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Original Research

Reproductive factors associated with breast cancer risk in Li–Fraumeni syndrome

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Abstract Li–Fraumeni syndrome (LFS) is a rare autosomal dominant cancer predisposition syndrome with exceptionally high lifetime cancer risks, caused primarily by germline *TP53* variants. Early-onset breast cancer is the most common cancer in women with LFS. Associations between female reproductive factors and breast cancer risk have been widely studied in the general population and *BRCA1/2* mutation carriers but not in LFS. We evaluated whether reproductive factors are associated with breast cancer in LFS. Questionnaire data were collected for 152 women with confirmed germline *TP53* variants enrolled in the National Cancer Institute's LFS study (NCT01443468); of which, 85 had breast cancer, confirmed by pathology/medical reports. Fisher's exact test and Cox proportional hazards were used to calculate the effect of reproductive factors on breast cancer risk. Lifetime breastfeeding for at least 7 months was associated with lower breast cancer risk (hazard ratio [HR] 0.57, $p = 0.05$). Parity did not independently change breast cancer risk (HR 1.08, $p = 0.8$) but suggested an increased risk with older age at first live birth (HR 2.14, $p = 0.05$). Age at menarche (HR 1.09, $p = 0.24$) and use of oral contraceptives (HR 0.88; $p = 0.7$) did not significantly affect breast cancer risk. In this first study of reproductive factors and breast cancer in women

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with LFS, breastfeeding was observed to be protective against breast cancer risk, especially with at least 7 months of lifetime breastfeeding. Older age at first live birth was suggested to slightly increase breast cancer risk. Larger prospective studies of reproductive factors are warranted in women with LFS before making definitive clinical recommendations.
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1. Background

Li–Fraumeni syndrome (LFS) is a rare inherited cancer predisposition syndrome with very high lifetime risks of developing multiple cancer types, beginning in childhood [1]. Early-onset/premenopausal breast cancer, bone and soft tissue sarcomas, brain tumours and adrenocortical carcinoma are 'core' LFS cancers in affected families. Individuals with LFS are also at a high risk of developing multiple primary cancers during their lifetimes, with more than 50% of those diagnosed with a primary cancer developing a subsequent primary malignancy [2,3]. First described in 1969, classic LFS is diagnosed based on a personal history of early-onset sarcoma and a specific cancer family history pattern based on age at onset and cancer type [4]. Less stringent classifications have been used more recently to guide clinical genetic testing for LFS [5,6]. Pathogenic germline variants in *TP53*, inherited in an autosomal dominant pattern, are the only known genetic cause for LFS and have been estimated to account for between 60% and 80% of families with classic LFS [7,8].

The lifetime risk of cancer in people with LFS has been previously reported to be nearly 100% by the age of 60 years in women and 73% in men [9], with an overall cumulative incidence of 50% by the age of 40 years [10]. We previously reported a cumulative cancer incidence of 50% by the age of 31 years in women and the age of 46 years in men with LFS [11]. Age at onset and cancer type can be highly variable within families carrying the same mutation, suggesting that other genetic and non-genetic factors modify the inherited risk [12]. In addition, a recent study of cancer in more than 2000 carriers of pathogenic germline *TP53* variants reported incomplete penetrance with about 80% of individuals developing cancer by the age of 80 years [12].

This sex difference of cancer incidence in LFS is mainly driven by the exceptionally high risk of early-onset breast cancer in women, which can reach 49% by the age of 60 years, with a median age at diagnosis of 32 years [11]. In the general population, female reproductive factors including early parity and longer duration of breastfeeding independently lower the overall risk of breast cancer. Although this reduction in breast cancer risk is postulated to be associated with lifetime exposure to ovarian hormones, which influences the number of cumulative ovulatory cycles and differentiation of breast lobules [13], large meta-analyses have not shown significant change in breast cancer risk by menopausal status, and the underlying biological mechanisms of hormonal breast carcinogenesis are not fully elucidated [14–16]. Female reproductive factors in the setting of heritable breast cancer due to pathogenic variants in *BRCA1/2* have been extensively studied, and breastfeeding has been consistently observed to be protective, with up to a 32% reduction in breast cancer risk in *BRCA1* women who breastfed for at least 12 months [17].

There are scarce data on potential non-genetic cancer risk modifiers of breast cancer in LFS. In this study, we evaluated the association of female reproductive factors and breast cancer risk in women with LFS.

2. Methods

2.1. Study participants

This retrospective observational study consisted of participants enrolled in the National Cancer Institute's Institutional Review Board–approved LFS study (11-C-0255, ClinicalTrails.gov; identifier NCT01443468; www.lfs.cancer.gov) [3] between 2011 and 2016. Written informed consent was obtained from all participants. Detailed family history and individual information questionnaires (IIQs) were completed. The IIQ includes self-reported data on the individual's demographics, medical and surgical history and all cancer diagnoses. Women also reported on reproductive factors such as age at menarche, number of pregnancies, childbirth and breastfeeding, fertility experiences and use of oral contraceptives (OCPs). Adult participants who self-identified as woman, completed an IIQ and had a known pathogenic/likely pathogenic germline *TP53* variant were included in this analysis. We confirmed breast cancer diagnoses and hormone receptor status (oestrogen receptor [ER], progesterone receptor [PR] and human epidermal growth factor receptor 2 (HER2)/neu) through the evaluation of pathology reports, surgical operative notes, consultation reports and/or medical provider notes. Breast sarcomas and malignant phyllodes tumours were excluded from this analysis. Parity was defined as having reported at least one live birth. Breastfeeding was defined as the total number of months of lifetime breastfeeding reported. Germline

genetic testing reports were examined to confirm the presence of a known germline *TP53* variant.

2.2. Statistical analysis

Odds ratios (ORs) on contingency tables of breast cancer status vs. dichotomised cumulative breastfeeding duration (e.g., less than 12 months, more than 12 months) were calculated using Fisher's exact test. Cox proportional hazards models were used to calculate the effect of hormonal factors on breast cancer risk. Hazard rates were derived by comparing women based on similar dichotomised breastfeeding duration (e.g., less than 3 months, more than 3 months) at each monthly time point. Parity and number of live births were treated as time-varying covariates, and the participants were censored at the date of death, end of the study, mastectomy or study dropout. As mastectomy and breast cancer diagnosis may occur concurrently or within nearly the same time frame in women with *TP53* mutations, women who had a mastectomy (unilateral or bilateral) before a cancer diagnosis were censored at the time of mastectomy if it occurred more than one year before their diagnosis and excluded from the analyses. Women who reported unilateral or bilateral mastectomy after breast cancer diagnosis were included. Survival curves were visualised using Kaplan–Meier curves and non-parametric graphical representations accounting for time-varying covariate status [18]. All analyses were performed using statistical software R version 3.4 [19], using survival package version 2.38 [20].

2.3. Role of the funding source

The funding source for this study had no role in study design, data collection, interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

This study evaluated reproductive factors in 152 women with a pathogenic or likely pathogenic germline variant in *TP53* (Supplemental Table 1). Eighty-five women (56%) developed at least one breast cancer, and 13 (15%) of these women had bilateral synchronous breast cancers. The median age at first breast cancer diagnosis was 32 years (range: 20–54 years). Six of these women were postmenopausal at diagnosis. Twenty of the 85 women (23%) were diagnosed with a subsequent primary breast cancer at a median age of 40 years (range: 29–63 years), two of whom also developed a third primary breast cancer. Of the 64 first breast cancers with available hormone receptor status data, 60% were ER/PR+, and of the 48 cancers with available HER2/neu status, 57% were HER2/neu+, compared with a prior report of hormone status in women with germline *TP53* variants that showed 76% ER+/67% PR+ and 65% HER2/neu+ breast cancers [11]. Of the 85 women with breast cancer, only one woman reported a risk-reducing bilateral oophorectomy after her breast cancer diagnosis. None of the 67 breast cancer-free women had undergone mastectomy at the time of IIQ completion. None of the women reported significant problems with menstrual cycles or infertility. Fifteen of the 85 women (18%) had a prior cancer diagnosis before developing breast cancer. Of these 15, four reported receiving radiation therapy for their previous cancer. One of the four women developed a subsequent breast cancer in the field of prior radiation therapy, 28 years after her radiation treatment. Two women reported having received chemotherapy before breast cancer diagnosis, and one woman received prior immunotherapy.

In parous women, breastfeeding for any length of time was associated with reduced breast cancer risk. The strongest association occurred with lifetime breastfeeding for at least 7 months (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.33–1.00; $p = 0.05$). This association of reduced breast cancer risk was consistent through at least 12 months of lifetime breastfeeding (HR: 0.49; 95% CI: 0.26–0.89; $p = 0.02$) (Table 1, Fig. 1). Breast cancer risk was reduced with each month of breastfeeding with the log OR decreasing by 0.19 per month in logistic regression models. The protective effect of lifetime breastfeeding for at least 12 months remained consistent after controlling for age of the participant and age at first breast cancer diagnosis (HR: 0.48; 95% CI: 0.26–0.90; $p = 0.02$). There was no statistically significant difference in the ER/PR status of the breast cancers between women who breastfed for less

Table 1
Risk of breast cancer associated with each cumulative month of lifetime breastfeeding in women with Li–Fraumeni syndrome due to known germline *TP53* variants.

Lifetime breastfeeding reported (months)	Number of women	Number of women with breast cancer	Hazard ratio (vs. < months)	95% CI	p-value
≥1	67	43	0.97	0.48–1.97	0.94
≥2	63	37	0.84	0.45–1.57	0.59
≥3	59	34	0.73	0.41–1.33	0.3
≥4	57	32	0.69	0.39–1.23	0.21
≥5	53	30	0.70	0.40–1.24	0.22
≥6	53	30	0.70	0.40–1.24	0.22
≥7	48	26	0.57	0.33–1.0	0.05
≥8	47	25	0.56	0.32–0.99	0.04
≥9	42	22	0.55	0.31–0.97	0.04
≥10	39	21	0.61	0.34–1.08	0.09
≥11	35	17	0.49	0.26–0.89	0.02
≥12	35	17	0.49	0.26–0.89	0.02

CI; confidence interval.
Hazard ratios calculated in comparison with women who breastfed for less than the 'lifetime breastfeeding months' reported.
Analysis performed only in women who reported at least one live birth.

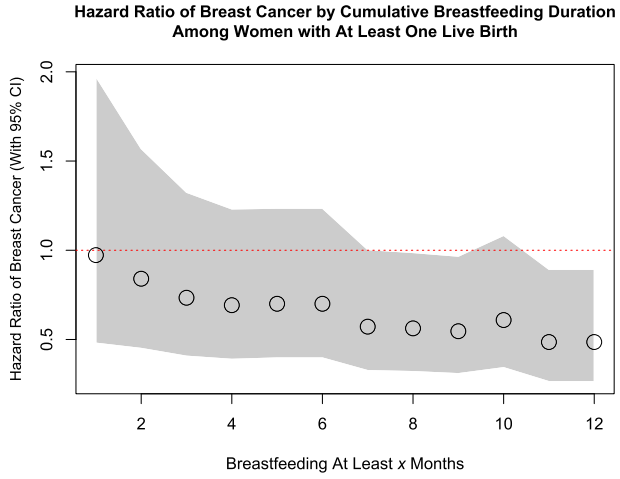

Fig. 1. **Breast cancer risk by cumulative breastfeeding duration among women with Li–Fraumeni syndrome due to known germline *TP53* variants who had at least one live birth.** Red dotted line denotes a hazard ratio of 1.0. The circles denote the hazard ratio, and the grey area encompasses the corresponding 95% confidence intervals for each added month of cumulative breastfeeding. CI, confidence interval.

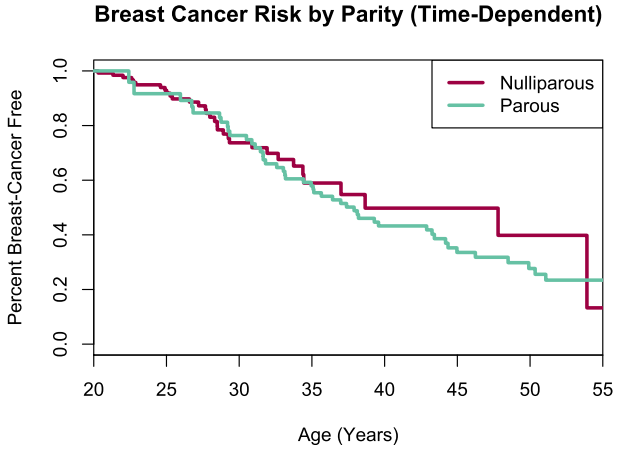

Fig. 2. **Parity as an independent risk factor for breast cancer in women with Li–Fraumeni syndrome due to known germline *TP53* variants.** Parous = at least one live-born child. Parity analysed as a time-dependent covariate, meaning anytime a woman had a live-born child, she automatically crossed over to the 'parous' group.

than or at least 12 months (OR: 0.57 for ER+ breast cancer; 95% CI: 0.1–3.1; p = 0.48). Similarly, there was no difference in the age at breast cancer diagnosis between women who breastfed for less than or at least 12 months (HR: 0.7; 95% CI: 0.41–1.2; p = 0.23).

There was no observed evidence of a difference in breast cancer risk between nulliparous and parous women with LFS, when parity was independently evaluated as a time-varying covariate, and after adjusting for age at first live birth (HR: 1.08; 95% CI: 0.65–1.78; p = 0.8) (Table 2, Fig. 2). When stratifying the data to account for women who had not developed breast cancer and were alive at the age of 40 years, there was no evidence that parity affected breast cancer risk after the age of 40 years (Table 2). The number of live births in

Table 2
Parity as an independent risk factor for breast cancer in women with Li–Fraumeni syndrome due to known germline *TP53* variants.

Parameter	Number of women without breast cancer	Number of women with breast cancer	Hazard ratio	95% CI	p-value
Effect of parity on breast cancer risk (all women)					
Nulliparous	34	33	–		
Parous	33	52	1.07	(0.66, 1.77)	0.8
Effect of parity on breast cancer risk stratified by age at study entry					
≤ 40 years					
Nulliparous	43	30	–		
Parous	43	34	1.12	(0.66. 1.91)	0.7
>40 years					
Nulliparous	4	3	–		
Parous	21	11	0.85	(0.24. 3.07)	0.8
Number of live births					
Nulliparous	37	30	–		
1	5	13	1.23	(0.69. 2.19)	0.5
2	16	32	1.13	(0.61. 2.09)	0.7
3	5	6	0.82	(0.31. 2.20)	0.7
4+	5	3	0.29	(0.04. 2.12)	0.23
Per live birth			0.93	(0.76. 1.14)	0.5
Age at first live birth (years)					
Nulliparous	33	33	–		
<25	23	16	0.71	(0.38. 1.41)	0.29
25–29	7	21	1.44	(0.83. 2.97)	0.26
≥30	5	14	2.14	(1.1. 5.24)	0.05

CI; confidence interval.
Parous = at least one live-born child.

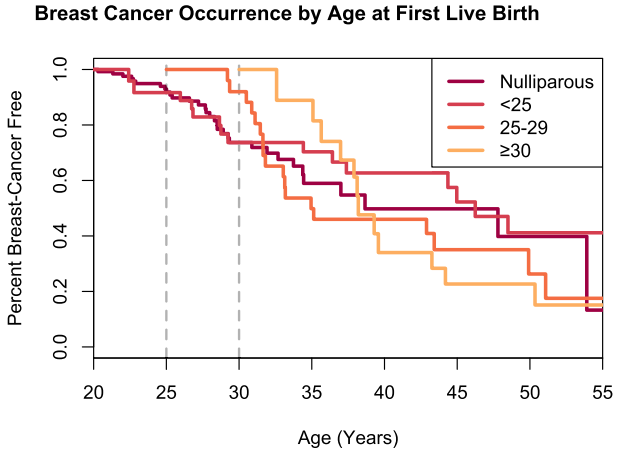

Fig. 3. **Occurrence of breast cancer stratified by age at first live birth in women with Li–Fraumeni syndrome due to known germline *TP53* variants.** Y-axis is the probability a woman is breast cancer free, based on age at first live birth in years as a time-dependent covariate.

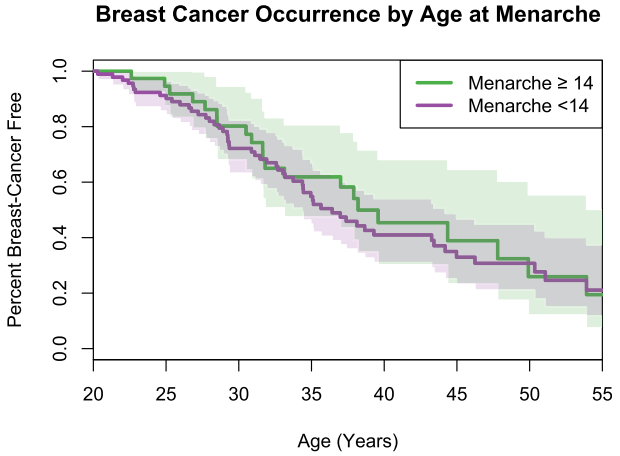

Fig. 4. **Breast cancer occurrence by age at menarche in women with Li–Fraumeni syndrome due to known germline *TP53* variants.** Y-axis depicts the probability a woman is breast cancer free by age with years on the x-axis. Coloured areas show the corresponding 95% confidence intervals. Green line = age at menarche at least 14 years or older (n = 39), purple line = age at menarche below 14 years (n = 104). Age at menarche was not available for nine women.

parous women was not associated with significant change in breast cancer risk. However, there was a borderline statistically significant excess risk among women who had their first live birth after the age of 30 years (HR: 2.14; 95% CI: 0.99–4.6; p = 0.05) (Fig. 3, Table 2).

Breast cancer risk was not associated with self-reported OCP use in women with LFS (OR: 2.06; 95% CI: 0.79–5.6; p = 0.12; age-adjusted analysis conferred a HR = 0.89; 95% CI: 0.44–1.78; p = 0.7). Assuming continuous use of OCPs for the reported duration, the risk of breast cancer was suggested to slightly increase with increasing duration of OCP use (HR: 1.07; 95% CI: 1.02–1.12; p = 0.01).

The overall median age at menarche for women in this study was 12 years (range: 9–18 years). The median age at menarche was not different among women with or without breast cancer at study entry (median age at menarche in women with breast cancer: 13 years, range: 9–17 years; median age in women without breast cancer: 12 years, range: 10–18 years; p > 0.05). Our data show that younger age at menarche did not significantly affect breast cancer risk of women with LFS (OR: 1.09; 95% CI: 0.94–1.27; p = 0.24) (Fig. 4).

LFS is considered a radiation-sensitive syndrome, and genotoxic therapy such as chemotherapy and/or radiation therapy has been shown to increase the risk of development of subsequent primary malignancies in a mouse model of LFS [21]. Therefore, we performed the same statistical analyses excluding the five women who received genotoxic therapy before their breast cancer diagnosis. In this evaluation of 81 women, the associations between breastfeeding, parity, age at first live birth, OCP use and age at menarche were robust and consistent with the results reported previously (data not shown).

4. Discussion

Female reproductive factors are associated with the risk of breast cancer in the general population and among carriers of pathogenic germline variants in *BRCA1/2* [15,22–25]. However, this association has not yet been explored in germline *TP53* mutation carriers. We report a protective effect of breastfeeding on breast cancer risk in *TP53* mutation carriers, with breastfeeding for at least 7 months conferring a 43% risk reduction. This effect of breastfeeding is consistent with findings in the general population and among *BRCA1/2* mutation carriers. In the general population, large-scale pooled epidemiological analyses have reported that breast cancer risk decreased by more than 4% for every 12 months of breastfeeding [13]. Evaluations of *BRCA1/2* cohorts have shown consistently that breastfeeding is protective in *BRCA1* carriers, with up to a 32% reduction in breast cancer in women who breastfed for 12 months [17,26].

Studies of parity and breast cancer risk in both the general population and in women with pathogenic germline *BRCA1/2* variants have had variable results. Some have reported a protective effect of younger age at first childbirth and higher risk with first live birth at older ages [25,27]. However, other studies in women with *BRCA1/2* mutations *vs* non-carriers showed no difference in breast cancer risk by mean age at first live birth or between parous and nulliparous women [23]. Additional studies of *BRCA1/2*-associated breast cancer stratified outcomes of full-term pregnancies or looked independently at age at first full-term pregnancy and the

number of children [23,25,27]. We defined parity as a pregnancy resulting in reported live birth but were unable to capture other outcomes of full-term pregnancies such as stillbirth or late foetal loss. Our analyses did not find that parity was associated with breast cancer risk in LFS; however, our data suggest that women with live birth after the age of 30 years may have an increased breast cancer risk, regardless of how long they breastfed.

In the general population, OCP use has been associated with a slightly higher breast cancer risk that appears to decrease after cessation of OCPs [28,29]. Reports in *BRCA1/2* cohorts have shown slightly conflicting results between studies and depending on the particular gene, with some data showing increasing duration of OCPs being associated with increased breast cancer risk [26,27,30]. Our data did not identify an association between OCP use and breast cancer risk in LFS. However, it must be noted that only 25 of the 154 women in the study reported never having used OCPs, making our comparison group limited by the sample size.

In this LFS cohort, age at menarche was not associated with alteration in breast cancer risk in contrast to the slightly higher risk of breast cancer with younger age at menarche in the general population [27,31,32]. The age of 14 years was chosen as a statistical cut-off based on global estimates of average age at menarche. The lack of significant association between menarchal age and breast cancer could be due to the earlier age at onset of breast cancer in LFS (a median age at diagnosis of 32 years in LFS and 62 years in the general population), with fewer cumulative ovulatory cycles and reproductive hormone exposure before breast cancer diagnosis, compared with the women in the general population and those with *BRCA1/2* predisposition.

The effect of genotoxic cancer therapy on subsequent development of malignancy in LFS has not been quantified in humans, but mouse models show that chemotherapy and radiation therapy increase the risk of subsequent cancers [21]. The exclusion of women who received genotoxic therapy before breast cancer diagnosis did not significantly change the effect of each reproductive factor on breast cancer risk, suggesting that these factors may impact breast cancer risk independent of prior therapy in these women. However, the understanding of the potential impact cancer therapy has on subsequent malignancies and breast cancer in women with LFS is an important factor to consider in future larger cohort studies of LFS.

The relatively small sample size is a limitation of this study. However, an important strength of our study was the detailed clinical data, which permitted a comprehensive evaluation of the reproductive factors in breast cancer in LFS. Because our data is self-reported, there is a potential for survival bias in women who report their prior cancer history, and we acknowledge the critical need for continued follow-up of women with LFS who have not yet developed breast cancer. Breastfeeding was reported as lifetime duration, without detailed stratification of breastfeeding per childbirth for women with more than one live-born child. Of the 86 women in our study who developed breast cancer, 15 (17%) had a previous cancer diagnosis. However, none of these women reported medical/surgical menopause or fertility concerns before breast cancer diagnosis.

It is important to consider the medical benefits of breastfeeding in the context of cancer screening and prevention in women with LFS. The American Academy of Pediatrics and World Health Organisation, among other expert consensus, strongly recommend breastfeeding for the medical and emotional benefits in infants and mothers, such as decreased postpartum bleeding in the mother and decreased occurrence of infections and immune-mediated disorders in the infant [33]. In LFS, where the median age of breast cancer development is 32–33 years [11,12] and breast cancer accounts for more than a quarter of the cancer diagnoses [12], balancing a woman's reproductive choices such as breastfeeding against the high risk of early-onset breast cancer is an important discussion. Women with LFS who continue to have breast tissue through their reproductive years have the additional burden of screening with annual breast Magnetic resonance imaging (MRI) ± mammography [34]. Further consideration of cancer-screening recommendations during pregnancy and lactation is important to discuss on a continuum in women with LFS.

In conclusion, we report a statistically significant protective effect of breastfeeding on breast cancer risk in LFS. Parity and OCP use were not seen to be independent risk factors for breast cancer. While we acknowledge that these results require replication in a larger sample of women with LFS due to pathogenic germline *TP53* variants, our data provide critical information to build future studies of breast cancer and hormonal carcinogenesis in LFS. If confirmed, our results suggest a main effect of breastfeeding among the reproductive risk factors for breast cancer risk in LFS. This may inform clinical and reproductive decision-making in women with LFS, specifically those who are weighing their reproductive options and established benefits of breastfeeding against those of prophylactic risk-reducing mastectomies.

Author contributions

P.P.K. and M.I.A. contributed to study conceptualisation and design. A.F.B. and P.P.K. were involved in the analyses of the study. P.P.K., J.T.L., J.F.F. and S.A.S. contributed to data collection. P.P.K., A.F.B., M.I.A. and S.A.S. were involved in the interpretation of the results. P.P.K., A.F.B., J.F.F., J.T.L., M.I.A. and S.A.S. contributed to manuscript writing and editing.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.005.

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