IMPACT OF CANCER THERAPY ON FEMALE FERTILITY: A SYSTEMATIC REVIEW

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Abstract

Background: Cancer has become highly prevalent in developing countries, and Africa is not far from it. The treatment of these cancers increases the risk of infertility in women. This review aims to understand the effects of different types of cancer treatments on the fertility in women.

Method: PRISMA guidelines were followed for scrutinizing the articles. Original research articles were searched and obtained from online databases including Pub Med, Pub Med Central, Springer, Nature, Web of Sciences, Semantic Scholar, Medline, Science Direct, Directory of Open Access Journals, Google Scholar, Research Gate, EMBASE, National Center for Biotechnological Information etc. After removing irrelevant, duplicated, and less correlated articles from the total of 1671 obtained articles, 19 studies were included in the systematic analysis.

Results: Among The 19 Studies Included, 14 Were Retrospective. Based On The Systematic Analysis Performed, Overall Fertility Deficits Were Observed In Female Survivors Of Cancers. Sex, Age At Diagnosis, Pre-Diagnosis Parenthood, And Diagnostic Period All Had An Effect On Fertility After Cancer Treatment. Treatment with alkylating agents, second line therapy, and age>35 years also influence the chances of pregnancy. Pre-term delivery was also found to be linked to cancer-related therapy. The probability of having a first live birth among cancer survivors was low. The site of cancer and age at the onset of cancer were independent predictors of a reduced probability of giving birth after diagnosis. Pelvic radiation was found to be more damaging than abdominal or supradiaphragmatic radiation.

Conclusion: The present review suggests that future measures should be taken to include an assessment of women's desire for future fertility and also provide fertility preservation options. Fertility preservation strategies for cancer-affected women in their reproductive years. Long-term fertility data on cancer survivors in South Africa are needed. Counseling tools and guidelines for referral to onco-fertility specialists should be developed for newly diagnosed young patients.

Key words: Cancer; Survivor; Fertility; Chemotherapy; Radiotherapy; Treatment

Introduction

Recently, cancer has become highly prevalent in developing countries, and Africa is not far from it[1]. More than 1 million people suffer from cancer in the world every year, and these are mostly people of reproductive age[2]. Cancer contributed to 650 000 new cases in Africa in 2002, among which sub-Saharan Africa comprised 530 000 people (311 000 males and 338 000 females)[3]. Despite high rates, cancer has not been a highly recognized issue in Africa. Some of the most common cancers in women are liver cancer (5%), cervical cancer (23.3%), Kaposi's sarcoma (5.1%), breast cancer (19.3%), ovarian cancer (3.7%) and non-Hodgkin's lymphoma (3.8%)[4,5]. The treatment of these cancers increases the risk of infertility in women. It is the main reason for infertility in cancer survivors. The side effects of the treatment negatively impact the reproductive capacity, mainly through premature menopause[6,7]. Although clinicians are well aware of the issue of infertility in such women, they emphasize the utmost importance of patient survival rather than fertility preservation[8]. Fertility also influences emotional health in women[9]. In recent times, cancer-related infertility has been on the rise in South Africa. Therefore, oncologists should map out treatment strategies that render the therapies harmless to the reproductive potential of female patients. The current published literature has focused on the effects of cancer treatments on the fertility of women in South Africa.

Cancer treatments and their effects on fertility have been investigated in various studies, mainly focusing on pregnancy and childbirth[10–14]. The mechanism of cancer therapy related injury in terms of ovarian reserve has not been comprehensively understood. Some of the effects include faster primordial follicle recruitment ("burn-out" effect), ovarian vascularization impairment[15], and direct DNA damage to oocytes and granulosa cells. The specific agents, their dosage and threshold determine the magnitude of damage in a dose-dependent manner. Alkylating agents, although unsafe for patients, have been used to treat cancers and preserve life. Radiotherapy may also damage ovaries if given to the whole body, or abdominal, pelvic, or spinal regions of the body[16]. However, many cancer sites have been providing contradictory data, and not much information is available on South African women. Such a scenario does not allow an overall understanding of the topic of infertility in female cancer patients.

Aim: This particular systemic review aims to understand the effects of different types of cancer treatments on the fertility of South African women and also assesses their chances of fulfilling their desire for parenthood.

Importance: This study might be helpful in future counselling of such patients and their families on the impact of oncologic treatment on fertility and might also seek their decisions on fertility preservation, if possible, in the future.

Methodology

Literature search: The literature search was performed on scientific journals, databases, and websites, including PubMed, PubMed Central, Google Scholar, Nature,

Springer, Web of Sciences, Semantic Scholar, Medline, Science Direct, Directory of Open Access Journals, Google Scholar, Research Gate, EMBASE, National Center for Biotechnological Information etc., The period of survey ranged from 2002 to 2022.A systematic review of the published literature was performed on the topic of the effects of cancer treatment on the fertility of women in South Africa initially. This yielded only one randomized control trial(RCT) on cancer therapy and fertility, specifically from South Africa[17]. The studies across other countries and continents were also considered, so that some basic ideas on how cancer therapies affect fertility in women of reproductive age could be known. The search was limited to studies in humans. The key terms used were "cancer", "breast cancer", "non-Hodgkin's lymphoma", "Hodgkin's lymphoma", "soft tissue cancer", "central nervous system cancer", "liver cancer", "GI tract cancer", "kidney cancer", "thyroid cancer", "cancer therapies", "leukemia", "chemotherapy", "radiotherapy", "hormone therapy", "biologics", and "fertility, pregnancy, or childbirth". This study included RCTs, case controls, cross-sectional studies, and published cohorts (retrospective or prospective). Their references were also searched manually for a few relevant articles. Unpublished studies and studies published in languages other than English were excluded.

Adherence to PRISMA: This systematic review was carried out in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18] for conducting and writing systematic reviews. This review summarizes the data after the collection of articles, followed by systematically discussing their results.

Article screening: The literature search was done on the databases for relevant publications. Primary screening was done according to the title and the abstracts by two independent authors. In the event of any discrepancy, consensus meetings and discussions were carried out between both authors to reach a common agreement. The titles and abstract of the articles that are not relevant to the present investigation were excluded for the secondary screening. The selected articles after the first screening were screened for full text for eligibility criteria of the present study. The full-text articles that did not fall under our title criteria were excluded. Full-text articles with ambiguous data, no control group, and no information on cancer subtypes were also omitted. Systematic review articles were not included in the study.

Data extraction: The selected studies were scrutinized, and relevant data was extracted from the selected articles using an excel spreadsheet. The following data pertaining to aim, study design, inclusion and exclusion criteria, ethnicity of the population, age of patients, type of cancer, type of cancer therapy, and main findings were obtained and recorded.

Results

Literature search: An initial search of databases with the key words yielded a total of 1671 articles. After screening for duplications, 596 articles were retained. After further exclusion of articles for title, abstract, and full text, the articles that were relevant and

available in full text were 42 in number. The literature search resulted in 19 articles that were further considered for final inclusion in the study. Finally, exclusions based on the criteria of irrelevant text, systematic review, unclear data, no control group, and no information on cancer subtypes led to the inclusion of 19 final articles for this review (Figure 1).

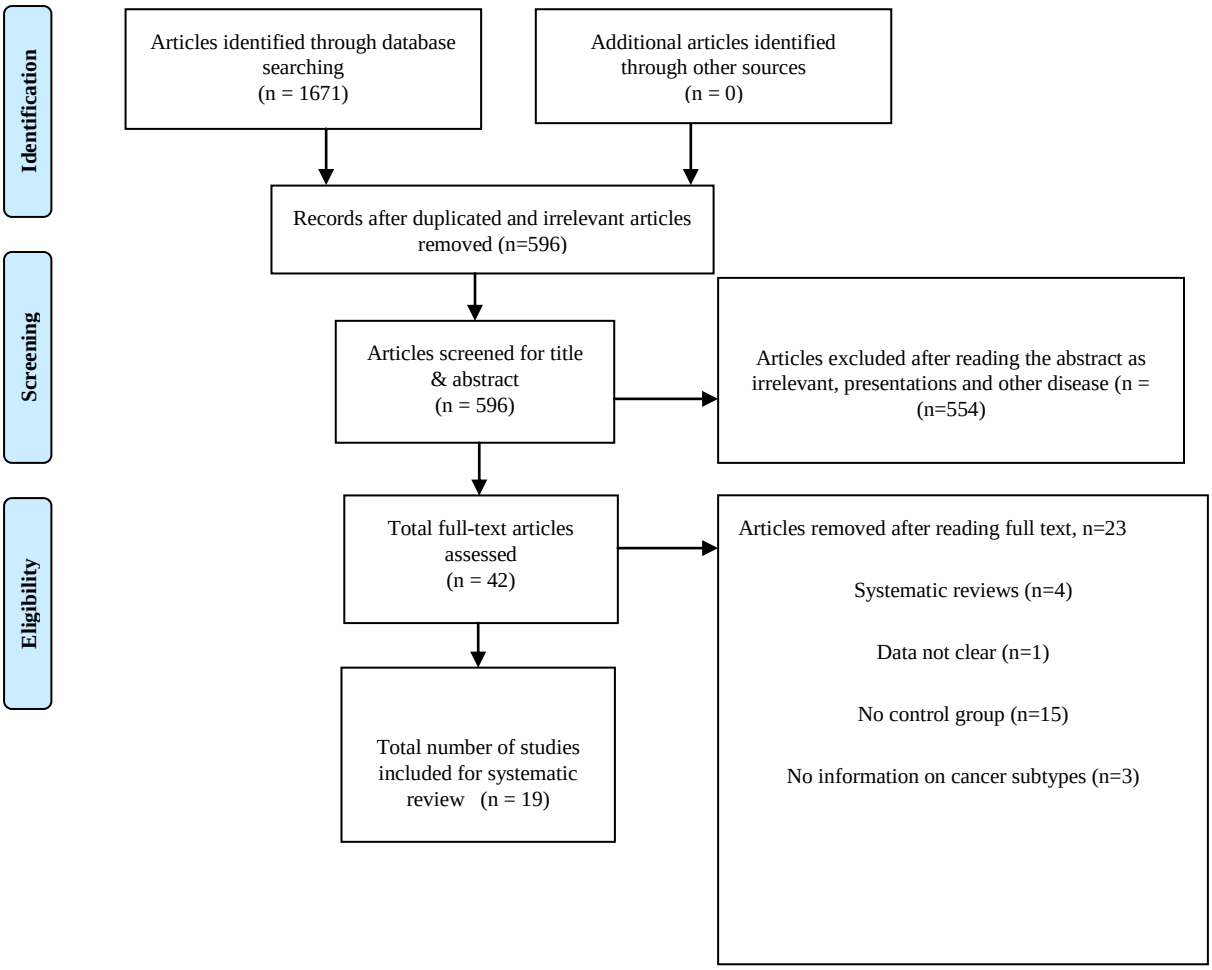

Figure 1: PRISMA chart

Literature over the years

The present literature search from the study showed that studies are published over a span of 20 years at regular intervals. However, only one or two studies have been published each year. Some countries where these types of studies have been done are Norway, the USA, Canada, UK, Sweden, Philadelphia, Scotland, and Finland (Table 1). From the geographical distribution of origin of studies, it is observed that countries from Asia and Africa have not been actively publishing on this topic. Hence, very few or no publications were reported during the literature search for Asian and African countries. Only one South African study was reported to be published in 2020, which was not in exact accordance with the current study's goal, but was included because it represented the area from which this study originated and would provide some information on cancer treatment and infertility for women in South Africa. Its primary aim was to understand the contraceptive needs and fertility intentions of women with breast cancer in Cape Town, South Africa.

Fourteen of the 19 studies included here were retrospective, which means that data or information was extracted from online cancer registry databases in most countries. In few studies, control groups were non-cancer healthy individuals, survivors' siblings or friends. The fertility rates were compared to the fertility rates of the general population whose data was provided by those countries' Register Data centers. Two studies were actually done on females by the Children's' Cancer Group and Princess Margaret Hospital for Hodgkin's lymphoma[19,20]. One study from Philadelphia included participants from the Children's Hospital of Philadelphia Survivorship Program and the Transition Program at Penn's Living Well after Cancer Survivorship Program. Through Penn-affiliated health practices and advertising, unexposed controls of similar age to cancer survivors were discovered[21]. One study compared parenting in female Hodgkin's lymphoma survivors enrolled in five German Hodgkin's disease studies to parenthood in a German female population control group in a prospective longitudinal study[12]. One multi-centric study that was included in this study was by Chow et al.[22] which involved 27 institutions in the USA and Canada (Childhood Cancer Survivor Study). In this study also, the controls were siblings[22]. The participants were quite young (<21 years) at the time of diagnosis. One study that was published in Cape Town, South Africa, was qualitative in-depth interviews of women diagnosed with breast cancer and health care providers[17].

Cancer types and subtypes: The most common types of cancer that were reported in most of the articles were breast cancer and cervical cancer. Our results show that a wide variety of cancers were responsible for initiating fertility related studies in different parts of the world. The types of cancers that were covered were leukemia, ovary, brain, cervix uteri, breast, bone, non-Hodgkin's lymphoma, Hodgkin's lymphoma, eye, endocrine, skin, kidney, thyroid, central nervous system, soft tissue, germ cell, trophoblastic, gonadal cell, gynecological, non-heritable retinoblastoma, heritable retinoblastoma, melanoma, digestive tract, head and neck, urinary tract, and colorectal cancers.

Age: The age of the participants who were considered in their respective articles was from 15–45 years (broad range). Most of the studies considered children as young as 15 years[13,14,19,20,22–24], but some considered people aged 18-44[10,25–27]. While one article considered only middle-aged participants for its study, that is, 20-34 years[11]. Heterogeneity in age would help us to understand the influence of age on cancer therapy in infertility better.

Chemotherapy and Radiotherapy: Chemotherapy and radiotherapy were the modes of treatment of cancer in almost all the articles. Cranial radiotherapy protocols 101, 105, 106,123,139,141, 141A, 162, 162A, 163, 903, and 9998 of the Children's Cancer Group were used to treat leukemia[19]. ABVD chemotherapy was used to treat Hodgkin's lymphoma, CNS cancer, and retinoblastoma[20][28]. Among 19 studies considered, only three studies reported detailed treatments for cancer, whereas the other 16 types did not report the mode of treatment used[10,11,13,14,17,21,23–25].

Fertility protection strategies: In accordance with the responsible oncologists, any woman between the ages of about 14 and 40 who receives chemotherapy with a significant

chance of impairing ovarian function should obtain advice on fertility preservation techniques from a physician skilled in reproductive medicine. Few strategies include cryopreserving unfertilized and fertilized oocytes after ovarian stimulation, cryopreservation of ovarian tissue, using antagonists for gonadotropin-releasing hormone, and ovarian transposition. These techniques may be used separately or in a combined manner[29].The percentage of females who undergoes fertility protection strategies ranges from 2 to 50%[30].

Investigated outcome: The results of the included studies were analysed and found to be consistent with the anticipated outcome of the current investigation. A few that primarily investigated pregnancy were[10,19–21,26,31]. Other articles that investigated childbirth as their primary outcome were[11,13,14,23–25,27,28,32]. It is to be noted that pregnancy may not always result in a live childbirth. In the articles included in the present studies, childbirth is a live birth and is a result of a successful pregnancy. One article considered both pregnancy and childbirth as its primary outcome[22], and one article from South Africa studied the impact of breast cancer on future fertility intentions and contraceptive use[17].

Follow up time: The table of included studies shows that the maximum time of follow up was for 15 years by Bramswig et al. and the minimum was 25 months by Dillon et al.[21].Other articles did not report clearly the time duration or the extent of time. Instead, they just mentioned the month and year up till which the follow up was done.

Main findings: According to the current literature review, overall fertility deficits were observed in female cancer survivors. This was directly reported by a few of the articles, such as[19,26,32]. The mentioned articles have clearly highlighted lower post-cancer reproduction than that of the general population. Byrneet al.,[19] reported this in female survivors treated with cranial radiotherapy. It has also been observed to be influenced by sex, age at diagnosis, prediagnosis parenthood, and diagnostic period with more favorable rates in males than in females[26]. Moreover, treatment with alkylating agents, second line therapy, and age> 35 years seem to influence the chances of pregnancy[32].

Age-related difficulty in pregnancy was also reported by Hodgson et al.[20]. On the contrary, Hodgson et al.[20] observed that there was no association between age at the time of treatment and the number of cycles of chemotherapy and pregnancy among Hodgkin's lymphoma. Female Hodgkin's lymphoma patients who had attempted conception after ABVD and survived without recurrence for more than or equal to 3 years did not have substantial subfertility[20].In ovarian cancer, fertility preservation attempts have been successful (Steinsheim et al). Additionally, a few of the studies also discussed the percentage of difficulty in having a first live childbirth in comparison to subsequent ones. When compared to the general population, first-birth rates among cancer patients were only around 25% lower, according to Syse et al.[25].Higher-order birth rates for females were 36% below those of the general population.[13]found a lower likelihood of having a first live birth among cancer survivors. Overall, including in breast cancer, cervical cancer, and Hodgkin's lymphoma, the benefit was reduced with a longer treatment term, while it was constant in leukemia and brain and CNS tumors[31]. One of the articles reported that liver birth within 10 years of diagnosis occurred in <10% of breast cancer patients. However, there was a risk of pre-term delivery[33]. Pre-term delivery was also observed in childhood female cancer

survivors who received abdominal radiotherapy and were at a three-fold increased risk of delivering preterm, a two-fold increased risk of low birth weight, and a small increased risk of miscarriage[28]. Patients with abdominal and brain radiotherapy also reported a reduced probability of producing offspring[27,28] found that cancer site (reproductive organs), age at onset of cancer (<12 years), and parity status were all significant and independent predictors of a lower likelihood of giving birth after diagnosis.. And even so, achieving pregnancy and childbirth was all the more difficult for those who received pelvic radiation compared with those who received abdominal and supradiaphragmatic radiation (Bramswig).

Discussion

Young cancer patients' fertility may be universally compromised by cancer treatments like chemotherapy, radiotherapy, or surgery[34]. It is shown that cancer treatments like radiotherapy and chemotherapy to the pelvis in a woman may have side effects like vaginal changes, fatigue, and emotional problems, thereby affecting their sexual behaviour. De Roo et al.[35] proposed a worldwide oncofertility index to help specialists assess the scope of the problem and design educational tools to define access to reproductive technology. The International Late Effects of Childhood Cancer Guideline Harmonization Group POI guideline identified major gaps in information about safe treatment dosages, the safety of novel therapies, and the role of genetic susceptibility on subsequent POI (premature ovarian insufficiency) risk in survivors. Oncofertility is a recently developed field of medicine that functions as a bridge between oncology (the study of cancer) and reproductive biology in humans. Its sole purpose is to either preserve the reproductive capacity of cancer patients or maximize the reproductive capacity of cancer survivors. Since incidences of cancer are increasing, fertility preservation is also gaining importance for women, men, and children. Many fertility-preservation options exist such as shielding, ovarian transposition, gonadotropin agonist, egg banking, embryo banking, in vitro maturation, sperm banking, testicular sperm aspiration and extraction, and tissue banking. These practices are growing in developing countries, but with regard to South Africa, not much is seen in the field of oncofertility. Some common difficulties faced here are lack of proper knowledge and awareness, strict religious guidelines, lack of coverage of insurance and related expenses. These barriers must be overcome to promote the speciality of oncofertility in South Africa[36].

In the present study, the overall fertility deficits were observed in female survivors of cancers. The majority of the articles reported the association between age, first birth or later birth, and the body part receiving the therapy, with pregnancy and live childbirth. Apart from that, pre-term delivery was also found to be linked to cancer-related therapy[37].A reduced probability of having a first live birth among cancer survivors has also been observed[13]. Additionally, different cases of pregnancy post-cancer treatment have also been observed in the articles selected in the present study. The fertility protection strategies commonly used in the gynecology field after undergoing a cytotoxic therapy has also been summarized in the current analysis. This article overall summarizes the effect of cancer-related therapy on pregnancy in female patients of reproductive age. In such a scenario, it would be an injustice not to have discussed the mechanism by which therapy-related infertility is brought about in the survivors. Hereby, we discussed some of the mechanisms of cancer-related therapy on pregnancy and childbirth in cancer survivors.

Mechanisms

Cancer treatments involving chemotherapy, radiation, surgery, and endocrine therapies dispense their consequences just beyond scars. It affects every phase of fertility that would ultimately lead to reproductive failure in cancer survivors of reproductive age[38,39].

Chemotherapy: The main mechanism of action of chemotherapeutic agents, especially alkylating agents and anti-tumour antibiotics like actinomycin D, is to disrupt the process of cell replication, its transcription, and DNA synthesis. Some agents may directly damage the DNA structure, while others, like adriamycin, may damage the plasma membrane. Plant-based taxanes interrupt the tubulin function that is critical for the mitotic process to function normally[34]. Cyclophosphamide and chlorambucil cause DNA damage to the follicles of the ovaries. While drugs like Etoposide, 5-fluorouracil, Adriamycin, and Methotrexate are deemed less damaging, they still have other damaging mechanisms for the ovaries. Hence, chemotherapy drugs may cause the follicular cells' death by directly damaging the primordial follicles[40]. The depletion of the female reproductive hormone oestrogen because of ovarian failure can also cause added sexual dysfunctions like vaginal stenosis and inelasticity, dyspareunia, coital bleeding, vaginal atrophy and dryness, and risk of fistula[41–43]. Other toxicities of the antineoplastic drugs include endovascular damage[44]. Chemotherapy also induces focal fibrosis of the cortex of the ovaries along with blood vessel injury. Chemotherapy-induced damage is most commonly encountered in mature follicles, largely driven by certain endocrine mechanisms. The larger follicles secrete a specific hormone called anti-Müllerian hormone (AMH), the level of which significantly drops in the course of therapy[45,46].

Radiotherapy: Radiotherapy is also well established for its dose-dependent damaging effects on ovarian and reproductive function[47,48]. The predictable median lethal dose (LD50) to cause damage to the oocyte is < 4 Gy (46). A study has found that whole-abdominal irradiation of 20 - 30 Gy in childhood leads to ovarian failure that is exhibited as primary amenorrhoea in 71% of patients and premature menopause at the median age of 23.5 years in the rest[48]. Radiotherapy may also damage the uterus by reducing the uterine elasticity and volume[49,50]. The incidences of intrauterine growth restriction, miscarriages, and premature delivery are high among them[51]. Endometrial sampling measures uterine damage after radiotherapy to assess the endometrial function. However, the reproductive outcome may not be evident from the assessment[34]. Women undergoing cranial radiation may require careful assessment of their hormones and the periodic menstrual cycle may merely not reveal the functionality of the hypothalamic-pituitary axis[42]. Other adverse outcomes of cancer survivors are small gestational age of children, preterm delivery, and low birth weight infants[39,52,53]. The female cancer survivors are found to experience higher rates of early pregnancy loss and infertility [54]. Moreover, a comparatively lower rate of natural pregnancy is reported in female cancer survivors than in the general population[38,39].

Fertility protection strategies: As per previous reports by Lambertiniet al.[55], the reports on fertility protection strategies are too limited and the level of evidence is ≤3 so far. The fertility rate in breast cancer patients has been reported to be relatively lower after

treatment[10].Fertility and pregnancy after undergoing treatment for cancer are not considered safe[56].Ruddy et al.[57] have reported that females opt for embryo cryopreservation more thanoocyte cryopreservation and luteinizing hormone-releasing hormone analog administration. Limitations in fertility protection strategies include insufficient ovarian reserve, increased susceptibility to complications, or an emergent need for chemotherapy.

In summary, it can be said that women with bone, breast, brain, or kidney cancer have decreased chances of childbirth compared to controls. On the other hand, there are some chances of childbirth, and reassurance can be given to such survivors of thyroid cancer, melanoma, and non-Hodgkin's lymphoma. There is also a need for biomarkers that can help in the prediction of infertility.

Conclusion

Female cancer survivors of reproductive age have fertility risks owing to their diagnosis, disease, and treatment. Future studies are required, especially in the region of South Africa, where not much work has been done on this. The present study indicates that future measures should be taken to include an assessment of women’s desire for future fertility and also provide fertility preservation options. A very strong survey or RCT is very much required in South Africa. In addition to focusing on survival, oncologists should consider fertility preservation strategies for female candidates of reproductive age, as well as their decision to consider child birth in the future. Emphasis must be laid on generating long-term fertility data for such patients. The development and implementation of counselling tools and standards for referral to oncofertility specialists may also aid newly diagnosed young cancer patients and survivors.

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Appendix

Table 1: Summary of included studies

Author Name and Year	Study Design	Aim of the Study	Cancer type/subtype	Chemotherapy/Radiotherapy	Age	Diagnosis time period	Outcome investigated	Follow-up length	Main findings
Byrne et al., [19]	Females treated according to Children's Cancer Group. Controls were siblings.	To investigate functional impairment of fertility in women who were long-term survivors of acute lymphoblastic leukemia (ALL) with a retrospective cohort study.	Leukaemia.	Protocols 101, 105, 106,123, 139,141, 141A, 162, 162A, 163, 903, 9998 of the Children's Cancer Group.	Childhood	1970–1987	Pregnancy	Not reported	Significant fertility deficits were noted in female survivors treated with cranial radiotherapy (CRT) at any dose around the time of menarche

Syse et al., [25]	Data from Cancer Registry of Norway.	To find the effect of several cancer forms on fertility at a population level	Ovary; brain; cervix uteri; leukaemia; breast; bone; non-Hodgkin's lymphomas; Hodgkin's lymphoma; eye; endocrine; skin.	Not reported	17–44	1965–2001	Childbirth	uptill 31 December 2001.	First-birth rates among persons with cancer were reduced by only about 25% when compared with the general population. higher-order birth rates for females were 36% below those of the general population. Reductions in fertility were most pronounced for reproductive cancer forms, presumably related to subfecundity. However, also cancer forms unrelated to reproductive function led to reduced fertility,

									perhaps suggesting underlying social mechanisms.

Hodgson et al., [20]	Females treated at Princess Margaret Hospital for Hodgkin's lymphoma. Controls were friends/siblings.	To estimate success rate of women attempting pregnancy following ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)	Hodgkin's lymphoma.	ABVD[a]	<45 years (treatment)	1983–1999	Pregnancy	Not reported	Age at treatment and the number of cycles of chemotherapy were not associated with pregnancy rate among HL survivors. Female HL patients who had survived without recurrence > or =3 years and who had attempted pregnancy after ABVD did not experience significant sub-fertility.

Madanat et al., [23]	Data from Finnish Cancer Registry records linked to the Population Register Centre data.	To evaluate in a population-based setting the postdiagnosis parenthood among survivors compared with the fertility patterns of siblings.	Leukaemia; Hodgkin's lymphoma; non-Hodgkin's lymphoma; CNS; SNS; kidney; thyroid; breast; bone; soft tissue; germ cell; trophoblastic and other gonadal tumours.	Not reported	0–34 (diagnosis)	1953–2004	Childbirth	Not reported	The relative probability of parenthood increased over calendar time among young adult cancer patients. The relative probability of parenthood following early onset cancer was overall significantly reduced by approximately 50%. Parenting a second child, however, was not reduced among pediatric and adolescent survivors, and only slightly reduced among early adulthood cancer survivors

									compared to siblings.
Cvancarova et al., [26]	Data from Norwegian Radium Hospital registry and of the Cancer Registry of Norway. Each patient was birth	To compute 10-year first postdiagnosis cumulative reproduction rates (10-PDRs) and hazard ratios (HRs) avoiding	Malignant lymphoma /leukaemia; gynaecologic cancer; breast cancer.	Table 1 of Cvancarova et al.	15–44 (diagnosis)	1971–1997	Pregnancy	10 years	Postcancer reproduction is lower than that of the general population and influenced by sex, age at diagnosis, prediagnosis parenthood, and

	year-matched with five randomly selected individuals from the Norwegian Population Registry.	these limitations.							diagnostic period with more favorable rates in males than in females. Post-1988+ fertility-saving strategies may have improved the reproduction rates for select genital cancers.
Reulen et al., [28]	Data from National Registry of Childhood Tumours. No. of live births was compared to thate expected from population of England and Wales.	(a) To quantify the risk of adverse pregnancy outcomes in survivors of childhood cancer in relation to cancer type and treatment and (b) To assess live birth rates	Hodgkin's lymphoma; CNS; non-heritable retinoblastoma; heritable retinoblastoma.	Chemotherapy and abdominal or brain irradiation (specific protocols not reported)	Childhood	1940–1991	Childbirth	Not reported	Female survivors of childhood cancer treated with abdominal radiotherapy are at 3-fold increased risk of delivering preterm, 2-fold increased risk of low birth weight, and a small increased risk of miscarriage. Overall, female survivors

		relative to the general population.							produce considerably fewer offspring than expected, particularly those treated with abdominal or brain radiotherapy.
Pivetta et al., [24]	Cases taken from Italian Off-Therapy Registry. Fertility rates compared to general population given by Italian Institute of Statistics.	To describe the patterns of marriage and parenthood in a cohort of childhood cancer survivors included in the Off-Therapy Registry maintained	Acute lymphoblastic leukaemia; acute non-lymphoblastic leukaemia; Hodgkin's lymphoma; non-Hodgkin's	Not reported	<15 years (diagnosis)	1960–1998	Childbirth	uptill 30 October 2006	Childhood cancer survivors are less likely to marry and to have children than the general population

		by the Italian Association of Pediatric Hematology and Oncology.	lymphoma ; CNS.						
Stensheim et al., [10]	Data 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	To analyze postcancer pregnancy rates in Norway	Breast; cervix uteri; ovary; melanoma ; brain; thyroid; non-Hodgkin's lymphoma ; Hodgkin's lymphoma ; leukaemia .	Not reported	16–45 (diagnosis)	1967–2004	Pregnancy	Not reported	Fertility-preserving attempts have succeeded in patients with ovarian or testicular cancer and in males with Hodgkin lymphoma.

	Registrar.								
van der Kaaij et al., [32]	Cases from 9 consecutive RCTs from 1964 and 2004. Controls were matched to case by sex, country of residence, education level, and year of birth.	To investigate the impact of Hodgkin lymphoma (HL) on parenthood, including factors influencing parenthood probability, by comparing long-term HL survivors with matched general population	Hodgkin's lymphoma.	Table 1 of van der Kaaij et al.	>15	1964–2004	Childbirth	Not reported	Treatment with alkylating agents, second-line therapy, and age older than 35 years at treatment appeared to reduce the chances of spontaneous post-treatment parenthood.

		controls.							
Hartman et al., [27]	Data from Swedish Multi-Generation Register and Swedish Cancer Register. Compared to background population matched according to attained age and year of birth.	To investigate independent factors associated with reduced birth rates among cancer survivors	Breast; ovary; brain; eye; hematopoietic; bone; digestive tract; head and neck; thoracic; skin; reproductive (minus ovary) .	Not reported	16–45	1958–2001	Childbirth	untill age 45 years	Cancer site (reproductive organs), age at onset of cancer (< 12 years), and parity status were all significant and independent predictors of a reduced probability of giving birth after diagnosis.
Baxter et al., [11]	Data from Ontario	To investigate	Brain; breast;	Not reported	20–34	1992–1999	Childbirth	13 years	Long-term female young

	Cancer Registry. Women diagnosed with non-gynaecologic malignancies age matched to 5 randomly selected cancer-free women.	childbirth in female young adult survivors of non-gynecologic malignancies.	Hodgkin's lymphoma; non-Hodgkin's lymphoma; thyroid; melanoma.						adult survivors of malignancies are less likely than controls to have childbirth after diagnosis; the overall effect is small and is influenced by prediagnosis childbirth and malignancy type.
Dillon et al.,[21]	Participants from Children's Hospital of Philadelphia Survivorship Program and the Transition Program at Penn's Living Well After Cancer Survivorship Program.	To compare measures of ovarian reserve (MOR) and pregnancy rates in young female cancer survivors and similar-aged controls.	Not specified.	Not reported	15–39	2006–2010	Pregnancy	25 months	Survivors achieved pregnancy at a rate similar to controls despite impaired MOR.

	Controls of similar age.								
Brämswig et al.,[12]	Prospective longitudinal study, comparison of 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	To assess the frequency of parenthood in female survivors of Hodgkin's lymphoma younger than 18 years at diagnosis, and to compare it with that in a female population control group.	Hodgkin's lymphoma.	Table 1 of Brämswig et al.	<18 years (diagnosis)	1978–1995	Childbirth	15 years	Parenthood was significantly reduced in survivors receiving pelvic radiation compared with those who received abdominal and supradiaphragmatic radiation. an overall favourable prognosis for parenthood in female survivors of Hodgkin's lymphoma.

	control group.								
Chow et al.,[22]	Cohort study from 27 Institutions in the USA and Canada (Childhood Cancer Survivor Study) . Controls were siblings.	To establish the effects of these chemotherapeutic drugs on pregnancy in male and female survivors of childhood cancer not exposed to pelvic or cranial radiotherapy .	Leukaemia; CNS; Hodgkin's lymphoma; non-Hodgkin's lymphoma; kidney; neuroblastoma; soft-tissue sarcoma; bone.	Table 1, Table 2 and Table 3 of Chow et al.	<21 (diagnosis)	1970–1999	Pregnancy and childbirth.	8 years	Chemotherapy-specific effects on female pregnancy were generally few. Contrary results in male survivors.

Armuand et al., [13]	Cases were from Swedish Patient Register. Controls were two age- and sex-matched individuals per case born on the same day identified using the Total Population Register.	To compare the probability of a first live birth, age at time of birth, and time between diagnosis/referent date and birth between childhood and adolescent cancer survivors and an age-matched comparison group.	Leukaemia; CNS; Hodgkin's lymphoma; thyroid; soft tissue; urinary tract; eye.	Not reported	<21 (diagnosis)	Women born 1973–1977	Childbirth	uptill 31 December 2012	Reduced probability of having a first live birth among cancer survivors diagnosed during childhood or adolescence; men were particularly vulnerable.
Anderson et al., [33]	Data from Scottish Cancer Registry data linked to national	To investigate the the impact of cancer in females	Colorectal; liver; bone; skin; soft tissue; breast;	Table 2 of Anderson et al.' for chemo/radiotherap	0-39	1981–2012	Pregnancy	uptill 31 December 2014	Cancer survivors achieved fewer pregnancies. The chance of achieving a first pregnancy was

	general and maternity hospital discharge records to find out pregnancies.	aged ≤39 years on subsequent chance of pregnancy.	cervix uteri; ovary; kidney; eye; CNS; thyroid, Hodgkin's lymphoma; non-Hodgkin's lymphoma; leukaemia.	y status (specific protocol not reported)					also lower. The effect was reduced with more recent treatment period overall and in cervical cancer, breast cancer and Hodgkin lymphoma, but was unchanged for leukaemia or brain/CNS cancers.
Thouvenin-Doulet et al., [14]	Cases from Euro2K cohort and from the Childhood Cancer Registry of the Rhône-Alpes Region (ARCERRA) cohort.	To describe fecundity in female survivors of childhood cancer and consider the correlation with quality of life (QOL).	Lymphoma; CNS; SNS; retinoblastoma; kidney; bone; soft tissue; germ cells.	Not reported	<15 (diagnosis)	1948–1992	Childbirth	till 2010	Women treated for childhood cancer demonstrated impaired fecundity that correlated with poor QOL, as registered by the SF-36.
Anderson et al., [33]	Data from North Carolina	To examine the incidence of	Breast.	Table 1 of Anderson	15–39	2000–2013	Childbirth	5–10 years	<10% of AYA breast cancer survivors had a

	Central Cancer Registry records linked to North Carolina birth certificate files.	live birth and the prevalence of adverse birth outcomes according to tumor and treatment characteristics amongthe incidence of live birth and the prevalence of adverse birth outcomes according to tumor and treatment characteristics among adolescents and young adults with breast cancers with		et al. for chemo/radiotherapy status (specific protocol not reported)					live birth within 10 years of their diagnosis. However, there was a risk of pre-term delivery.

		breast cancer.							
Harries et al., [17]	Qualitative in depth interviews	To understand the contraceptive needs and fertility intentions of women with breast cancer in Cape Town, South Africa.	Breast.	Chemotherapy, details not reported	18-49	2105-2020	Impact of breast cancer on future fertility intentions and contraceptive use		Most women did not receive information around fertility preservation options, and few were familiar with the concept. Providers focus was more on preventing pregnancy during treatment and ensuring a patient was on a non-hormonal contraceptive method. Providers supported a more holistic, multidisciplinary approach to breast cancer patient's contraceptive and

									future fertility needs a Only types with quantitative data available are listed.