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Original Research

Survival after breast cancer in women with a subsequent live birth: Influence of age at diagnosis and interval to subsequent pregnancy

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KEYWORDS
Breast cancer;
Survivorship;
Pregnancy;
ER status;
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Abstract ***Background:*** There remains a considerable concern among both patients and oncologists that having a live birth (LB) after breast cancer might adversely impact survival.
Methods: analysis of survival in a national cohort of women with breast cancer diagnosed at age 20–39 years between 1981 and 2017 (n = 5181), and subsequent LB using Scottish Cancer Registry and national maternity records. Cases had at least one subsequent LB, each was matched with up to six unexposed cases without subsequent LB, accounting for guaranteed time bias.
Results: In 290 women with a LB after diagnosis, overall survival was increased compared to those who did not have a subsequent LB, HR 0.65 (95%CI 0.50–0.85). Women with subsequent LB who had not had a pregnancy before breast cancer showed increased survival (HR 0.56, 0.38–0.82). There was a progressively greater interaction of subsequent LB with survival with younger age, thus for women aged 20–25 years, HR 0.30 (0.12–0.74) vs. those aged 36–39, HR 0.89 (0.42–1.87). In women with LB within five years of diagnosis, survival was also increased (HR 0.66; 0.49–0.89). Survival following LB was similar to unexposed

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women by ER status (both positive and negative) and in those known to have been exposed to chemotherapy.

Conclusions: This analysis provides further evidence that for the growing number of women who wish to have children after breast cancer, LB does not have a negative impact on overall survival. This finding was confirmed within subgroups, including the youngest women and those not previously pregnant.

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1. Introduction

Breast cancer is the most commonly diagnosed malignancy in women of reproductive age [1]. Societal changes in many developed countries have resulted in a later age at childbirth, thus increasingly women have not started or completed their families when diagnosed with breast cancer. The wider use of chemotherapy and other treatments has improved survival, increasing emphasis on the quality of life in cancer survivors, but few women have children after treatment for breast cancer [2,3], likely to be due to a complex interaction of biological/medical and psychosocial factors [4].

Biomedical aspects of post-treatment fertility include the gonadotoxicity of standard alkylating-based chemotherapy, resulting in an increased risk of premature ovarian insufficiency and infertility [5]. Adjuvant endocrine treatment is recommended for women with hormone-sensitive tumours, increasingly for ten years duration [6,7], during which time conception is contraindicated [8]. When combined with the natural decline in fertility with age, this will preclude chances of successful childbirth in many women, although pre-treatment fertility preservation is increasingly recommended and used [9,10]. Importantly, there are also concerns among both women and their clinicians regarding the potential detrimental effect of a subsequent pregnancy on disease recurrence [11,12], reflecting the hormonal sensitivity of the disease and the high levels of both oestrogen and progesterone during pregnancy. These concerns are particularly relevant in the presence of hormone receptor-positive breast cancer, where evidence on the safety of pregnancy following treatment completion remains limited [2].

In addition to the relative infrequency of the event, the analysis of the potential effect of a subsequent pregnancy and birth on survival from breast cancer is complicated by the necessarily observational nature of the data. There may be bias resulting from both those women having a subsequent pregnancy not being representative of the general population of women with breast cancer. We aimed to use national cancer register data to minimise the latter bias and to account for guaranteed time survival and tumour stage to minimise the former to investigate the impact of subsequent childbirth on survival, and the patient and disease factors that impact this.

2. Methods

Women with breast cancer (ICD-50 codes) diagnosed at age <40 years were identified from Scottish cancer registry records from 1981 through 2017 and linked to national maternity and death records from 1981 to December 2018. Exposed cases were identified as a subset of this study population; unexposed cases were taken from the instances remaining after the removal of exposed cases, and hence comprise a random sample from the general population that gave rise to the cases. The Scottish cancer registry is highly validated, with data quality subject to national and international indicators (https://www.isdscotland.org/Health-Topics/Cancer/Scottish-Cancer-Registry/Quality-Assurance/).

Exposed cases were diagnosed at age 20–39 years, were not pregnant at diagnosis, and had at least one subsequent live birth (LB). Age 40 was used as this is the upper limit for 'young age' at diagnosis of breast cancer [13]. Pregnancy at the time of diagnosis was defined as LB or other conclusions of pregnancy within 40 weeks of diagnosis: all such cases were individually examined to ensure correct classification. Cases enter study at date of LB, with the primary outcome being subsequent survival. To account for guaranteed time bias, following a methodology used in our prior studies [14,15], up to six matched unexposed cases with no subsequent LB for each subject were chosen at random (min = 4, mean = 5.8), matched by similar year of diagnosis (plus/minus three years) and were alive when their match had a LB (or last LB where there was more than one). Unexposed cases entered study at the date of LB for their match. For analysis of women with more than one LB, study entry was at the date of the last LB.

Subgroup analyses were performed to investigate the potential impact of having had a pregnancy prior to diagnosis (Yes or No); tumour stage (1 or 2–3; using pathological staging or clinical staging where pathological not available); age at diagnosis (20–25 years, 26–30 years, 31–35 years, or 39–39 years), interval between diagnosis and LB (earlier than five years or later than five

years); ER status (positive or negative) and where ER positive, by LB earlier of later than five years after diagnosis, where there was known treatment with chemotherapy, and by the period of diagnosis (pre-1995, 1995–2004, and after 2004). Tumour and ER status data were recorded from 1997 onwards, and other tumour information (e.g., HER2 status) was not available.

3. Statistical methods

For each study question Kaplan–Meier curves, numbers at risk and p-values for the log-rank test for the null hypothesis that survival curves are the same for all groups were calculated. For each Kaplan–Meier comparison, we report survival and 95% CI after approximately half the maximum follow period [16]. P-values were calculated from the chi-square distribution, but there is an inherent risk of a type II error due to low power when a Kaplan–Meier comparison involves few events. To guard against this, and after checking that the proportional hazards assumption holds for these data, Cox proportional hazard regression was used to calculate hazard ratios (HR), 95% CI for the HR, and p-values for the null hypothesis that the HR is 1. These p-values are more robust with respect to event frequency; similar p-values for Kaplan–Meier and HR tests increase confidence that calculated and actual statistical significance coincides for this study. Any missing data are not included in the Cox proportional hazard regression, as missingness is a criterion for our subgroup analyses; this also guards against biased estimates and loss of power to detect associations. Analyses were performed using the survminer and finalfit packages for R version 4.3.0.

The project was approved by the Scottish Public Benefits and Privacy Panel (Ref number 1819-0186) which has delegated authority from the UK NHS Research Ethics Service.

4. Results

A total of 5181 women with a new diagnosis of breast cancer were identified, with the median age at diagnosis of 36 years (IQR 33–38 years). Median follow-up was 12.2 yrs (IQR 5.2–21.1 years). Of these, 358 were aged 20–39 at diagnosis and had at least one subsequent LB. We excluded 70 women where breast cancer was diagnosed during pregnancy, with 68 pregnancies leading to LB. Thus, the study population (the 'exposed' group) consisted of 290 women with at least one LB after diagnosis (224 exactly one; 66 more than one). Additionally, 2652 women had a LB before but not after diagnosis, and 2171 had no LB recorded. Thus, these combined groups (n = 4823) provided the unexposed group of women with breast cancer who did not have a LB after diagnosis. Matching resulted in a population of 1682 unexposed women for the primary analysis. To assess potentially confounding factors, patient and tumour characteristics for the exposed and unexposed groups as well as for the whole cohort are shown in Table 1.

LB after diagnosis occurred in 5.7% of the study population, with a median interval of 4.1 years (IQR 2.6–6.3 years) after diagnosis. Overall survival was increased in women who had a subsequent LB (HR 0.65; 95% CI 0.50–0.85, p = 0.002, Fig. 1a and Table 2), compared to unexposed cases matched by the period of diagnosis, and for guaranteed survival. Further analysis separated those women with one subsequent LB and those with more than one. Women with only one subsequent LB (n = 224) showed increased overall survival compared to matched unexposed women (HR 0.73; 95% CI 0.54–0.98, p = 0.033), while survival was similar in women with more than one subsequent LB to matched unexposed women (n = 66, HR 0.84, 95% CI 0.46–1.50, p = 0.57; Table 2; Fig. 1 b and c).

Subgroup analyses were performed by pregnancy before diagnosis, tumour stage, age at diagnosis, interval to LB, ER status, and known exposure to chemotherapy (Table 2). Women with a subsequent LB who had not had a pregnancy before breast cancer diagnosis showed increased survival (HR 0.56, 95% CI 0.38–0.82, p = 0.003; Fig. 1d), whereas this effect was not found in women who had had a previous pregnancy (HR 0.76, 95% CI 0.53–1.09, p = 0.13; Fig. 1e).

Table 1
Characteristics of study population, divided into those women with subsequent live birth after breast cancer, and those withoout.

Characteristic	Exposed (LB)		Unexposed (no LB)		Whole cohort	
N	290		1682		5181	
Age (yrs)	31 (29–34)		32 (30–37)		36 (33–38)	
Follow-up (yrs)	15.8 (10.9–23.2)		14.7 (8.9–22.1)		12.2 (5.2–21.1)	
Tumour stage 1	95	(32.8)	521	(31.0)	1094	(21.1)
Tumour stage 2 or 3	58	(20.0)	348	(20.7)	1097	(21.2)
Tumour stage unknown	137	(47.2)	813	(48.3)	2990[a]	(57.7)[a]
Pregnancy prior to diagnosis	148	(51.0)	888	(52.8)	3521	(68.0)
ER negative	65	(22.4)	390	(23.2)	839	(16.2)
ER positive	102	(35.2)	612	(36.4)	1768	(34.1)
ER unknown	109	(42.3)	680	(40.4)	2574	(49.7)
Exposure to chemotherapy	184	(63.4)	1000	(59.5)	3024	(58.4)

Note: Age and follow-up are median (IQR), other data are number of subjects (%). Tumour stage and ER status were recorded from 1997 onwards.
[a] Includes 89 tumour stage 4 instances that were excluded from the analysis.

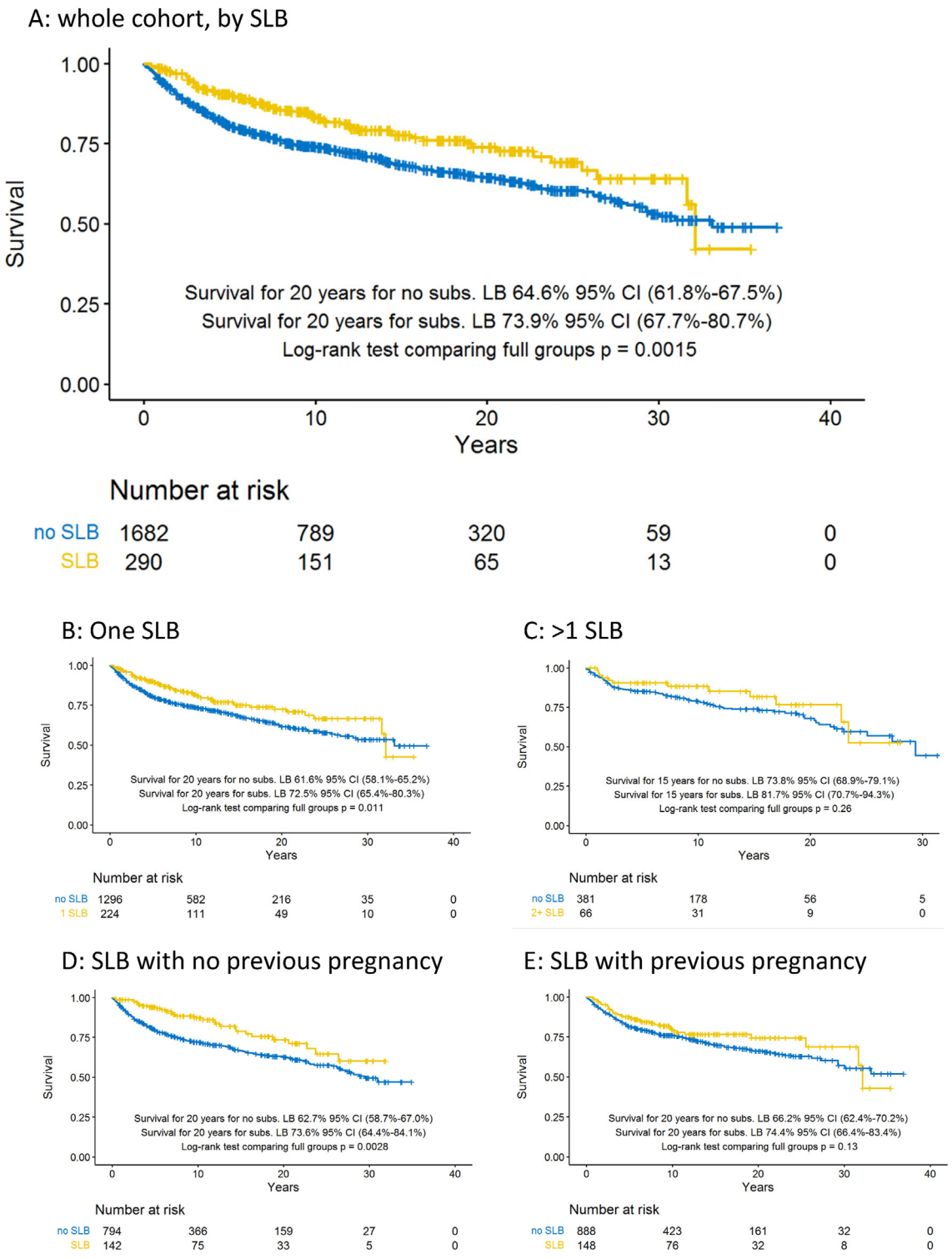

Fig. 1. (a) Overall survival in women with breast cancer by the occurrence of subsequent live birth (SLB) (yellow) or no SLB (blue) following diagnosis. (b) Overall survival in women who had a single SLB (yellow) or no SLB (blue), and (c) in women who had more than one subsequent LB (yellow) or no LB (blue). (d) Overall survival in women who had not been pregnant prior to breast cancer diagnosis, by SLB (yellow) or no SLB (blue), and (e) in women who had been pregnant prior to breast cancer diagnosis, by SLB (yellow) or no SLB (blue). Data are shown by time in years following live birth or matched time point in unexposed cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
The effect of subsequent live birth on survival after breast cancer: whole cohort, and subgroup analyses.

	Exposed (LB)	Unexposed (no LB)	Hazard Ratio (95% CI)
1: Cohort: subsequent LB	290	1682	0.65 (0.50–0.85, p = 0.002)
1a: one subsequent LB	224	1343	0.73 (0.54–0.98, p = 0.033)
1b: more than 1 subsequent LB	66	396	0.84 (0.46–1.50, p = 0.57)
2: Pregnancy before diagnosis			
2a: Yes	148	888	0.76 (0.53–1.09, p = 0.134)
2b: No	142	794	0.56 (0.38–0.82, p = 0.003)
3: Tumour stage			
3a: 1	95	521	0.74 (0.40–1.35, p = 0.328)
3b: 2 or 3	58	348	0.71 (0.37–1.37, p = 0.303)
4: Age at diagnosis (years)			
4a: 20–25	31	161	0.30 (0.12–0.74, p = 0.009)
4b: 26–30	97	580	0.58 (0.38–0.88, p = 0.011)
4c: 31–35	126	756	0.67 (0.44–1.01, p = 0.057)
4d: 36–39	36	216	0.89 (0.42–1.87, p = 0.756)
5: Interval to LB (years)			
5a: Within 5 years from diagnosis	182	1065	0.66 (0.49–0.89, p = 0.006)
5b: More than 5 years from diagnosis	108	617	0.63 (0.36–1.13, p = 0.121)
6: ER status			
6a: Positive	102	612	0.66 (0.37–1.18, p = 0.160)
6b: Negative	65	390	0.72 (0.38–1.35, p = 0.301)
7: ER positive			
7a: LB with 5 years from diagnosis	51	306	0.54 (0.26–1.1, p = 0.091)
7b: LB more than 5 years from diagnosis	51	306	0.79 (0.31–2.0, p = 0.629)
7: Exposure to chemotherapy	184	1104	0.86 (0.64–1.20, p = 0.33)
8: Period of diagnosis			
8a: Pre-1995	86	533	0.68 (0.47–1.0, p = 0.048)
8b; 1995:2004	104	617	0.65 (0.40–1.0, p = 0.067)
8c: Post-2004	100	523	0.61 (0.33–1.1, p = 0.105)

Note: Analysis of hazard ratio (with 95% CI) for overall survival in the whole cohort, and by subgroups, comparing cases with subsequent live birth (LB) with matched unexposed cases (no LB). Data under 'exposed' and 'unexposed' are numbers of subjects.

Both age at diagnosis and interval to subsequent LB had a significant interaction with survival in women who had a subsequent LB. For analysis of the effect of age at diagnosis, women were divided into five-year age groups (Table 2). This showed a progressively greater interaction of subsequent LB on survival with younger age at diagnosis. For the youngest group, age 20–25 years, HR for survival was 0.30, 95% CI 0.12–0.74 (p = 0.009); for those aged 26–30, HR was 0.58, 95% CI 0.38–0.88 (p = 0.011); for those aged 31–36, HR was 0.67, 95% CI 0.44–1.01 (p = 0.057); and for those aged 36–39, HR was 0.89, 95% CI 0.42–1.87 (p = 0.76). In women who had a LB within five years of diagnosis, survival was increased (HR 0.66; 95% CI 0.49–0.89, p = 0.006, Fig. 2a). Fewer women had a LB five or more years after diagnosis (n = 108 vs 182 within five years), and there was no clear effect on survival in these women (HR 0.63, 95% CI 0.36–1.13, p = 0.12; Fig. 2b).

The analysis of survival in women with stage 1 disease did not show an effect of subsequent LB (HR 0.74, 95% CI 0.40–1.35, p = 0.33; Fig. 2c) with similar results in women with stage 2 or 3 disease (HR 0.71, 95% CI 0.37–1.37, p = 0.31; Fig. 2d). Survival of women with a subsequent LB was also not impacted by ER status, for either ER + ve or ER-ve cancers. For women with ER + ve disease, HR was 0.66 (95% CI 0.37–1.18, p = 0.16), and for women with ER-ve disease, HR was 0.72 (95% CI 0.38–1.35, p = 0.30; Table 2 and Fig. 2e and f). For women with ER + ve disease, the impact of LB within or later than five years from diagnosis was also analysed (Table 2). For those with subsequent LB within five years, HR was 0.54 (95% CI 0.26–1.1, p = 0.091), and for those with LB after five years, HR was 0.79 (95% CI 0.31–2.0).

Treatment with chemotherapy was known in approximately 60% of the population, with a similar proportion of women treated with chemotherapy among those who did (63.4%) or did not (59.5%) have a subsequent LB. Survival was similar in chemotherapy-treated women who did or did not have a subsequent LB (HR 0.86; 95% CI 0.64–1.20, p = 0.33; Table 2 and Fig. 3).

The potential impact of period of diagnosis was also investigated (Table 2). In women diagnosed prior to 1995, HR for survival was 0.68 (95% CI 0.47–1.0, p = 0.048). For women diagnosed between 1995 and 204, HR was 0.65 (95% CI 0.40 = 1.0, p = 0.067), and after 2004, HR was 0.61 (95% CI 0.33–1.1, p = 0.105).

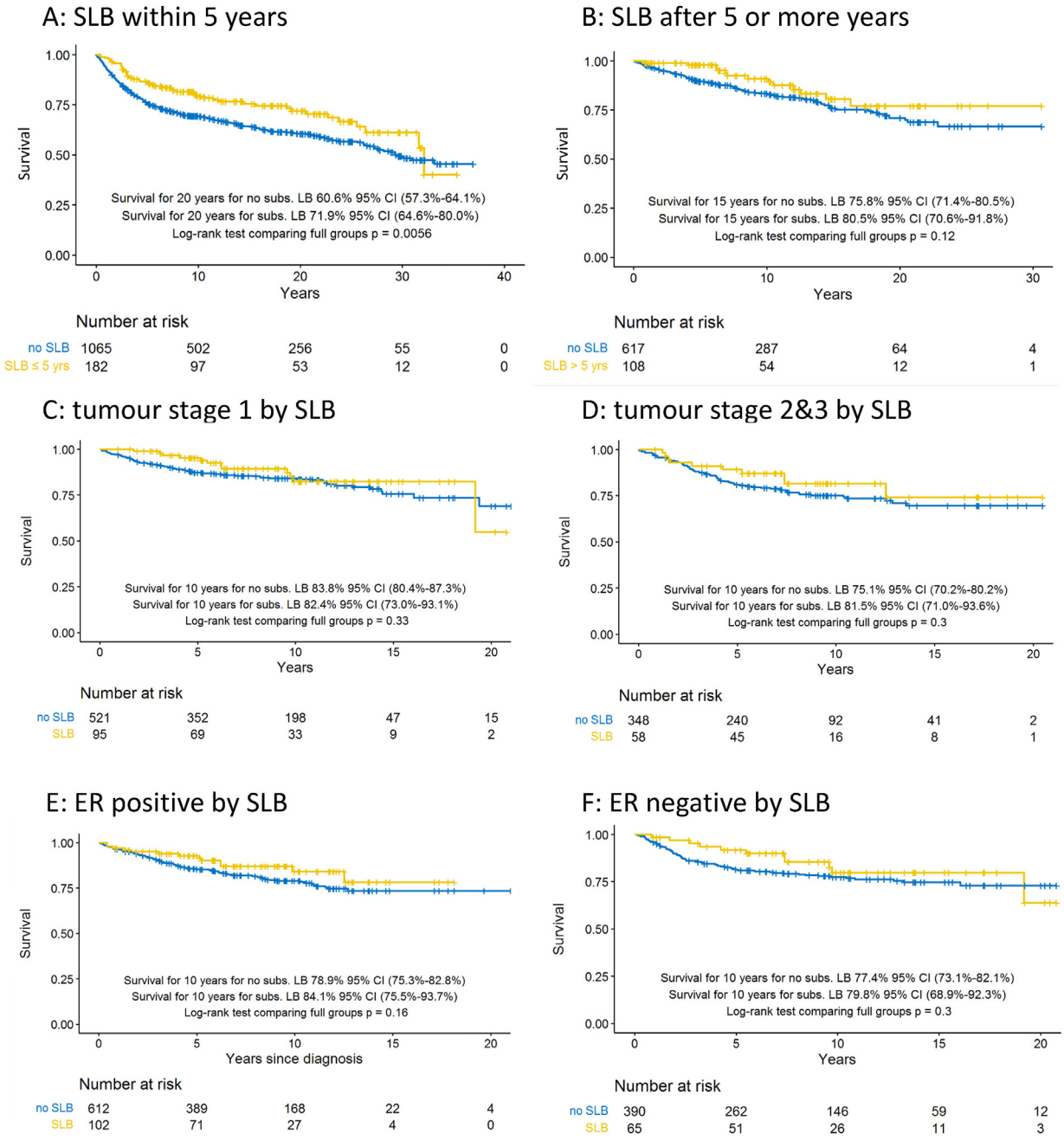

Fig. 2. Overall survival in women with breast cancer by the occurrence of subsequent live birth (SLB) (yellow) or not (blue) following diagnosis in subgroups by (a) occurrence of SLB within five years of diagnosis (yellow) or no SLB (blue); (b) occurrence of SLB five years or more after diagnosis (yellow) or no SLB (blue); (c) tumour stage 1 (d) or stages 2–3 by ER status, (e) positive, or (f) negative. Data are shown by time in years following live birth or matched time point in unexposed cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

5. Discussion

This analysis provides further evidence of the lack of adverse effect on the survival of a subsequent pregnancy and LB in women previously treated for breast cancer. With 290 women with LB after breast cancer in an overall study group of over 5000 patients, this is one of the largest analyses, with both a long period of follow-up and the inclusion of women with a relatively recent diagnosis and treatment. We also provide novel evidence for a positive effect on survival in women who had not been pregnant before their breast cancer diagnosis, and in the women who were youngest at diagnosis. Additionally, we identify the lack of negative prognostic effect of LB after breast cancer in women having births both early (within five years of diagnosis) and after a longer interval, and in women with both ER-positive and ER-negative tumours. These findings are particularly reassuring and important

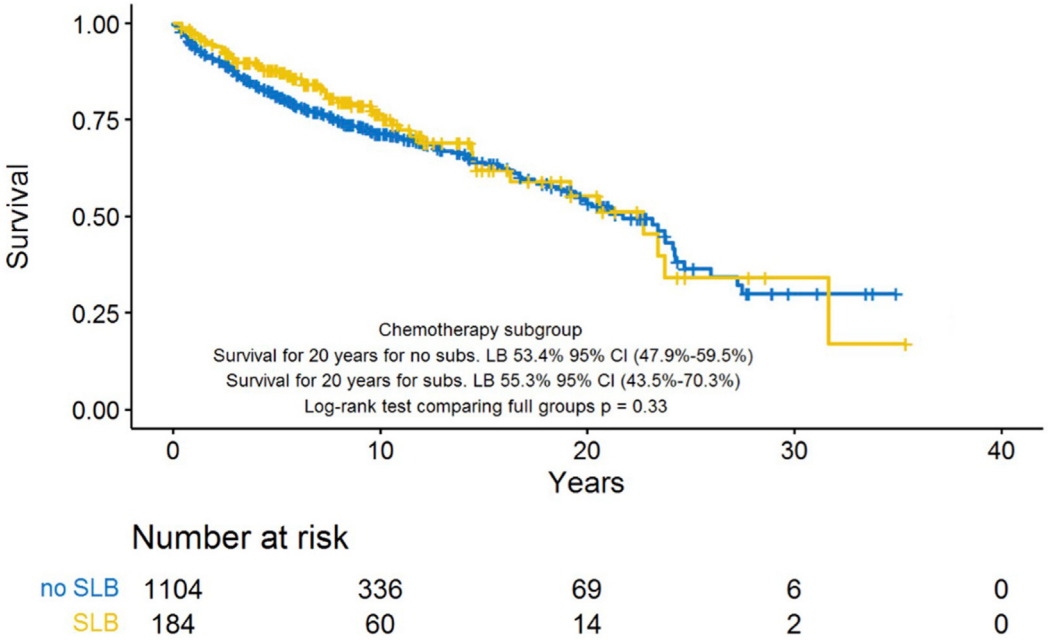

Fig. 3. Overall survival in women with breast cancer who had received chemotherapy by the occurrence of subsequent live birth (yellow) or not (blue) following diagnosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

to young women who are considering starting a family after treatment for breast cancer at a young age and to their oncologists.

There are several converging factors making these findings of growing importance. Sociodemographic changes in age at childbirth are rising, and both the prevalence of breast cancer in young women and survival rates are also increasing. Thus, there is a growing population of women previously treated for breast cancer who have not started or completed their family. In this analysis, only 5.7% of women had a LB after a breast cancer diagnosis, although the duration of follow-up in women diagnosed more recently means that this will be an underestimate of the true final prevalence of childbirth in this population. Pregnancy rates after breast cancer are less than half of that in age-matched women in the general population [17,18]; the present finding is similar to previous analyses, with only 4.2% of women having a pregnancy after breast cancer [2]. We have also recently shown that even in women who do achieve pregnancy after breast cancer, family size is reduced [3].

As analyses such as this cannot have the rigour of randomised selection, minimisation of bias is essential for the validity of the data. The use of well-curated national databases avoids selection bias and increases the size of the population studied. Moreover, we accounted for guaranteed time bias to minimise the 'healthy mother' effect. Our selection of matched unexposed cases minimises bias introduction since it is a random sample from the general population of women with breast cancer that gave rise to the cases. Cancer survival analysis can suffer from date of study entry being date at diagnosis, with the exact time of cancer occurrence being unknown. In this study, both exposed and unexposed cases enter at a date of LB, which is exact. Only four studies have assessed impact on survival in women with a completed pregnancy, with a wide range of HRs reported in the individual studies [14,19–21]. Meta-analysis of these studies showed an overall HR 0.58 (95% CI 0.29–1.17) [2], in comparison with 0.65 (95% CI 0.50–0.85) here, with a duration of follow-up of up to more than 30 years. Furthermore, matching by tumour stage with only women with stage 1 disease, or with stages 2–3 combined, showed no adverse effect of subsequent LB on survival (HRs of 0.74 and 0.71, respectively), nor did restricting the analysis to women known to have been exposed to chemotherapy (HR 0.86). Therefore, while we cannot exclude that other confounding positive factors for survival might be more prevalent in women with a subsequent LB, these data strongly add to the evidence that pregnancy and LB after breast cancer treatment do not adversely affect overall survival.

Although breast cancer is increasingly less prevalent with younger age, such women will have the largest future fertility needs. There are also concerns that breast cancer in young women aged <35 years may have an adverse prognosis [22,23] which may impact on the intensity of treatment administered [13]. The prognostic impact of LB after breast cancer by age at diagnosis has not been previously investigated. We found that despite

the small group size, there was evidence of improved overall survival in the youngest group of women at diagnosis (HR 0.30). This effect declined with increasing age such that it was non-significant in the group diagnosed at age 31–35 years, despite this being the largest group, and in the group aged 36–39 years.

An additional novel finding is that whether or not a woman had had a previous pregnancy impacted the effect of a subsequent LB on survival. Thus, in women who had a pregnancy before breast cancer diagnosis, subsequent LB did not affect survival (HR 0.76, 95% CI 0.53–1.09). However, in women who had not been previously pregnant, there appeared to be a positive impact of a subsequent LB on survival (HR 0.56, 95% CI 0.38–0.82). Prior reproductive events have well-recognised effects on the risk of developing breast cancer, with increased risk associated with early menarche, later first pregnancy and recent pregnancy [24], but with a protective effect of previous pregnancies [22,25]. These findings may be consistent with these previous data regarding the beneficial impact of pregnancy and provide further reassurance to women who have not started their family at the time of breast cancer diagnosis, as well as to women who wish further children to complete their families. Additional reassurance is also provided that having more than one LB after breast cancer does not negatively impact survival, although the sample size of that analysis is limited, and the use of guaranteed survival in the analysis may have limitations where there are multiple LBs since there is a choice of dates for study entry for both exposed and unexposed cases.

There are few data on the potential impact of timing of a pregnancy after breast cancer on overall survival. One study of women diagnosed before 1995 showed no effect of a pregnancy within one year of diagnosis [20]. Increased survival was found in women who had a pregnancy at least six months after diagnosis [26], and a similar result was reported in women who conceived more than two years after diagnosis [27], with a non-significant improvement for pregnancy after six months. However, no matching was performed in those analyses. In the present analysis, we used a cut-off of LB before or after five years from diagnosis and found increased overall survival in both groups. While this was statistically significant in the group with early LB (HR 0.66, 95% CI 0.49–0.89), the HR was similar but non-significant in the group with later LB (HR 0.63, 95% CI 0.36–1.13), likely due to the smaller number of women who had a later LB. Many women wishing to conceive after treatment for breast cancer will be concerned that their treatment has reduced their fertility, additionally impacted by the need to defer attempts at conception for a period of time after treatment, especially when endocrine therapy is advised, compounded by increasing age. These data are reassuring that relatively early pregnancy and LB after breast cancer diagnosis do not adversely affect survival.

Given the hormonal sensitivity of breast cancer, albeit with remaining uncertainties around the effects of both oestrogen and progesterone [28,29], ER status is an important consideration for subsequent pregnancy. We found a non-significant increased overall survival in women with both ER-positive and ER-negative tumours (HR 0.66 and 0.72, respectively). Previous analysis found improved overall survival with pregnancy in women with ER-negative tumours with no effect in those with ER-positive tumours [2,14]. Additionally, we found no adverse impact on overall survival in women with ER-positive tumours who had a LB within five years of diagnosis (HR 0.54, CI 0.26–1.1). This is of particular relevance to women taking adjuvant endocrine therapy for ER-positive tumours, where the current POSITIVE trial (ClinicalTrials.gov identifier: NCT02308085) is investigating the impact of interruption of endocrine therapy in women wishing to conceive [30].

Recent decades have seen considerable changes in the diagnosis and treatment of breast cancer, including more widespread use of chemotherapy in early disease, with consequent improvements in overall survival. Analysis of the impact of subsequent LB in both women known to have received chemotherapy and by the period of diagnosis showed no evidence for an adverse effect in women exposed to chemotherapy or diagnosed during the different time periods.

This study has strengths in its size, the use of carefully maintained national databases to ensure compete ascertainment of cases and outcomes, the long duration of follow-up, and the use of guaranteed time bias and other matches for selecting matched unexposed cases. The size of the database allows for valuable subgroup analysis, but limitations include the evolving nature of data collection. This means that some patient/tumour information was not collected for women diagnosed in the earlier time periods, and there is a lack of detailed treatment information. It is also possible that we have not identified potentially clinically meaningful effect sizes with CI crossing 1 due to the sample size of some subgroups, despite the use of a national database including all women diagnosed with breast cancer over a 36-year period.

In conclusion, this analysis provides evidence for use in counselling the growing number of women who wish to be able to have children after breast cancer that pregnancy and LB do not have a negative impact on overall survival. This important finding was confirmed within subgroups by age at diagnosis, previous pregnancy and timing of subsequent pregnancy, ER status, and known treatment with chemotherapy.

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Author contributions

RAA: conceptualisation, interpretation, drafting and finalising ms. ML: study development, interpretation, editing and finalising ms. PSH: interpretation, editing and finalising ms. WHW; interpretation, editing and finalising ms. DM: interpretation, editing and finalising ms. TWK: primary data analysis, interpretation, editing and finalising ms.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **RAA** has undertaken consultancy work for Roche Diagnostics. **ML** has undertaken consultancy work for Roche, Lilly, AstraZeneca and Novartis; and has received speaker honoraria from Takeda, Roche, Lilly, Pfizer, Sandoz and Novartis.

The other authors report no potential conflicts of interest.

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