013	America	Retro. cohort	119	394	Pregnancy + <5 year postpartum	35.7	3	OS, DFS
Bell [41]	2013	Australia	Prospec. cohort	13	377	Pregnancy + <1 year postpartum	<48	5	OS, DFS
Johansson 2 [73]	2013	Sweden	Retro. CCS	317	3915	Pregnancy + <2 years postpartum	<44	9	OS
Framarino-Dei-Malatesta [42]	2014	Italy	Retro. CCS	22	45	Pregnancy	37.2	10	OS*
Yang [43]	2014	Taiwan	Retro. CCS	26	104	Pregnancy + <1 year postpartum	34	5	OS*
Madaras [44]	2014	Hungary	Retro. CCS	31	31	Pregnancy + <1 year postpartum	34	10	OS*, DFS *
Strasser-Weipl [3]	2015	China	Retro. cohort	109	1274	Pregnancy + <5 year postpartum	<45	5	DFS
Baulies [45]	2015	Italy	Retro. CCS	56	73	Unspecified	–	5	DFS*
Genin [46]	2015	France	Retro CCS	87	174	Pregnancy + <1 year postpartum	35	9	OS ρ DFS

Studies in bold are unique to this meta-analysis and were not included in previous meta-analyses

*Studies for which OR was calculated from crude data

+ Studies for which HR was calculated from KM Curves

ρ HR was obtained by contacting the author

Table 2 Study characteristics (pregnancy after diagnosis) ($n = 19$)

First author	Year	Country	Study type	Cases	Controls	Age	Follow-up (years)	Outcomes measured	HME bias?
Cooper [48]	1970	America	CCS	28	56	<40	5	OS*	No
Ribeiro [49]	1977	United Kingdom	CCS	40	120	<45	10	OS+	No
Mignot [50]	1986	France	CCS	68	136	<45	10	OS+	No
Ariel [51]	1989	America	CCS	46	900	<45	10	OS*	No
Sankila [26]	1994	Finland	CCS	91	471	<40	15	OS	No
Von Schoultz [1]	1995	Sweden	Population based	50	2069	<50	7	DFS	Yes
Lethaby [52]	1996	New Zealand	Population based	14	334	<45	10	OS*	Yes
Valentgas [53]	1999	America	CCS	53	265	<45	15	OS	No
Gelber [57]	2001	International	CCS	94	188	<42	10	OS	No
Mueller [58]	2003	America	CCS	329	2002	<45	17	OS	No
Blakely [74]	2004	America	Hospital based	47	323	<35	22	OS*, DFS	Yes
Ives [59]	2007	Australia	Population based	123	2416	<45	21	OS	Yes
Kroman [60]	2008	Denmark	Population based	199	10,037	<45	30	OS	No
Largillier [56]	2009	France	Hospital based	118	762	<35	10	OS, DFS	Yes
Rippy [54]	2009	United Kingdom	Cohort	18	244	<45	5	OS*	Yes
Kranick [55]	2010	America	CCS	107	344	<45	12	OS, DFS	No
Cordoba [34]	2012	Spain	Population based	18	97	<36	5	OS*	Yes
Azim [27]	2013	Belgium	CCS	333	874	<48	5	OS, DFS	No
Valentini [40]	2013	Canada	Population based	53	269	<45	15	OS	No

Studies in bold are unique to this meta-analysis and were not included in previous meta-analyses

* Studies for which OR was calculated from crude data

+ Studies for which HR was calculated from KM curves

articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. The search was limited to humans. A search for unpublished literature was performed; however, no additional studies were found.

Study selection

Pregnancy before breast cancer diagnosis

We included studies that met the following inclusion criteria: (1) PABC was recognised on clinical diagnosis and/or confirmed histologically; (2) cases were defined as those diagnosed during pregnancy or up to 5 years postpartum; (3) the study reports outcomes in terms of OS and/or DFS; (4) the risk point estimate was reported as a hazard ratio (HR), or the data were presented such that an OR could be calculated; (5) the 95 % confidence interval (CI) was reported, or the data were presented such that the CI could be calculated.

Pregnancy after breast cancer diagnosis

We included studies that met the following inclusion criteria: (1) Breast cancer was recognised on clinical diagnosis and/or confirmed histologically; (2) cases were defined as pregnancy occurring up to 5 years after diagnosis; (3) the study reports outcomes in terms of OS and/or DFS; (4) the risk point estimate was reported as a HR or OR, or the data were presented such that an OR could be calculated; (5) the 95 % CI was reported, or the data were presented such that the CI could be calculated.

Data extraction

The data extraction was performed using a standardised data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, temporal direction, population type, country, continent, case control matching, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs and data used to calculate CIs. Authors were contacted for missing data. Adjusted ratios were extracted in preference to non-adjusted ratios; however, where ratios were not provided, unadjusted ORs and CIs were calculated from the published crude data using 2×2 contingency tables. Where more than one adjusted ratio was reported, we chose the ratio with the highest number of adjusted variables. Where multiple risk estimates were available in the same study, for example due to

the use of different comparator groups, they were included as separate risk estimates. Where only KM curves were provided, the Parmar method [29] was used to extract the HR. The studies were then allocated into one of two groups: those for which HR was provided or extracted from KM curves, and those for which OR was calculated from crude data. In order to be statistically sound, we conducted separate analyses on these two groups. For the analysis of pregnancy occurring during or before breast cancer, there were 13 studies consisting of 488 cases for which OR had to be calculated for OS and 8 studies consisting of 439 cases for which OR had to be calculated for DFS. For the analysis of pregnancy occurring after breast cancer diagnosis, there were 6 studies consisting of 171 cases for which OR had to be calculated for OS.

Statistical analysis

Pooled OR and 95 % CI were calculated using a random effects model [30]. In our study, a HR or OR > 1 indicated an increased risk of death, or an increased risk of disease recurrence. We tested heterogeneity with Cochran's Q statistic, with $p < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25, 50 and 75 % corresponded to low, moderate and high degrees of heterogeneity, respectively [31]. We quantified publication bias using the Egger's regression model [32], with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to yield a statistically non-significant effect. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n + 10$, with n being the number of studies included in the meta-analysis [33]. All analyses were performed with Comprehensive Meta-analysis (version 3.0), Biostat, Englewood, NJ (2014).

Results

From 6492 citations screened by our search, we identified a total of 60 studies that met our inclusion criteria (Fig. 1). 41 of these studies examined pregnancy occurring before or concurrently with breast cancer diagnosis up to 5 years postpartum, whilst 19 examined pregnancy followed a breast cancer diagnosis. Tables 1 and 2 show selected characteristics of the identified studies. In terms of study design, 44 were case control studies and 16 were cohort studies. 27 studies examined populations from Europe, 22 from North America, 6 from Asia, 3 from Oceania, 1 from South America and 1 was a global multicentre study. In the data collection process, adjusted and calculated HR were used and where they were not provided nor could be extracted from KM survival curves, OR were manually calculated by 2×2 contingency tables. Our results are summarised in Table 3.

Pregnancy occurring before breast cancer diagnosis or concurrently with breast cancer diagnosis

41 studies (34 case control and 7 cohort) comprising of 4929 cases and a total of 65,970 individuals were identified for the meta-analysis. 18 studies had data available for both OS and DFS, whilst 18 had data on OS only and 4 had data on DFS only.

Overall survival (OS)

37 studies (32 case control and 5 cohort) comprising of 5583 cases and a total of 124,277 individuals were identified for the meta-analysis on OS. There was no publication bias as analysed by funnel plot based on Egger's regression ($p = 0.19$) (Fig. 2). There was an overall increased risk of death for patients compared to controls with a pooled hazard ratio (pHR) of 1.57 (95 % CI 1.35–1.82) (Fig. 4). There was significant heterogeneity ($I^2 = 84.90$, $p = 0.001$). When cases were limited to those diagnosed up to 2 years postpartum, the pHR increased significantly to 1.96 (95 % CI 1.87–2.05) but did not change when the definition was limited to up to 1 year postpartum, HR 1.97 (95 % CI 1.88–2.06) (Table 3). There was however, significant heterogeneity up to 1 year postpartum ($I^2 = 84.31$, $p = 0.001$), as well as up to 2 years postpartum ($I^2 = 83.97$, $p = 0.001$).

PABC (pregnant and postpartum) 23 studies comprising of 3150 cases with a total of 34,445 individuals were identified for the PABC sub-analysis. This sub-analysis examined where diagnosis occurred either during pregnancy or up to 5 years postpartum, and excluded studies that exclusively examined the postpartum period. PABC individuals were at an increased risk of death, with a pHR of 1.46 (95 % CI 1.17–1.82) (Fig. 4). There was significant heterogeneity ($I^2 = 75.45$, $p < 0.001$). When cases were defined as up to 1 year postpartum, the pHR increased marginally to 1.53 (95 % CI 1.11–2.11) (Table 3). The pooled OR of studies where OR was calculated provided similar results [OR 1.56; 95 % CI 1.10–2.21) (Table 3) with mild heterogeneity that was not significant ($I^2 = 37.61$, $p = 0.11$).

Pregnancy 13 studies comprising of 906 cases with a total of 45,082 individuals were identified for the pregnancy only sub-analysis. This included studies where diagnosis of breast cancer occurred exclusively during

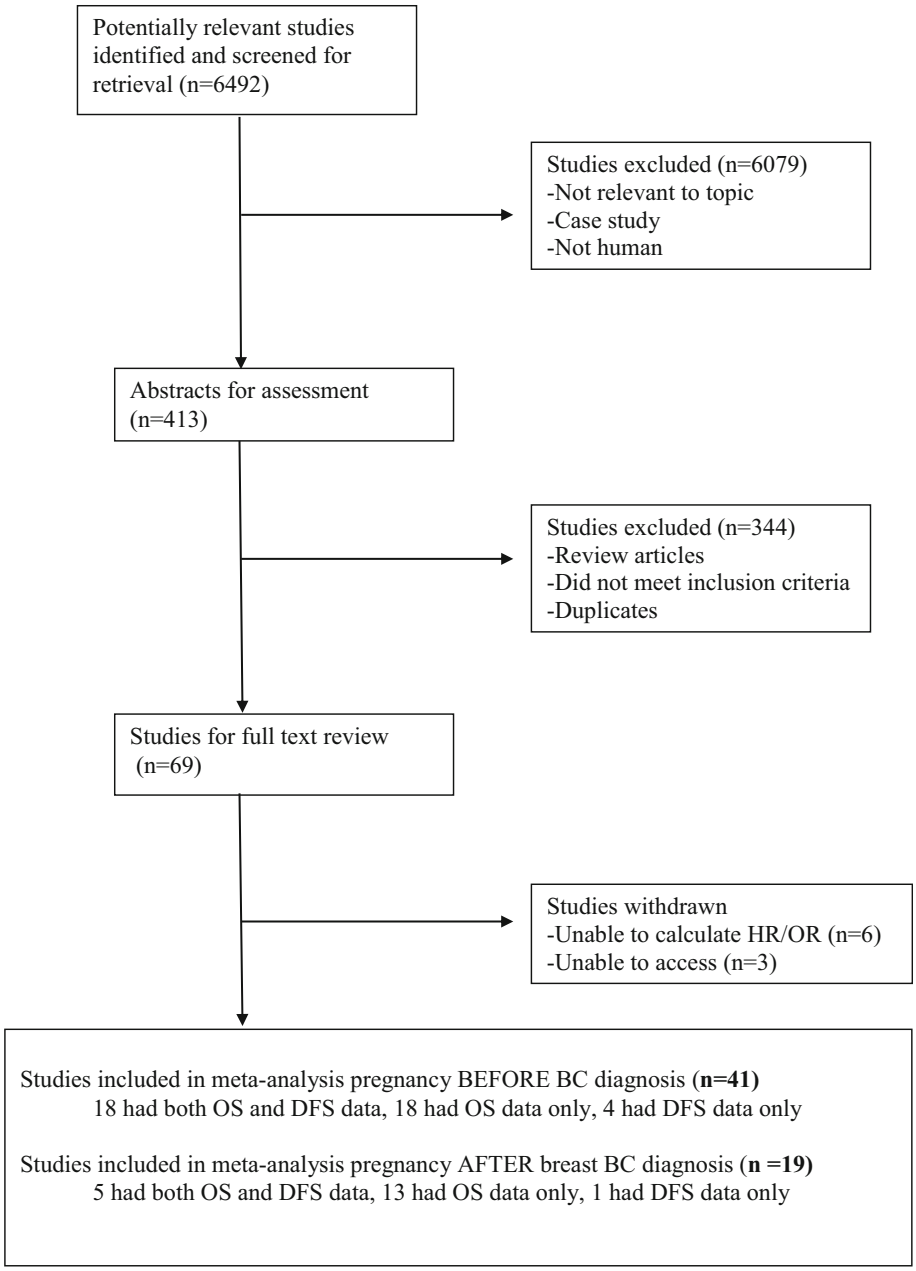


Fig. 1 Flowchart of the search strategy

pregnancy. There was an increased risk of death for patients diagnosed during pregnancy compared to non-pregnant controls, with a pHR of 1.47 (95 % CI 1.04–2.08) (Table 3). There was substantial heterogeneity ($I^2 = 83.11$, $p < 0.001$).

Postpartum 8 studies comprising of 1439 cases with a total of 44,662 individuals were identified for the post-partum only sub-analysis. Postpartum individuals were at an increased risk of death up to 5 years postpartum, with a pHR of 1.79 (95 % CI 1.39–2.29) (Fig. 4). There was significant heterogeneity ($I^2 = 83.67$, $p < 0.001$). When cases were defined as up to 1 year postpartum the pHR increased further to 1.99 (95 % CI 1.90–2.09) (Table 3) with no significant heterogeneity ($I^2 = 0.00$, $p = 0.64$).

Disease-free survival (DFS)

23 studies comprising of 1857 cases and a total of 9798 individuals were identified for the meta-analysis on DFS. There was no publication bias as analysed by funnel plot based on Egger's regression ($p = 0.07$) (Fig. 3). Patients were at an increased risk of relapse or progression up to 5 years postpartum, with a pHR of 1.51 (1.22–1.88) (Fig. 5). There was significant heterogeneity ($I^2 = 60.75$, $p = 0.01$). When the definition of PABC was narrowed to

Table 3 Meta-analyses conducted

Meta-analysis	Time period	No. of studies	Cases	Controls	HR (95 % CI)	*p* value	OR (95 % CI)	*p* value
OS for all cases	≤5 years postpartum	37	5583	118,694	1.57 (1.35–1.82)	0.00	1.22 (0.91–1.62)	0.18
	≤2 years postpartum	35	4777	104,019	1.96 (1.87–2.05)	0.00		
	≤1 years postpartum	32	3531	85,184	1.97 (1.88–2.06)	0.00		
OS for PABC	≤5 years postpartum	23	3150	31,295	1.46 (1.17–1.82)	0.00	1.56 (1.10–2.21)	0.01
	≤1 year postpartum	22	1987	12,769	1.53 (1.11–2.11)	0.01		
OS for pregnant cases only	Pregnancy	13	906	44,176	1.47 (1.04–2.08)	0.03	0.76 (0.46–1.23)	0.26
OS for postpartum cases only	≤5 years postpartum	8	1439	43,223	1.79 (1.39–2.29)	0.00		
	≤2 years postpartum	6	633	28,548	1.99 (1.90–2.09)	0.00		
	≤1 year postpartum	5	550	28,239	1.99 (1.90–2.09)	0.00		
DFS for all cases	≤5 years postpartum	23	1857	7941	1.51 (1.22–1.88)	0.00	1.66 (1.09–2.52)	0.02
	≤2 years postpartum	20	1489	4851	1.52 (1.23–1.88)	0.00		
DFS for PABC	≤5 years postpartum	16	1111	5146	1.54 (1.16–2.04)	0.00	2.84 (1.70–4.73)	0.00
	≤2 years postpartum	15	938	3406	1.62 (1.29–2.05)	0.00		
DFS for pregnant cases only	Pregnancy	5	551	1445	1.13 (0.69.1.85)	0.62	0.52 (0.25 –1.10)	0.09
DFS for postpartum cases only	≤5 years postpartum	2	195	1350	1.86 (1.17–2.93)	0.01		
OS for pregnancy after diagnosis	Pregnancy occurring up to 5 years after diagnosis	17	1707	19,741	0.63 (0.51–0.79)	0.00	0.65 (0.46–0.92)	0.02
OS for pregnancy after diagnosis accounting for "healthy mother effect"	Pregnancy occurring up to 5 years after diagnosis	12	1387	15,662	0.65 (0.52–0.81)	0.00	0.79 (0.53–1.20)	0.27
DFS for pregnancy after diagnosis	Pregnancy occurring up to 5 years after diagnosis	5	655	4372	0.84 (0.69–1.02)	0.07		
DFS for pregnancy after diagnosis accounting for "healthy mother effect"	Pregnancy occurring up to 5 years after diagnosis	2	440	1218	0.93 (0.68–1.28)	0.66		

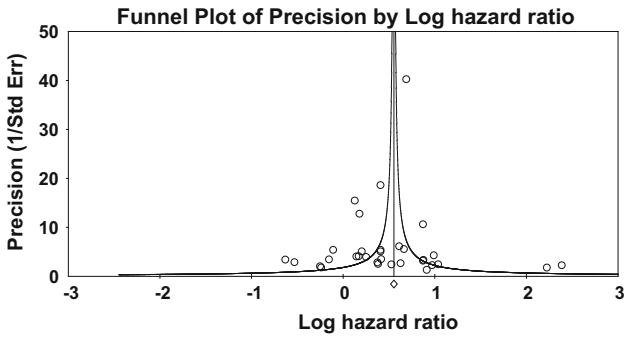
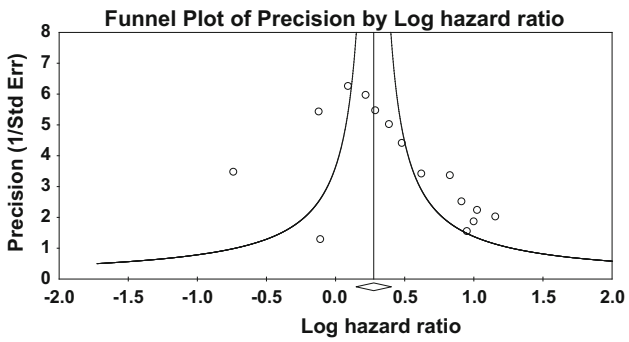


Fig. 2 Funnel plot to assess publication bias. *Circles* indicate individual studies. *Diamond* indicates summary estimates. *SE* standard error



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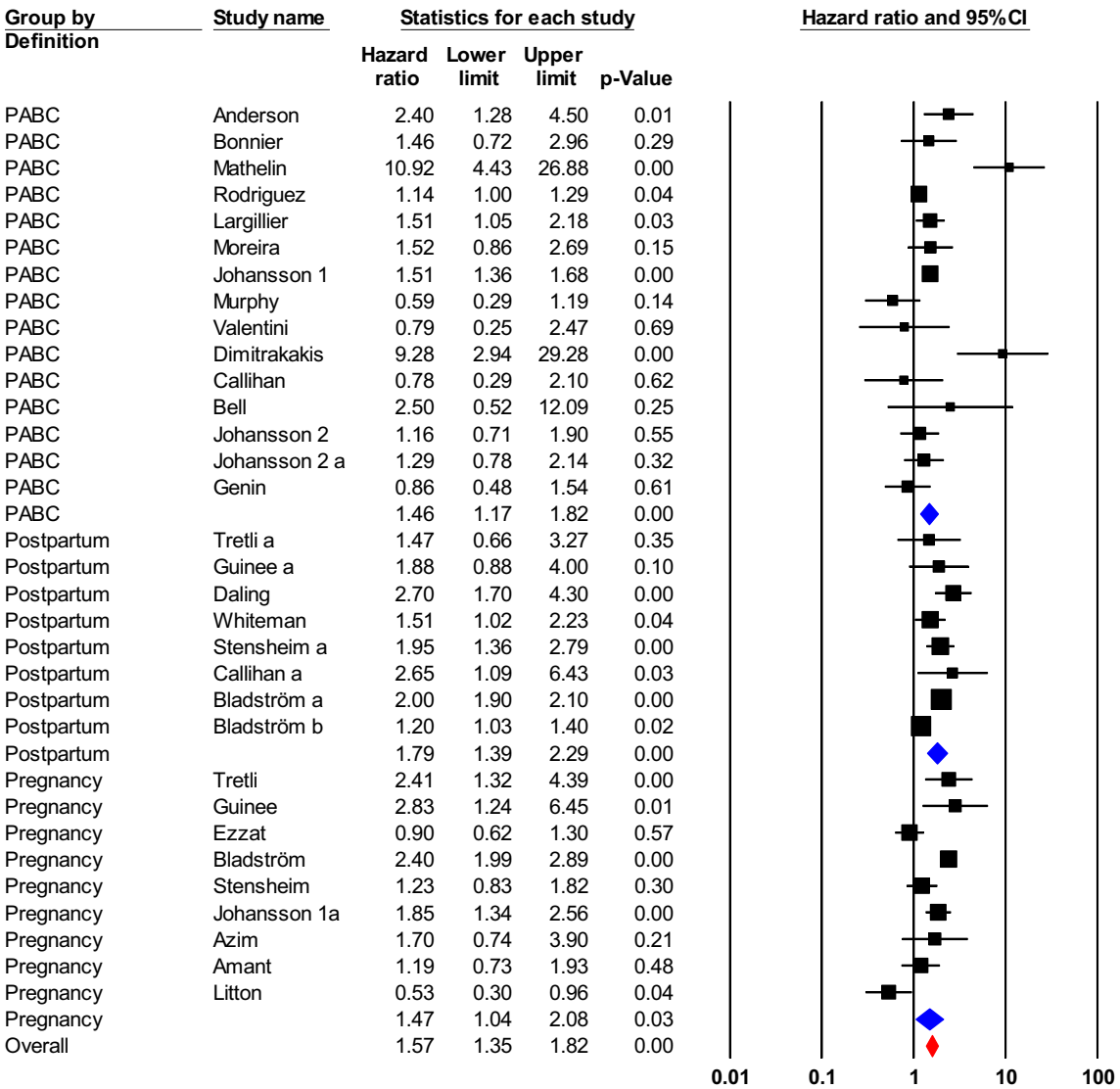

Fig. 4 Meta-analysis of the association between breast cancer and pregnancy diagnosed during pregnancy or up to 5 years postpartum on OS. Test for heterogeneity Overall: $I^2 = 84.90$, $p = 0.001$, PABC: $I^2 = 75.45$, $p < 0.001$, Postpartum: $I^2 = 83.67$, $p < 0.001$, Pregnancy: $I^2 = 83.11$, $p \leq 0.001$. Each study is shown by a hazard ratio estimate with the corresponding 95 % CI

up to 2 years postpartum, the pHR did not differ, 1.52 (95 % CI 1.23–1.88) (Table 3). The pooled OR provided similar results [OR 1.66; 95 % CI 1.09–2.52] (Table 3) with substantial heterogeneity ($I^2 = 72.41$, $p = 0.001$).

PABC (pregnant and postpartum) 16 studies comprising of 1111 cases with a total of 6257 individuals were identified for the PABC sub-analysis. This sub-analysis examined where diagnosis occurred either during pregnancy or up to 5 years postpartum. PABC individuals had a worse DFS with a pHR of 1.54 (95 % CI 1.16–2.04) (Fig. 5). There was moderate heterogeneity; however, it was not significant ($I^2 = 46.61$, $p = 0.06$). When cases were defined as up to 2 years postpartum, the pHR increased marginally to 1.62 (95 % CI 1.29–2.05) (Table 3). The pooled OR indicated a worse DFS 2.84 (1.70–4.73) with moderate heterogeneity that was not significant ($I^2 = 52.38$, $p = 0.05$).

Pregnancy Five studies comprising of 551 cases with a total of 1996 individuals were identified for the pregnancy only sub-analysis. This included studies where diagnosis of breast cancer occurred during pregnancy. There was an increased risk of relapse or disease progression with a pHR of 1.13 (0.69–1.85) (Fig. 5); however, the result was not significant. There was no heterogeneity ($I^2 = 0.00$, $p = 1.00$).

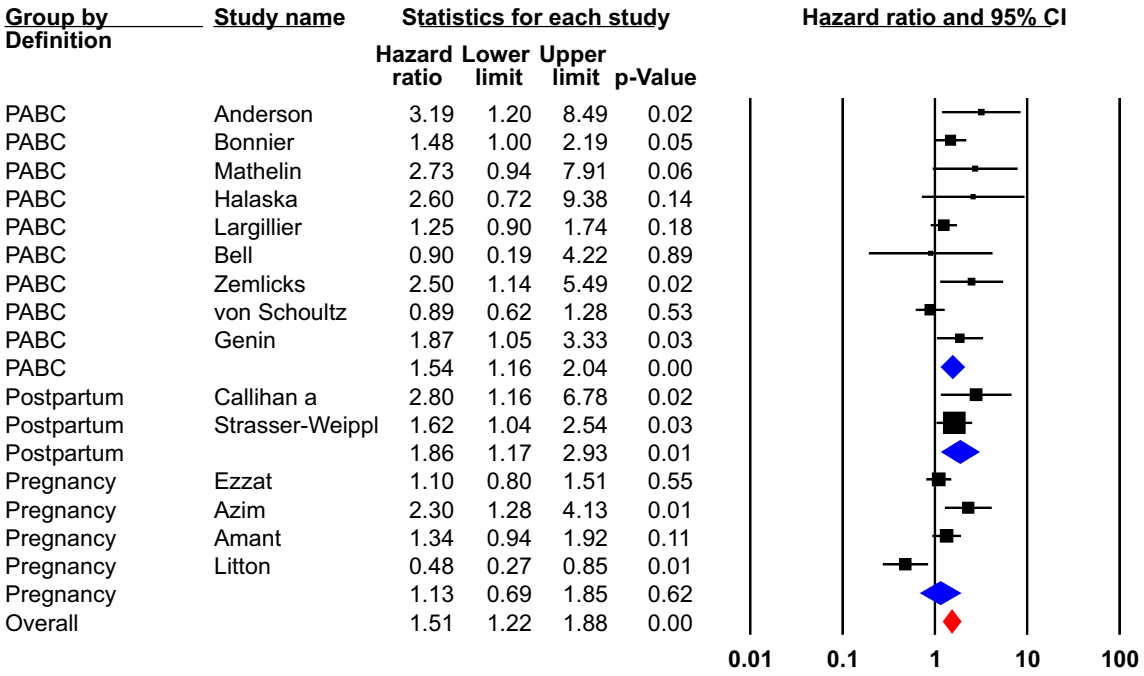

Fig. 5 Meta-analysis of the association between breast cancer and pregnancy diagnosed during pregnancy or up to 5 years postpartum on DFS. Test for heterogeneity Overall: $I^2 = 60.75$, $p < 0.001$, PABC: $I^2 = 46.61$, $p = 0.06$, Postpartum: $I^2 = 13.86$, $p = 0.28$. Each study is shown by a hazard ratio estimate with the corresponding 95 % CI

Postpartum Two studies comprising of 195 cases and 1 545 individuals were identified for this sub-analysis. Those diagnosed during the postpartum period up to 5 years following childbirth had an increased risk of relapse or disease progression, HR 1.86 (95 % CI 1.17–2.93) (Fig. 5). There was no heterogeneity ($I^2 = 13.86$, $p = 0.28$).

Pregnancy after breast cancer diagnosis

Nineteen studies (10 case control and 9 cohort) comprising of 1828 cases and a total of 23,736 individuals were identified for the meta-analysis. Four studies had data available for both OS and DFS, whilst 14 had data on OS only and 1 had data on DFS only. There was no publication bias as analysed by funnel plot based on Egger's regression ($p = 0.53$).

Overall survival (OS)

Seventeen studies (10 case control and 7 cohort) comprising of 1707 cases and a total of 21,448 individuals were identified for sub-analysis. Women who became pregnant after a diagnosis of breast cancer had a significantly reduced risk of death compared to those who did not become pregnant, pHR 0.63 (95 % CI 0.51–0.79) (Fig. 6). There was significant ($I^2 = 50.52$, $p = 0.02$). One cohort study [34] with a relatively small sample size was not included in the analysis because calculation of the OR resulted in a zero in a single cell. The pooled OR similarly indicated an improved prognosis for such women, OR 0.65 (95 % CI 0.46–0.92) (Table 3) with no significant heterogeneity ($I^2 = 12.98$, $p = 0.33$).

Controlling for the "healthy mother effect" The "healthy mother effect" [26] is a selection bias where only women who have had favourable outcomes following diagnosis are likely to conceive. Studies control for this bias by matching for nodal status, ER status, disease-free interval and treatment. 12 studies (10 case control and 2 cohort) comprising of 1 387 cases and a total of 17 049 individuals were identified for sub-analysis. When including only those studies that accounted for the "healthy mother effect" bias, women who become pregnant after a diagnosis of breast cancer had a reduced risk of death, pHR 0.65 (95 % CI 0.52–0.81) (Table 3). There was no significant heterogeneity ($I^2 = 44.54$, $p = 0.06$). The pooled OR indicated similar findings, although the result was not significant (Table 3).

Disease-free survival (DFS)

Five studies (2 case control and 3 cohort) comprising of 655 cases and a total of 4372 individuals were identified for sub-analysis. There was a decreased risk of recurrence or disease progression amongst women who became pregnant following a diagnosis of breast cancer compared to those

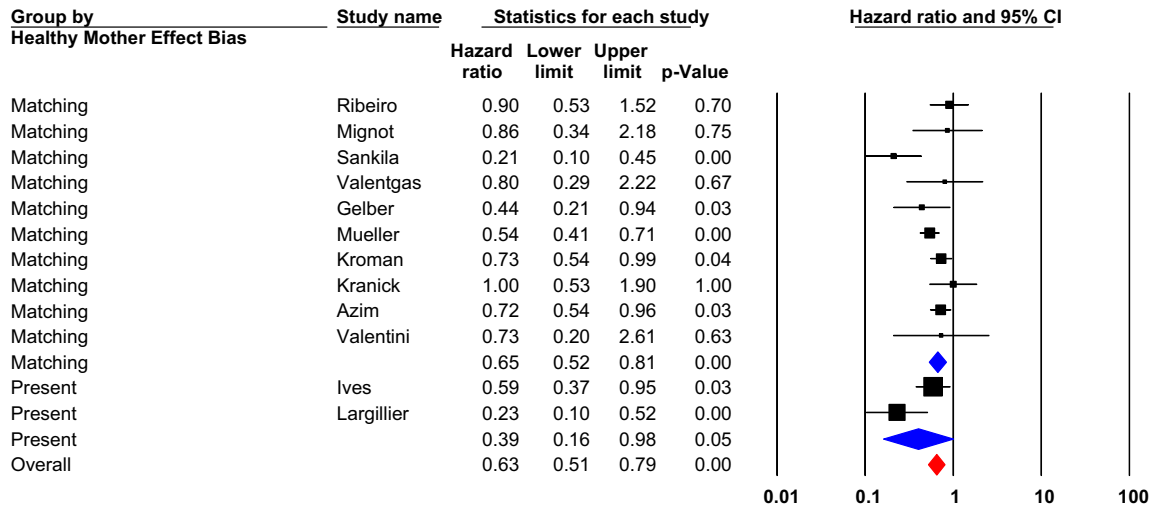

Fig. 6 Meta-analysis of the association between pregnancy and breast cancer diagnosed before pregnancy on OS. Test for heterogeneity: Overall: $I^2 = 50.52$, $p = 0.02$, Matching: $I^2 = 44.54$, $p = 0.06$, Present: $I^2 = 73.54$, $p = 0.05$. Each study is shown by a hazard ratio estimate with the corresponding 95 % CI

who did not become pregnant [pHR 0.84; 95 % CI 0.69–1.02] (Table 3); however, the result was not significant. There was no significant heterogeneity ($I^2 = 0.00$, $p = 0.41$).

Controlling for the "healthy mother effect" Two studies (2 case controls) comprising of 440 cases and a total of 4909 individuals were identified for sub-analysis. There was a decreased risk of recurrence and disease progression for women who became pregnant following diagnosis of breast cancer [pHR 0.93; 95 % CI 0.68–1.28] (Table 3). However, these results were not significant and data were only pooled across two studies. There was no significant heterogeneity ($I^2 = 35.12$, $p = 0.21$). There is a large difference in HR between this subgroup and the overall group. The protective effect of pregnancy appears less pronounced in studies that have accounted for the "healthy mother effect" bias as would be expected.

Discussion

Pregnancy before or during breast cancer diagnosis

Our meta-analysis shows that women with PABC up to 5 years postpartum are at an increased risk of mortality and a substantially increased risk of disease recurrence compared to controls. Our subgroup analysis showed that those diagnosed in the postpartum period had a worse prognosis compared to those diagnosed during either pregnancy alone or in the pregnancy or postpartum (PABC) subgroup. Cases diagnosed postpartum are therefore likely to be driving the overall increased risk. Our results are consistent with a previous meta-analysis of 30 studies conducted in 2012 [24]; however, the negative effect of pregnancy on OS appears to be more pronounced in our study overall and within each subgroup. Similarly, we demonstrated that those diagnosed postpartum had poorer outcomes compared to those diagnosed during pregnancy. We demonstrated this same trend for postpartum cases on DFS.

In our study, the results for both overall survival and disease-free survival were highly heterogeneous. This was likely due to significant differences in sample size, the definition of PABC, the definition of a pregnancy, treatment interventions and the follow-up length. Additionally, the studies used different criteria in the matching of cases for case control studies, and different variables were adjusted for where multivariate analysis was completed.

Our results show that PABC individuals are at an increased risk of death. Of the 37 studies included, there were 21 studies that found a negative [35] or null association [2, 5, 11–17, 21, 36–46] between PABC and mortality. In a recent study, Litton et al. [35] showed that women treated with FAC chemotherapy during pregnancy had OS and DFS comparable to, if not better than controls who received the same treatment. This promising result, however, may be due to the small sample size of the study. Callihan et al. [2] did not find a significant result when cases were defined as during pregnancy or up to 1 year postpartum. When cases were defined within 5 years postpartum however, there was an increased risk of both death [HR 2.65; 95 % CI 1.09–6.42] and distant recurrence [HR 2.80; 95 % CI 1.12–6.57] compared to nulliparous controls when adjusted for tumour biological subtype, stage and year of diagnosis. The authors suggest that pregnant and postpartum cases are distinct subsets of

PABC and further research should treat them as such in order to clarify whether events subsequent to pregnancy such as breast involution impact breast cancer. They also proposed the definition of PABC should be expanded, with further studies needed to delineate the exact outer limit of the relevant postpartum timeframe. In our analysis, we found there was a significantly increased risk of death in all time frames, but the risk was worse when a more conservative definition of the postpartum period was used. The DFS on the other hand did not meaningfully change with variation in the postpartum period. As such, we found the most relevant period for increased risk for patients is during pregnancy and up to 1 year postpartum; however, an increased risk is evident up to 5 years postpartum.

In contrast, Dimitrakakis et al. [47] found an increased risk of death amongst women with PABC. The study compared 39 cases of PABC up to 1 year postpartum with 39 controls that were matched for stage, age, year of diagnosis and treatment with a 5-year follow-up. The study resulted with a hazard ratio (HR) of 9.28 (95 % CI 2.94–29.27) when adjusted for stage, ER status, grade and age at diagnosis. A well-designed case–control study by Azim et al. [21] reported no difference in OS survival but an inferior DFS (HR 2.3; 95 % CI 1.3–4.2) when comparing 65 pregnant patients with non-pregnant controls after adjustment for age, pT, pN, neoadjuvant chemotherapy, ki-67, HER2 and perivascular invasion. Whilst the exact mechanism is unknown the authors hypothesise the hormonal environment characterising pregnancy may be responsible for pregnancy being a poor prognostic factor for breast cancer. Specifically, it has been postulated that the high levels of growth hormone present in pregnancy may exert an effect on the mammary stem cells that have been shown to transiently overexpress GH receptors during pregnancy [21].

Pregnancy after breast cancer diagnosis

Our meta-analysis shows that women who have had a previous diagnosis of breast cancer and who subsequently became pregnant have a significantly reduced risk of death compared to those who do not become pregnant following diagnosis. The time between diagnosis and pregnancy is clearly a critical issue however, and future studies should determine this time period. These results are consistent with the previous meta-analysis of 14 studies conducted by Azim et al. [25]. There was moderate heterogeneity in our study which resolved after we accounted for the healthy mother effect bias. Our study showed that there was also a decreased risk of recurrence; however, this result was not significant, most likely due to the small sample size.

Our results demonstrate that pregnancy is safe following a breast cancer diagnosis, and indeed associated with an improved prognosis. This result is reassuring for women who have received treatment for breast cancer and are concerned that a pregnancy may worsen their chance of survival. Of the 17 studies included in the analysis on OS, there were 9 studies that found a positive or null association [40, 48–55] between pregnancy following breast cancer and mortality. Kranick et al. [55] found no significant prognostic difference between women who had a pregnancy subsequent to diagnosis and those who did not. A small non-significant adverse effect was found for women who conceived within 12 months of diagnosis. The result was likely due to small sample size. Similarly, a recent study by Valentini et al. [40] of 53 women with BRACA 1/2 mutation did not find that pregnancy following diagnosis adversely affected survival.

In contrast, several studies have demonstrated improved survival outcomes for women conceiving after treatment for breast cancer [26, 27, 56–60]. These findings, however, may be a result of the "healthy mother" effect [26], a selection bias whereby women who have had favourable outcomes are more likely to conceive than those who have relapsed thereby skewing the true effect. To overcome this bias, a study by Azim et al. [27] ensured cases and controls were matched according to disease-free interval, as well as ER status, nodal status, treatment, age and year of diagnosis. The study consisted of a large cohort of 333 patients and found that women who became pregnant after diagnosis experienced better OS (HR 0.72; 95 % CI 0.54–0.97) than the controls who did not, with no interaction according to ER status. Additionally, women who became pregnant within 2 years of diagnosis had increased DFS compared to matched controls, whilst those who became pregnant more than 2 years after diagnosis had comparable outcomes. Interestingly, there was no statistical difference in DFS between patients who had an abortion or miscarriage with their controls. We conducted a subgroup analysis of the studies that accounted for the "healthy mother effect" bias and produced similar results to Azim et al. [25]; however, the protective effect of pregnancy in our study was significant and more pronounced.

In another large study, Mueller et al. [58] found that there was a decreased risk of mortality for women who gave birth 10 months or more after diagnosis compared to controls. Furthermore, Kroman et al. [60] found that women who had a full-time pregnancy after a breast cancer diagnosis had a reduced risk of dying. This result was not modified by age at diagnosis, tumour size, nodal status or pregnancy history before diagnosis. Whilst the exact mechanism of the apparent protective effect of pregnancy is unclear, several hypotheses have been proposed. Janerich [61] suggests that in pregnancies following breast cancer an alloimmunisation against the cancer occurs. This hypothesis speculates that because breast cancer cells and

foetal cells share common antigens [62], a mother's immune system is activated during pregnancy and eliminates not only circulating foetal cells but also quiescent tumour cells, resulting in improved prognosis. A second hypothesis suggests that the substantial increase in oestrogen levels in pregnancy after deprivation may induce apoptosis in oestrogen-responsive breast cancer cells [63].

Strengths and limitations

Our study has several strengths. This is the largest and most current meta-analysis conducted in this field. We performed a comprehensive literature search involving multiple databases, which was not limited by language. We searched unpublished studies and scanned reference lists for further studies. Only studies with a recognised clinical diagnosis of breast cancer were included. There were a large number of studies and there was no publication bias. Study populations were derived from a wide range of countries, increasing the relevance of this study to most populations. Whilst many of the individual studies were unable to detect a significant result due to small sample size, the large number of patients provided us with adequate statistical power to detect an effect. Azim et al. earlier meta-analysis on PABC was restricted to cases occurring up to 1 year postpartum, whilst their study on pregnancy following breast cancer was limited to studies up until 2009 and had a substantially smaller sample size than our study. In contrast, our study adopted a broad definition of the postpartum period up to 5 years following delivery, reported on both groups of women, and contained more recent studies as well as those omitted by previous meta-analyses. We also performed separate analyses based on whether HR was provided or whether OR was calculated from crude data. It therefore includes all the available evidence for women with pregnancy-related breast cancer.

There were also a number of limitations that should be taken into consideration when interpreting our results. Many OR had to be manually calculated, as they were not provided in the study and thus not adjusted for co-variants. Our study was also heterogeneous with regard to study design, particularly in regard to the definition of PABC, the definition of pregnancy, the follow-up time and treatment. Lastly, data were based on published rather than original patient data. It would be useful for future studies to specifically research each subset of PABC, that is, those diagnosed during pregnancy and those diagnosed postpartum in greater detail. Further studies should also ascertain the 'cut-off' time of the increased risk that exists for postpartum cases. Previous studies have been unable to assess any difference in survival for women according to oestrogen receptor status with pregnancy. Future studies should perform sensitivity analysis according to oestrogen receptor status to ascertain whether there are any differences in outcomes for those who become pregnant with endocrine-responsive tumours compared to non-responsive tumours. Further investigation is also needed regarding the interval between diagnosis and pregnancy to ascertain the safest period in which to conceive following treatment. It would also be interesting to examine the effect of assisted reproductive technology (ART) on patients with breast cancer diagnosed before and after pregnancy.

Conclusion

Our meta-analyses demonstrated that women who are diagnosed with breast cancer during or after pregnancy are at an increased risk of both death and recurrence compared to those diagnosed with non-pregnancy-related breast cancer. On the other hand, women with a history of breast cancer who subsequently become pregnant have improved survival rates compared to those who do not become pregnant.

Compliance with ethical standards

Conflicts of interest All authors declare no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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