Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Cancer Therapy, Gonadal Function, and Fertility Preservation: Systematic Review and Meta-analysis

Student Investigator's Name

Christopher O. Eden

Date of Submission *(mm/dd/yyyy)*

03/08/2022

Graduation Year

2022

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Projects Curriculum

Co-Investigators *(Names, departments; institution if not OHSU)*

Alyson Haslam, Ph.D., Vinay Prasad M.D. M.P.H (Department of Epidemiology and Biostatistics, University of California, San Francisco) and Peter Mayinger

Mentor's Name

Peter Mayinger Ph.D., Alyson Haslam Ph.D., and Vinay Prasad M.D. M.P.H.

Mentor's Department

Molecular and Cellular Biosciences, School of Medicine

Scholarly Project Final Report

Concentration Lead's Name

Peter Mayinger, Ph.D.

Project/Research Question

1. How much do different chemotherapy regimens for various cancers affect fertility?
2. What is the rate of referral for fertilization preservation for cancer patients?
3. How many cancer patients cryopreserve oocytes, sperm, and embryos? What is the viability of these frozen products?
4. How cancer patients have more offspring with fertility preservation?
5. How effective is ferto-protective therapy?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Systematic review and meta-analysis

Key words *(4-10 words describing key aspects of your project)*

Cancer therapy, fertility preservation, chemotherapy, radiation, ferto-protective therapy, cryopreservation

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

N/A

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

N/A

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

N/A

Scholarly Project Final Report

Next Steps
What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

Additional next steps that would build upon the current results could include sub-group analyses of different cancers and therapies for meta-analysis, forest plots of percent normal, assessing risk of bias within individual studies, and figuring out which studies used a control arm of healthy people.

Unanswered research questions include how many people use frozen products for fertility since we were unable to find any studies that addressed this. Additionally, new research could be focused on the "rules" of how long cryopreserved oocytes, sperm, and embryos are kept in freezers.

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

https://ohsu.ca1.qualtrics.com/jfe/form/SV_3ls2z8V0goKiHZP

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X

Student's full name

Mentor's Approval *(Signature/date)*

Scholarly Project Final Report

Report: *Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Cancer therapy frequently results in decreased fertility. About 1 in 10 of total cancer cases arise in adults of reproductive age, and the most common cancers in this cohort include breast, bowel, cervical, and testicular cancers (1). If harm to reproductive organs from therapy is inevitable, preserving gametes, embryos, or tissue may help to preserve fertility.

Both female and male fertility may be impaired following chemotherapy, bone marrow transplant, and/or radiotherapy for cancer. Chemotherapy comprises the largest set of therapies used to treat cancer. Some cancer treatment regimens, historically considered to cause infertility, have had overstated estimates of damage. Researchers have described the reproductive toxicity of frequently used chemotherapy regimens, which can assist with risk stratification before starting therapy, but this has proved difficult given the heterogeneity of regimens, patients, and cancers (2).

Several options are currently available for the preservation of fertility including oocyte cryopreservation, sperm cryopreservation, ovarian tissue cryopreservation, and embryo cryopreservation (3).

Currently, there is a lack of knowledge about how much cancer therapies affect fertility, which patients choose fertility preservation, and of the patients who do how successful is the utilization of these products for conception. There is no consistent incidence for infertility following cancer therapy. Furthermore, the degree to which infertility guidance and recommendations are employed in clinical practice is unclear.

To tackle gaps in this important topic, we aim to answer five questions:

1. How much do bone marrow transplant, chemotherapy, and radiation regimens for various cancers affect fertility?
2. What is the rate of referral for fertilization preservation for cancer patients?
3. How many cancer patients cryopreserve oocytes, sperm, and embryos? What is the viability of these frozen products?
4. How many cancer patients have more offspring with fertility preservation?
5. How effective is ferto-protective therapy?

Our hypothesis is that the number of eligible patients that undergo fertility preservation is suboptimal, and a vast majority of cryopreserved ova and sperm may never be used. This could be due to failures in preservation (e.g., collected oocytes and sperm might be less viable than embryos) and there might be additional reasons why costs have constrained the system's limit collection.

Our approach to answering these questions is to conduct a systematic review and meta-analysis by analyzing a number of published studies found in different databases. As a retrospective, cross-sectional study, this project is highly feasible and attainable.

Methods *(≥250 words)*

This systematic review and meta-analysis were conducted in accordance with PRISMA and with PROSPERO. Methodology was based on previous work by Prasad et al. as well as Talic et al. (2021) (18).

Eligibility criteria:
Articles that met the population, intervention, comparison, outcome, and study design criteria were eligible for inclusion in this systematic review.

We excluded case reports, case studies, reviews and non-empirical studies (e.g., commentaries, editorials, government reports) that provided results without strong well-documented statistical assessments.

Information sources:
We conducted an extensive search in the following databases: Embase (1991-2021), Google Scholar (1991-2021), and PubMed (1991-2021) (Figure 1). Chris Eden developed the initial search strategy, which was validated by Dr. Haslam. Our broad computerized search strategy was built upon using the keywords chemotherapy, radiation, and fertility. The updated search strategy was last performed on 1 December 2021. All citations identified from the database searches were uploaded to Excel.

Studies with the following designs were included: 1) randomized controlled trials, according to the Cochrane Collaboration guidelines; 2) controlled clinical trials, experiments in which eligible subjects are allocated in a nonrandomized manner to the treatment and the control groups; 3) other designs, including patient series and pre-post studies. Only full-length articles or full written reports were considered for inclusion in the review.

Study Selection:
We independently screened the titles and abstracts and excluded studies that did not match the inclusion criteria (article type: clinical trial, randomized controlled trial, or other designs, which included clear statistical results; species: human; year: 1991-2021). We retrieved full text articles and determined whether to include or exclude studies no the basis of predetermined selection criteria. We determined whether each article answered one or multiple of our questions. Information obtained from the full text articles included: title, journal/book, question, database found in, tissue, intervention, country, objective(s), setting, patient population, study type/statistical methods used, outcome(s), results (statistics included), conclusions, limitations, study duration, cancer type, publication year, and DOI (Supplemental Table 1, not all columns displayed due to readability). Studies were sorted by question and then sub-divided by cancer type, and outcome(s) (e.g., hormone level, number of gametes).

Statistical analysis:
Because of the differences in the effect metrics reported by the individual studies, we could only perform descriptive qualitative data synthesis and analysis for the five questions. Pie charts displaying the study characteristics were created in Excel.

Future next steps with data would include transforming effect metrics derived from different studies to allow for pooled meta-analysis. The Dersimonian Laird random effects model would be used to estimate pooled effect estimates. Heterogeneity among individual studies would be assessed using the Cochran Q test and the I^2 test. All P values would be two tailed, with P = 0.05 considered to be significant.

Public and patient involvement:
No patients or members of the public were directly involved in this study as no primary data were collected.

Results *(≥500 words)*

1. How cancer treatments affect fertility?

24 studies provided estimates on the effect of bone marrow transplant, chemotherapy, and radiation regimens on fertility outcomes in different cancers (Figure 2, Supplemental Table 1). Most studies focused exclusively on groups of patients with a specific diagnosis. Out of the 24 studies, seven of the studies assessed fertility in patients with Hodgkin's lymphoma treated with chemotherapy, five assessed testicular cancer treated with chemotherapy (four articles) or irradiation (one article), and the remaining studies assessed various other cancers including acute lymphoblastic leukemia, acute myeloid leukemia, breast cancer, and non-Hodgkin's lymphoma treated with bone marrow transplant, chemotherapy, or radiation. Measured outcomes serving as surrogate measures for fertility were heterogeneous, but within the 24 studies, roughly 33% looked at semen analysis, 17% looked at ovarian tissue analysis, and 50% looked at hormonal labs (Figure 2).

The results of studies that assessed fertility indicate that cancer patients face wide variation in outcomes attributable to age at diagnosis, disease, and treatment. However, studies that examined chemotherapy showed rates of infertility are high among women receiving chemotherapy regimens that contain heavy alkylator exposure (articles 1-4, 7-8, 12, 19, 21-23 in table 1). Among the studies, for women, anti-mullerian hormone seems to be the best measurable outcome correlated with fertility. Dillon et al. (2013) (article 4 in table 1) is the best example of how anti-mullerian hormone measured both before and after treatment can be useful in management of women concerned about fertility potential (4).

Infertility among men has been less studied, but semen analysis is more reliable compared to markers of ovarian reserve (articles 6, 7, 8, 10, 13, 20 in table 1). High follicular stimulating hormone (FSH) levels are frequently employed as indirect markers of fertility dysfunction but their reliability is questionable (5).

Interestingly, our review shows that is important to consider the impact of underlying malignancies on fertility just as much or more so than therapy. For example, in Hodgkin's lymphoma, the data is very complicated. Although patients with Hodgkin's lymphoma have high overall response rates to therapies, almost 90% of patients develop azoospermia (article 6 in table 1) (5). The pre-therapy semen quality of patients with cancers such as Hodgkin's lymphoma can be low. Sieniawski et al. (2008) (article 6 in table 1) showed that newly diagnosed Hodgkin's lymphoma 23% patients had normozoospermia and 77% patients had dysspermia. These researchers showed that a minority of patients showed improved sperm counts after receiving chemotherapy.

2. What is the rate of referral for fertility preservation?

Only two studies assessed rate of referral for fertility preservation (6, 7). Both studies were in concordance with low fertility preservation at medical centers. Surveys from these studies suggest that important discrepancies exist in fertility counseling rates across European countries with rates ranging from 15% to 40% of eligible candidates (7).

3. How many cancer patients cryopreserve oocytes, sperm, and embryos?

Eight studies were included in the analysis that examined how many patients underwent fertility preservation (7-14). Heterogeneity among studies was substantial. van der Kaaij and colleagues reported that 40% of men treated for Hodgkin lymphoma cryopreserved sperm prior their treatment used (6). In a 2017 European study that included 38 centers with expertise in children and adolescents, the authors reported that a total of 29% of patients had a fertility preservation procedure performed (7).

4. How many cancer patients have more offspring with fertility preservation?

Only one study (which also answered questions 2 and 3) reported the association between increased offspring and fertility preservation. The 2014 study assessed men treated for Hodgkin lymphoma and showed that semen cryopreservation doubled the odds of fatherhood after treatment; with 20% of children conceived using cryopreserved semen (6).

5. How effective is ferto-protective therapy?

Overall, 49 articles provided estimates on the effectiveness of ferto-protective therapy (Supplemental Table 2). Out of the 49 studies, 32 articles assessed gonadotropin-releasing hormone agonists (GNRHa), 5 articles assessed luteinizing hormone-releasing hormone agonists (LHRHa), 3 articles assessed tamoxifen, and the remaining 9 articles assessing other ferto-protective therapies. The most commonly measured outcomes were premature ovarian insufficiency and post-treatment pregnancy rate. Our preliminary meta-analysis shows that treatment with GnRHa fails to provide a protective fertility effect with studies showing contradictory results (Supplemental Table 2).

Discussion *(≥500 words)*

More than 80% of children with cancer become long-term survivors, and fertility is an obvious concern in cancer patients of childbearing age (15). Fertility and fertility preservation for cancer patients is a developing field. The potential effect of cancer therapies on fertility, the use of ferto-protective therapies, referral patterns for fertility preservation, risks of preservation, and disposition of cryopreserved sperm, oocytes, and embryos are all topics requiring more evidence.

The first question of our project aimed to research the effects of different cancer therapies on fertility. The 24 studies found in our systematic review demonstrated that there are a wide variety of effects of cancer therapies (chemotherapy, bone marrow transplant, and radiation) on fertility. Our review yielded a wide array of patient demographics (e.g., age, sex), cancers, treatments, site of administration, and doses. With all of these very diverse variables, there are innumerable combinations.

Retrospective cohort studies describe the affect of cancer therapies on fertility. Since chemotherapy regimens often consist of multiple drugs, the influence of specific drugs on fertility is difficult to discern. Throughout all of the studies, though, it did appear that chemotherapy regimens with alkylating agents (represented by cyclophosphamide) posed a strong risk of infertility. We recommend characterization by risk stratification to specify each regimen accurately (2). Additionally, calculating cyclophosphamide equivalent dosing may provide further standardization (16). Unfortunately, our study reveals that there is significant inconsistency in monitoring the effects of fertility. Poor surrogate outcomes, lack of patient follow-up, and no control groups contribute to ambiguity among the effects of cancer therapies on fertility. With development of new tools, we hope that it will be much easier to estimate the impact of therapies on fertility.

Consideration of fertility preservation before cancer treatment remains a possibility to maximize the reproductive potential of patients newly diagnosed with cancer. The second, third, and fourth questions of our project aimed to address this component. Overall, fertility preservation is very understudied, as we showed there are very few studies that look into this topic. From the data we collected, fertility preservation referral rates remain low, and the number of cryopreserved fertility products is unknown. Literature has shown that oncologists lack knowledge about fertility preservation (17). We postulate that there are significant barriers to fertility preservation given the cost, public perceptions, limited research, and institutional factors such as lack of practice guidelines. Cultural, economic, and religious factors also certainly play a role in determining which patients get referred for cryopreservation, what products are preserved, and where cancer-specific fertility information is available.

Scholarly Project Final Report

The last and fifth question in our systematic review and meta-analysis analyzed ferto-protective therapies. This is one of the best-studied topics within the realm of fertility and cancer therapies. We provided evidence from numerous studies of the unclear role of protecting gonadal tissue with GnRHa chemotherapy. Clinical trials found in our review have suggested conflicting results, questioning the benefit of ferto-protective therapies with hormone suppression.

The methodology of this project utilized existing electronically active articles. This process quickly revealed that there is very limited research on fertility preservation in cancer (questions 2-4). Studies analyzed for each of our five questions revealed substantial differences in assessed outcomes, which made it difficult to create a meta-analysis. Future work would include conducting a randomized control study.

This project raises a number of questions surrounding fertility preservation and there is a strong need for studies that follow cancer patients who undergo fertility preservation. Who gets referred? What are the risks? How long should cryopreserved fertility products be stored? What is the viability of cryopreservation?

Conclusions *(2-3 summary sentences)*

Our analysis is the first attempt at a systematic review of all currently published articles on fertility and fertility cryopreservation in cancer patients. Despite the limitations of existing data, and the pressing need for more comprehensive analysis of fertility in the context of cancer, the literature very clearly shows the impact of some cancers and treatments on fertility.

Figures

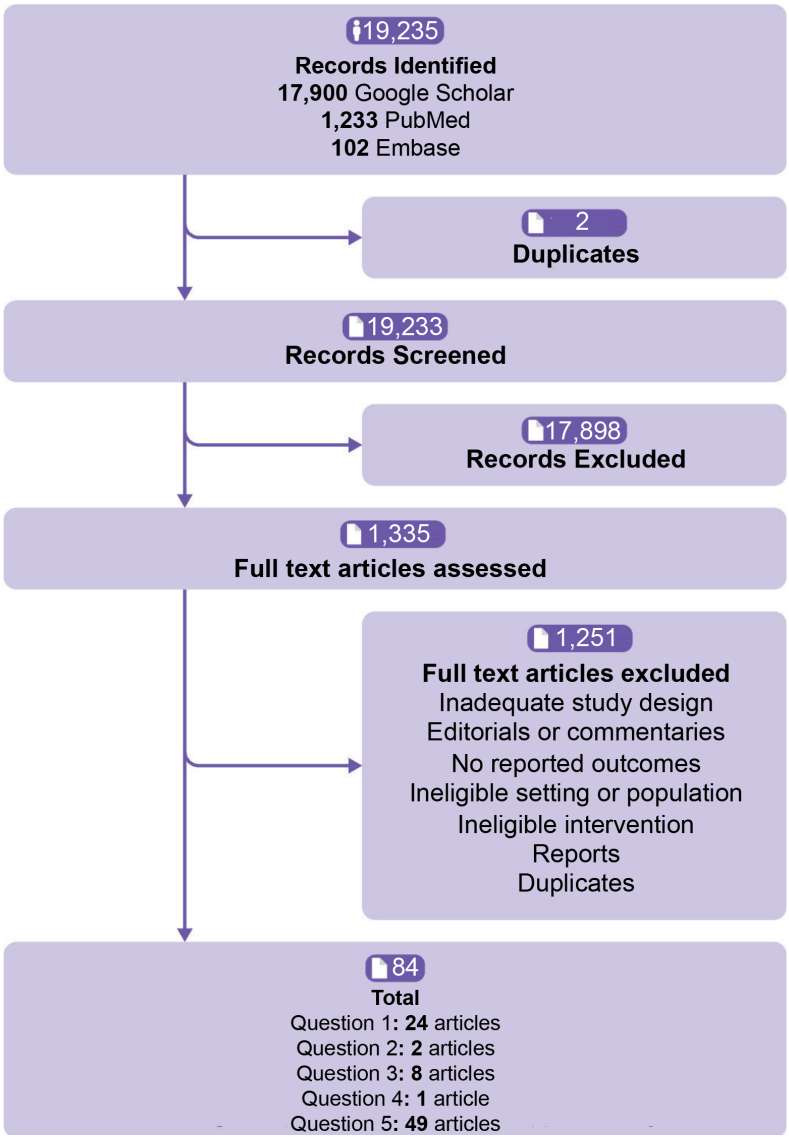

Figure 1. Flow of articles through the review. Figure adapted from Talic et al. (2021) (18).

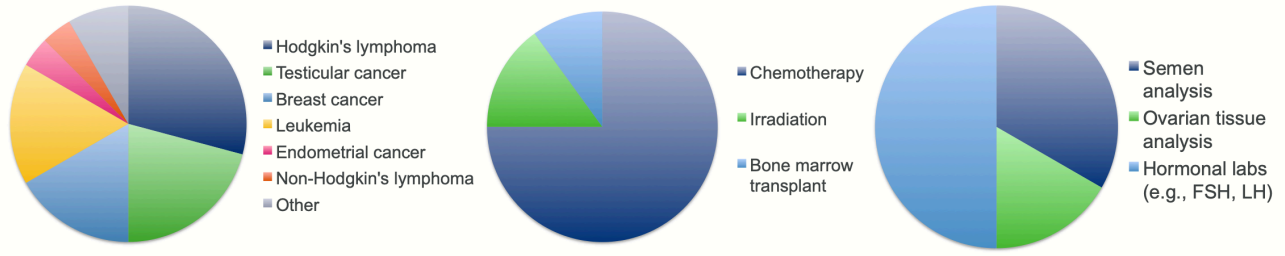

Figure 2. Cancers, therapies, and outcomes assessed for question 1.

Scholarly Project Final Report

#	Title	Journal/Book	Question 1/Outcome(s)	Intervention	Cancer	Publication Year	DOI
1	Age at Birth of First Child and Fecundity of Women Survivors of Childhood Acute Lymphoblastic Leukemia (1987-2007): A Study of the Childhood Cancer Registry of the Rhône-Alpes Region in France (ARCERRA)	Pediatr Hematol Oncol	Yes, chemotherapy, chemo and radiotherapy, conditioning allograft	Chemotherapy	Acute Lymphoblastic Leukemia	2015	10.3109/08880018.2015.1020178
2	Gonadal function and fertility after stem cell transplantation in childhood: comparison of a reduced intensity conditioning regimen containing melphalan with a myeloablative regimen containing busulfan	Br J Haematol	Yes, busulfan and cyclophosphamide, fludarabine and melphalan	Chemotherapy	Acute myeloid leukemia, myelodysplastic syndrome, variety of hematological and congenital disorders	2015	10.1111/bjh.13497
3	Individualized Prediction of Menses Recovery After Chemotherapy for Early-stage Breast Cancer: A Nomogram Developed From UNICANCER PACS04 and PACS05 Trials	Clin Breast Cancer	Yes, menses recovery at 3, 6, and 18 months after the end of adjuvant chemotherapy.	Chemotherapy	Breast Cancer	2019	10.1016/j.clbc.2018.08.005
4	Pre-Treatment AMH Determines Rate of Post-Therapy Ovarian Reserve Recovery: Acute Changes in Ovarian Reserve During and After Chemotherapy	Fertil Steril	Yes, baseline ovarian reserve and alkylating agent exposure effect the magnitude of acute changes in ovarian reserve from chemotherapy	Chemotherapy	Breast, leukemia, lymphoma, sarcoma, brain, Wilm's, germ cell	2013	10.1016/j.fertnstert.2012.09.039
5	Long-Term Oncologic and Reproductive Outcomes in Young Women With Early Endometrial Cancer Conservatively Treated: A Prospective Study and Literature Update	Int J Gynecol Cancer	Yes, pregnancy and live birth rates		Endometrial Cancer	2016	10.1097/IGC.0000000000000825
6	Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG)	Blood	Yes, leomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone	Chemotherapy	Hodgkin lymphoma	2008	10.1182/blood-2007-02-073544
7	Rapid recovery of spermatogenesis after mitoxantrone, vincristine, vinblastine, and prednisone chemotherapy for Hodgkin's disease	J Clin Oncol	Yes, mitoxantrone, vincristine, vinblastine, and prednisone chemotherapy	Chemotherapy	Hodgkin's disease	1997	10.1200/JCO.1997.15.12.3488
8	Evaluation of the efficacy of the VEEP regimen in adult Hodgkin's disease with assessment of gonadal and cardiac toxicity	J Clin Oncol	Yes, vincristine, epirubicin, etoposide, and prednisolone	Chemotherapy	Hodgkin's disease	1995	10.1200/JCO.1995.13.2.387
9	Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial	Lancet Oncol	Yes, serum antimŸllerian hormone and follicle-stimulating hormone measurements		Hodgkin's lymphoma	2018	10.1016/S1470-2045(18)30500-X
10	Gonadal function in males after chemotherapy for early-stage Hodgkin's lymphoma treated in four subsequent trials by the European Organisation for Research and Treatment of Cancer: EORTC Lymphoma Group and the Groupe d'Etude des Lymphomes de l'Adulte	J Clin Oncol	Yes, various combinations of radiotherapy and chemotherapy, with or without alkylating agents, or with radiotherapy alone	Chemotherapy and irradiation	Hodgkin's lymphoma	2007	10.1200/JCO.2006.10.2020

11	Impact of cancer chemotherapy before ovarian cortex cryopreservation on ovarian tissue transplantation	Hum Reprod	Yes, ovarian function recovery, ovarian graft survival, and incidence of pregnancy		Hodgkin's lymphoma, non-Hodgkin disease	2019	10.1093/humrep/dez047
12	Fertility and ovarian function are preserved in women treated with an intensified regimen of cyclophosphamide, adriamycin, vincristine and prednisone (Mega-CHOP) for non-Hodgkin lymphoma	Hum Reprod	Yes, cyclophosphamide, adriamycin, vincristine and prednisone	Chemotherapy	non-Hodgkin lymphoma	2005	10.1093/humrep/dei018
13	Testicular function in poor-risk nonseminomatous germ cell tumors treated with methotrexate, paclitaxel, ifosfamide, and cisplatin combination chemotherapy	J Androl	Yes, methotrexate, paclitaxel, ifosfamide, and cisplatin	Chemotherapy	Nonseminomatous germ cell tumors	2009	10.2164/jandrol.108.006437
14	Stage I seminoma of the testis: a bi-institutional retrospective analysis of patients treated with radiation therapy only	BJU Int	Yes, paternity after irradiation	Irradiation	Seminoma of the testis	2003	10.1046/j.1464-410x.2003.04273.x
15	Effect of low-dose testicular irradiation on sperm count and fertility in patients with testicular seminoma	J Androl	Yes, radiation	Irradiation	Stage I seminoma of the testicle	1994	
16	No long-term increase in sperm aneuploidy rates after anticancer therapy: sperm fluorescence in situ hybridization analysis in 26 patients treated for testicular cancer or lymphoma	Clin Cancer Res	Yes, anticancer therapy on sperm aneuploidy rates		Testicular cancer	2004	10.1158/1078-0432.CCR-04-0582
17	Treatment outcome, body image, and sexual functioning after orchiectomy and radiotherapy for Stage I-II testicular seminoma	Int J Radiat Oncol Biol Phys	Yes, questionnaire with concerns of fertility	Irradiation	Testicular seminoma	2002	10.1016/s0360-3016(02)02849-3
18	Severe adverse impact on sexual functioning and fertility of bone marrow transplantation, either allogeneic or autologous, compared with consolidation chemotherapy alone: analysis of the MRC AML 10 trial	Cancer	Yes, bone marrow transplant	Bone marrow transplant	Acute myeloid leukemia	1999	10.1002/(sici)1097-0142(19991001)86:7<1231::aid-cncr18>3.0.co;2-y
19	Ovarian reserve after chemotherapy in breast cancer: A systematic review and meta-analysis	J Pers Med.	Yes, but systematic review and meta-analysis of anti-Mullerian hormone	Chemotherapy	Breast Cancer	2021	10.3390/jpm11080704
20	ABVD and BEACOPP regimens' effects on fertility in young males with Hodgkin lymphoma	Clin Transl Oncol	Yes, ABVD and BEACOPP regimens	Chemotherapy	Hodgkin lymphoma	2021	10.1007/s12094-020-02483-8
21	Comparing the gonadotoxicity of multiple breast cancer regimens: Important understanding for managing breast cancer in pre-menopausal women	Breast Cancer (Dove Med Press)	Yes	Chemotherapy	Breast Cancer	2021	10.2147/BCTT.S274283
22	Pregnancy Outcomes After a Breast Cancer Diagnosis: A Systematic Review and Meta-analysis	Clin Breast Cancer	Yes, pregnancy outcomes after breast cancer treatment	Chemotherapy	Breast Cancer	2017	10.1016/j.clbc.2017.06.016
23	Pregnancy and live birth after successful cancer treatment in young women: the need to improve fertility preservation and advice for female cancer patients	Expert Rev Anticancer Ther.	Yes, pregnancy and live birth after cancer treatment	Irradiation and chemotherapy	Childhood cancers	2018	10.1080/14737140.2018.1404453
24	How does bone marrow transplantation affect ovarian function and fertility?	Curr Opin Obstet Gynecol.	Yes, bone marrow transplant	Bone marrow transplant	Many cancers	2012	10.1097/GCO.0b013e328353bb57

Supplemental Table 1. Individual studies assessing question 1. The full Excel tables include columns of title, journal/book, question, database found in, tissue, intervention, country, objective(s), setting, patient population, study type/statistical methods used, outcome(s), results (statistics included), conclusions, limitations, study duration, cancer type, publication year, and DOI.

Scholarly Project Final Report

#	Title	Journal/Book	Question 5/Specific therapy	Cancer	Publication Year	DOI
1	Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonadotoxicity in young women by GnRH-a	J Natl Cancer Inst Monogr	Yes, GnRH agonist	Lymphoma, leukemia, nonmalignant autoimmune diseases	2005	10.1093/jncimonographs/lgi015
2	No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial	J Clin Oncol	Yes, GnRH agonist	Lymphoma	2016	10.1200/JCO.2015.65.8864
3	Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study	Fertil Steril	Yes, GnRH agonist	Adenocarcinoma of the breast	2009	10.1016/j.fertnstert.2007.12.044
4	Ovarian rescue/protection from chemotherapeutic agents	J Soc Gynecol Investig	Yes, GnRH agonist	Lymphoma, leukemia	2001	10.1016/s1071-5576(00)00112-x
5	GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial	Ann Oncol	Yes, GnRH agonist	Breast cancer	2017	10.1093/annonc/mdx184
6	Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report	Gynecol Oncol	Yes, GnRH agonist		2001	10.1006/gyno.2001.6181
7	No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a phase II trial from the German Hodgkin Study Group	Ann Oncol	Yes, GnRH agonist	Hodgkin lymphoma	2010	10.1093/annonc/mdq066
8	Gonadatrophin suppression to prevent chemotherapy-induced ovarian damage: a randomized controlled trial	Obstet Gynecol	Yes, GnRH agonist	Breast cancer	2013	10.1097/aog.0b013e31827374e2
9	Gonadotropin-releasing hormone agonists cotreatment during chemotherapy in borderline ovarian tumor and ovarian cancer patients	Chin Med J (Engl)	Yes, GnRH agonist	Ovarian cancer	2013	
10	Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer	J Clin Oncol	Yes, GnRH agonist	Breast cancer	2012	10.1200/JCO.2011.34.6890
11	Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma	Fertil Steril	Yes, GnRH agonist	Hodgkin lymphoma	2008	10.1016/j.fertnstert.2007.02.010

12	Gonadotropin-releasing hormone agonists during chemotherapy for ovarian function and fertility preservation for patients with early-stage breast cancer	Cancer Manag Res.	Yes, GnRH agonist	Breast cancer	2019	10.2147/CMAR.S204069
13	Fertility preservation by endocrine suppression of ovarian function using gonadotropin-releasing hormone agonists: The end of the controversy?	J Clin Oncol.	Yes, GnRH agonist		2018	10.1200/JCO.2018.78.9347
14	Pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients	Cancer Res	Yes, GnRH agonist		2018	10.1158/1538-7445.SABCS17-GS4-01
15	Gonadotropin-releasing hormone agonists for ovarian protection during cancer chemotherapy: systematic review and meta-analysis	Ultrasound Obstet Gynecol.	Yes, GnRH agonist		2018	10.1002/uog.18934
16	Perspectives on the co-treatment with GnRHa in female patients undergoing hematopoietic stem cell transplantation	Endocrine Connections	Yes, GnRH agonist		2017	10.1530/EC-17-0246
17	Gonadotropin-releasing hormone analogs for gonadal protection during gonadotoxic chemotherapy: A systematic review and meta-analysis	Reprod Sci.	Yes, GnRH agonist		2019	10.1177/1933719118799203
18	Debated role of ovarian protection with gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in women with cancer	J Clin Oncol.	Yes, GnRH agonist		2017	10.1200/JCO.2016.69.2582.
19	Appraising the biological evidence for and against the utility of GnRHa for preservation of fertility in patients with cancer	J Clin Oncol.	Yes, GnRH agonist		2016	10.1200/JCO.2016.67.1693
20	GnRH agonist leuprolide acetate neither activates anti-apoptotic genes nor protects human ovary and granulosa cells from DNA damage and apoptosis induced by cyclophosphamide	Fertility and Sterility	Yes, GnRH agonist		2015	10.1016/j.fertnstert.2015.07.192
21	Preserving fertility when choosing chemotherapy regimens-the role of gonadotropin-releasing hormone agonists	Expert Opinion on Pharmacotherapy	Yes, GnRH agonist		2015	10.1517/14656566.2015.1031654
22	GnRH agonist for gonadal protection during chemotherapy	Human Reproduction	Yes, GnRH agonist		2015	10.1093/humrep/dev258
23	Protection of ovarian function by GnRH agonists during chemotherapy: A meta-analysis	International Journal of Oncology	Yes, GnRH agonist		2014	10.3892/ijo.2014.2296
24	An ounce of prevention is worth a pound of cure': The case for and against GnRH-agonist for fertility preservation	Ann Oncol.	Yes, GnRH agonist		2014	10.1093/annonc/mdu036

25	Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: Systematic review and meta-analysis of randomized trials	Minerva Ginecol.	Yes, GnRH agonist		2017	10.23736/S0026-4784.17.04067-9
26	Utility of GnRH-agonists for fertility preservation in women with operable breast cancer: Is it protective?	Curr Breast Cancer Rep.	Yes, GnRH agonist		2013	10.1007/s12609-013-0123-y
27	Gonadotropin-releasing hormone for preservation of ovarian function during chemotherapy in lymphoma patients of reproductive age: A summary based on 434 patients	PLoS One	Yes, GnRH agonist	Lymphoma	2013	10.1371/journal.pone.0080444
28	GnRH agonist for the prevention of chemotherapy-induced ovarian failure in lymphoma	J Clin Oncol.	Yes, GnRH agonist	Lymphoma	2013	10.1200/JCO.2012.42.8185
29	GnRH-analogues for ovarian protection in childhood cancer patients: How adult hypotheses are relevant in Prepubertal females	Curr Drug Targets	Yes, GnRH agonist		2013	10.2174/138945011314080005
30	GnRH analogs for fertility preservation - Let's not jump to conclusions	Breast Care	Yes, GnRH agonist		2012	10.1159/000345902
31	Gonadotropin-releasing hormone agonist for preservation of ovarian function during (neo) adjuvant chemotherapy for breast cancer	J Clin Oncol.	Yes, GnRH agonist		2012	10.1200/JCO.2011.34.6890
32	Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: A systematic review and meta-analysis	Fertil Steril.	Yes, GnRH agonist		2011	10.1016/j.fertnstert.2010.11.017
33	Primary hormonal treatment for early endometrial carcinoma	Eur J Gynaecol Oncol	Yes, hormonal treatment	Endometrial cancer	1998	
34	Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study	J Clin Oncol	Yes, letrozole and gonadotropins	Breast cancer	2008	10.1200/JCO.2007.14.8700
35	Protective effect of leuprolide on ovarian function in young women treated with adjuvant chemotherapy for early breast cancer: a multicenter phase II study	J Chemother	Yes, leuprolide	Breast cancer	2008	10.1179/joc.2008.20.6.740
36	Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy	N Engl J Med	Yes, LHRH agonist	Breast	2015	10.1056/NEJMoa1413204
37	Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC)	Breast Cancer Res Treat	Yes, LHRH agonist	Breast cancer	2008	10.1007/s10549-007-9745-y
38	LH-RH analogues in the treatment of young women with early breast cancer: long-term follow-up of a phase II study	Int J Oncol	Yes, LHRH agonist	Breast cancer	2015	10.3892/ijo.2014.2811

39	Ovarian Function Suppression With Luteinizing Hormone-Releasing Hormone Agonists for the Treatment of Hormone Receptor-Positive Early Breast Cancer in Premenopausal Women	Front Oncol.	Yes, LHRH agonist	Breast cancer	2021	10.3389/fonc.2021.700722
40	Goserelin reduces ovarian failure associated with breast cancer chemotherapy, study shows	BMJ	Yes, LHRH agonist	Breast cancer	2015	10.1136/bmj.h1274
41	Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women	J Clin Oncol	Yes, medroxyprogesterone acetate	Endometrial carcinoma	2007	10.1200/JCO.2006.08.8344
42	Medroxyprogesterone acetate plus metformin for fertility-sparing treatment of atypical endometrial hyperplasia and endometrial carcinoma: trial protocol for a prospective, randomised, open, blinded-endpoint design, dose-response trial (FELICIA trial)	BMJ Open	Yes, Medroxyprogesterone acetate plus metformin	Endometrial cancer	2020	10.1136/bmjopen-2019-035416
43	Phase II study of medroxyprogesterone acetate plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer	Ann Oncol	Yes, metformin	Endometrial cancer	2016	10.1093/annonc/mdv539
44	Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial	BJOG	Yes, metformin plus megestrol acetate	Endometrial cancer	2020	10.1111/1471-0528.16108
45	The safety and efficacy of controlled ovarian hyperstimulation for fertility preservation in women with early breast cancer: A systematic review	Hum Reprod.	Yes, ovarian hyperstimulation	Breast cancer	2017	10.1093/humrep/dex027
46	Fertility preservation with ovarian stimulation and time to treatment in women with stage II-III breast cancer receiving neoadjuvant therapy	Breast Cancer Res Treat	Yes, ovarian stimulation	Breast cancer	2017	10.1007/s10549-017-4288-3
47	Stimulation of the ovaries in women with breast cancer undergoing fertility preservation: Alternative versus standard stimulation protocols; the study protocol of the STIM-trial	Contemp Clin Trials	Yes, tamoxifen		2017	10.1016/j.cct.2017.07.009
48	Five-year changes in ovarian function restoration in premenopausal patients with breast cancer taking tamoxifen after chemotherapy: An ASTRRA study report	Eur J Cancer	Yes, tamoxifen	Breast cancer	2021	10.1016/j.ejca.2021.03.017
49	Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation	J Clin Oncol	Yes, tamoxifen and letrozole	Breast cancer	2005	10.1200/JCO.2005.05.037

Supplemental Table 2. Individual studies assessing question 5. The full Excel tables include columns of title, journal/book, question, database found in, tissue, intervention, country, objective(s), setting, patient population, study type/statistical methods used, outcome(s), results (statistics included), conclusions, limitations, study duration, cancer type, publication year, and DOI.

References *(JAMA style format)*

1. Cancer Research UK (2011) . Cancer incidence by age- UK statistics Retrieved 6 March, 2022, from http://info.cancerresearchuk.org/cancerstats/incidence/age/#Adults.

2. Poorvu PD, Frazier AL, Feraco AM, Manley PE, Ginsburg ES, Laufer MR, LaCasce AS, Diller LR, Partridge AH. Cancer Treatment-Related Infertility: A Critical Review of the Evidence. JNCI Cancer Spectr. 2019 Apr 9;3(1):pkz008.
3. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360(9):902-911.
4. Dillon KE, Sammel MD, Prewitt M, Ginsberg JP, Walker D, Mersereau JE, Gosiengfiao Y, Gracia CR. Pretreatment antimüllerian hormone levels determine rate of posttherapy ovarian reserve recovery: acute changes in ovarian reserve during and after chemotherapy. Fertil Steril. 2013 Feb;99(2):477-83.
5. Sieniawski M, Reineke T, Nogova L, Josting A, Pfistner B, Diehl V, Engert A. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). Blood. 2008 Jan 1;111(1):71-6.
6. M.A.E. van der Kaaij, J. van Echten-Arends, N. Heutte, P. Meijnders, E. Abeilard-Lemoisson, M. Spina, et al. Cryopreservation, semen use and the likelihood of fatherhood in male Hodgkin lymphoma survivors: an EORTC-GELA Lymphoma Group cohort study. Hum Reprod. 2014 Mar;29(3): 525-33.
7. Diesch T, Rovo A, von der Weid N, Faraci M, Pillon M, Dalissier A, Dalle JH, Bader P. Fertility preservation practices in pediatric and adolescent cancer patients undergoing HSCT in Europe: a population-based survey. Bone Marrow Transplant. 2017 Jul;52(7):1022-1028.
8. Chow EJ, Stratton KL, Leisenring WM, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2016;17(5): 567-576.
9. Seshadri T, Gook D, Lade S, et al. Lack of evidence of disease contamination in ovarian tissue harvested for cryopreservation from patients with Hodgkin lymphoma and analysis of factors predictive of oocyte yield. Br J Cancer. 2006;94(7):1007-1010.
10. Agarwal A, Shekarriz M, Sidhu RK, Thomas AJ Jr. Value of clinical diagnosis in predicting the quality of cryopreserved sperm from cancer patients. J Urol. 1996 Mar;155(3):934-8.
11. Gabrielsen A, Agerholm I, Toft B, Hald F, Petersen K, Aagaard J, Feldinger B, Lindenberg S, Fedder J. Assisted hatching improves implantation rates on cryopreserved-thawed embryos. A randomized prospective study. Hum Reprod. 2004 Oct;19(10):2258-62.
12. Lin MH, Morshedi M, Srisombut C, Nassar A, Oehninger S. Plasma membrane integrity of cryopreserved human sperm: an investigation of the results of the hypoosmotic swelling test, the water test, and eosin-Y staining. Fertil Steril. 1998 Dec;70(6):1148-55.
13. Goldrat O, Van Den Steen G, Gonzalez-Merino E, Dechène J, Gervy C, Delbaere A, Devreker F, De Maertelaer V, Demeestere I. Letrozole-associated controlled ovarian hyperstimulation in breast cancer patients versus conventional controlled ovarian hyperstimulation in infertile patients: assessment of oocyte quality related biomarkers. Reprod Biol Endocrinol. 2019 Jan 3;17(1):3.
14. Fabbri R, Vicenti R, Magnani V, Pasquinelli G, Macciocca M, Parazza I, Paradisi R, Battaglia C, Venturoli S. Cryopreservation of ovarian tissue in breast cancer patients: 10 years of experience. Future Oncol. 2012 Dec;8(12):1613-9.
15. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014 Mar-Apr;64(2):83-103. doi: 10.3322/caac.21219.
16. Green DM, Liu W, Kutteh WH, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. Lancet Oncol. 2014;15(11):1215-1223.
17. Fuchs A, Kashanian JA, Clayman ML, Gosiengfiao Y, Lockart B, Woodruff TK, Brannigan RE. Pediatric Oncology Providers' Attitudes and Practice Patterns Regarding Fertility Preservation in Adolescent Male Cancer Patients. J Pediatr Hematol Oncol. 2016 Mar;38(2):118-22.
18. Talic S, Shah S, Wild H, Gasevic D, Maharaj A, Ademi Z, Li X, Xu W, Mesa-Eguiagaray I, Rostron J, Theodoratou E, Zhang X, Motee A, Liew D, Ilic D. Effectiveness of public health measures in

reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. BMJ. 2021 Nov 17;375:e068302.