

Family size and duration of fertility in female cancer survivors: a population-based analysis

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Objective: To assess family size and timescale for achieving pregnancy in women who remain fertile after cancer.

Design: Population-based analysis.

Setting: National databases.

Patient(s): All women diagnosed with cancer before the age of 40 years in Scotland, 1981–2012 (n = 10,267) with no previous pregnancy; each was matched with 3 population controls.

Intervention(s): None.

Main Outcome Measure(s): The number and timing of pregnancy and live birth after cancer diagnosis, to 2018.

Result(s): In 10,267 cancer survivors, the hazard ratio for a subsequent live birth was 0.56 (95% confidence interval, 0.53–0.58) overall. In women who achieved a subsequent pregnancy, age at live birth increased (mean $\pm$ SD, 31.2 $\pm$ 5.5 vs. 29.7 $\pm$ 6.1 in controls), and the family size was lower (2.0 $\pm$ 0.8 vs. 2.3 $\pm$ 1.1 live births). These findings were consistent across several diagnoses. The interval from diagnosis to last pregnancy was similar to that of controls (10.7 $\pm$ 6.4 vs. 10.9 $\pm$ 7.3 years) or significantly increased, for example, after breast cancer (6.2 $\pm$ 2.8 vs. 5.3 $\pm$ 3.3 years) and Hodgkin lymphoma (11.1 $\pm$ 5.1 vs. 10.1 $\pm$ 5.8 years).

Conclusion(s): These data quantify the reduced chance of live birth after cancer. Women who subsequently conceived achieved a smaller family size than matched controls, but the period of time after cancer diagnosis across which pregnancies occurred was similar or, indeed, increased. Thus, we did not find evidence that women who were able to achieve a pregnancy after cancer had a shorter timescale over which they have pregnancies. (Fertil Steril® 2022;117:387–95. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Fertility, cancer, reproductive lifespan, survivorship



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The diagnosis of cancer and its treatments, including chemotherapy, radiotherapy, and surgery, have established adverse effects on fertility in both women and men (1–3). This effect is evident across cancer diagnostic groups, with an overall reduction in the number of

women achieving a pregnancy after cancer of approximately 38% compared with population controls (4). Direct effects on the reproductive system in women include loss of ovarian follicles with an increased risk of infertility and premature ovarian insufficiency (POI) (5, 6) and damage

to the uterus (7, 8), with these effects varying with treatment type and dose and age (3, 9, 10). The risk of early menopause also varies by treatment type (11, 12). Effects on the hypothalamus and pituitary gland impacting reproductive function may also result from cranial irradiation or surgery (13). Additionally, pregnancy complications are more common in cancer survivors (14): radiotherapy to a field that includes the uterus is the most established risk factor (15, 16), but there is also some evidence that chemotherapy can be associated with pregnancy complications (17).

There are additionally several other factors that influence the likelihood of pregnancy after cancer, including effects on rates of cohabitation/marriage,

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sexuality, and the impact of other long-term health consequences (generally termed “late effects”) of cancer treatment (18–23). Concerns regarding health status and disease recurrence may also be significant in decisions regarding family building after treatment (24); others may be voluntarily childless (25). Thus, there is a complex interplay of biologic, psychologic and social factors that determine postcancer fertility (26).

Studies that assess the achievement of successful pregnancy generally report this as a bimodal event, for example, a live birth was achieved or not, in relation to cancer diagnosis and treatment modality and regimen, with few studies assessing the fertility of women who are able to conceive after cancer treatment. There is some evidence that in the absence of POI, cancer survivors have a greater prevalence of infertility (27, 28). Studies assessing ovarian reserve biomarkers as a surrogate endpoint indicate that several women have reduced anti-Müllerian hormone (AMH) levels after cancer treatment, indicating a possible risk of later loss of fertility and POI (29–31). There is little information on completed family size in cancer survivors or whether, as suggested by the reduced ovarian reserve identified in several survivors, the remaining ovarian function results in a reduced reproductive lifespan. In this study, we analyzed all pregnancies and live births in an unbiased, population-based cohort of cancer survivors to address the questions of whether the number of births to female cancer survivors who are able to achieve pregnancy is different from the matched controls and whether the time distribution of those pregnancies indicates an effect on the period of time over which pregnancy and childbirth can be achieved, as an index of fertile lifespan.

MATERIALS AND METHODS

The Scottish cancer registry records from 1981 through 2012 were linked to maternity and death records from 1981 to September 2018. The primary exposed group was extracted as all females with a cancer diagnosis at the age of <40 years and no previous pregnancy before cancer diagnosis. Maternity records are hospital based and, thus, are not comprehensive for early miscarriage. For each exposed subject, 3 controls from the population were matched using the unique personal Community Health Index number allocated to each person in Scotland at birth or on first registration with the National Health Service. Matching was by age at diagnosis, period of diagnosis by decade, previous pregnancy history, and socioeconomic status using deprivation index quintiles on the basis of Scottish postal address data (32). Any ages at death were recorded for the exposed group, and the competing risk of maternity events was censored (accounted for by excluding maternity records) for a control after the date of death for her exposed match.

Hazard ratios (HRs) for live birth were calculated using the Cox proportional hazard models with event as first live birth, time to event as the difference between the date of delivery and date of diagnosis, and groups exposed or controls and are reported with 95% confidence intervals. Fertile survivors were those cancer registry patients with at least 1 subsequent pregnancy recorded in the maternity records. These

were compared against their controls—adjusted for competing risks—in terms of age at live birth, family size, and the time period between diagnosis and last pregnancy as an index of fertile lifespan. The means and standard deviations were calculated, with an unpaired t-test adjusted where necessary for unequal variance for the null hypothesis that the means were equal. Density charts were produced, subset by diagnosis. The area under the curves for both the exposed and control groups was 1, with the charts showing how time from diagnosis to last live birth is distributed for both groups. All data linking, chart production, and analysis were performed using R version 3.6.1.

This analysis was approved by the National Health Service Scotland Public Benefit and Privacy Panel for Health and Social Care (reference 1819-0186).

RESULTS

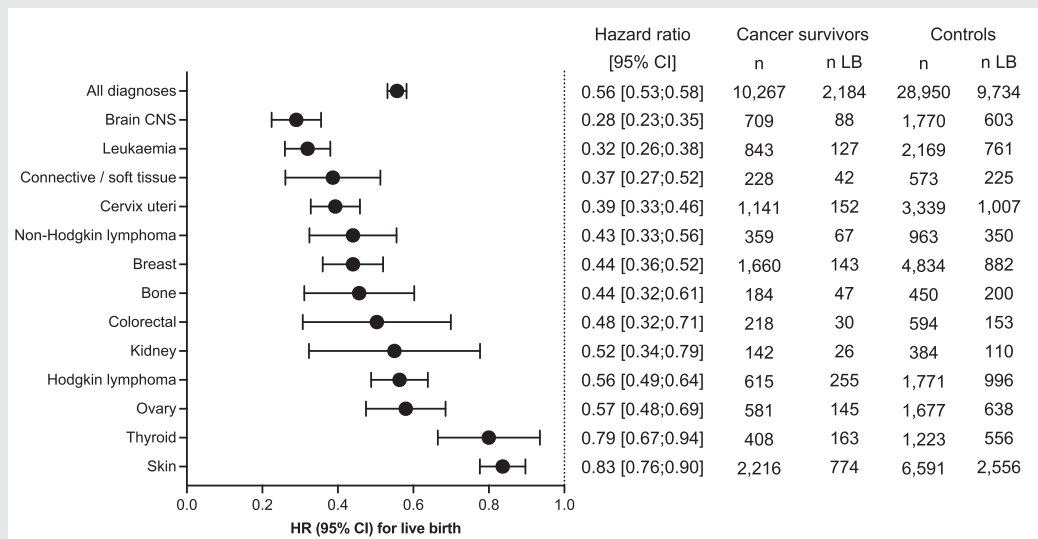
Effect of cancer on live birth rates

A total of 10,267 cancer survivors aged <40 years at cancer diagnosis and who had not been pregnant before diagnosis were identified; of these, 2,261 women had at least 1 pregnancy, and 2,184 had at least 1 live birth over the period of analysis (median, 16.3 years' follow-up; interquartile range, 7.8–26.4 years). These were compared with 28,950 controls, matched for age, time period, and deprivation score, who likewise had not been pregnant before entry into the study. Of these controls, 10,010 had a pregnancy and 9,734 had a live birth over the same period of analysis (Fig. 1). Thus, women were less likely to have a live birth after a cancer diagnosis, with an overall HR of 0.56 (95% confidence interval, 0.53–0.58). Analysis by specific cancer diagnostic groups showed the wide range of diagnoses associated with a reduction in the likelihood of live birth after cancer, with among the more common diagnoses, HRs as low as 0.29 for brain/central nervous system (CNS) cancer and below 0.5 for cervical, breast, colorectal, and bone cancers, non-Hodgkin lymphoma, and leukemia (Fig. 1). Skin and thyroid cancers were also associated with significantly reduced HRs (0.83 and 0.79, respectively).

Impact of Cancer on Age at Live Birth

Subsequent analyses investigated reproductive function in “fertile survivors,” defined as women achieving at least 1 pregnancy after cancer diagnosis. These were compared with their matched controls. The mean age at first live birth was greater in cancer survivors overall (31.2 ± 5.5 vs. 29.7 ± 6.1 years, $P < .001$), and this was confirmed across most diagnoses (Table 1), indicating a cancer-related delay in age at childbirth. This was not seen, however, for cervical cancer, where the mean age at live birth was similar in cancer survivors (32.8 ± 4.3 vs. 33.0 ± 4.2 years, $P = .41$). How age at live birth varied with age at diagnosis was explored in 3 conditions, that is, breast cancer, Hodgkin lymphoma, and leukemia, representing diagnoses with peak incidence in adulthood, adolescence, and childhood, respectively (Table 1). In all 3 conditions, however, the pattern was fairly consistent. In breast cancer, with an overall mean age at live birth of 1.2 years older than controls,

FIGURE 1



Hazard ratio (HR) and 95% confidence interval (CI) for live birth after cancer for subsequent live birth (LB) in women with cancer diagnosed at the age of <40 years, with diagnosis from 1981 through 2012, with births up to the end of 2018, compared with matched controls. CNS = central nervous system.

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the differences were 1.0, 1.2, and 1.2 years in 3 groups spanning age at diagnosis from 25–29, 30–34, and 35–39 years, respectively ($P < .05$ to $< .001$ vs. controls). In Hodgkin lymphoma, the overall difference was 1.7 years older, and the differences were 0.7 ($P = .45$), 1.9 ($P < .001$), and 1.2 ($P < .01$) years

in age groups 0–14, 15–24, and 25–29 years, respectively. In leukemia, the overall mean difference was 1.1 years older, and the differences were 1.1 ($P < .05$), 1.5 ($P < .05$), and 0.8 ($P = .88$) years across the same 3 age groups as for Hodgkin lymphoma.

TABLE 1

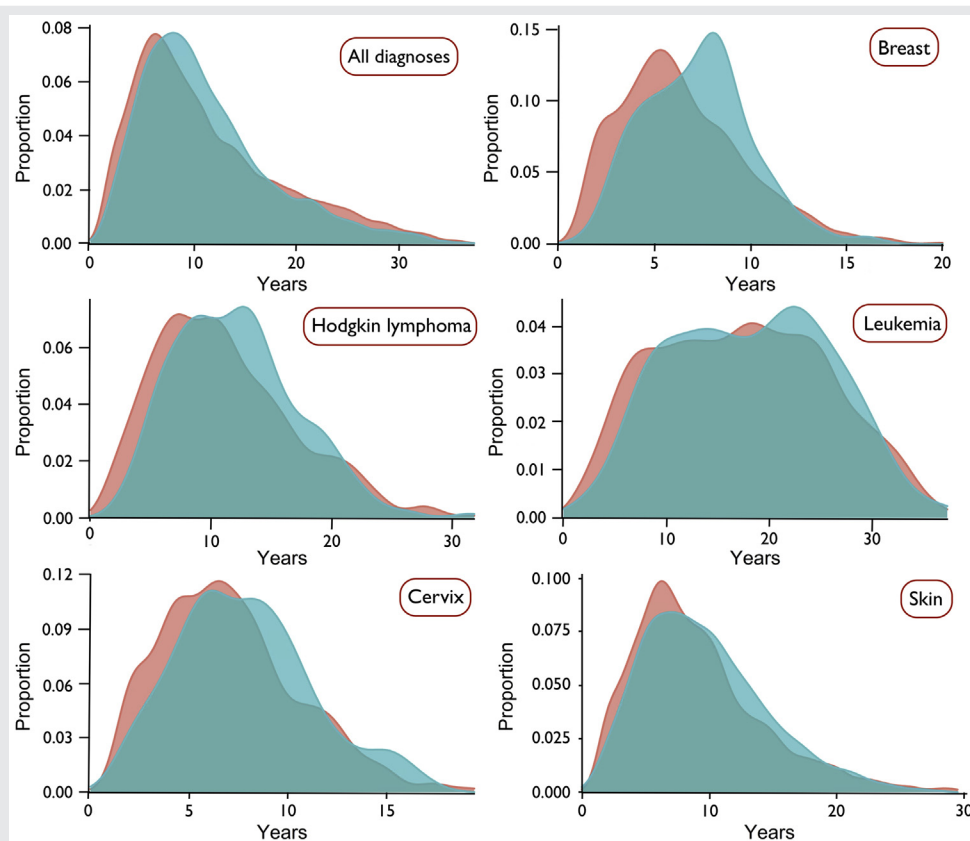
Age at live birth, family size (number of live births), and interval to last pregnancy in women with cancer who achieved at least 1 subsequent pregnancy.

Cancer type	n FS	Age at LB (mean; SD)			Family size (mean; SD)			Interval to last pregnancy (mean; SD)		
		FS	Controls	P	FS	Controls	P	FS	Controls	P value
All diagnoses	2,265	31.2; 5.5	29.7; 6.1	<.001	2.0; 0.8	2.3; 1.1	<.001	10.7; 6.4	10.9; 7.3	.57
Colorectal	31	32.9; 5.6	31.1; 6.1	<.05	1.8; 0.7	2.2; 1.0	<.001	9.1; 6.9	7.2; 4.4	.07
Skin (melanoma and nonmelanoma)	794	32.5; 4.9	31.3; 5.3	<.001	2.0; 0.8	2.2; 1.0	<.001	8.7; 4.9	8.1; 5.1	<.001
Connective and soft tissue	45	29.7; 5.2	27.4; 6.0	<.001	2.1; 0.8	2.4; 1.0	<.01	12.8; 6.6	13.0; 6.9	.86
Breast, all ages	156	35.6; 4.4	34.4; 4.4	<.001	1.7; 0.8	1.8; 0.7	<.05	6.2; 2.8	5.3; 3.3	<.001
Breast, 25–29	48	32.9; 3.3	31.9; 3.2	<.05	1.5; 0.6	2.0; 0.6	<.001	6.1; 2.7	6.4; 3.1	.97
Breast, 30–34	59	36.7; 2.4	35.5; 2.9	<.001	1.8; 0.9	1.8; 0.7	.93	6.0; 2.4	4.8; 2.9	<.001
Breast, 35–39	45	40.6; 2.4	39.4; 2.5	<.01	1.6; 0.7	1.5; 0.6	.37	5.0; 2.2	3.4; 2.3	<.001
Cervix uteri	153	32.8; 4.3	33.0; 4.2	.41	2.0; 0.8	2.0; 0.8	.60	6.8; 3.4	6.0; 3.6	<.001
Ovary	149	30.1; 5.1	30.3; 5.6	.58	2.0; 0.9	2.3; 1.3	<.001	9.3; 5.6	8.8; 5.8	.18
Brain CNS	94	27.4; 5.3	26.9; 6.0	.34	2.2; 1.1	2.5; 1.2	<.01	16.4; 8.2	15.1; 8.2	<.05
Thyroid	167	31.2; 5.0	30.2; 5.8	<.01	2.0; 0.9	2.2; 1.0	<.01	8.7; 4.8	8.4; 5.1	.39
Hodgkin lymphoma, all ages	261	29.9; 5.2	28.2; 5.5	<.001	2.0; 0.8	2.4; 1.1	<.001	11.1; 5.1	10.1; 5.8	<.001
Hodgkin lymphoma, 0–14	36	25.9; 6.3	25.2; 6.0	.45	2.3; 1.2	2.7; 1.6	<.05	17.2; 5.4	16.9; 5.9	.69
Hodgkin lymphoma, 15–24	157	29.0; 4.4	27.1; 5.0	<.001	1.9; 0.8	2.4; 0.9	<.001	11.4; 4.3	10.4; 5.1	<.01
Hodgkin lymphoma, 25–29	64	32.8; 3.1	31.6; 3.8	<.01	2.0; 0.7	2.1; 1.0	.06	7.8; 2.4	7.1; 4.0	<.05
Non-Hodgkin lymphoma	69	30.9; 5.6	29.0; 6.2	<.01	2.0; 0.8	2.3; 1.1	<.001	11.8; 6.1	11.0; 7.1	.18
Leukemia, all ages	137	27.4; 5.8	26.3; 6.0	<.05	2.0; 0.8	2.6; 1.4	<.001	17.1; 7.7	16.4; 8.2	.15
Leukemia, 0–14	86	25.7; 5.1	24.6; 5.5	<.05	2.0; 0.8	2.7; 1.4	<.001	20.8; 6.4	21.1; 6.5	.46
Leukemia, 15–24	37	28.4; 4.8	26.9; 5.4	<.05	2.0; 0.8	2.6; 1.4	<.001	11.8; 5.0	11.5; 5.3	.67
Leukemia, 25–29	12	32.8; 2.6	32.0; 3.7	.88	1.5; 0.6	2.1; 0.7	.13	5.8; 1.5	6.9; 3.3	.21

Note: Age in years. FS = fertile survivor (i.e., women achieving at least 1 pregnancy after cancer diagnosis).

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FIGURE 2



Time distribution of live births in fertile survivors (women with cancer who achieved at least 1 pregnancy thereafter, green) and matched controls (orange). The graphs show the proportion of births achieved in each group by interval since diagnosis (years). The panels show data for all cancer diagnoses and the specific diagnoses of breast cancer, Hodgkin lymphoma, leukemia, and cervical and skin cancers, as indicated. The area under each curve has been normalized to 1.

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Impact of Cancer on the Number of Births Achieved

Family size (total number of live births achieved) was consistently different from controls, being lower overall (2.0 ± 0.8 live births vs. 2.3 ± 1.1 in controls, $P < .001$) and across several diagnoses (Table 1). Larger differences were noted in women with colorectal and connective/soft tissue cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and particularly leukemia, where the mean family size was 2.0 ± 0.8 vs. 2.6 ± 1.4 ($P < .001$) in controls (Table 1). In women with breast cancer, the greatest difference was in those diagnosed in the youngest age group ($25\text{--}29$ years, 1.5 ± 0.6 vs. 2.0 ± 0.6 , $P < .0001$), with smaller but still significant deficits in women diagnosed at later ages. In women with leukemia, the deficit was similar across age at diagnosis groups. Women with cervical cancer were the only diagnostic group with a similar family size to controls.

Impact on Interval to Last Pregnancy

To determine the index of reproductive lifespan, the time from diagnosis to last pregnancy in the fertile survivors was calculated (Table 1). Overall, this was very similar in cancer

survivors to controls, at 10.7 ± 6.4 vs. 10.9 ± 7.3 years ($P = .57$). In several diagnostic groups, time to last pregnancy was actually significantly longer after cancer. Thus, in women with breast cancer, it was 6.2 ± 2.8 vs. 5.3 ± 3.3 years in controls ($P < .001$), and in Hodgkin lymphoma, it was 11.1 ± 5.1 vs. 10.1 ± 5.8 years ($P < .001$), whereas in leukemia, which was the diagnostic group with the longest time to last pregnancy, it was not significantly different (17.1 ± 7.7 vs. 16.4 vs. 8.2 years, $P = .15$). In women with breast cancer, similarly, an increased time to last pregnancy was noted in the 2 older age at diagnosis groups (differences of 1.2 and 1.6 years, both $P < .001$), whereas the $25\text{--}29$ years old group showed a nonsignificant reduction in time to last pregnancy (6.1 ± 2.4 vs. 6.4 ± 2.9 years, $P = .97$). Women with Hodgkin lymphoma showed an increased time to last pregnancy in all 3 age at diagnosis groups (Table 1).

To explore this further, the distribution of live birth over time after diagnosis was investigated. Consistently, and in keeping with the aforementioned increase in the mean age at live birth, there was a shift to the right showing a reduced proportion of births during the initial years after diagnosis and an increase in the age at which the peak proportion of

TABLE 2

Age at live birth, family size, and interval to last pregnancy in female fertile breast cancer survivors known to have received chemotherapy and their matched controls.

Variable analysed	Known chemotherapy exposure	Controls	P value
N	90	263	
Age at LB (mean; SD)	36.1; 4.8	34.7; 4.3	< .01
Family size (mean; SD)	1.6; 0.8	2.2; 1.8	< .01
Interval to last pregnancy (mean; SD)	5.9; 2.6	5.3; 3.2	.03

Note: LB = live birth; SD = standard deviation.

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live births was achieved. This was generally followed by a period when proportionally more live births were achieved in the fertile cancer survivors than in controls. The extreme tail of this distribution provided an index of the time to end of fertility: overall, and in specific diagnoses, this difference was very small (Fig. 2), and in no diagnosis was there evidence of a clear reduction in fertile lifespan. This distribution is illustrated for breast, skin, and cervical cancers, Hodgkin lymphoma, and leukemia in Figure 2, as the more common diagnoses and representative of distributions of the range of age at diagnosis and overall impact on reproductive impact after diagnosis (Table 1).

Effect of Chemotherapy in Women with Breast Cancer

Although treatment details are not available, we identified fertile survivors with breast cancer who were known to have received chemotherapy and their matched controls. As chemotherapy for breast cancer is potentially gonadotoxic, we hypothesized that this group would be likely to show an impact of treatment on family size and time to last pregnancy. This group showed an increased mean age at live birth and reduced family size compared with controls (Table 2). As seen in the whole breast cancer fertile survivor group, the interval to last pregnancy was, however, significantly increased compared with that in controls (5.9 ± 2.6 vs. 5.3 ± 3.2 years, $P=.03$); thus, in this subgroup with known chemotherapy exposure, there was no evidence of a reduced fertile lifespan.

DISCUSSION

Studies assessing fertility in women after cancer treatment have shown clear evidence of loss of fertility in several women, across a wide range of diagnoses and treatments, and that is confirmed in this study (2, 33–36). With a longer follow-up time than in our previous analysis (4) allowing extended data collection for those more recently diagnosed, we report the live birth rates across diagnostic groups, with data confirming a reduced chance of live birth after a wide range of cancer diagnoses. The size- and population-based approaches used provide an accurate evaluation of that reduction for specific diagnoses. In addition to cancer diagnoses where there is broad consistency of evidence of an impact

on subsequent fertility (reviewed by van Dijk et al [37]), these data confirm that women with other diagnoses, specifically Hodgkin lymphoma and non-Hodgkin lymphoma; skin, colorectal, and thyroid cancers; and leukemia, do have a reduced likelihood of having a child after their cancer diagnosis.

Few studies have investigated remaining fertility in those women who were able to achieve a pregnancy after cancer treatment and whether the duration of fertility was affected (38). The present data show that women who were able to achieve pregnancy after cancer were slightly older at childbirth, by a mean of 1.5 years, and achieved fewer live births than matched controls. This pattern was found consistently across a range of different diagnoses, although fertile survivors of cervical, brain/CNS, and ovarian cancers had a similar mean age at childbirth and, for cervical cancer, similar family size. In women diagnosed in adulthood, this may in part reflect that pregnancy is not advised during and for a period after treatment, but it is significant to note that this delay was also noted in women diagnosed during childhood and early adulthood, where there is a long interval between diagnosis/treatment and the wish to conceive. This finding, therefore, illustrates the complexities of cancer survivorship, both medical and psychosocial, rather than a purely biologic impact on reproductive function.

The effect of age at diagnosis was analyzed for breast cancer, Hodgkin lymphoma, and leukemia because these are common cancers, with peak incidence in women in their later reproductive years, adolescence, and childhood, respectively. Women with breast cancer showed the greatest loss of family size when diagnosed at a younger age. Overall, only 8.6% of breast cancer survivors achieved a live birth after diagnosis, similar to the findings in a recent meta-analysis (39). For these younger women with breast cancer, these data illustrate the impact of the conflicts involved, including between family desires, ongoing endocrine treatment, and concerns over relapse. For both Hodgkin lymphoma and leukemia, there were reductions in family size for the 2 younger age groups (0–14 and 15–24 years at diagnosis), with no significant reduction in the 25–29 years age group. The older group was very small for leukemia; thus, this is likely to be a limitation of the power of the analysis, but this was not the case for this subgroup with Hodgkin lymphoma, which was substantially larger than the youngest age group. We are not aware of previous studies documenting in detail achieved family size across diagnoses.

A key novel finding of this study is that in women who are able to conceive after cancer, the time interval to last pregnancy is not reduced and, indeed, may be increased in some women. We hypothesized that if cancer treatments had adversely affected women's ovarian reserve, then we would expect to see a reduction in the interval to their last pregnancy. This was assessed in 2 ways, by the analysis of the interval between diagnosis and final pregnancy and analysis of the time distribution of all live births after diagnosis, focusing on later births achieved. These analyses, however, showed no reduction in the time to last pregnancy after cancer overall or in any specific diagnostic group. In fact, there was a longer interval to last pregnancy in women after cancer in several specific diagnostic groups, including breast, cervical,

skin, and brain/CNS cancers and Hodgkin lymphoma, and in women after breast cancer, the interval to last pregnancy was most increased in the older age group. This increase was also specifically confirmed in women with breast cancer known to have received chemotherapy. There is considerable evidence that cancer treatment adversely affects the ovarian reserve, as revealed by the measurement of AMH. This is noted across diagnoses and ages at treatment (29–31, 40, 41), and specifically, chemotherapy for breast cancer includes alkylating agents and taxanes which are well recognized to have significant gonadotoxicity (42–44). However, in women with remaining ovarian function after treatment, there is evidence for a plateau in the AMH levels, without a more rapid decline (31, 45). This is consistent with such women retaining their fertility for longer than would be expected for the degree of initial reduction in the AMH levels, with possible underlying compensatory changes in the rates of follicle activation. There are few data on the age of menopause in cancer patients, but an increased risk of POI has been reported in childhood cancer survivors and in adult survivors of Hodgkin lymphoma associated with radiotherapy to the ovaries and higher doses of alkylating agents (6, 11, 12). Intriguingly, low gonadotoxicity treatment for Hodgkin lymphoma has been suggested to result in an increase in nongrowing follicle density (46). These data suggest that those women who are able to conceive after breast and other cancers are able to start and increase their family size for a similar or even slightly longer time than the general population, albeit with a reduction in their attained family size. The potential contribution of assisted reproduction, including the use of oocyte donation, cannot be assessed from the data available to be analyzed here. While interpretation of our findings needs to acknowledge the complexity of both the biologic capacity for conception and the psychosocial issues surrounding that after cancer and its treatment, it provides significant information for women seeking to build their desired family size after cancer diagnosis.

The present data also do not directly address whether women experienced infertility or not. The reduced family size may in part reflect the decline in fertility with age as the mean age at childbirth was older. While some women may run out of time to complete their families, this appears unlikely to be a major contribution to reduced family size in those diagnosed at a young age, for example, with leukemia and Hodgkin lymphoma. The wide range of reasons that may influence women's choice to have a pregnancy or achieve a certain family size after cancer may be more important than biologic reproductive function for several survivors (24, 47). A recent survey indicated that 21% of young women cancer survivors (mean age, 31.8 years) were voluntarily childless (25), and this was independent of diagnosis and medical comorbidities. Others, however, have found a similar desire to have children among cancer survivors compared with their siblings (23). Women are less likely to be partnered/married after some cancer diagnoses (18, 19), although divorce rates are similar to population norms (19, 48).

A key strength of this analysis is the use of national databases to ensure complete ascertainment of a large

population of nulliparous at diagnosis cancer survivors and the outcomes of all subsequent pregnancies in the period of analysis, with carefully matched controls from the general population. This avoids selection bias and gives precision to the analysis. However, this approach also has limitations, notably the absence of data relating to treatment administered and the impact of choice on achieving pregnancy and live birth. In some diagnoses, the range of treatments may vary from high to low gonadotoxicity, which cannot be assessed here. For all but kidney cancers and leukemia, the proportional hazards assumption for Table 1 does not hold; thus, the HRs for most cancer types are likely to be large in early years of follow-up and then decline. There is also a necessarily limited follow-up period for women diagnosed in more recent years. These findings provide a basis for further studies into these aspects of postcancer fertility.

In conclusion, these data provide unbiased and comprehensive evidence on the impact of cancer and its treatment on the chance of childbirth after diagnosis in women who had not been previously pregnant. We provide novel evidence that in those women who do achieve a pregnancy after diagnosis, family size is reduced, and this is remarkably consistent across several diagnoses. There is a delay in childbirth after cancer, present even in those diagnosed as children. However, this analysis did not find that women who are able to achieve a pregnancy after cancer have a shortened time to their last pregnancy compared with age-matched controls. Interestingly, in women diagnosed with breast cancer at later ages and in those known to have received chemotherapy, the interval to their last pregnancy was increased compared with that in matched controls. This information will be of value in counseling girls and women, both at the time of cancer diagnosis and after treatment.

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REFERENCES

1. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2009;27:2677–85.
2. Chow EJ, Stratton KL, Leisenring WM, Oeffinger KC, Sklar CA, Donaldson SS, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol* 2016;17:567–76.
3. van Dorp W, Haupt R, Anderson RA, Mulder RL, van den Heuvel-Eibrink MM, van Dulmen-den Broeder E, et al. Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult cancer: a review. *J Clin Oncol* 2018;36:2169–80.
4. Anderson RA, Brewster DH, Wood R, Nowell S, Fischbacher C, Kelsey TW, et al. The impact of cancer on subsequent chance of pregnancy: a population-based analysis. *Hum Reprod* 2018;33:1281–90.

5. Morgan S, Anderson RA, Gourley C, Wallace WH, Spears N. How do chemotherapeutic agents damage the ovary? *Hum Reprod Update* 2012;18:525–35.
6. van der Kaaij MA, Heutte N, Meijnders P, Abeilard-Lemoisson E, Spina M, Moser EC, et al. Premature ovarian failure and fertility in long-term survivors of Hodgkin's lymphoma: a European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Etude des Lymphomes de l'Adulte Cohort Study. *J Clin Oncol* 2012;30:291–9.
7. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. *J Natl Cancer Inst Monogr* 2005;34:64–8.
8. Griffiths MJ, Winship AL, Hutt KJ. Do cancer therapies damage the uterus and compromise fertility? *Hum Reprod Update* 2020;26:161–73.
9. Jayasinghe YL, Wallace WHB, Anderson RA. Ovarian function, fertility and reproductive lifespan in cancer patients. *Expert Rev Endocrinol Metab* 2018;13:125–36.
10. Goldfarb SB, Turan V, Bedoschi G, Taylan E, Abdo N, Cigler T, et al. Impact of adjuvant chemotherapy or tamoxifen-alone on the ovarian reserve of young women with breast cancer. *Breast Cancer Res Treat* 2021;185:165–73.
11. Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, et al. Risk of premature menopause after treatment for Hodgkin's lymphoma. *J Natl Cancer Inst* 2014;106:dju207.
12. Sklar CA, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Natl Cancer Inst* 2006;98:890–6.
13. Meirou D, Biederman H, Anderson RA, Wallace WHB. Toxicity of chemotherapy and radiation on female reproduction. *Clin Obstet Gynecol* 2010;53:727–39.
14. van der Kooi ALF, Kelsey TW, van den Heuvel-Eibrink MM, Laven JSE, Wallace WHB, Anderson RA. Perinatal complications in female survivors of cancer: a systematic review and meta-analysis. *Eur J Cancer* 2019;111:126–37.
15. Signorello LB, Cohen SS, Bosetti C, Stovall M, Kasper CE, Weathers RE, et al. Female survivors of childhood cancer: preterm birth and low birth weight among their children. *J Natl Cancer Inst* 2006;98:1453–61.
16. Rozen G, Rogers P, Chander S, Anderson R, McNally O, Umstad M, et al. Clinical summary guide: reproduction in women with previous abdominopelvic radiotherapy or total body irradiation. *Hum Reprod Open* 2020;2020:hoaa045.
17. Hartnett KP, Mertens AC, Kramer MR, Lash TL, Spencer JB, Ward KC, et al. Pregnancy after cancer: does timing of conception affect infant health? *Cancer* 2018;124:4401–7.
18. Frobisher C, Lancashire ER, Winter DL, Jenkinson HC, Hawkins MM. Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. *Int J Cancer* 2007;121:846–55.
19. Janson C, Leisenring W, Cox C, Termuhlen AM, Mertens AC, Whitton JA, et al. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev* 2009;18:2626–35.
20. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. *J Clin Oncol* 1998;16:501–14.
21. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104:386–405.
22. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355:1572–82.
23. van Dijk M, van den Berg MH, Overbeek A, Lambalk CB, van den Heuvel-Eibrink MM, Tissing WJ, et al. Reproductive intentions and use of reproductive health care among female survivors of childhood cancer. *Hum Reprod* 2018;33:1167–74.
24. Schover LR. Motivation for parenthood after cancer: a review. *J Natl Cancer Inst Monogr* 2005;2–5.
25. Lam CM, Shliakhtsava K, Stark SS, Medica ACO, Pinson KA, Whitcomb BW, et al. Reproductive intentions in childless female adolescent and young adult cancer survivors. *Fertil Steril* 2020;113:392–9.
26. Peate M, Meiser B, Hickey M, Friedlander M. The fertility-related concerns, needs and preferences of younger women with breast cancer: a systematic review. *Breast Cancer Res Treat* 2009;116:215–23.
27. Letourneau JM, Ebbel EE, Katz PP, Oktay KH, McCulloch CE, Ai WZ, et al. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. *Cancer* 2012;118:1933–9.
28. Barton SE, Najita JS, Ginsburg ES, Leisenring WM, Stovall M, Weathers RE, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol* 2013;14:873–81.
29. Anderson RA, Themmen APN, Al-Qahtani A, Groome NP, Cameron DA. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. *Hum Reprod* 2006;21:2583–92.
30. Thomas-Teinturier C, Allodji RS, Svetlova E, Frey MA, Oberlin O, Millischer AE, et al. Ovarian reserve after treatment with alkylating agents during childhood. *Hum Reprod* 2015;30:1437–46.
31. Su HI, Kwan B, Whitcomb BW, Shliakhtsava K, Dietz A, Stark SS, et al. Modeling variation in the reproductive lifespan of female adolescent and young adult cancer survivors using AMH. *J Clin Endocrinol Metab* 2020;105:2740–51.
32. Carstairs V, Morris R. Deprivation and health in Scotland. *Health Bull (Edinb)* 1990;48:162–75.
33. Reulen RC, Zeegers MP, Wallace WH, Frobisher C, Taylor AJ, Lancashire ER, et al. Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev* 2009;18:2239–47.
34. Reulen RC, Bright CJ, Winter DL, Fidler MM, Wong K, Guha J, et al. Pregnancy and labor complications in female survivors of childhood cancer: the British Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2017;109:djx056.
35. Green DM, Sklar CA, Boice JD Jr, Mulvihill JJ, Whitton JA, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009;27:2374–81.
36. van Dijk M, van Leeuwen FE, Overbeek A, Lambalk CB, van den Heuvel-Eibrink MM, van Dorp W, et al. Pregnancy, time to pregnancy and obstetric outcomes among female childhood cancer survivors: results of the DCOG LATER-VEVO study. *J Cancer Res Clin Oncol* 2020;146:1451–62.
37. Busnelli A, Vitagliano A, Mensi L, Acerboni S, Bulfoni A, Filippi F, et al. Fertility in female cancer survivors: a systematic review and meta-analysis. *Reprod Biomed Online* 2020;41:96–112.
38. Madanat LM, Malila N, Dyba T, Hakulinen T, Sankila R, Boice JD Jr, et al. Probability of parenthood after early onset cancer: a population-based study. *Int J Cancer* 2008;123:2891–8.
39. Lambertini M, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, et al. Pregnancy after breast cancer: a systematic review and meta-analysis. *J Clin Oncol* 2021;39:3293–305.
40. Lie Fong S, Lugtenburg PJ, Schipper I, Themmen AP, de Jong FH, Sonneveld P, et al. Anti-Müllerian hormone as a marker of ovarian function in women after chemotherapy and radiotherapy for haematological malignancies. *Hum Reprod* 2008;23:674–8.
41. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. *Fertil Steril* 2012;97:134–40.e1.
42. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013;31:2500–10.
43. ESHRE Guideline Group on Female Fertility Preservation, Anderson RA, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, et al. ESHRE guideline: female fertility preservation. *Hum Reprod Open* 2020;2020:hoaa052.
44. Lambertini M, Peccatori FA, Demeestere I, Amant F, Wyns C, Stukenborg JB, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2020;31:1664–78.

45. Cameron K, Sammel MD, Prewitt M, Gracia C. Differential rates of change in measures of ovarian reserve in young cancer survivors across the reproductive lifespan. *J Clin Endocrinol Metab* 2019;104:1813–22.
46. McLaughlin M, Kelsey TW, Wallace WH, Anderson RA, Telfer EE. Non-growing follicle density is increased following adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy in the adult human ovary. *Hum Reprod* 2017;32:165–74.
47. Benedict C, Hahn AL, McCready A, Kelvin JF, Diefenbach M, Ford JS. Toward a theoretical understanding of young female cancer survivors' decision-making about family-building post-treatment. *Support Care Cancer* 2020; 28:4857–67.
48. Frobisher C, Lancashire ER, Winter DL, Taylor AJ, Reulen RC, Hawkins MM, et al. Long-term population-based divorce rates among adult survivors of childhood cancer in Britain. *Pediatr Blood Cancer* 2010;54:116–22.

Tamaño de la familia y duración de la fertilidad en mujeres sobrevivientes de cáncer: un análisis poblacional.

Objetivo: Evaluar el tamaño de la familia y el tiempo para lograr embarazo en mujeres que permanecieron fértiles después del cáncer.

Diseño: Análisis poblacional.

Ámbito: Bases de datos nacionales.

Paciente(s): Todas las mujeres diagnosticadas con cáncer antes de los 40 años en Escocia, 1981–2012 ($n = 10,267$) sin embarazo previo; cada uno fue emparejada con 3 controles de población.

Intervención(es): Ninguna.

Medida(s) de resultado principal: El número y el momento de embarazo y nacido vivo después del diagnóstico de cáncer, hasta 2018.

Resultado(s): en 10 267 sobrevivientes de cáncer, la razón de riesgo para un nacimiento vivo posterior fue 0,56 (intervalo de confianza del 95 %, 0,53 –0,58) en general. En las mujeres que lograron un embarazo posterior, la edad en el momento del nacido vivo aumentó (media DE, $31,2 \pm 5,5$ frente a $29,7 \pm 6,1$ en los controles) y el tamaño de la familia fue menor ($2,0 \pm 0,8$ frente a $2,3 \pm 1,1$ nacidos vivos). Estos hallazgos fueron consistentes a través de varios diagnósticos. El intervalo desde el diagnóstico hasta el último embarazo fue similar al de los controles ($10,7 + 6,4$ frente a $10,9 + 7,3$ años) o aumentó significativamente, por ejemplo, después del cáncer de mama ($6,2 + 2,8$ frente a $5,3 + 3,3$ años) y el linfoma de Hodgkin ($11,1 + 5,1$ frente a $10,1 + 5,8$ años).

Conclusión(es): Estos datos muestran la probabilidad reducida de nacido vivo después del cáncer. Las mujeres que posteriormente concibieron lograron un tamaño de familia más pequeño que los controles emparejados, pero el período de tiempo después del diagnóstico de cáncer en el que ocurrieron los embarazos fue similar o, de hecho, aumentó. Por lo tanto, no encontramos pruebas de que las mujeres que pudieron lograr un embarazo después del cáncer tuvieran un período de tiempo más corto para tener embarazos.