RBMO

REVIEW

Fertility in female cancer survivors: a systematic review and meta-analysis

BIOGRAPHY

Andrea Busnelli graduated in Obstetrics and Gynaecology in 2018. He is currently a PhD student in Community Health at the University of Milan, Italy. His activity and research interest cover the whole field of reproductive medicine.

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KEY MESSAGE

Women with a history of bone, breast, brain or kidney cancer have reduced chances of childbirth compared with unaffected controls. On the contrary, thyroid cancer, melanoma and Non-Hodgkin's lymphoma survivors can be reassured about their reproductive prognosis.

ABSTRACT

Data on the effects of cancer treatments on fertility are conflicting. The aim of the present systematic review and meta-analysis was to determine the chances of childbirth in women survivors of different types of cancer. *PubMed*, *MEDLINE*, *Embase* and *Scopus* were searched from database inception to 17 July 2019 for published cohort, case-control and cross-sectional studies that investigated the reproductive chances in women survivors of different cancer types. Random-effects models were used to pool childbirth hazard ratios, relative risks, rate ratios and odds ratios, and 95% confidence intervals were estimated; 18 eligible studies were identified. Childbirth chances were significantly reduced in women with a history of bone cancer (HR 0.86, 95% CI 0.77 to 0.97; I^2 = 0%; P = 0.02 (two studies); RaR 0.76, 95% CI 0.61 to 0.95; I^2 = 69%; P = 0.01 (two studies); breast cancer (HR 0.74, 95% CI 0.61 to 0.90 (one study); RaR 0.51, 95% CI 0.47 to 0.57; I^2 = 0%; P < 0.00001 (two studies); brain cancer (HR 0.61, 95% CI 0.51 to 0.72; I^2 = 14%; P < 0.00001 (three studies); RR 0.62, 95% CI 0.42 to 0.91 (one study); RaR 0.44, 95% CI 0.33 to 0.60; I^2 = 95%; P < 0.00001 (four studies); OR 0.49, 95% CI 0.40 to 0.60 (one study); and kidney cancer (RR 0.66, 95% CI 0.43 to 0.98 (one study); RaR 0.69, 95% CI 0.61 to 0.78 (one study). Reproductive chances in women survivors of non-Hodgkin's lymphoma, melanoma and thyroid cancer were unaffected. Women with a history of bone, breast, brain or kidney cancer have reduced chances of childbirth. Thyroid cancer, melanoma and non-Hodgkin's lymphoma survivors can be reassured.

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KEYWORDS

Cancer
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Female fertility
Fertility preservation

INTRODUCTION

The significant improvement in the effectiveness of oncological treatment has led to an increase in overall survival rates of children, adolescents and young adults with cancer, which now exceed 80% at 5 years in several high-income countries (*Barr et al., 2016*; *Chow et al., 2016*). In cancer survivors, one of the strongest predictors of emotional satisfaction is maintaining fertility (*Knopman et al., 2010*). The fear of long-term harm on reproductive health, therefore, either as a result of cancer itself or of gonadotoxic therapies, is an issue of utmost relevance.

In women, cancer treatments could irrevocably damage the non-renewable pool of primordial follicles through direct and indirect mechanisms causing a decrease in the so-called ovarian reserve (*van Dorp et al., 2018*). *Oktem and Oktay (2007)*, using a xenograft model, showed that the injection of a single dose of cyclophosphamide was able to induce oocyte and granulose cell damage and follicle loss. Not surprisingly, compared with siblings, cancer survivors have an increased risk of non-surgical premature ovarian insufficiency (POI), with a cumulative incidence of about 8–10% by the age of 40 years (*Sklar et al., 2006*; *van Dorp et al., 2016*; *Chemaitilly et al., 2017*; *Levine et al., 2018*).

To date, the mechanisms of chemotherapy-related injury to ovarian reserve have only partially been elucidated (*Morgan et al., 2012*; *Wallace et al., 2016*; *Oktem et al., 2018*; *Somigliana et al., 2019*). They include an accelerated recruitment of primordial follicles ('burn-out' effect) (*Kalich-Philosoph et al., 2013*), an impairment of ovarian vascularization (*Meirow et al., 2007*) and a direct damage to DNA of oocytes and granulosa cells (*Morgan et al., 2012*). The magnitude of the damage depends on the specific agents used (*Somigliana et al., 2019*). A large body of evidence supports that alkylating agents cause a dose-dependent damage to ovarian reserve (*Overbeek et al., 2017*). At present, however, no definite threshold dose of alkylating agents has been demonstrated to be safe (*van Dorp et al., 2016*). The ovaries may also be damaged by radiation therapy if they are within the treatment field, e.g. total body, abdominal, pelvic or spinal irradiation. The magnitude of the effect is related to dose, fractionation schedule and age at the time of treatment. The oocyte is extremely sensitive to radiation, with 2 Grays representing the estimated dose required to destroy 50% of primordial follicles (*Wallace et al., 2005*; *van Dorp et al., 2016*). On a rational basis, one could suggest a possible mechanism of ovarian damage by molecular-target agents, such as monoclonal antibodies and kinase inhibitors (*van Dorp et al., 2016*). Nevertheless, evidence is scant and definitive conclusions cannot be drawn.

For many years, the decrease in the number of primordial follicles was considered linearly related to the decrease of the reproductive potential, and the biomarkers of ovarian reserve were used as a sort of fertility test (*Steiner et al., 2017*). Accordingly, fertility-preservation techniques, including cryopreservation of oocytes, embryos, or, more experimentally, ovarian tissue, have spread on a large scale and are commonly proposed to patients before treatment. Recent substantial evidence, however, has denied a relationship between ovarian reserve and fertility (*Santoro, 2017*; *Steiner et al., 2017*). Only women with compromised ovarian reserve causing anovulatory cycles or POI face infertility (*Somigliana et al., 2019*). The damage produced by oncologic therapies on fertility, therefore, are no longer obvious.

Several epidemiological studies have investigated the effects of cancer treatments on fertility considering the chances of pregnancy and childbirth as a main outcome (*Hodgson et al., 2007*; *Syse et al., 2007*; *Madanat et al., 2008*; *Cvancarova et al., 2009*; *Reulen et al., 2009*; *Pivetta et al., 2011*; *Stensheim et al., 2011*; *van der Kaaij et al., 2012*; *Baxter et al., 2013*; *Hartman et al., 2013*; *Brämswig et al., 2015*; *Chow et al., 2016*; *Armuand et al., 2017*; *Anderson et al., 2018a*; *2018b*; *Thouvenin-Doulet et al., 2018*). Conflicting data, however, have been reported for the different cancer sites, and a global interpretation of the results is not possible owing to the different weight of the individual studies. In the absence of a data synthesis, it is therefore not possible at present to provide accurate counselling for patients on fertility damage of oncologic treatments and to share decisions about fertility-preservation options.

Against that background, the aim of this systematic review and meta-analysis was, therefore, to determine the chances of female survivors of different types of cancer to fulfil their reproductive desire after treatment.

MATERIALS AND METHODS

Search strategy and selection criteria

This literature overview was reported according to the PRISMA guidelines for systematic reviews (*Moher et al., 2009*; *Deeks et al., 2018*), and the meta-analysis was conducted according to the MOOSE guidelines (*Stroup et al., 2000*). Since published de-identified data were used, this study was exempt from institutional review board approval. The study is registered with PROSPERO, number CRD42019119786.

The present systematic review and meta-analysis was restricted to published research articles that investigated the chances of pregnancy or live birth in women who underwent treatment for different types of cancer. *PubMed*, *MEDLINE*, *Embase* and *Scopus* were systematically searched from database inception to 17 July 2019. Searches were limited to studies in humans and were conducted using the following terms: 'cancer' OR 'leukaemia' OR 'breast cancer' OR 'Hodgkin's lymphoma' OR 'non-Hodgkin lymphoma' OR 'central nervous system (CNS) cancer' OR 'soft tissue cancer' OR 'liver cancer' OR 'digestive tract cancer' OR 'kidney cancer' OR 'thyroid cancer' AND 'fertility' OR 'pregnancy' OR 'live birth' OR 'childbirth'.

Published cohort (retrospective or prospective), case-control and cross-sectional studies were eligible for inclusion. All pertinent articles were retrieved, and the relative reference lists were systematically reviewed to identify further reports that could be included in the meta-analysis. Moreover, review articles and meta-analysis published on fertility after cancer in the same time span were consulted, and their reference lists searched for potential additional studies. No attempt was made to identify unpublished studies.

Two authors (A Busnelli and L Mensi) independently conducted an initial screening of title and abstract of all articles to exclude citations deemed irrelevant by both the observers. In

case of doubt, studies were discussed in consensus meetings with two other authors (S Acerboni and A Bulfoni). Studies were excluded if crude or adjusted effect estimates with corresponding 95% confidence intervals or results allowing their calculation were not reported; and control population was not clearly defined. Case reports, letters to the editor and reviews were also excluded.

Reports were classified according to the study design into case-control studies, prospective and retrospective cohort studies. The quality of case-control and cohort studies was evaluated by means of the Newcastle–Ottawa scale, a validated tool for assessing the quality of observational and non-randomized studies (*Wells et al., 2000*). The scale uses a score system based on three major criteria: selection of participants, comparability of study groups and assessment of exposure. The quality checklist includes eight items with a score of either 0 or 1 for each item except for 'comparability of cohorts', where a score of 0, 1 or 2 can be awarded. Therefore, the quantitative appraisal of the overall quality of each study ranged from 0 to 9. Only studies with a rating of 7 or higher were considered high quality and included.

Data analysis

Three authors (A Busnelli, A Vitagliano and F Filippi) independently evaluated all articles and extrapolated data on standardized forms. A final abstraction form was compiled from the three evaluation forms, after resolution of all the discrepancies among reviewers through discussion. Study design, the considered cancer registry, cancer type, women's age, diagnosis and treatment period, investigated outcomes, i.e. pregnancy or live birth achievement, reported effect estimates, follow-up length and the sub-analysis criteria were recorded (TABLE 1).

From each selected article, the information on the rate of women who achieved at least one pregnancy or one live birth was extracted separately for cancer survivors and controls. If spurious data were not reported, the effect estimates were extracted, i.e. hazard ratio (HR), relative risk (RR), rate ratio (RaR) and odds ratio (OR) (*Deeks et al., 2018*).

The calculated and extracted effect estimates were combined in meta-analyses using the generic inverse variance method, with the *DerSimonian and Laird random-effects model (1986)* (*DerSimonian and Kacker, 2007*; *Anderson et al., 2018b*). The effect estimates were combined as they were extrapolated from the studies and no attempts were made to convert one effect estimate into another. To compare data from different studies, definitions and cut-offs of risk factors were harmonized between studies whenever possible.

To minimize heterogeneity, studies were a-priori included in separate meta-analyses based on a default distinction between cancer subtypes, i.e. bone cancer (osteosarcoma and Ewing sarcoma), soft tissue cancer, breast cancer, brain and central nervous system cancer, leukaemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, thyroid cancer, kidney cancer, skin cancer, digestive tract cancer, liver cancer, retinoblastoma and neuroblastoma. All the results of the individual studies and the overall estimate from the meta-analyses were graphically displayed in forest plots.

The inconsistency of studies' results was measured using Cochrane Q and the I^2 statistics (*Higgins et al., 2003*). Negative values of I^2 are set equal to 0 so that I^2 lies between 0 and 100%. According to the *Cochrane Handbook for Systematic Reviews of Intervention*, an I^2 value of 0% indicates no observed heterogeneity, whereas I^2 values from 30–60% may represent moderate heterogeneity, I^2 values from 50–90% may indicate substantial heterogeneity and I^2 values from 75–100% express considerable heterogeneity (*Higgins et al., 2003*; *Deeks et al., 2018*; *Busnelli et al., 2019*).

To establish the effect of cancer and its treatment on fertility regardless of the well-known effect of age on the probability of ovarian failure, whenever possible, a sub-analysis pooling results only from studies that included women under the age of 21 years was conducted.

Some investigators have conducted sub-analyses based on other potentially relevant factors, i.e. period of diagnosis, chemotherapeutic agents used and parity status. The results of these sub-analyses could not be meta-analysed owing to the discrepancy of the cut-offs considered by the various investigators, but they were used to interpret the studies' findings.

Role of funding source

No source of funding was available for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

The process of search strategy and study is presented in FIGURE 1. The literature search yielded 645 studies. Fifty duplicates were removed. After review of the titles and abstracts, 41 studies were identified as potentially eligible for inclusion. After full review, four systematic reviews were excluded (*Levine et al., 2015*; *Lopategui et al., 2017*; *van Dorp et al., 2016*; *Burkart et al., 2019*), one publication because data could not be extracted (*Zynda et al., 2012*), 15 original studies because of the absence of a healthy control group (*Carter et al., 2006*; *Kiserud et al., 2007*; *Sudour et al., 2010*; *Speiser et al., 2011*; *Hamre et al., 2012*; *Hansen et al., 2013*; *Reinmuth et al., 2013*; *Shepherd et al., 2006*; *Greaves et al., 2014*; *Naessén et al., 2014*; *Hoshi et al., 2015*; *Wu et al., 2015*; *Yonemoto et al., 2016*; *Shandley et al., 2017*; *Nichols et al., 2018*) and three additional studies because they generically referred to reproductive prognosis after cancer without splitting data for cancer subtypes (*Green et al., 2009*; *Reulen et al., 2009*; *Dillon et al., 2013*).

Data on effect estimates (HR, RR, RaR, and OR) of pregnancy and live birth were extracted from the remaining 18 articles, all of which were published in peer-reviewed journals between 2004 and 2018 (*Byrne et al., 2004*; *Hodgson et al., 2007*; *Syse et al., 2007*; *Madanat et al., 2008*; *Cvancarova et al., 2009*; *Reulen et al., 2009*; *Pivetta et al., 2011*; *Stensheim et al., 2011*; *van der Kaaij et al., 2012*; *Baxter et al., 2013*; *Dillon et al., 2013*; *Hartman et al., 2013*; *Brämswig et al., 2015*; *Chow et al., 2016*; *Armuand et al., 2017*; *Anderson et al., 2018a*; *2018b*; *Thouvenin-Doulet et al., 2018*). Details of the characteristics of the included studies are presented in TABLE 1.

Fertility after bone cancer

Two of the included studies investigated whether a history of treated bone cancer may affect the chances of pregnancy (*Chow et al., 2016*; *Anderson et al., 2018a*). Pooling of results did not show a significant effect of this anamnestic

TABLE 1 CHARACTERISTICS OF THE INCLUDED STUDIES

Study	Study design	Cancer types[a]	Chemotherapy/ radiotherapy protocols	Womens' age s	Diagnosis period	Inves- tigated outcome	Risk estimate	Follow-up length	Sub-ananlysis criteria	Newcas- tle– Ottawa score
Byrne et al. (2004)	Cases were females treated on protocols of the Children's Cancer Group. Controls were the survivors' siblings.	Leukaemia.	Protocols 101, 105, 106,123,139,141, 141A, 162, 162A, 163, 903, 9998 of the Children's Cancer Group.	Childhood.	1970–1987	Pregnancy.	RR	NR	NA	7
Syse et al. (2007)	Cases were extracted from the Cancer Registry of Norway. Effect estimate was calculated using data from the general population.	Ovary; brain; cervix uteri; leukaemia; breast; bone; non-Hodgkin's lymphoma; Hodgkin's lymphoma; eye; endocrine; skin.	NR	17–44 years.	1965–2001	Childbirth.	OR	To 31 December 2001.	Parity status; years since diagnosis.	7
Hodgson et al. (2007)	Cases were females treated at the Princess Margaret Hospital for Hodgkin's lymphoma. Controls were friends or siblings of cases.	Hodgkin's lymphoma.	ABVD[b]	<45 years at the time of treatment.	1983–1999	Pregnancy..	HR	NR	NA	7
Madanat et al. (2008)	Finnish Cancer Registry records linked to the Population Register Centre data.	Leukaemia; Hodgkin's lymphoma; non-Hodgkin's lymphoma; CNS; SNS; kidney; thyroid; breast; bone; soft tissue; germ cell; trophoblastic and other gonadal tumours.	NR	0–34 years at diagnosis.	1953–2004	Childbirth.	RR	NR	Age at diagnosis.	7
Cvancarova et al. (2009)	Linking of the Norwegian Radium Hospital registry and of the Cancer Registry of Norway. Each patient was birth year-matched with five randomly selected individuals from the Norwegian Population Registry	Malignant lymphoma/ leukaemia; gynaecologic cancer; breast cancer.	See **Table 1** of Cvancarova et al.	15–44 years at diagnosis.	1971–1997	Pregnancy.	HR	10 years	Parity status; diagnosis before 1988 or 1988 and after.	8
Reulen et al. (2009)	Data extracted from records of the National Registry of Childhood Tumours. Observed number of live births was compared with that expected based on the general population of England and Wales.	Hodgkin's lymphoma; CNS; non- heritable retinoblastoma; heritable retinoblastoma.	Chemotherapy and abdominal or brain irradiation (specific protocols NR)	Childhood.	1940–1991	Childbirth.	RaR	NR	Radiotherapy site; maternal age.	7
Pivetta et al. (2011)	Cases were identified using the Italian Off-Therapy Registry. The fertility rates in the cohort of cases were compared with those of the general population, provided by the Italian Institute of Statistics.	Acute lymphoblastic leukaemia; acute non-lymphoblastic leukaemia; Hodgkin's lymphoma; non-Hodgkin's lymphoma; CNS.	NR	<15 years at diagnosis.	1960–1998	Childbirth.	RaR	To 30 October 2006	Age at diagnosis; period of diagnosis.	7
Stensheim et al. (2011)	Information on cases extracted from The Cancer Registry of Norway (CRN) . Controls were five age- and sex-matched individuals per patient who were selected from the data compiled by Office of the National Registrar.	Breast; cervix uteri; ovary; melanoma; brain; thyroid; non-Hodgkin's lymphoma; Hodgkin's lymphoma; leukaemia.	NR	16–45 years at diagnosis.	1967–2004	Pregnancy.	HR	NR	Treatment time period.	7
van der Kaaij et al. (2012)	Cases were extracted from nine consecutive randomized trials conducted between 1964 and 2004. Controls were matched to case by sex, country of residence, education level, and year of birth.	Hodgkin's lymphoma.	Treatment with or without alkylating agents and radiation site reported in **Table 1** of van der Kaaij et al.	>15 years.	1964–2004	Childbirth.	OR; RR	NR	Age at start of treatment; parity status; period of treatment; chemotherapy agent; radiation site; education level.	8
Hartman et al. (2013)	Linking of Swedish Multi-Generation Register and Swedish Cancer Register. Comparison was background population matched according to attained age and year of birth.	Breast; ovary; brain; eye; hematopoietic; bone; digestive tract; head and neck; thoracic; skin; reproductive (minus ovary) .	NR	16–45 years.	1958–2001	Childbirth.	RaR	Until age 45 years	Year of diagnosis; attained age; time since diagnosis; socioeconomic status; parity status.	8

Table 1 – (continued)

Study	Study design	Cancer types[a]	Chemotherapy/ radiotherapy protocols	Womens' age s	Diagnosis period	Inves-tigated outcome	Risk estimate	Follow-up length	Sub-ananlysis criteria	Newcas-tle– Ottawa score
Baxter et al. (2013)	Retrospective, population-based cohort study using the Ontario Cancer Registry linked to administrative data sets. Women diagnosed with non-gynaecologic malignancies age matched to 5 randomly selected cancer-free women.	Brain; breast; Hodgkin's lymphoma; non-Hodgkin's lymphoma; thyroid; melanoma.	NR	20–34 years.	1992–1999	Childbirth..	HR	13 years	Parity status.	7
Dillon et al. (2013)	Survivors recruited from the Children's Hospital of Philadelphia Survivorship Program and the Transition Program at Penn's Living Well After Cancer Survivorship Program. Unexposed controls of similar age to cancer survivors were identified through health practices affiliated with Penn and advertising.	Not specified.	NR	15–39 years.	2006–2010	Pregnancy.	RR	25 months	NA	7
Brämswig et al. (2015)	Prospective longitudinal study comparing parenthood in female Hodgkin's lymphoma survivors enrolled in five Deutsche Arbeitsgemeinschaft für Leukämieforschung Hodgkin's disease studies with parenthood in a German female population control group.	Hodgkin's lymphoma.	See **Table 1** of Brämswig et al.	<18 years at diagnosis.	1978–1995	Childbirth.	RR; HR	15 years	Age at diagnosis; laparotomy; therapy group; cycles of procarbazine; alkylating agent dose score; treatment protocol; radiation field.	8
Chow et al. (2016)	Cohort study from 27 Institutions in the USA and Canada (Childhood Cancer Survivor Study) . Controls were siblings.	Leukaemia; CNS; Hodgkin's lymphoma; non-Hodgkin's lymphoma; kidney; neuroblastoma; soft-tissue sarcoma; bone.	See **Table 1**, **Table 2** and **Table 3** of Chow et al.	<21 years old at diagnosis.	1970–1999	Pregnancy and childbirth.	HR	8 years	Age at follow-up; chemotherapy drug and dose; exposure to alkylating drugs.	8
Armuand et al. (2017)	Cases were identified using the Swedish Patient Register. Controls were two age- and sex-matched individuals per case born on the same day identified using the Total Population Register.	Leukaemia; CNS; Hodgkin's lymphoma; thyroid; soft tissue; urinary tract; eye.	NR	<21 years old at diagnosis.	Women born 1973–1977	Childbirth.	HR	To 31 December 2012	Childhood or adolescent diagnosis; diagnosis before 1988 or after	8
Anderson et al. (2018a)	Scottish Cancer Registry data linked to national general and maternity hospital discharge records to ascertain subsequent pregnancies.	Colorectal; liver; bone; skin; soft tissue; breast; cervix uteri; ovary; kidney; eye; CNS; thyroid, Hodgkin's lymphoma; non-Hodgkin's lymphoma; leukaemia.	See **Table 2** of Anderson et al.' for chemo/ radiotherapy status (specific protocol NR)	0–39 years.	1981–2012	Pregnancy.	RaR; HR	To 31 December 2014	Women age at cancer diagnosis; deprivation category at cancer diagnosis; period of cancer onset; chemotherapy; radiotherapy	8
Thouvenin-Doulet et al. (2018)	Cases extracted from the Euro2K cohort and from the Childhood Cancer Registry of the Rhône-Alpes Region (ARCERRA) cohort. The number of children expected was estimated by applying the fecundity rates by age in the French reference population.	Lymphoma; CNS; SNS; retinoblastoma; kidney; bone; soft tissue; germ cells.	NR	<15 years old at diagnosis.	1948–1992	Childbirth.	RaR	To 2010	Age at questionnaire completion; self-reported late effects	7
Anderson et al. (2018b)	North Carolina Central Cancer Registry records linked to North Carolina birth certificate files.	Breast.	See **Table 1** of Anderson et al. for chemo/ radiotherapy status (specific protocol NR)	15–39 years.	2000–2013	Childbirth.	RaR	5–10 years	NA	7

CNS, central nervous system; HR, hazard ratio; NA, not applicable; NR, not reported OR, odds ratio; RaR, rate ratio; RR, risk ratio; SNS, sympathetic nervous system.

[a] Only types with quantitative data available are listed.

[b] Doxorubicin, bleomycin, vinblastine, dacarbazine chemotherapy without pelvic radiation therapy.

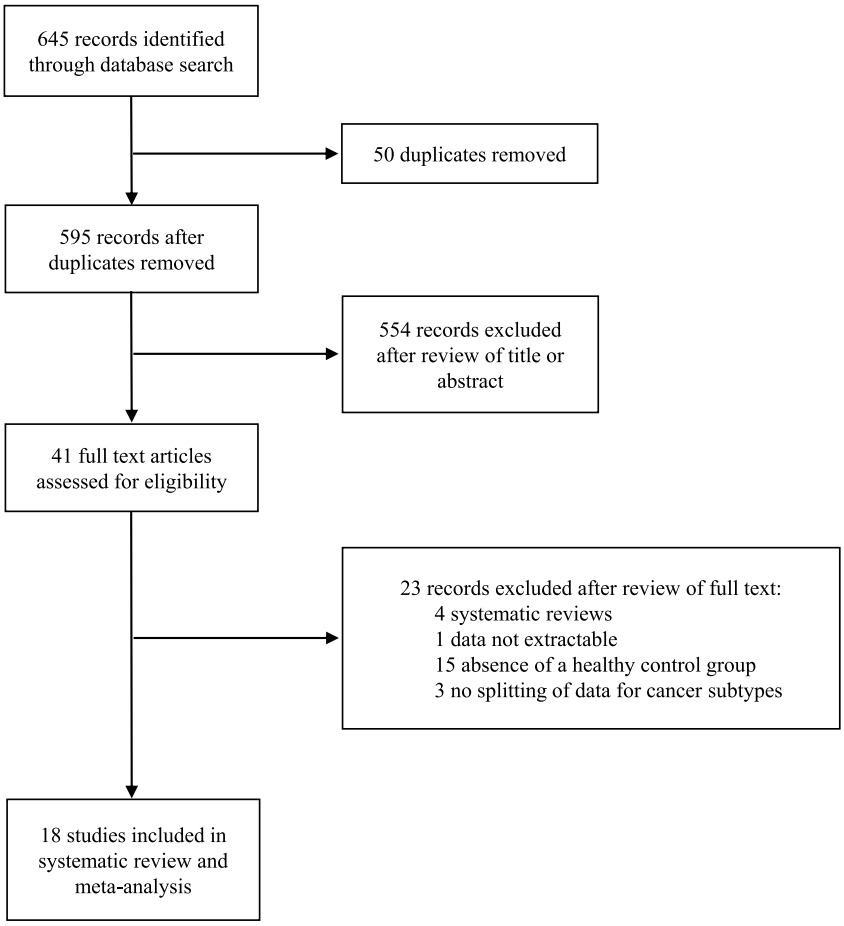


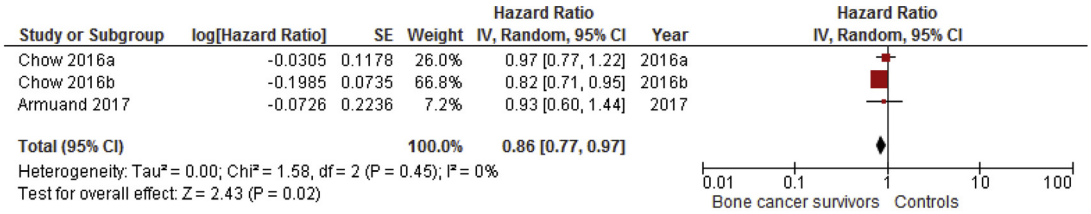
FIGURE 1 Study selection.

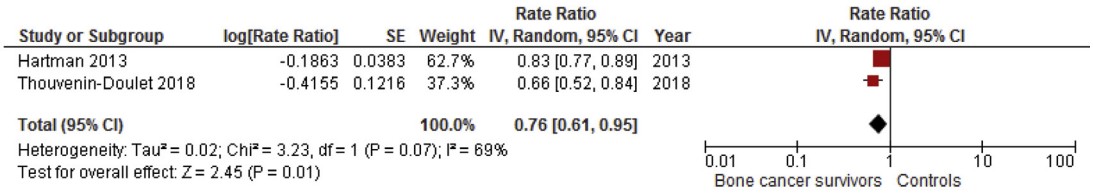
data on the rate of women who achieved at least one pregnancy: HR 0.66, 95% CI 0.37 to 1.16; I^2 = 96%; P = 0.14. Differently, the meta-analysis of studies investigating the chances of live birth agree in showing a negative effect of a history of bone cancer: HR 0.86, 95% CI 0.77 to 0.97; I^2 = 0%; P = 0.02 (*Chow et al., 2016*; *Armuand et al., 2017*); and RaR 0.76, 95% CI 0.61 to 0.95; I^2 = 69%; P = 0.01 (*Hartman et al., 2013*; *Thouvenin-Doulet et al., 2018*) (FIGURE 2A). The effect in the study by *Madanat et al. (2008)* failed to reach statistical significance: RR 0.65, 95% CI 0.43 to 1.00; I^2 = 81%; P = 0.05. The harmful effect was also confirmed after limiting the analysis to studies that included only patients under the age of 21 years: HR 0.86, 95% CI 0.77 to 0.97; I^2 = 0%; P = 0.02 (*Chow et al., 2016*; *Armuand et al., 2017*); and RaR 0.66, 95% CI 0.52 to 0.84; I^2 = 69%; P = 0.0006 (*Thouvenin-Doulet et al., 2018*); RR 0.50, 95% CI 0.33 to 0.76; I^2 = 71%; P = 0.001 (*Madanat et al., 2008*). In a sub-analysis, *Chow et al. (2016)* calculated hazard ratios for pregnancy and live birth separately for patients treated with and without alkylating agents, showing a detrimental effect of the exposure to alkylating agents on both outcomes. *Armuand et al. (2017)* reported almost similar hazard ratios of live birth in women diagnosed before 1988 and those diagnosed in 1988 or after. They also stratified results by age at diagnosis showing the absence of any effect in women who had be en diagnosed during childhood (<14 years). *Syse et al. (2007)* reported a reduced probability of first born in the first 5 years after the diagnosis and of higher order birth after more than 5 years from diagnosis.

Fertility after soft tissue cancer

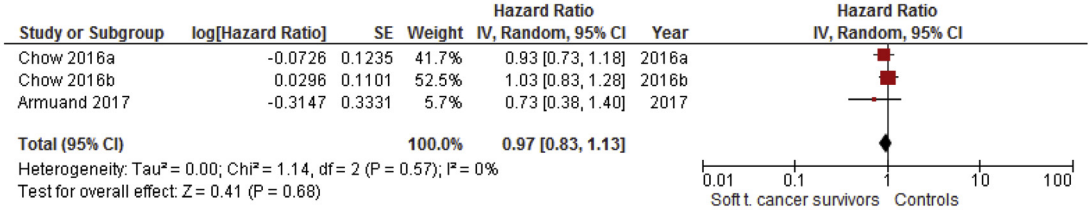
Chow et al. (2016) and *Anderson et al. (2018a)* investigated the effect of soft tissue cancer on fertility. Pooling of results did not show any influence on the chances of pregnancy: HR 0.64, 95% CI 0.27 to 1.48; I^2 = 97%; P = 0.29. Data on live birth rate (LBR) are conflicting. Results of studies reporting hazard ratios: HR 0.97, 95% CI 0.83 to 1.13; I^2 = 0%; P = 0.68 (*Chow et al., 2016*; *Armuand et al., 2017*) (FIGURE 2B) and relative risk deny any negative effect: RR 0.78, 95% CI 0.57 to 1.08 (*Madanat et al., 2008*). On the contrary, *Thouvenin-Doulet et al. (2018)* reported a detrimental effect: RaR 0.67, 95% CI 0.57 to 0.79. All four studies included only patients under the age of 21 years (*Madanat et al., 2008*; *Chow et al., 2016*; *Armuand et al., 2017*; *Thouvenin-Doulet et al., 2018*).

Chow et al. (2016) failed to show a worse prognosis in women treated with alkylating or similar agents. *Armuand et al. (2017)* stratified their results according to diagnostic era (before 1988 or from 1988 onwards) and age at diagnosis without observing any influence of these factors. *Madanat et al. (2008)* reported a negative effect of a history of soft tissue cancer on the live birth chances but only in women diagnosed between 20 and 34 years of age: RR 0.43, 95% CI 0.36 to 0.53.

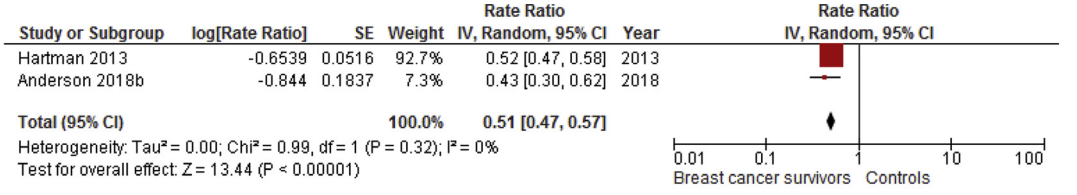




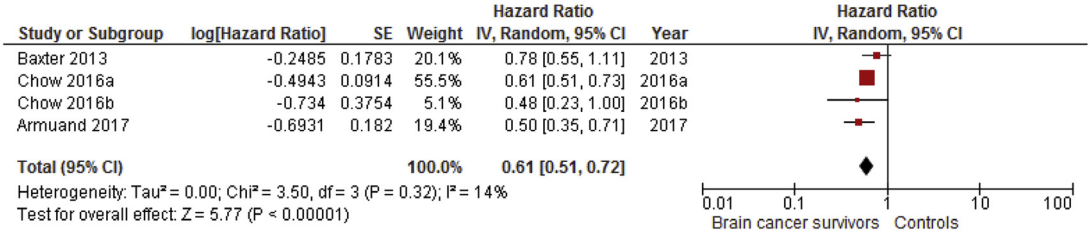
Panel A

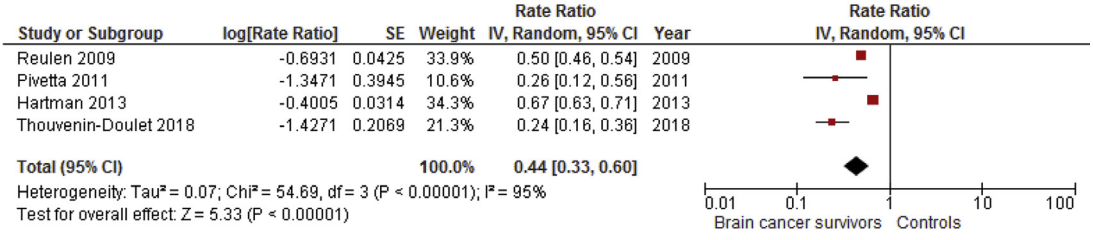


Panel B



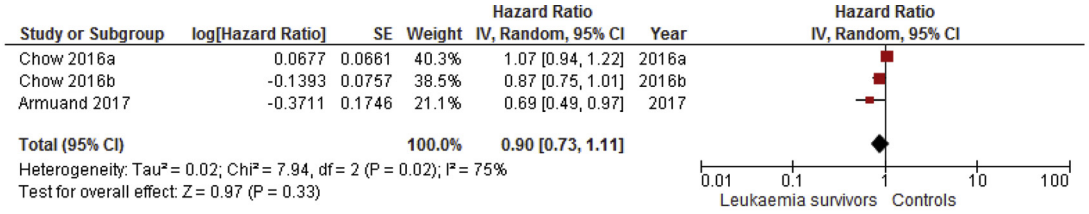
Panel C



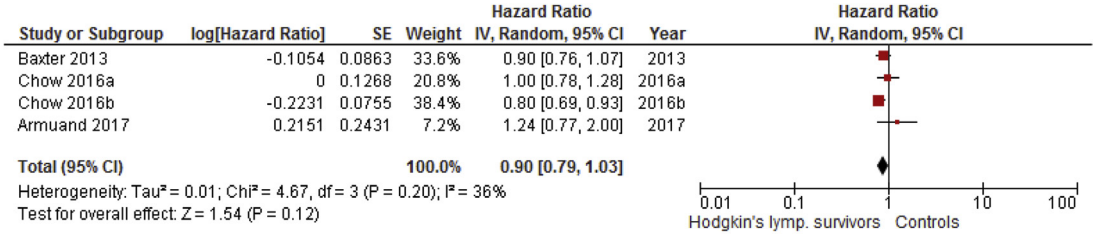


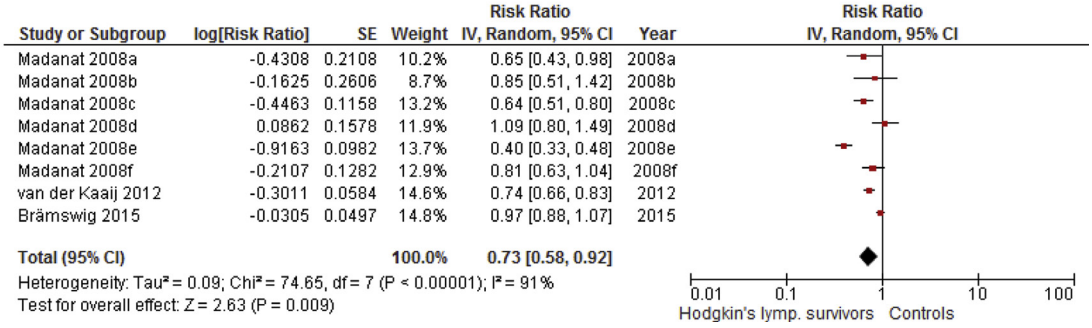
Panel D

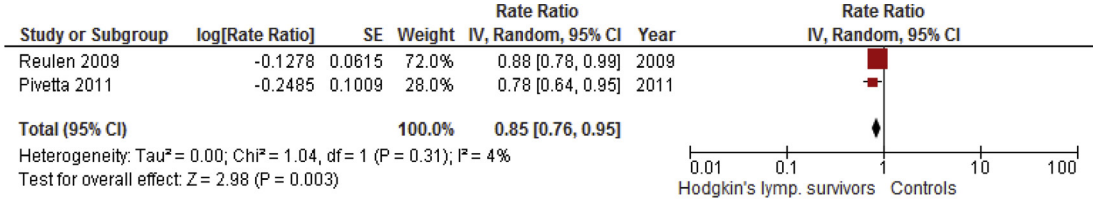
FIGURE 2 Effect estimates of childbirth in women with a history of bone cancer (Panel A), soft tissue cancer (Panel B), breast cancer (Panel C), brain and central nervous system (CNS) cancer (Panel D), leukaemia (Panel E), Hodgkin's lymphoma (Panel F), non-Hodgkin's lymphoma (NHL) (Panel G). *Chow et al. (2016*a) refers to women not exposed to alkylating or similar agents; *Chow et al. (2016*b) refers to women exposed to alkylating or similar agents; *Madanat et al. (2008*a) refers to paediatric survivors (0–14 years) with 1 child after diagnosis; *Madanat et al. (2008*b)



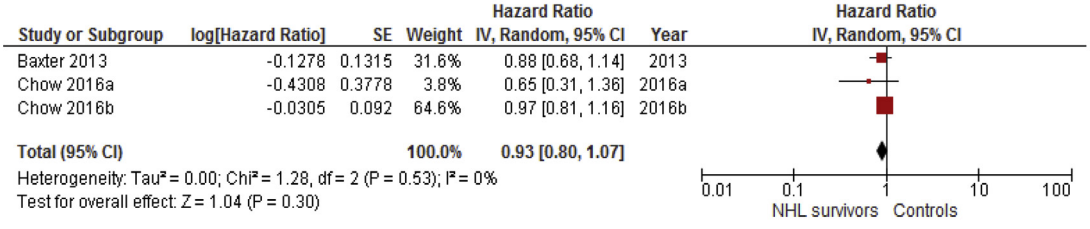
Panel E







Panel F



Panel G

FIG. 2 (Continued) refers to paediatric survivors (0–14 years) with two children after diagnosis; *Madanat et al. (2008*c) refers to adolescent survivors (15–19 years) with one child after diagnosis; *Madanat et al. (2008*d) refers to adolescent survivors (15–19 years) with two children after diagnosis; *Madanat et al. (2008*e) refers to adult survivors (20–34 years) with one child after diagnosis; *Madanat et al. (2008*f) refers to adult survivors (20–34 years) with two children after diagnosis.

Fertility after breast cancer

Meta-analysis of three studies (*Cvancarova et al., 2009*; *Stensheim et al., 2011*; *Anderson et al., 2018a*) showed a significantly reduced hazard ratio of pregnancy in women with a history of treated breast cancer: HR 0.34, 95% CI 0.29 to 0.40; I^2 = 38%; P < 0.00001. Results of studies investigating the effect of breast cancer on the rate of women who achieved at least one live birth confirmed the possible detrimental influence: HR 0.74, 95% CI 0.61 to 0.90 (*Baxter et al., 2013*); and RaR 0.51, 95% CI 0.47 to 0.57; I^2 = 0%; P < 0.00001 (*Hartman et al., 2013*; *Anderson et al., 2018b* (FIGURE 2C).

Baxter et al. (2013) and *Hartman et al. (2013)* controlled their results for pre-diagnosis parity and confirmed a significantly reduced hazard ratio and RaR only in survivors with a pre-diagnosis childbirth: HR 0.45, 95% CI 0.29 to 0.68 (*Baxter et al., 2013*); and RaR 0.35, 95% CI 0.31 to 0.4 (*Hartman et al., 2013*). *Madanat et al. (2008)* observed a significantly reduced LBR exclusively in women aged between 20 and 34 years at the time of diagnosis and parenting their first child after diagnosis: RR 0.17, 95% CI 0.14 to 0.21. *Syse et al. (2007)* reported a significantly impaired probability of a firstborn in the first 5 years after diagnosis and of a higher order birth regardless of time since diagnosis. *Anderson et al. (2018b)* evaluated potential variation in childbirth probability according to demographic, cancer and treatments characteristics. Specifically, they reported a more pronounced reduction in childbirth rate among women with regional or distant disease than among those with in-situ or localized disease. Furthermore, they observed that women diagnosed at an older age were less likely to have a post-diagnosis birth than those diagnosed at younger age. In analyses of cancer treatment, women treated with chemotherapy were less likely to have a live birth compared with those treated with surgery alone (*Anderson et al., 2018b*). Compared with oestrogen receptor-positive women, women with oestrogen receptor negative breast cancer were 1.31 times as likely to have a live birth (HR 51.31; 95% CI 0.97 to 1.78); this was largely driven by the lower cumulative incidence of birth among oestrogen receptor positive women over the first 8 years of follow-up . At 10 years, however, the cumulative incidence of live birth was 10% in both groups. Among women with oestrogen receptor positive tumours, those receiving endocrine therapy were less likely to have a live birth over most of the study period than those not receiving it (HR 50.47; 95% CI 0.31 to 0.71), although the cumulative incidence among endocrine therapy users actually exceeded that in non-users by 10 years after diagnosis (11% versus 10%) (*Anderson et al., 2018b*).

Fertility after brain and central nervous system cancer

Three of the included studies investigated the possible effect of a previous brain or central nervous system (CNS) cancer on subsequent chances of obtaining a pregnancy (*Stensheim et al., 2011*; *Chow et al., 2016*; *Anderson et al., 2018a*). Pooling of results showed a detrimental impact: HR 0.40, 95% CI 0.21 to 0.78; I^2 = 98%; P = 0.006. Meta-analysis of studies reporting the chances of live birth found a negative influence: HR 0.61, 95% CI 0.51 to 0.72; I^2 =14%; P < 0.00001 (*Baxter et al., 2013*; *Chow et al., 2016*; *Armuand et al., 2017*); and RaR 0.44, 95% CI 0.33 to 0.60; I^2 = 95%; P < 0.00001 (*Reulen et al., 2009*; *Pivetta et al., 2011*; *Hartman et al., 2013*; *Thouvenin-Doulet et al., 2018*) (FIGURE 2D). *Madanat et al. (2008)* (RR 0.62, 95% CI 0.42 to 0.91) and *Syse et al. (2007)* (OR 0.49, 95% CI 0.40 to 0.60) confirmed the detrimental effect. The harmful effect was also confirmed after limiting the analysis to studies that included only patients under the age of 21 years: HR 0.58, 95% CI 0.50 to 0.68; I^2 = 0%; P < 0.00001 (*Chow et al., 2016*; *Armuand et al., 2017*); and RaR 0.33, 95% CI 0.18 to 0.60; I^2 = 86%; P = 0.0002 (*Reulen et al., 2009*; *Pivetta et al., 2011*; *Thouvenin-Doulet et al., 2018*).

Stensheim et al. (2011) and *Hartman et al. (2013)* stratified their results on parity before cancer diagnosis but failed to detect any influence of this factor on the chances of both pregnancy and live birth. *Chow et al. (2016)* analysed the effect of different therapeutic agents and did not find any effect of alkylating agents on the chances of live birth: HR 0.48, 95% CI 0.23 to 1.03. Importantly, they excluded any radiation therapy that might have affected reproductive function. *Madanat et al. (2008)* controlled their results for the age at diagnosis without reporting any influence. *Pivetta et al. (2011)* repeated this sub-analysis and confirmed the detrimental effect only in females diagnosed between the ages of 5 and 14 years. The same investigators also analysed the results based on the diagnosis period and observed a negative trend progressing towards more recent years (test for a trend, P = 0.006) (*Pivetta et al., 2011*). *Syse et al. (2007)* reported an impaired probability of both firstborn and higher-order birth regardless of time since diagnosis.

Fertility after leukaemia

Three studies investigated the effect of a personal history of treated leukaemia on the chances of pregnancy. It was not possible to include in this meta-analysis the data provided by *Cvancarova et al. (2009)* because they did not report pregnancy rates separately for leukaemia and malignant lymphoma. Pooling of results did not show any significant influence: HR 0.52, 95% CI 0.26 to 1.05; I^2 = 98%; P = 0.07 (*Stensheim et al., 2011*; *Chow et al., 2016*; *Anderson et al., 2018a*). One study specifically investigated the effect of acute lymphoblastic leukaemia on reproduction, reporting a significantly reduced chance of pregnancy in previously affected women: RR 0.67, 95% CI 0.52 to 0.88 (*Byrne et al., 2004*). Results of meta-analysis investigating the effect on the LBR are conflicting. Pooling of results of studies reporting hazard ratios did not show any significant influence: HR 0.90, 95% CI 0.73 to 1.11; I^2 = 75%; P = 0.33 (FIGURE 2E) (*Chow et al., 2016*; *Armuand et al., 2017*). Both studies included only patients under the age of 21 years. On the contrary, *Madanat et al. (2008)* found a significant negative effect: RR 0.56, 95% CI 0.35 to 0.89. Sub-analyses conducted by *Steinsheim et al. (2011)* deny any influence of the diagnosis period but confirmed a negative effect on the chance of pregnancy only in women with at least one child born before cancer diagnosis. According to the results of *Chow et al. (2016)*, treatment with alkylating or similar agents did not modify the chances of live birth. *Pivetta et al. (2011)* separately investigated the reproductive prognosis in women affected by acute lymphoblastic and acute non-lymphoblastic leukaemia reporting a reduced chance of live birth in both groups: RaR 0.60, 95% CI 0.54 to 0.66; and RaR 0.53, 95% CI 0.32 to 0.88, respectively. *Armuand et al. (2017)* observed a detrimental effect of leukaemia on future chances of delivery only in women diagnosed before 1988.

Syse et al. (2007) observed an impaired chance of firstborn in the first 5 years after diagnosis and of a higher order born regardless of time since diagnosis.

Fertility after Hodgkin's lymphoma

Four studies investigated the possible effect of Hodgkin's lymphoma on the chances of pregnancy (Hodgson et al., 2007; Stensheim et al., 2011; Chow et al., 2016, Anderson et al., 2018a). Pooling of results showed a negative effect: HR 0.71, 95% CI 0.53 to 0.95; I^2 = 91%; P = 0.02. The evidence on the effect on LBR is conflicting. In fact, studies reporting hazard ratio as effect estimate failed to observe any influence: HR 0.90, 95% CI 0.79 to 1.03; I^2 = 36%; P = 0.12 (Baxter et al., 2013; Chow et al., 2016; Armuand et al., 2017) (FIGURE 2F). On the contrary, those reporting relative risk and RaR suggest a detrimental effect: RR 0.73, 95% CI 0.58 to 0.92; I^2 = 91%; P = 0.009 (Madanat et al., 2008; van der Kaaij et al., 2012; Brämswig et al., 2015); and RaR 0.85, 95% CI 0.76 to 0.95 ; I^2 = 4%; P = 0.003 (Reulen et al., 2009; Pivetta et al., 2011) (FIGURE 2F). Results are conflicting even after limiting the analysis to patients under the age of 21 years: HR 0.93, 95% CI 0.74 to 1.17; I^2 = 56%; P = 0.53 (Chow et al., 2016; Armuand et al., 2017); RaR 0.85, 95% CI 0.76 to 0.95; I^2 = 4%; P = 0.003 (Reulen et al., 2009; Pivetta et al., 2011); and RR 0.83, 95% CI 0.66 to 1.05; I^2 = 73%; P = 0.11 (Madanat et al., 2008; Brämswig et al., 2015). Stensheim et al. (2011) stratified their results according to the period of diagnosis (1967–1987 and 1988–2004) and to the parity status at diagnosis, and showed a constant, negative effect of cancer in all considered subgroups (Stensheim et al., 2011). Also, Baxter et al. (2013) controlled their findings for the parity status and observed a detrimental effect only in survivors with a childbirth before cancer diagnosis (Baxter et al., 2013). Van der Kaaij et al. (2012) confirmed this finding and showed an association between a patient age of 35 years and older at the start of treatment, alkylating chemotherapy and second-line treatment and a reduced probability of spontaneous pregnancy among survivors (van der Kaaij et al., 2012).Madanat et al. (2008) stratified results based on age at diagnosis. Calculated effect estimates showed a decreased chance of live birth regardless of age. On the contrary, Pivetta et al. (2011) observed a detrimental effect only in patients aged between 10 and 14 years at diagnosis. Brämswig et al. (2015) investigated the possible effect of multiple factors and concluded that parenthood was similar between Hodgkin's lymphoma survivors aged between 20 and 39 years and female German population of same age. Procarbazine in cumulative doses up to 11400 mg/m^2, cyclophosphamide in cumulative doses up to 6000 mg/m^2, alkylating agent dose scores of 1–5, therapy group, treatment protocol, abdominal and supradiaphragmatic radiation and age at treatment had no significant or only minor effects on parenthood. Major effects were documented only in patients who received pelvic radiation and patients who were aged 40–44 years at diagnosis (Brämswig et al., 2015). Analysed the effect of therapeutic agents on the chances of pregnancy and live birth. The investigators observed significantly reduced hazard ratios only in survivors who were treated with alkylating or similar agents. Syse et al. (2007) reported an impaired chance of higher order birth regardless of time since diagnosis.

Fertility after non-Hodgkin's lymphoma

Three of the included studies investigated the effect of a previous treated non-Hodgkin's lymphoma on the chances of pregnancy and failed to show any effect: HR 0.65, 95% CI 0.36 to 1.17; I^2 = 96%; P = 0.15 (Stensheim et al., 2011; Chow et al., 2016; Anderson et al., 2018a).

The evidence on the effect on the LBR also failed to observe any influence: HR 0.93, 95% CI 0.80 to 1.07; I^2 = 0%; P =0.30 (FIGURE 2G); RR 0.75, 95% CI 0.55 to 1.03; RaR 0.82; 95% CI 0.60 to 1.12 (Madanat et al., 2008; Pivetta et al., 2011; Baxter et al., 2013; Chow et al., 2016). The absence of any effect was confirmed also after limiting the analysis to studies that included only women under the age of 21 years: HR 0.94; 95% CI 0.76 to 1.16; I^2 = 6%; P = 0.56 (Chow et al., 2016); RR 0.82; 95% CI 0.60 to 1.11; I^2 = 29%; P = 0.20 (Madanat et al., 2008); RaR 0.82; 95% CI 0.60 to 1.12 (Pivetta et al., 2011).

Stensheim et al. (2011) stratified their results according to the parity status at diagnosis and showed a negative effect in patients with at least one child. Also, Baxter et al. (2013) controlled their findings for this factor but failed to show any influence. Pivetta et al. (2011) reported the effect estimates in different age categories and observed a detrimental effect exclusively in patients aged between 10 and 14 years at diagnosis. Furthermore, they failed to observe any negative effect in those diagnosed after 1980 (Pivetta et al., 2011). Chow et al. (2016) stratified their results according to the treatment agent used but confirmed the absence of any detrimental effect in all sub-categories (Chow et al., 2016). Madanat et al. (2008) observed a decreased probability of having a first child in women diagnosed between 0 and 14 years old and in those diagnosed between the ages of 20 and 34 years. Syse et al. (2007) observed an impaired chance of both first and higher order birth exclusively in the first 5 years after diagnosis.

Fertility after thyroid cancer

Two of the included studies investigated the effect of a personal history of treated thyroid cancer on the chances of pregnancy. Meta-analysis failed to show any influence: HR 0.81, 95% CI 0.59 to 1.11; I^2 = 89%; P = 0.19 (Stensheim et al., 2011; Anderson et al., 2018a). Four studies investigated the possible effect of previous thyroid or other endocrine gland cancers on the subsequent chances of live birth. Pooling of results reported by Baxter et al. (2013) and Armuand et al. (2017) did not show any influence: HR 1.07, 95% CI 0.96 to 1.20; I^2 = 0%; P = 0.22. Hartman et al. (2013) and Madanat et al. (2008) confirmed this finding: RaR 0.98, 95% CI 0.93 to 1.03 and RR 0.75, 95% CI 0.55 to 1.01, respectively. Armuand et al. (2017) controlled their results for the age at diagnosis (childhood or adolescence) and for the diagnostic era (before 1988 or from 1988 onwards) without observing any significant influence of both these factors. Also, limiting the analysis to women younger than 21 years of age confirmed the absence of any effect (Madanat et al., 2008; Armuand et al., 2017).

Fertility after kidney cancer

A history of kidney cancer does not seem to affect future chances of achieving a pregnancy: HR 0.56, 95% CI 0.27 to 1.14; I^2 = 89%; P = 0.11 (Chow et al., 2016; Anderson et al., 2018a). On the contrary, this factor negatively affected the delivery rate: RR 0.66, 95% CI 0.43 to 0.98 (Madanat et al., 2008); and RaR 0.69, 95% CI 0.61 to 0.78 (Thouvenin-Doulet et al., 2018).

Fertility after skin cancer

Anderson et al., (2018) reported a significant reduced pregnancy hazard ratio in women with a history of skin cancer (melanoma/non-melanoma): HR 0.66, 95% CI 0.62 to 0.72. Syse et al. (2007) reported an impaired chance of live birth exclusively in survivors who had already had at least one child and only in the first 5 years after diagnosis.

Studies investigating melanoma exclusively failed to observe any significant effect of the exposure factor on chances of pregnancy (Stensheim et al., 2011) and live birth: RaR 1.04, 95% CI 0.99 to 1.10 (Hartman et al., 2013); HR 1.11, 95% CI 0.95 to 1.30 (Baxter et al., 2013).

Fertility after digestive tract cancer

Anderson et al. (2018a) showed a detrimental effect of a history of treated colorectal cancer on the chances of pregnancy: HR 0.26, 95% CI 0.18 to 0.38 (Anderson et al., 2018a). Hartman et al. (2013) observed a negative influence of a previous digestive tract cancer on the LBR: RaR 0.90, 95% CI 0.83 to 0.98.

Fertility after liver cancer

Anderson et al. (2018a) investigated the possible effect of liver cancer on future fertility and observed a detrimental effect on the chances of pregnancy: HR 0.27, 95% CI 0.12 to 0.61.

Fertility after retinoblastoma

Two studies investigated the chances of live birth in women previously treated for retinoblastoma. Meta-analysis of results shows a detrimental effect: RaR 0.58, 95% CI 0.39 to 0.88; I^2 = 88%; P = 0.009) (Reulen et al., 2009; Thouvenin-Doulet et al., 2018). Both studies included only women under the age of 21 years.

Fertility after neuroblastoma

Chow et al. (2016) investigated the possible effect of neuroblastoma on future fertility. Sub-analysis showed a detrimental effect on the chances of live birth only in women treated with alkylating or similar agents: HR 0.70, 95% CI 0.52 to 0.94.

DISCUSSION

The present meta-analysis found that the reproductive prognosis of cancer survivors may vary considerably depending on the type of cancer. For the sake of clarity, we then discuss the available evidence separately for each cancer site.

Fertility after bone and soft tissue cancers

Results of our meta-analyses support an impairment of reproductive performance in women survivors of bone cancer, i.e. osteosarcoma and Ewing sarcoma. Chemotherapeutic drugs could play a role. As proof of this, Chow et al. (2016) confirmed the detrimental effect only in women treated with alkylating or similar agents. Data supporting damage from alkylating drugs on the gonadal function has already been published for men with osteosarcoma. An Italian survey showed that 15 out of 16 patients with osteosarcoma (94%) who had received 24000–60000 mg/m^2 of ifosfamide had oligospermia or azoospermia (Longhi et al., 2003; Chow et al., 2016).

In contrast, the evidence about the possible effect of soft tissue cancer and its treatment on fertility is reassuring. In fact, the only study reporting a reduced chance of childbirth among previously affected women is limited by the inclusion of patients diagnosed since 1948 when treatment options were extremely backward (Thouvenin-Doulet et al., 2018).

Fertility after breast cancer

Impairment of ovarian function is a known undesirable consequence of breast cancer treatments. Chemotherapy treatment has been shown to cause chemotherapy-induced amenorrhoea (CIA) in 21–70% of women under the age of 40 years treated for breast cancer (Minton et al., 2002; McCray et al., 2016).

Gonadotrophin releasing hormone agonists have been proposed as treatments to prevent subfertility and premature ovarian failure in young women undergoing cytotoxic treatments. Published evidence is promising. Indeed, in a recent meta-analysis of randomized controlled trials, Munhoz et al. (2016) showed that the addition of gonadotrophin releasing hormone agonists during chemotherapy, given in the neoadjuvant or adjuvant setting, was associated with ovarian function preservation as assessed by the rate of recovery of regular menses in young women with early breast cancer. All the effect estimates calculated in the present meta-analysis coincide in demonstrating a reduction of the reproductive potential in survivors of breast cancer compared with healthy controls. A previous childbirth was proposed as a possible factor negatively influencing the fertility of women after a diagnosis of breast cancer (Baxter et al., 2013). Initial evidence seems to confirm this hypothesis, but further data are warranted (Baxter et al., 2013; Hartman et al., 2013). Importantly, a sub-analysis by Anderson et al. (2018b) showed that post-diagnosis chances of live birth were significantly lower for women treated with chemotherapy and for those with a higher cancer stage at diagnosis. One could speculate that the use of cyclophosphamide, an alkylating agent often used in breast cancer treatment, may be associated with a worse reproductive prognosis owing to its certified ovarian toxicity (Walshe et al., 2006). Unfortunately, no study stratified the results by type and dose of chemotherapeutic agent used.

Our findings further justify the recommendations by the American Society of Clinical Oncology and the National Comprehensive Cancer Network that a documented fertility discussion and appropriate referral should become a new quality metric for dedicated breast cancer centres (McCray et al., 2016). A documented fertility discussion should include assessing women's desire for future fertility, the potential effect of each treatment regimen on future fertility and, possibly, an exploration of options for fertility preservation (McCray et al., 2016). In this setting, fertility preservation procedures become urgent, even if there is generally enough time to set up an ovarian stimulation cycle before starting the planned treatment (Peccatori et al., 2018). The recent development of random start and repetitive stimulation protocols, e.g. 'DuoStim' may improve the effectiveness of this approach (Kuang et al., 2014)). Ovarian tissue freezing and transplantation is an alternative option (De Vos *et al*., 2014), although the success of this approach is predominantly inherent to ovarian reserve at cancer diagnosis. Moreover, the carcinological risk of ovarian tissue transplantation in women with breast cancer remains an unresolved issue (Peccatori et al., 2018).

In the clinical management of young women with a history of breast cancer,

timing of a subsequent pregnancy is a crucial issue. Pregnancy does not impair breast cancer prognosis (*Danforth, 1991*; *Velentgas et al., 1999*; *Rosenberg et al., 2004*; *Azim et al., 2013*), but there is a consensus that childbearing should be delayed until 3–5 years after completion of treatment. This recommendation, however, might vary according to cancer biology and stage (*Averette et al., 1999*; *Ives et al., 2007*). In this respect, both chronological and biological age play an essential role, as delaying pregnancy for women in their late thirties or for those with reduced ovarian reserve might definitively impair fertility. In patients with endocrine responsive tumours, who are candidates for 5–10 years' adjuvant treatment (*Davies et al., 2013*), the timing of pregnancy is also controversial, although, as alluded above, studies assessing the possibility of a temporary interruption of endocrine therapy are ongoing (*Pagani et al., 2015*).

Fertility after brain and central nervous system cancer

Brain and CNS cancer incidence among young women is high, although these tumours are heterogeneous histotypes, treatments and prognoses. Patients with primary brain tumours are at risk for amenorrhoea owing to a potential damage of the hypothalamic–pituitary axis exerted by the tumour itself, cranial surgery or radiotherapy. In addition, chemotherapy, particularly alkylating agents such as temozolomide, a specific drug which is of common use in the treatment of primary brain tumours, can deplete the pool of oocytes (*Meirow et al., 2010*; *Stone et al., 2017*). Our results are worrying: the chances of both pregnancy and childbirth were found to be significantly reduced in patients with a history of treated brain and CNS cancer. On the other hand, possible confounding factors could have worsened the estimates. In fact, brain and CNS tumour survivors are the subset of cancer survivors at highest risk for neurocognitive sequelae with social effects such as reduced cohabiting and marriage rates (*Hartman et al., 2013*; *Anderson et al., 2018a*). Nonetheless, such a compromised picture highlights the need for interventions to protect fertility in these patients and to support them considering pregnancy once treatment is completed (*Anderson et al., 2018a*).

Fertility after leukaemia

Leukaemia is globally the most common malignancy in children (aged 0–14 years), except in Africa (*Bonaventure et al., 2017*). Therefore, it would be of crucial importance to outline the reproductive performance of survivors of leukaemia. Unfortunately, definitive conclusions cannot be drawn from our literature synthesis because of conflicting results. A possible explanation of such discrepancy was suggested by *Armuand et al. (2017)* who showing a detrimental effect on LBR only in those women diagnosed with cancer before 1988. This could be associated with the drastic modifications in chemotherapy protocols over the past decades, resulting in a lower reproductive impairment for those women treated for leukaemia in more recent times. In support of this, any detrimental effect of acute lymphoblastic leukaemia on the chances of childbirth disappeared in women diagnosed with cancer after 1990 in the study by *Pivetta et al. (2011)*. Conversely, studies on patients treated until the mid-1980s observed a significant reduction of the reproductive chances after treatment (*Byrne et al., 2004*). These findings are encouraging but limited. Furthermore, specific information on the effect of treatment with total body irradiation or conditioning chemotherapy required before haematopoietic stem cell transplantation is limited, which is a key part of treatment for some leukaemias. Worryingly initial evidence shows a fertility impairment in 57% of exposed females after a median time of 2.3 years after haematopoietic stem cell transplantation (*Pfitzer et al., 2015*).

Further studies focusing on the effect of current therapy for leukaemia on the reproductive function are warranted.

A further limitation of our findings is inherent to the heterogeneity of cancer variants reported under the designation of leukaemia. Indeed, leukaemia is a generic term that refers to a group of diseases of mostly unknown origin. Although it is still unclear, we may speculate that the reproductive prognosis of survivors may vary according to the specific variant of leukaemia, disease severity and treatments used. The reduced chances of pregnancy and live birth observed in women with a history of acute lymphoblastic leukaemia indirectly support this hypothesis (*Byrne et al., 2004*; *Pivetta et al., 2011*). To provide reliable information, future research should serially evaluate the reproductive effect of each leukaemia subtype.

Fertility after Hodgkin's lymphoma

Our meta-analyses suggest a negative effect of a history of Hodgkin's lymphoma on future fertility. These results cannot be judged as definitive because of the high heterogeneity among studies. Interesting insights, emerge, however, from the sub-analyses. Of special interest are the data from two studies showing that treatment with alkylating or similar agents significantly worsens the reproductive prognosis (*van der Kaaij et al., 2012*; *Chow et al., 2016*). Additionally, the age at cancer diagnosis seems to play a fundamental role in the reproductive prognosis. Interestingly, *Brämswig et al. (2015)* noted no significant difference in parenthood between groups aged younger than 18 years divided by age at diagnosis (<10 years, 10 to <15 years, and ≥15 to <18 years) (*Brämswig et al., 2015*). This result suggests that a sufficient number of oocytes may survive in women younger than 18 years treated for Hodgkin's lymphoma, as shown by a trend in parenthood comparable to the general population. On the other hand, one can speculate that gonadotoxic treatment in adult female patients carries a higher age-related risk of infertility, owing to the decreasing number and increased vulnerability of oocytes. In this regard, one should also consider that the reproductive window, i.e. years to attempt childbearing, may be significantly reduced if diagnosis is made in adulthood (*Somigliana et al., 2019*). In line with these speculations, *Van der Kaaij et al. (2012)* and *Chow et al. (2016)* found a significantly more detrimental effect of a history of Hodgkin's lymphoma in older patients at the time of diagnosis. Noteworthy, two studies controlled their findings for the parity status and observed a detrimental effect on LBR only in survivors with a diagnosis before childbirth (*van der Kaaij et al., 2012*; *Baxter et al., 2013*). Assessing the meaning of this finding is difficult, however. In fact, multiparity might not be directly associated with a worse reproductive prognosis, but rather suggest an older age at cancer diagnosis compared with nulliparous women. In addition, reproductive behaviours after recovery may also differ between women who did and did not have children at the time of cancer diagnosis because of psychological reasons.

Importantly, *Brämswig et al. (2015)* reported significantly reduced chances of parenthood in survivors receiving pelvic radiation compared with those who received abdominal and supradiaphragmatic radiation. These data confirm the severe gonadotoxicity of pelvic radiotherapy. Therefore, patients should receive adequate information about the implications of these therapies for their future fertility, including the high risk of acute ovarian failure and premature menopause (*Brämswig et al., 2015*).

Fertility after non-Hodgkin's lymphoma

An optimistic view emerges from a critical analysis of the available evidence on the effect of non-Hodgkin's lymphoma on the survivors' reproductive potential. The only counter-trend study is the one conducted by *Madanat et al. (2008)*. The recruitment period, however, was extremely wide ranging from 1 January 1953 to 31 December 2004. Inevitably, therapeutic advance limits the reliability of results. Two studies suggest a worse prognosis in patients diagnosed at younger age (*Madanat et al., 2008*; *Pivetta et al., 2011*). The investigated age ranges, however, are not perfectly overlapping and, therefore, definitive conclusions cannot be drawn.

Fertility after thyroid cancer

The evidence on the effect of thyroid cancer on reproductive prognosis is reassuring. This is of particular relevance as most new diagnoses refer to differentiated thyroid cancers (papillary or follicular thyroid cancers). These cancers are highly curable, with a 5-year relative survival of 98% for all stages combined (*Anderson et al., 2017*). The standard treatment for differentiated thyroid cancers is thyroidectomy, which is often followed by radioactive iodine (RAI) treatment for delivery of adjuvant therapy or ablation of any postoperative remnant thyroid tissue (*Nixon et al., 2013*). The benefits of RAI treatment should be carefully evaluated, especially in younger patients. In fact, RAI was associated with transient elevations in serum gonadotrophins and temporary oligomenorrhoea or amenorrhoea, potentially causing long-term damage to gonadal tissue (*Souza Rosario et al., 2005*; *Sawka et al., 2008*). Women treated with RAI may also have an earlier average age at menopause and an increased risk of miscarriage in the first year after treatment (*Sawka et al., 2008*). *Anderson et al. (2017)* specifically investigated the effect of this treatment on the subsequent fertility in women affected by differentiated thyroid cancer. Interestingly, the proportion of women who had a child after diagnosis did not significantly differ between those treated and not treated with RAI, suggesting little effect of RAI on future reproductive potential.

Miscellaneous

The effect of the other types of cancer on the reproductive potential has been less investigated. Evidence suggests impaired childbirth chances in women with a history of kidney, digestive tract, liver cancer, retinoblastoma and neuroblastoma treated with alkylating or similar agents. The prognosis is more reassuring in patients with melanoma. Considering the limited available data, further studies are needed before drawing definitive conclusions.

Strengths and limitations

Some limitations of the present meta-analysis deserve mention. First, most studies included in the analysis involve women of a wide age range, and at least five of them include women over the age of 40 years. This might undermine the reliability of the results considering the well-known detrimental effect of age on oocytes quality. To limit the effect of this weakness, for each cancer type, whenever possible, results were pooled only from studies that involved women under the age of 21 years when the process of oocytes competence alteration has not yet begun. Such sub-analyses could be conducted for bone cancer, brain and CNS cancer, Hodgkin's and non-Hodgkin's lymphoma and thyroid cancer to establish the overall effect. As for soft tissue cancer, leukaemia, retinoblastoma and neuroblastoma, the overall analysis already includes studies involving young women.

Second, one could speculate that factors such as the extent of the disease, diagnostic era, women's age and parity status may influence the reproductive prognosis in female cancer survivors. Only a few published studies that carried out sub-analyses took these factors into account. Unfortunately, the results of these sub-analyses could not be meta-analysed owing to the discrepancy of the cut-offs considered by the various investigators. To mitigate the effect of this limitation and to provide the most detailed and precise information, we reported for each type of cancer the available data on the effect of the various prognostic factors on the reproductive chances of survivors and the effect of possible confounders on the studied associations.

Importantly, the variability between studies in type of cancer treatment inevitably limits the reliability of the estimates. For example, the heavily relied-on study by *Chow et al. (2016)* specifically excludes patients treated with total body irradiation whose deleterious effect on subsequent reproductive function is well-established.

Third, possible confounding variables may limit the reliability of the results, e.g. the effect estimates calculated for bone and soft tissue cancer. In fact, amputation is routinely carried out on patients with high-grade bone and soft tissue tumours in the extremities. Limb-preserving surgery with a wide margin achieves positive outcomes in selected cases; however, loss of limb function remains an unsolved problem (*Hoshi et al., 2015*). The psychological sequelae of such aggressive therapies inevitably affect the relationship life. It therefore cannot be ruled out that this factor confounds the association between cancer or cancer treatment and fertility. In the other tumours, these sequelae are less common but could nonetheless occur and influence the results. Until the possible role of these factors is clarified, girls and young women with brain and CNS cancer should be considered at high risk of infertility.

Although the above limitations should always be carefully considered before drawing definitive conclusions, the present systematic review and meta-analysis fills a significant gap of knowledge in oncofertility. Children and women of reproductive age who are diagnosed with cancer are currently counselled based on data on the effects of cancer treatments on surrogate and poorly reliable markers of fertility, i.e. ovarian reserve, age at menopause, and on the reproductive chances cumulatively calculated for many cancer sites. An estimate of reproductive success by type of cancer as precise as possible is, therefore, of utmost importance to counsel patients and to accurately assess the risk–benefit

TABLE 2 EVIDENCE ON THE EFFECTS OF DIFFERENT TYPES OF CANCER ON THE CHANCES OF CHILDBIRTH IN WOMEN

Cancer	Number of studies[a]	Number of patients	Quality of the evidence	Effect estimates	Conclusions
Bone cancer	5	3408	High	Concordant	Bone cancer, its treatments, or both, probably reduce the chances of childbirth.
Soft tissue cancer	4	1463	High	Conflicting	Published evidence is insufficient to establish the effect of soft tissue cancer, its treatment, or both, on childbirth chances.
Breast cancer	5	19468	Medium	Concordant	Breast cancer, its treatments, or both, probably reduce the chances of childbirth.
Brain/CNS cancer	6	6175[b]	Medium	Concordant	Brain and CNS cancer, its treatments, or both, probably reduce the chances of childbirth.
Leukaemia	5	4331	Medium	Conflicting	Published evidence is insufficient to establish the effect of leukaemia, its treatment, or both, on childbirth chances.
Hodgkin's lymphoma	9	3843[b]	Medium	Conflicting	Published evidence is insufficient to establish the effect of Hodgkin's lymphoma, its treatment, or both, on childbirth chances.
Non-Hodgkin's lymphoma	5	1394	Medium	Concordant	Non-Hodgkin lymphoma, its treatment, or both, probably do not affect the chances of childbirth.
Thyroid cancer	4	6024	High	Concordant	Thyroid cancer, its treatment, or both, probably do not affect the chances of childbirth.
Kidney cancer	2	633	Medium	Concordant	Published data and the quality of evidence are insufficient to draw reliable conclusions.
Melanoma	2	5135	High	Concordant	Melanoma, its treatment, or both, probably do not affect the chances of childbirth.
Digestive tract cancer	1	2439	High	Concordant	Published data are insufficient to draw reliable conclusions.
Retinoblastoma	2	76[b]	Medium	Concordant	Published data are insufficient to draw reliable conclusions.
Neuroblastoma	1	525	High	Concordant	Published data are insufficient to draw reliable conclusions.

[a] Refers to studies with quantitative data available.

[b] *Reulen et al.(2009)* did not report the number of affected women.CNS, central nervous system.

ratio before starting fertility preservation programmes.

In conclusion, this systematic review and meta-analysis shows that women with a history of bone, breast, brain or kidney cancer have reduced chances of childbirth compared with unaffected controls. On the contrary, thyroid cancer, melanoma and non-Hodgkin's lymphoma survivors can be reassured. Further evidence is needed to assess the reproductive probabilities of women with a history of soft tissue cancer or Hodgkin's lymphoma. Reproductive prognosis of women affected by leukaemia probably depends on the type of leukaemia but data confirming this hypothesis are warranted (TABLE 2).

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