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Sexual dysfunction and infertility as late effects of cancer treatment

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ABSTRACT

Sexual dysfunction is a common consequence of cancer treatment, affecting at least half of men and women treated for pelvic malignancies and over a quarter of people with other types of cancer. Problems are usually linked to damage to nerves, blood vessels, and hormones that underlie normal sexual function. Sexual dysfunction also may be associated with depression, anxiety, relationship conflict, and loss of self-esteem. Innovations in cancer treatment such as robotic surgery or more targeted radiation therapy have not had the anticipated result of reducing sexual dysfunction. Some new and effective cancer treatments, including aromatase inhibitors for breast cancer or chemoradiation for anal cancer also have very severe sexual morbidity. Cancer-related infertility is an issue for younger patients, who comprise a much smaller percentage of total cancer survivors. However, the long-term emotional impact of being unable to have a child after cancer can be extremely distressing. Advances in knowledge about how cancer treatments may damage fertility, as well as newer techniques to preserve fertility, offer hope to patients who have not completed their childbearing at cancer diagnosis. Unfortunately, surveys in industrialised nations confirm that many cancer patients are still not informed about potential changes to their sexual function or fertility, and all modalities of fertility preservation remain underutilised. After cancer treatment, many patients continue to have unmet needs for information about restoring sexual function or becoming a parent. Although more research is needed on optimal clinical practice, current studies suggest a multidisciplinary approach, including both medical and psychosocial treatment options.

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1. Introduction

Reproductive problems are among the most common and distressing consequences of cancer treatment. Infertility caused by cancer treatment only affects a minority of cancer patients, since most are beyond the age of wanting to have a child. Sexual dysfunction is a more universal threat. For most men and women, reproductive problems persist long after cancer treatment. We summarise the mechanisms of damage to reproductive health from cancer treatment and suggest ways to provide information and effective medical and psychosocial interventions to cancer patients and survivors. We also summarise recommendations for research and practice from the authors, who comprised a panel of experts at the first European Organisation for Research and Treatment of Cancer (EORTC) Survivorship Summit.

2. The prevalence of sexual dysfunction related to cancer

Close to two-thirds of cancer survivors in the United States were treated for pelvic or breast tumors [1], with at least a 50% prevalence of long-term, severe sexual dysfunction [2]. The situation is likely to be similar across Europe, given comparable prevalence and types of cancer [3]. Most sexual problems are not caused by the cancer itself, but by toxicities of cancer treatment [2]. Although sexual problems are more distressing for those under age 65 [4–6], and among patients who are sexually active at cancer diagnosis [7–10], sexuality remains important even for many geriatric cancer survivors [11,12]. Damage during cancer treatment to pelvic nerves, blood vessels, and organ structures leads to the highest rates of sexual dysfunction [10,11,13–20], but problems are common even after lung cancer [8,21], haematologic malignancies [22], or head and neck tumors [23]. Rates of sexual problems are close to 33% in survivors of childhood cancer, with women twice as likely as men to report dysfunction [24,25]. People treated for central nervous system tumors in childhood or adolescence may be limited in their adult relationships by learning disabilities and continued dependence on their families of origin [24]. In both men and women, other side effects of cancer treatment can lead to discontinuation of sexual activity, particularly persistent fatigue [26], nausea, or urinary and bowel incontinence [27–29].

2.1. *Sexual problems in men*

In men, the most common sexual problems are loss of desire for sex and erectile dysfunction (ED) [2]. Less common, but certainly distressing, are changes in the quality of orgasm, difficulties reaching orgasm, and pain with erection or orgasm [29,30]. Despite innovations such as laparoscopic robotic radical prostatectomy, few men recover normal erections after pelvic cancer surgery. Even among men who had excellent erections at baseline and are under age 65, fewer than 25% retain or recover their former erection quality [31–33]. Similarly, techniques to limit damage from radiation therapy have been disappointing, with little evidence of superior erectile function after intensity-modulated radiation therapy or proton therapy compared to computer guided external beam protocols [34–39], and disappointing long-term results after brachytherapy [20,34,39]. It is clear that a history of prostate cancer is a major predictor of sexual dysfunction, even for men on active surveillance. In the Scandinavian Prostate Cancer Group Study, at 12-year follow-up, 84% of men reported erectile dysfunction after radical prostatectomy, as did 80% on active surveillance, compared to only 43% of matched control men who had not had prostate cancer [40]. In the United States, the 10-year follow-up for the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, revealed that over 95% of men in each prostate cancer treatment group had erection problems, again significantly worse than rates in controls [41]. Another prospective cohort study recently reported that by 15-yr follow-up, 87% of men with localised disease have erectile dysfunction [20].

Men who have surgery for bladder [42] or rectal cancer [14,43], or chemoradiation for anal cancer [44] also have high rates of ED. Sexual problems are not exclusive to men who have treatment to the pelvic organs. Hypogonadism and damage to pelvic nerves may lead to sexual dysfunction after intensive chemotherapy [26,45,46], or in men treated with either pelvic radiotherapy or total body irradiation [39,47,48]. Survivors of testis cancer or lymphoma also may have excess rates of sexual inactivity and low desire [49,50], though evidence remains equivocal [51]. Causes may be multifactorial, including hypogonadism, fatigue, and negative mood [45].

Animal studies suggest that obtaining erections several times a week by using treatments such as phosphodiesterase-5-inhibitors, penile injection therapy, or vacuum erection devices may protect the erectile tissue in the penis from atrophy, allowing better recovery of erections over time. Unfortunately, adherence to such treatments, often called penile rehabilitation, is so poor that it has been difficult to demonstrate clear benefit [52].

2.2. *Sexual problems in women*

In women the most common sexual problems are vaginal dryness and other genital changes that lead to pain during sexual activity, or loss of sexual desire, usually accompanied by difficulty feeling arousal and pleasure during sex [2]. Cancer treatments that increase the risk of sexual dysfunction for women include any that cause abrupt, premature ovarian failure in women who had not yet begun menopause [53,54]. Women whose combination chemotherapy leads to permanent ovarian failure seem to have a higher risk for sexual problems than those who continue to menstruate or have just a temporary cessation of menses [55,56]. The risk of permanent ovarian failure increases with the woman's age, especially for women over age 35, and with alkylating drugs and higher total doses of chemotherapy. As in men, any pelvic radiation therapy contributes strongly to the risk of sexual dysfunction, from a combination of ovarian failure and direct tissue damage to genital areas in the radiation field [11,19,39,57]. Use of gonadotropin agonists or antagonists to create a temporary state of ovarian failure also causes sexual problems, although the dysfunctions may resolve once hormonal therapy is discontinued [13]. Bilateral oophorectomy increases the prevalence of sexual dysfunction whether per-

formed as part of cancer surgery or as prophylactic surgery in women with genetic mutations that increase gynaecologic cancer risk [54]. Although oestrogen replacement helps somewhat with vaginal dryness, it does not restore normal sexual function [54]. Hormonal therapy also may cause sexual problems. Women given tamoxifen to prevent or treat breast cancer have negligible changes in sexual function if they did not have prior chemotherapy [53,55], but aromatase inhibitors may cause severe vaginal dryness and pain with sex [10,13]. At least a quarter of women who have systemic graft versus host disease after allogeneic stem cell or bone marrow transplantation develop irritation and then scarring on the vulva and in the vagina. If not treated early, genital graft versus host disease can make intercourse impossible, essentially obliterating a woman's vagina [58].

3. Communication about Sexual Function in Oncology Practice

Although most research on communication about sexuality between health care professionals (HCPs) and cancer patients is qualitative, or based on surveys with limited numbers of participants [59–61], results agree strongly on the major issues, across developed countries. Cancer patients want their HCPs to provide information and help with the sexual consequences of cancer treatment, but rarely receive such care [6,21,62]. HCPs believe that patients who want help with sexuality will bring up the topic themselves [61,63]. Some endorse the value of discussing sex with patients [63], but each profession—oncologists, nurses, mental health professionals—fails to take responsibility to provide such discussions, suggesting it is someone else's job [43,64,65]. Barriers to discussing sex cited by HCPs include lack of time, lack of knowledge, a lack of a network of specialists who can act as referrals, and personal discomfort with the topic of sexuality [63,43,66–68]. HCPs tend to be most reluctant to discuss sex with patients who are different from them, including opposite gender, different sexual orientation, the unmarried, the much younger or older, or patients from a different ethnicity or culture [61,64]. Patients want help with a broad array of sexual issues, not only including sexual function, but also self-concept and relationships, whereas most HCPs discuss sex at best in a narrow, medicalised fashion, focusing on problems such as erectile dysfunction or vulvovaginal atrophy that would prevent penile/vaginal intercourse [60,63,66,69–75]. HCPs report similar patterns of inadequate communication about sexual issues in other areas of care, such as cardiology [76], gynaecologic practice [77,78], general practice [79,80], or psychological practice [81].

4. Assessment of sexual function

Although erections and vaginal blood flow can be measured physiologically, most tests have limited relevance in clinical practice for diagnosing sexual dysfunction or in creating a treatment plan [82,83]. Since sexual desire, arousal, and pleasure are subjective, assessment of changes with cancer treatment often relies on interviews or patient-reported outcome questionnaires [84]. A variety of standardised questionnaires have been used to assess sexual function in oncology settings [84]. Some are specific to one type of cancer, such as the Expanded Prostate Cancer Index Composite (EPIC), which measures sexual function, urinary and bowel incontinence, and symptoms related to hormonal therapy [85]. The Female Sexual Function Index, a 19-item multiple-choice measure for women, has been validated for cancer patients [86]. In the United States, the National Cancer Institute has sponsored research to create brief screening questionnaires for cancer-related sexual dysfunction, as well as a larger bank of problem-specific items that researchers can utilise for a particular research project [69,87]. In Europe, the EORTC Quality of Life (QLG) Sexual health working group has begun qualitative and survey research to develop a more multifaceted Sexual Health Measure for cancer patients and cancer survivors that will include concepts such as body image, self-esteem, and relationship changes as well as assessing actual sexual function (Elfriede Griemel, PhD, personal communication).

5. Interventions for cancer-related sexual dysfunction

Fewer than 20% of most male or female cancer survivors seek professional care (psychological or medical) for their sexual problems [88–90], although close to half would like such help if it were accessible and affordable [88,89]. Over half of men who have radical prostatectomy get medical help for ED, but their rates are exceptional because of surgeons' attention to preserving erectile function through penile rehabilitation [62,91]. Sexuality is rated as a high priority issue by a quarter to three-quarters of survivors [23,62,69], and is ranked as an important unmet need during cancer survivorship [23,42,62,92,93]. Sexual dysfunction after cancer is consistently associated with poor perceived quality of life [5,15,17,93–96].

6. Rationale for a multidisciplinary approach

Research on interventions to improve sexual function and satisfaction in cancer patients and survivors suggests that a multidisciplinary approach, combining medical and psychosocial care, is the most effective strategy [2,97]. Although dysfunctions typically result from physiological damage related to cancer treatment, resuming a satisfying sex life requires good communication between partners [98], taking a view that sexual pleasure and intimacy may include a variety of activities besides penetrative intercourse [73,97–100], and being able to cope with the indignities and limitations of resuming sex after cancer. Providing information and counselling early in the process of treatment planning may be more effective than trying to restore sexual function after problems have become well-established [52,101].

Although a minority of men do try mechanical treatments for ED, satisfaction and adherence remain poor [90,97]. In the United States from 2003 to 2006, Medicare records of 39,000 men with localised prostate cancer showed that 26% used a phosphodiesterase-5-inhibitor after radical prostatectomy,

and only 9% did so after radiation therapy [91]. A number of studies show that men on adjuvant hormonal therapy are the least likely to use a medical treatment for erectile dysfunction. A review of surveys on erectile dysfunction treatment in prostate cancer survivors treated in academic medical centres suggests that 38–52% use oral medication, 7–18% use penile injection therapy, 5–19% use a vacuum erection device, 4–10% try a urethral suppository, and only 2% have penile prosthesis surgery [90,102–109]. Unfortunately, utilisation of these treatments is well below 50% after several months, except in men who have a penile prosthesis [110]. Barriers include the need to interrupt sexual activity, as well as limited partner acceptance.

Similarly, in women it is rare that simple use of vaginal dilation [111,112], lubricants [101], or oestrogen treatments [53,54,101,113] restore the vulva and vagina to a problem-free state. Vaginal dilation is best used as a preventive measure rather than to treat established vaginal atrophy, but it is difficult to convince women to use a dilator regularly [112]. However, innovative new vaginal moisturisers [114,115] and selective oestrogen receptor modifiers [116,117] may provide options to prevent and treat dyspareunia without increasing cancer risk, especially when combined with sexual counselling [113,118].

7. Structure of a sexuality clinic in oncology practice settings

One solution is better training for HCPs in general. A practical model could focus on training one or several team members (such as nurses, physician's assistants, social workers, or psychologists) in an oncology outpatient clinic to be the 'reproductive specialist' who can assess patients' concerns and provide educational resources and brief sexual counselling, using low intensity cognitive-behavioural therapy [119]. Patients who need more intensive medical treatment or cognitive behavioural sex therapy could then be referred to specialists.

Large cancer centres ideally should have in-house sexual dysfunction clinics including specialists in mental health, sexology, gynaecology, and urology, with outreach to cancer site-specific clinics across the institution to educate and encourage HCPs to ask about sexual issues, provide basic information, and make referrals. Such clinics are far from universally available, however. In community oncology offices or less specialised settings, such services are rarely available. At best, oncologists, gynaecologists and urologists provide purely medical suggestions and treatments. At least in the United States, as well as some European countries, poor insurance reimbursement for mental health care is a barrier to establishing counselling and supportive services. Furthermore, few mental health professionals who practice in oncology settings have expertise in treatment of sexual dysfunction. Conversely, most community-based specialists in sexual problems have little knowledge of oncology. Each practice setting should develop a referral network of in-house or community urologists, andrologists, and gynaecologists with expertise in treating medical aspects of sexual dysfunction.

Once a triage system is set up, with trained reproductive counsellors on the frontline and specialists available for referrals, sexual rehabilitation can become a routine part of quality care in oncology. Patients ideally should be informed about potential problems at the time of treatment planning. Further assessment of needs for help should take place at each follow-up visit. One attractive approach is to use electronic media to provide interactive, tailored education and counselling for patients [120], supplementing with human contact as needed [97,118]. When patients are treated at a tertiary referral centre away from home, telehealth options such as realtime online support groups or providing psychotherapy sessions via secure videochat may be helpful. Patients with chronically conflicted relationships [97] or complicated sexual histories [121] may need referral to a mental health professional with expertise in treating sexual dysfunction.

8. Priorities for research on sexuality and cancer

For too long, researchers have focused on defining the prevalence and types of sexual problems after various cancer treatments. Although some valuable work remains to be done on comparative effectiveness of cancer treatments that differ in their risk of reproductive side effects, the types of sexual problems that commonly occur and the cancer treatments that most increase risk for them are clear. The area that continues to be neglected is the design and evaluation of effective interventions to prevent or treat cancer-related sexual dysfunction. In particular, mental health and medical specialists need to collaborate to create cost-effective treatment programs to help prevent, or at least better manage, sexual problems that may interfere with adherence to life-saving cancer treatments, and that clearly damage quality of life in the long-term, even after successful cancer treatment. When helping patients make shared decisions about treatment options, a discussion of potential long-term sexual effects should be included. After evaluating and refining interventions, it will be important to study how best to disseminate and implement them so that they reach not only the affluent, educated patients treated at major urban cancer centres, but also the larger majority of people who rarely have adequate knowledge about cancer-related sexual problems, or skills for coping with them.

As part of the EORTC Survivorship Summit, our working group suggested the following high priority areas for research and future clinical services:

- Create and evaluate cost-effective programs of education and multidisciplinary treatment for sexual dysfunction that can be applied across a variety of oncology treatment settings
- Find ways to prevent cancer-related sexual dysfunction or at least provide early intervention to minimise problems

- Support the efforts of the EORTC QLG to create an instrument that will provide a comprehensive assessment of sexual issues important to cancer survivors, including physiological, psychological, and social aspects of sexuality.

9. The prevalence of cancer-related damage to fertility

Cancer patients aged 44 or less at diagnosis make up about 13% of newly diagnosed cases worldwide [122]. Although men 45 or older may still be interested in having future children [123], this is the age group most at risk for distress when childbearing is interrupted. Damage to fertility is usually linked to particular cancer treatments, but some types of cancer also may be associated with temporary or permanent subfecundity. For example, men with testicular cancer often have poor semen quality at diagnosis, and although most have better values after treatment, those initial semen analyses predict post-treatment sperm quality and genetic integrity [124]. Indeed the risk of several types of cancer is elevated in men with poor semen quality who present for infertility treatment [125]. In women, too, childlessness is associated with elevated risk of some types of ovarian cancer [126] and with hormone-sensitive breast tumors [127]. Women with mutations in the BRCA1 gene also may have a genetic risk for decreased ovarian reserve, leading to an earlier average age at menopause [128].

In general however, it is the treatments used for cancer that damage fertility. Chemotherapy regimens that include alkylating drugs are associated with the highest risk of infertility in both men and women, with damage to sperm or oocytes increasing with drug dose [129]. The testes are even more sensitive than the ovaries to damage from radiation therapy [130]. The mechanisms of damage to fertility may be similar for chemotherapy and for a significant dosage of radiation to the gonads [129,130]. In the ovaries, one recent theory is that the number of primordial follicles recruited for growth accelerates, ultimately resulting in apoptosis of successive waves of maturing oocytes, diminishing and ultimately eradicating the supply [131]. Blood flow to the ovaries has also been observed to decrease after some types of chemotherapy, and certainly decreases with tissue damage from radiation therapy [132]. Age is a greater factor in post-treatment fertility for women than for men with cancer [133]. When women reach their mid- to late thirties, oocytes are recruited and die at an accelerated rate, even without an environmental risk factor [132].

Because fertility preservation is a new option, with high costs and unknown long-term benefits, it would be helpful to have criteria to optimise patient selection. Levels of anti-müllerian hormone (AMH), a marker of the number of primordial follicles remaining in the ovaries, predict a woman's likelihood of having menstrual cycles after chemotherapy [133]. Very low levels of AMH are also associated with poor response to ovarian stimulation [134]. Obtaining AMH levels or using ultrasound imaging of the ovaries to examine volume and antral follicle counts may give some idea of an individual woman's ovarian reserve before or after cancer treatment, but neither measure is reliable enough to definitively guide decisions about whether a cycle of ovarian stimulation would be worthwhile [134]. Recently, concerns have been raised over the reliability of a new commercial AMH assay used in most clinical settings [135]. International standards for AMH values are also still lacking [134].

A woman's age, individual ovarian reserve, type and dose of chemotherapy and/or dose of radiation to the ovaries give a general idea of the likelihood that she will end up in permanent, premature ovarian failure after cancer treatment, but more prospective research is needed to develop predictive algorithms to use in individual clinical-decision making about fertility preservation [132–135]. Many women under age 35 at the time of cancer treatment will continue to menstruate or will recover menstrual cycles, but because their ovarian reserve has been depleted, they remain at significant risk to reach menopause years earlier than normal [132]. Furthermore, the presence of menstrual cycles has been used as the endpoint of much research on cancer and fertility, but is far from a guarantee that conception will be possible [132].

With data from a number of registry-based studies, becoming pregnant after completing cancer treatment does not appear to increase the risk of disease recurrence, even in women with hormone-positive breast cancer [136]. Occult damage to heart or lung function after a woman's cancer treatment may occasionally cause unexpected health problems during a pregnancy. More often, women have birth complications after cancer that include low birth weight infants, premature birth, miscarriage, or neonatal death, particularly in women who had uterine exposure to radiation in childhood [137].

For men, permanent infertility after cancer treatment results when all stem cells in the testes have been destroyed by either chemotherapy or radiation therapy [130,138]. About 3% to 18% of men are azoospermic at cancer diagnosis, before receiving any treatment [139]. Even if no sperm are found in a man's semen, islands of sperm production may remain. Exploration of the testes using microsurgery has allowed urologists to harvest mature sperm to use for cryopreservation before cancer treatment or for fertility treatment after cancer [139]. Recovery of spermatogenesis is common after chemotherapy or lower doses of radiation to the testes, but may take several years [130,138].

10. Health of children born to cancer survivors

Large studies of children born to parents who were treated for cancer before conception have largely been reassuring. No excess rate of congenital abnormalities or genetic disease has been found in offspring of childhood cancer survivors [140,141], or in the offspring of young adults treated for cancer [137]. Even most children exposed in utero to chemotherapy during a mother's cancer treatment for cancer appear to be healthy, as long as treatment is delayed until the second trimester of pregnancy [142].

11. Techniques of fertility preservation

Sperm banking has been available for post-pubertal men facing cancer treatment for decades, but became more widely

used after the advent of intracytoplasmic sperm injection in the early 1990s [130,138]. Even if only a few sperm cells with poor motility survived freezing and thawing, they could be used for conception with *in vitro* fertilisation. Still, records of utilisation of cryopreserved semen in many large registries continue to show that typically only about 10% to 20% of men retrieve their samples for infertility treatment [143]. Most men conceive using fresh sperm after cancer. Others die or decide not to have children. Although a number of cancer centres are cryopreserving small pieces of testicular tissue obtained from prepubertal boys who undergo cancer treatments with high risk of damaging fertility, we remain years away from having a way to use these samples for conception [130,138]. Human sperm cells have not yet been successfully matured *in vitro* or by autografting the tissue onto an immunodeficient mouse host. Autotransplantation of testicular tissue risks reintroducing cancer cells. A hope is that spermatogonial stem cells that manufacture sperm cells can be isolated and used to repopulate the cancer survivor's testis, but attempts have not been successful in humans [130].

Fertility preservation is even more complicated and expensive in women. For prepubertal girls, the only current option is again the experimental one of retrieving ovarian tissue for cryopreservation [144]. Later options would include autotransplantation of the thawed tissue, with its attendant risks of a cancer recurrence, or using primordial follicles with *in vitro* maturation, another procedure that is not yet technically possible, though advances are being made [145]. Recently, a live birth was reported after conception using a metaphase II oocyte harvested from the ovary of a young woman with ovarian cancer and matured *in vitro* before being fertilised in the laboratory [146]. Ovarian tissue cryopreservation is still considered experimental by the American Society of Reproductive Medicine [147], and autotransplantation of ovarian tissue has resulted in fewer than 30 live births worldwide [148]. It is now possible, however, to begin ovarian stimulation for fertility preservation at any point in the menstrual cycle with excellent results, so that the cycle can usually be accomplished in less than 2 weeks [149], minimising delays in starting cancer treatment. Since birth rates are now equal using cryopreserved oocytes subsequently thawed and fertilised, compared to those from using cryopreserved embryos, the options have increased for young cancer patients who are not in a stable relationship [148]. For women with breast cancer, protocols using letrozole as part of ovarian stimulation can minimise peak estradiol levels during fertility preservation without compromising results, potentially decreasing the risk that a cycle of hormone stimulation would lead to cancer recurrence [149].

Cancer treatments can sometimes be modified to spare fertility, for example avoiding the use of alkylating chemotherapy in treating Hodgkin lymphoma when the cancer prognosis is favourable [150,151]. When women are going to have pelvic radiotherapy, ovarian transposition (moving the ovaries out of the field to minimise their exposure) can often preserve hormonal function and fertility, though uterine capacity may still be damaged [152]. Other options that may be successful for both cancer treatment and fertility preservation include conisation for noninvasive cervical malignancies, trachelectomy for very early stage cervical cancer, which spare the uterus and ovaries [153], conservative surgery for germ cell, borderline, or early stage epithelial ovarian tumors [154], and treatment of early stage uterine cancer with progestogen therapy, followed by hysterectomy after pregnancy [155].

12. Utilisation of fertility preservation

Sperm banking, a relatively inexpensive and medically uncomplicated procedure, remains underutilised in industrialised nations [138,156], even in countries whose universal health system pays for sperm banking [157]. In a recent Swedish registry-based cohort, however, 68% of men recalled getting information on sperm banking and 54% preserved semen [158]. The most common barrier remains failure to get information to male patients in a timely way in oncology treatment settings [159]. The oncologist's recommendation is a crucial factor [155,156,159]. For teens, it is important to include the parents in the education and counselling as part of the decision process [160]. Despite relatively low rates of utilisation of banked semen, sperm banking remains a simple and effective type of fertility preservation. In a recent study of men treated for Hodgkin lymphoma, semen cryopreservation doubled the odds of fatherhood after treatment, with 20% of children conceived using cryopreserved semen [161].

Even fewer eligible women undergo some type of fertility preservation. The out-of-pocket costs to undergo ovarian stimulation or surgery to retrieve ovarian tissue for storage vary widely across the world. A high cost for *in vitro* fertilisation not only decreases the rate of usage in a nation's women, but also influences the number of embryos placed in a transfer cycle, with higher costs of care leading to the adverse outcome of more multiple births [162]. In the United States, where insurance rarely covers ovarian stimulation, only 12% of infertile women use any infertility services, with the great majority only having a medical consultation [163]. Women who use assisted reproductive technology are older, more affluent and educated, and more likely to be Caucasian [163]. These same demographic trends are seen in the small percentage of United States women with cancer who undergo fertility preservation [164–166]. Yet even in Canada, where fertility preservation is included in national health insurance, fewer than 5% of eligible women appear to have fertility preservation before cancer treatment [167]. In one academic centre in the Netherlands, only 2% of women had fertility preservation [168]. Young girls or adult women are less likely than men to be informed about fertility preservation [169]. In the same Swedish cohort with such high rates of sperm banking, only 12% of women had been offered fertility preservation and 2% proceeded [158]. Some women could only have a biological child with the help of a gestational carrier, but restrictive laws in many European states forbid such arrangements, leaving opportunities only for those wealthy enough to afford reproductive 'tourism,' with the added concern of exploitation of women living in poverty [170].

13. Information, decisional support, and counselling about fertility preservation

Surveys of adolescents and young adults with cancer show that a majority want information on damage to fertility and

options for parenthood, particularly those who have not yet begun having children [151,171–176]. Despite guidelines on counselling patients about fertility preservation originally published in 2006 by the American Society of Clinical Oncology, two surveys conducted several years later found than fewer than half of oncologists in the United States were making routine referrals [177,178]. In a recent survey of 100 oncologists in the United Kingdom, only 38% routinely provided written material on fertility preservation to eligible patients [179]. Despite a national system of sperm banking for oncology patients in the United Kingdom, 21% of cancer specialists who responded to a survey were unfamiliar with local policies, and many let their own beliefs influence which men they referred [180]. In a study of French oncologists, 54% had not referred a single female patient for fertility preservation in the past 6 months [181]. Common barriers found in research on oncologist communication include lack of time in busy clinics, lack of knowledge about fertility preservation, and not knowing how or where to refer patients. In addition, many oncologists do not discuss fertility preservation if they believe a patient would not be able to afford it financially, or if a patient has a poor prognosis or already has at least one child.

Some evidence already suggests that having the opportunity to consider fertility preservation and to make an informed decision can improve well-being in cancer survivors [182]. Actually storing reproductive material helps patients feel more optimistic about the future [182,183]. A survey of young women treated for cancer, 10 years after their diagnosis, revealed that those who had wanted a child and were unable subsequently to fulfil their desire remained significantly distressed about infertility [184]. Childless women were affected the most severely. A recent survey of young cancer survivors in Germany also found unmet needs for information and lingering distress, especially in women [185].

Because decisions about preserving fertility are complex and usually must be made within a narrow window of time that is already extremely stressful because of the unexpected diagnosis of cancer, efforts are being made to create educational materials and decision aids for patients [186–189]. Although the science of decision-making in health settings is advancing, few studies have evaluated the long-term outcomes of decision-aids on cancer patients' well-being [190]. More work is needed to find the best ways to educate patients about cancer-related infertility and to help them make choices that will improve their future satisfaction with life.

14. Parenthood options after successful cancer treatment

The major focus of research on fertility and cancer has been on modalities to prevent damage from cancer treatment. However, as illustrated above, the majority of cancer survivors who want to have children do not have cryopreserved genetic material. Women may want evaluation of their current ovarian reserve to help in deciding whether to try to conceive naturally, pursue assisted reproductive technology, or consider social parenthood by means of donated oocytes or embryos, or adoption [132,184]. Men often have not had a recent semen analysis, and are unsure whether they could father a pregnancy [143]. Although cancer survivors express more comfort with adoption than with using donor sperm or oocytes [171,172], their medical history may be a barrier to adopting in many international or domestic contexts [191]. One solution would be a multidisciplinary clinic that could assess current fertility in cancer survivors, offer appropriate options for fertility treatment, and also provide education and counselling on options to become a parent or to resolve grief about cancer-related infertility.

15. Priorities for research and clinical services regarding cancer and fertility

The working group suggests the following priorities related to cancer and fertility:

- Establish a European registry, including biomarkers that could be used to predict infertility in response to specific cancer treatments. Include periodic standardised surveys about clinical services such as counselling and referral regarding fertility preservation
- Create tools to facilitate shared decision-making for patients who are at risk for infertility from cancer treatment
- Create multidisciplinary programs to assess fertility after cancer treatment, help patients to make decisions about parenthood, and to offer a range of options for patients to become parents.

Conflict of interest statement

None declared.

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