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Reproductive Complications and Sexual Dysfunction in Cancer Survivors

Leslie R. Schover

Defining the Population at Risk for Reproductive Complications

This chapter will review risk factors and management for three types of reproductive complications of cancer treatment: infertility, menopausal symptoms, and sexual dysfunction. Each problem area affects unique, albeit overlapping, populations of cancer patients and survivors.

Risk Factors for Cancer-Related Infertility

The demographics of cancer survivorship and delayed childbearing ensure that increasing numbers of patients will have their family-building disrupted by cancer treatment. The success of cancer treatment for malignancies that affect young people, such as pediatric cancers, testicular cancer, and Hodgkin's Disease, has yielded a large population of cancer survivors. According to the National Health Information Survey of 2001,[1] 2.2% of adults aged 18 to 44 in the United States have been diagnosed with cancer. Extrapolating based on statistics for this age group from the United States 2000 Census,[2] approximately 2.5 million adults of childbearing age are cancer survivors. It is more difficult to specify how many have faced infertility, but most probably had treatment with gonadotoxic chemotherapy, and smaller numbers would be at risk for infertility because of surgery or radiation therapy affecting the reproductive system.

Another trend that increases the salience of cancer and fertility is delayed childbearing in American families. Birth rates for women in their thirties have been climbing steadily, reaching a high in 2001 of 95.6 per 1,000 women aged 30–34 and 41.4 per 1,000 women aged 35–39.[3] Births to women aged 40–44 have more than doubled since 1981 to 8.1 per 1,000 women. According to the United States Census report for 2000, the percentage of childless women age 30–34 has jumped from 19.8% in 1980 to 28.1% in 2000, and for women aged 35–39 from 12.1% in 1980 to 20.1% in 2000.[4] When these women are ready to conceive, some will receive the unwelcome news of a malignancy. Data on paternal age are not readily available, but in 1995 in the United States, men at marriage were on the average 2.7 years older than their brides so that men, too, would be more at risk currently to have cancer interfere with their fertility.[5]

Infertility Related Directly to a Malignancy

For a few types of malignancy, for example testicular cancer, the risk of infertility and risk of cancer are related. In a cohort of 3,530 Danish men who were born between 1945 and 1980 and developed testicular cancer from 1960 to 1993, the standardized fertility rate was significantly lower (ratio 0.93) than for all 1,488,957 Danish men born in the same era.[6] Fertility was particularly reduced in the two years leading up to cancer diagnosis, and for men with nonseminomatous tumors (ratio 0.87). Furthermore, men who developed testicular cancer were less likely than men in the general population to conceive male children, possibly indicating a genetic or environmental factor.

Skakkebæk and his colleagues believe that a testicular dysgenesis syndrome (TDS) is increasing in frequency in Western countries because of environmental influences in utero, perhaps combined with a genetic susceptibility factor. The syndrome includes testicular cancer, undescended testes, hypospadias, and decreased semen quality.[7] Although the evidence for TDS, and in particular the influence of endocrine disrupting pollutants, remains controversial, it is clear that men with testis cancer have a high percentage of abnormalities in the contralateral testis suggesting abnormal fetal development of these tissues.[8] The standardized incidence ratios of testis cancer in 32,442 men who had a semen analysis at the laboratory in Copenhagen between the years of 1963 and 1995 were compared with rates in the general population of Danish men.[9] Parameters of poor semen quality, including low count, poor motility, and abnormal morphology, were all associated with increased risk of testis cancer (standardized incidence ratios of 2.3–3.0).

In women, a recent evidence-based review of the link between infertility and cancer risk concluded that borderline ovarian tumors are slightly more common in women

diagnosed with infertility.[10] It is less clear whether infertile women are at increased risk for invasive ovarian cancer, but rates may be elevated in those who never achieve a pregnancy or among women with endometriosis. In contrast, infertility does not appear to be a risk factor for breast cancer.[10] Although most cohort and case-control studies have not demonstrated a link between using ovarian stimulating drugs to treat female infertility and subsequent cancer risk for any site,[11] a recent comparison of 4,575 women with breast cancer and 4,682 controls found that women who used human menopausal gonadotropin for at least 6 cycles had a greater relative risk of breast cancer (2.7–3.8).[12]

Infertility Caused by Cancer Treatment

Many cancer patients are put at risk for infertility by the therapies used to eradicate or control their malignancy. Surgical treatment for pelvic cancer may remove a critical part of the reproductive organ system, e.g. bilateral orchiectomy for prostate cancer or for asynchronous testicular tumors, or bilateral oophorectomy as part of treatment for gynecological malignancies or as prevention for breast or ovarian cancer in women with BRCA mutations.[13] Treatment of prostate or bladder cancer may entail removal of the prostate and seminal vesicles and the vagina or uterus may be removed to treat vaginal, cervical, or uterine cancer. Nerves controlling antegrade ejaculation of semen may be damaged in retroperitoneal lymphadenectomy for testicular cancer[14] or in surgery for colorectal cancer.[15]

Radiation therapy to the pelvis damages fertility because developing gametes and ovarian follicles, like cancer cells, are more likely to be in the genetically vulnerable, proliferative state.[16] Patients treated for prostate or cervical cancer, or those who have total body irradiation as preparation for bone marrow transplant, are the most common groups to experience radiation-associated infertility.

Chemotherapy drugs also interfere with gametogenesis because maturing sperm and oocytes are vulnerable to the toxins that damage rapidly-growing cancer cells.[17,18] Alkylating drugs (including the platinum-based chemotherapies) are most likely to damage fertility. The likelihood of permanent ovarian failure in women increases with cumulative dose and age, and is manifested as decreased numbers of follicles, atretic follicles, and fibrotic changes in the ovary.[19] Spermatogenesis is even more vulnerable to disruption by chemotherapy, with a similar pattern of risk factors in terms of dosage and type of drugs.[20] The impact of male age on fertility after cancer is unclear, but in general men over age 45 take longer to establish a pregnancy and have decreased conception rates.[21]

Preventing and Managing Cancer-Related Infertility

Preserving fertility is highly important to men and women diagnosed with cancer before completing their families. Although research on the psychosocial aspects of cancer-related infertility is limited, surveys and qualitative interview studies concur that most survivors feel healthy enough to be good parents, believe that their experience of cancer has increased the value they place on family closeness, are particularly distressed about infertility if childless, and are not getting enough information on options to spare or treat fertility.[22–26]

Utilization of infertility services in the United States is limited even for the population at large. Less than 50% of women with infertility seek medical consultation and only 1.6% use assisted reproductive technology.[27] Although male factors explain roughly half of infertility, no statistics are available on men's use of infertility services.[28] This gives some context for help-seeking among cancer survivors with infertility.

Preventing Cancer-Related Infertility

Obviously, it is preferable to prevent cancer-related infertility rather than to try treating it after the fact. Hormonal manipulation during chemotherapy may be used to try to minimize damage to the gonads. In addition, when treatment of a particular malignancy has become highly successful, efforts have been made to spare fertility in younger patients by using less toxic chemotherapy drugs or by limiting cancer surgery. Several options are available to cryopreserve gametes or embryos before cancer treatment for later use in conception, although assisted reproductive technology is typically required. Each of these options will be reviewed, and the level of evidence for its efficacy examined.

Hormonal Prevention

In men, efforts during chemotherapy to protect the spermatogonia A cells that produce mature spermatozoa have included prescribing GnRH analogues with or without accompanying testosterone. Despite promising results in animals, human trials have been uniformly disappointing.[29] Howell and Shalet speculate that continuing hormonal treatment for several months after finishing chemotherapy might have more success, allowing surviving stem cells to recover and renew spermatogenesis. If no spermatogonia survive chemotherapy or radiation therapy, however, continuing hormonal treatment will be fruitless. Even in the prepubertal testis, cancer therapies damage fertility because the Leydig, Sertoli, and germ cells are not truly quiescent, but continue to develop,[30] making them vulnerable to toxic cancer therapies.

Efforts at hormonal protection of the ovaries during chemotherapy in women have had more promising results, but double-blind randomized trials are still lacking. The largest case-control cohort has been followed by Blumenfeld in Israel.[31] An injectable GnRH agonist was administered, beginning 1 to 2 weeks before chemotherapy and continuing for up to 6 months, to a group of 60 women aged 15 to 40 being treated for lymphoma. All but 3 of the surviving women resumed menstruation by the end of the first year, compared to only 45% of 60 women treated with chemotherapy alone, without hormonal protection. Inhibin –A and –B levels decreased during GnRH administration, normalizing only in the women who resumed menstruation.[18] Although the GnRH and comparison groups did not differ on age, tumor type, cumulative dose of chemotherapy drugs, or exposure to radiation therapy, the comparison group consisted either of historical controls or women who were not seen in time to start the GnRH-agonist before chemotherapy.[31] Obviously, selection bias is possible.

The use of a GnRH-agonist during adjuvant chemotherapy for breast cancer is attractive because it not only may protect against ovarian failure in young women, but could potentially add to cancer control. In a Phase II pilot study, a group in Rome administered the long-acting GnRH analog goserelin for one year during adjuvant chemotherapy to 64 newly diagnosed women with breast cancer, aged 18 to 50 and without distant metastases.[32] Dosage and drug regimen depended on cancer stage. At a median follow-up time of 55 months, 86% of women had resumed menstruation after chemotherapy, including five who had stem cell transplantation. Although this was a lower rate of ovarian failure than would be expected, no comparison group was provided.

Chemoprotection Strategies

Even if hormonal protection helps preserve a greater number of primordial follicles during chemotherapy, many of those remaining would be damaged.[33] Another type of chemoprotection is suggested by advances in understanding how toxins like chemotherapy influence signaling pathways in the testis and ovary. A small lipid molecule, sphingosine 1-phosphate, may be able to prevent damage to the follicles as well as protecting against genetic damage to the oocyte.[34] Even more tantalizing is the recent discovery of stem cells in the human ovary, suggesting that females are not limited to the number of oocytes that survive fetal development, but have ongoing replenishment of primordial follicles.[35]

Cryopreservation of Reproductive Tissue for Future Conception

The most well-established form of reproductive tissue cryopreservation in cancer patients is sperm banking. Measures of the effectiveness of sperm banking include the success of using sperm cryopreserved by cancer patients in conceiving healthy offspring and the utilization of stored samples by cancer survivors.

Conception rates from banked sperm have increased radically since the advent of intracytoplasmic sperm injection (ICSI) in 1992. In this technique, only one live sperm is injected into each oocyte retrieved from in vitro fertilization (IVF). Rates of fertilization with ICSI do not differ when using sperm that was cryopreserved versus from a fresh ejaculate, nor has the use of cryopreserved sperm resulted in increased birth defects.[36]

Although many men diagnosed with cancer have impaired semen quality, samples from patients with suboptimal semen parameters survive freezing and thawing just as well as sperm from men of normal fertility.[37,38] Several prospective case series of men who cryopreserved sperm are presented in Table 19.1. Only about 6% to 18% of cancer patients are azoospermic and unable to bank at the time of attempted semen collection.[39,41,42,44] The most efficient use of stored samples is to attempt to conceive with IVF-ICSI,[41,43] unless the semen quality is unusually good.

It appears that less than 10% of men who store semen actually use their samples to try to conceive, but this rate may be accelerating with the availability of IVF-ICSI.[42–44] The percentage of couples who use their cryopreserved sperm with assisted reproductive technology (ART) and actually have a live birth varies widely from center to center, but is comparable to results for the general population of infertile couples.[41,43] With all cohorts in Table 19.1 combined, 37 healthy babies were born, with only one pregnancy terminated because a major fetal malformation was detected.[42]

Although specific rates of impaired fertility have been reported for a variety of chemotherapy combinations or radiation therapy doses and fields,[29] it is not possible to accurately predict recovery of fertility in any one man treated for cancer.[36] Therefore, sperm banking should be routinely offered when men are about to begin treatments that put fertility at risk. An adequate number of specimens can be banked without delaying cancer treatment in all but the most

TABLE 19.1. Long-term follow-ups of cohorts of consecutive cancer patients who cryopreserved sperm.

Reference	*Year*	*Number of Patients*	*Years follow-up*	*% able to store sperm*	*% using samples*	*Cycles of ART*	*Pregnancies per cycle*	*Live births*	*% couples attempting conception who achieved parenthood*	*Birth defects*
Lass et al.[39]	1998	191	8	83%	3%	IUI: 2 IVF: 9 ICSI: 4	100% 22% 50%	7	83%	0
Audrins et al.[40]	1999	258*	20	—	2%	IUI: 53 IVF: 14	4% 36%	7	33%	0
Kelleher et al.[41]	2001	930	22	90%	10%	IUI: 28 IVF: 28 ICSI: 35	43% 31% 21%	39	45%	2
Blackhall et al.[42]	2002	122*	22	94%	27%	—	—	11	27%	1
Agarwal et al.[43]	2002	318**	20	—	9% (26% in past 4 yrs.)	IUI: 37 IVF: 23 ICSI: 20	8% 26% 35%	12	44%	0
Ragni et al.[44]	2003	776	15	88%	5%***	IUI: 40 IVF: 6 ICSI: 42	8% 0% 26%	14	43%	1

*Hodgkin's disease only.

**Only N cryopreserving sperm was reported.

***Rates increase with duration of follow-up to 12% at 12 years.

emergent cases. A study of 95 cancer patients found that acceptable post-thaw semen quality could be obtained when men abstained for only 24 to 48 hours between collecting ejaculates.[45]

Despite low rates of usage of stored sperm, men do not appear to regret the trouble or expense. Hallak and colleagues examined the reasons that 56 (16%) of 342 cancer men who had banked sperm before cancer treatment in their clinic discarded their cryopreserved specimens.[46] Out of the 56 men, 21 had died and the families discarded the samples, 23 had already conceived all the children they wanted without using their stored sperm, 8 had a return of good semen parameters, and 4 had decided not to have children. The cost of banking sperm was not a factor in these decisions.

Unfortunately, recent surveys of oncologists reveal that many fail to give men information about sperm-banking, underestimating its importance to their male patients and overestimating the barriers of cost and availability of sperm banking facilities.[47–49] For those cancer patients interested in having future children, the most common reason cited for failure to bank sperm is lack of timely information. In our recent survey of young male survivors, only half recalled their oncology health care providers discussing the possibility of banking sperm.[23]

The pediatric oncology community has shown an increasing interest in giving teens with cancer the option of banking sperm. Out of 238 boys aged 12 to 19 referred to one center in London, 87% were able to produce an ejaculate for semen storage, with semen quality similar to that in adult cancer survivors.[50] A new experimental technique uses testicular biopsies to obtain spermatogonia from prepubertal boys for cryopreservation before cancer treatment, in the hope that they can be replaced through autografting to restore fertility later. Attempts at replacement in adult men have been disappointing, however, since it is not possible to inject the thawed suspension of cells directly into the fibrous seminiferous tubules.[29] Cryopreserved human spermatogonial stem cells have been transplanted into mouse testes and survived for up to 6 months, suggesting that xenotransplantation could some day be another option for producing mature sperm cells for IVF-ICSI, or at least for providing a research model.[51]

In women, progress is also being made with the use of a rapid freezing technique called *vitrification* to freeze mature, unfertilized oocytes, although pregnancy rates still do not approach those with cryopreserved embryos.[52] Another promising avenue is the use of sugars as cryoprotectants during freezing.[53] To have a true analogue to sperm banking in men, it would be necessary to cryopreserve primordial follicles and then to mature them in the laboratory. Although such techniques remain years away,[54] researchers are having some preliminary success with in vitro maturation of freshly retrieved antral follicles that are approaching full maturity.[55]

A number of centers around the world are removing and cryopreserving ovarian tissue for women about to undergo cancer treatment that could impair fertility.[54] Several cases of auto-transplantation have taken place, with promising results.[56,57] Technical problems include minimizing injury to ovarian tissue during the freezing itself and ischemia causing damage to follicles while the graft grows a new vascular system.[58] For some malignancies, concern about reintroducing cancer cells along with the ovarian tissue may limit this option.[58] An alternative use of the tissue could be in xenotransplantation to immunodeficient mice with subsequent harvest of mature oocytes. Recently an embryo was produced using an oocyte retrieved from transplanted ovarian tissue in a female cancer survivor, but no pregnancy resulted when the embryo was transferred to the woman's uterus.[59] Furthermore, the first primate has been born using this technique—a rhesus monkey.[60] Still, an ethical dilemma is that women facing cancer treatment and desperate to protect their future fertility are paying several thousand dollars in out-of-pocket costs to harvest, freeze, and store ovarian tissue with very low odds that a pregnancy will ever result.

Ovarian Transposition During Pelvic Radiation Therapy

When radiation therapy fields include the pelvis, the ovaries can be moved surgically to a more protected location. Although both medial positioning behind the uterus and lateral movement to the pelvic sidewall have been used, currently the most common procedure is to use laparoscopy to move the ovaries laterally just prior to starting radiotherapy. Although ovarian transposition can be performed during a staging laparotomy, it is less effective because the ovaries tend to migrate back to their original position.[61] The ideal position is above the pelvic brim, with the fallopian tubes remaining attached to the uterus.[62]

A recent literature review of the outcome of laparoscopic lateral ovarian transposition included only 44 cases of women under age 40 with a variety of malignancies. However, 89% had preserved menstrual function.[62] Oophoropexy can be complicated by vascular injury, infarction of the fallopian tube, or ovarian cyst formation. IVF is often required to conceive. Women with adenocarcinoma of the cervix or with more advanced stage disease may be at some risk for metastasis to a transposed ovary or to the site of trocar insertion for the laparoscopy.[63] Successful transposition may still be followed by early menopause because of reduced ovarian reserve after radiation therapy.[64]

Fertility-Sparing Surgery for Early-Stage Gynecological Malignancies

Young women diagnosed with early stage cervical or ovarian cancer may opt for conservative surgical procedures that allow them to retain fertility. For women with squamous cell carcinoma of the cervix that is invasive but still early stage, a trachelectomy can be substituted for a radical hysterectomy.[65–68] After the majority of the cervix is removed, the vaginal cuff is sewn back to the cervical remnants. As long as lymph nodes and surgical margins are clear, recurrence rates are comparable to those after radical hysterectomy. Although many women are able to become pregnant after trachelectomy, rates of miscarriage and prematurity are higher than normal. The cervical mucous plug that prevents infection of the amniotic membranes may be inadequate and there is an increased risk of cervical incompetence.

Women with adenocarcinoma of the cervix that is either in situ or very early stage can be treated with conization alone to preserve fertility, as long as surgical margins are clear.[69,70] Adenocarcinoma of the cervix is often multifocal or located high in the endocervical canal, however, and about 20% of

women with negative margins at the time of conization will have local recurrences.

In conservative surgery for young women with borderline or germ cell ovarian tumors, only the affected ovary is removed, preserving the uterus and contralateral ovary.[66] Results have been good, both in terms of fertility and cancer control, but only small case series have been published.[71,72] Recurrence rates after conservative surgery for borderline tumors are higher than after radical surgery, but survival rates remain similar[71] Conservative surgery has also been utilized for Stage I epithelial tumors.[73] The largest cohort study included women treated for germ cell tumors with a median follow-up of 122 months.[74] Of those who tried to conceive (N = 38), 76% have become pregnant.

Other Fertility-Sparing Modifications of Cancer Treatment

Other modifications made to cancer treatment to spare fertility have not been evaluated in randomized clinical trials, but instead have been compared to historical controls. Examples include the less gonadotoxic chemotherapy regimens for Hodgkin's disease[75]; surveillance protocols and nerve-sparing retroperitoneal lymphadenectomy for early stage testicular cancer[76]; and orthotopic bladder reconstruction with fertility preservation for men with bladder cancer.[77]

The Safety of Pregnancy After Cancer Treatment

It would be of little utility to promote fertility in women after cancer if pregnancy were a risk factor for cancer recurrence. However, evidence has accumulated that becoming pregnant after successful cancer treatment does not affect women's survival, even those who have had breast cancer.[78] Women diagnosed with breast cancer during pregnancy often have more advanced disease but do not have a survival disadvantage when matched to nonpregnant controls on medical factors such as cancer stage and histology.[79]

An area much in need of study is the psychosocial impact of experiencing cancer during pregnancy, and the development of supportive interventions for women in this predicament.[80] One recent survey found that reproductive concerns remain salient in women successfully treated for gestational trophoblastic disease and that 75% would have attended support groups if they had been available during treatment.[81] Young survivors often lack accurate information about pregnancy after cancer. In our pilot survey, 20% of breast cancer survivors and 18% of women with other cancer sites worried at least "a fair amount" that pregnancy could trigger a recurrence of cancer. Only 53% of women recalled any discussion by their oncology team of pregnancy after cancer.[22]

Survivors also lack knowledge about potential pregnancy complications related to impaired cardiac, pulmonary, or uterine function after cancer treatment. Few would plan evaluation by a high-risk obstetrician before trying to conceive.[22] In the largest study to date, 4,029 pregnancies of participants in the Childhood Cancer Survivor Study were reviewed.[82] A woman's history of chemotherapy was not associated with adverse outcomes, but women who had pelvic irradiation were more likely to have low birthweight infants. A higher than expected rate of voluntary pregnancy termination was observed, again suggesting that women may be worried about the safety of pregnancy or about the likelihood of having healthy offspring. Some women may also have been told in error that they were infertile, and thus did not use contraception to prevent an unwanted pregnancy. Higher rates of miscarriage and prematurity have also been observed in women with uterine exposure to radiotherapy as young adults, although the damage from childhood exposure is more severe.[83]

The Use of Assisted Reproductive Technology (ART) and Cancer

Although cryopreservation of embryos is far more successful than freezing unfertilized oocytes or ovarian tissue, undergoing IVF before cancer treatment presents some difficulties.[84,85] Women with a very aggressive malignancy such as acute leukemia may not have time to delay chemotherapy for several weeks of ovarian stimulation. Women who do not have a committed male partner have to use an anonymous sperm donor to create embryos. Women recently diagnosed with cancer often do not produce many mature oocytes in response to IVF. Women with untreated breast cancer risk exacerbating their disease by taking hormones for IVF. One alternative is natural cycle IVF, in which the one or two oocytes that mature without exogenous hormones are harvested and fertilized. Recently Oktay and colleagues developed an IVF protocol especially for women newly diagnosed with breast cancer, using tamoxifen for ovarian stimulation. The average number of embryos per cycle was 1.6 compared to 0.6 with a natural cycle, yielding a higher chance of an eventual pregnancy.[86] Ovarian stimulation regimens combining tamoxifen and follicle stimulating hormone (FSH) are yielding even better results.[87]

Women who wait until after chemotherapy to try IVF typically have a suboptimal response to the hormone stimulating drugs.[85] Creating embryos with oocytes from a donor is another option for the woman who has diminished fertility or is in ovarian failure after cancer treatment, but can still carry a pregnancy.[88,89] The cancer survivor herself does not undergo the risks of ovarian stimulation. If she is in ovarian failure, she may need some hormonal support to prepare her uterus for embryo transfer, as well as during the first weeks of a pregnancy, until the placenta begins to produce its own hormones. The hormone levels during these intervals are similar to those in a natural pregnancy. Pregnancy rates per cycle with donated oocytes are high, especially when both egg donor and recipient are under age 35. Women who have had pelvic irradiation still suffer the risk of prematurity and miscarriage, however. Along with survivors who have lost their uterus to cancer but have stored embryos or ovarian tissue, they may work with a gestational carrier to have a child. Only isolated case reports are available in the literature, however.[90]

For men with poor semen quality after cancer, IVF with ICSI is the preferred method of treatment. Some men do not have any mature spermatozoa in their semen, or no longer ejaculate seminal fluid after their cancer treatment. If they did not bank sperm before treatment, some options are still open to them. Men who do not ejaculate after node dissection for testis cancer or surgery for colorectal tumors may respond to medications that temporarily restore antegrade ejaculation. Viable sperm may also be retrieved from urine voided just after orgasm. Perhaps the most reliable means of

obtaining sperm from these men is via electrical stimulation of ejaculation with a probe in the anal canal.[91] This procedure must be performed under anesthesia, but yields samples that typically can be used for IVF with ICSI.[92] Some urologists have used electroejaculation to obtain ejaculates from young teens who are unable to collect semen through masturbation due to anxiety or religious constraints.[93]

About half of men with no sperm in their semen after chemotherapy do have islands of spermatogenesis in their testes. A few viable sperm can be retrieved in testicular biopsies and used for successful IVF with ICSI.[94,95] Although increased aneuploidy has been observed in the sperm of men recently treated for cancer,[96] and aneuploidy has been associated with poorer fertilization rates with ICSI,[97] the pregnancy rates using ICSI with testicular sperm from cancer survivors have been comparable to those with other causes of male factor infertility, with a quarter to a third of cycles resulting in a healthy baby.[94,95] In a recent case series of 33 male childhood cancer survivors, only 33% of had normal semen quality but the integrity of DNA in their spermatozoa did not differ from that in a group of control men, suggesting that offspring would not be at increased risk of birth defects or other health problems.[98]

Health of Offspring of Cancer Survivors

Despite concerns that children born to men or women who had been treated for cancer would have unusual rates of genetic abnormalities or fetal malformations,[99] the available data suggest reasonable cause for optimism. Karyotypes of 2,630 live-born children with a parent who had survived childhood cancer were available from the Danish Cytogenetic Registry.[100] The rate of abnormal karyotypes was not significantly greater than those in the children born to the siblings of the childhood cancer patients. No study has thus far documented an excess rate of birth defects in children born after one parent's cancer treatment, with the caveats that (1) a limited number of offspring have been studied; and (2) the nature and duration of follow-up of offspring has been limited.

Genetic damage from cancer treatment may impact rates of early miscarriage or the gender of surviving infants. In addition to the results of pregnancies from the females in the Childhood Cancer Survivor Study,[82] 2,323 pregnancies sired by the male cancer survivors were documented. The live birth rate of 69% was significantly less than that for the survivors' brothers, and a deficit of male offspring born to the survivors was also observed.[101] Partners of men exposed to more than 5,000 mg/m^2 of procarbazine had an increased risk of miscarriage. A large Scandinavian registry study did not document any increased lifetime cancer risk in offspring, except in families with known, autosomal dominant inherited cancer syndromes.[102] Most offspring in these studies have been born to childhood cancer survivors long removed from their active treatment when they conceived. On the other hand, some types of chemotherapy can be administered to pregnant women in the second and third trimesters without causing fetal malformations.[103]

A new issue is the impact on young adults' childbearing decisions of knowing they carry a mutation that increases lifetime cancer risk. For example, women with BRCA mutations increase their risk of breast cancer by having a pregnancy before age 40 and decrease their risk by early oophorectomy without estrogen replacement.[104,105] Technologies such as prenatal diagnosis and preimplantation genetic diagnosis are also available to identify known autosomal dominant mutations responsible for hereditary cancer syndromes,[106] bringing potential ethical dilemmas, especially whether they should be used for those syndromes with a relatively late onset.

Risk Factors for Cancer-Related Menopausal Symptoms

Since the incidence of cancer increases with aging, menopausal symptoms are probably of high concern for more survivors than infertility. Women treated for breast cancer and men receiving hormonal therapy for advanced prostate cancer are particularly at risk for troublesome hot flashes (see Chapters 11 and 12). Vaginal atrophy and dyspareunia are the major sexual consequences of menopause for women[107] and will be discussed in the sections on sexual function. Menopause-related risks for cardiovascular disease and osteoporosis fall outside of the scope of this chapter.

Psychosocial Factors and Hot Flashes

It is unclear whether cancer survivors experience more severe menopause symptoms than women in the community without a cancer history. The prevalence of menopausal symptoms has generally been overestimated. The Massachusetts Women's Health Study followed a large cohort of women through the transition to menopause.[108,109] Most women did not have hot flashes or depression, had neutral or positive attitudes to menopause, and did not seek any medical attention for menopausal symptoms. Women who had hysterectomy were a more distressed group, with indications that women with pre-existing psychological problems are more likely to have this surgery.[110] An analysis of sexual function in 200 of the participants found that estrogen levels were significantly correlated with reports of dyspareunia, but not with any other sexual problem. A woman's perceptions of her overall health and the quality of her dyadic relationship were stronger predictors of her sexual function than was her menopausal status.[111]

Psychosocial factors play an important role in women's menopause complaints. The best predictors of depression, general health, and utilization of medical services after menopause are a woman's physical and psychological health and history of medical consultation before menopause.[109,110,112,113] Hot flashes and the use of hormone replacement therapy (HRT) are both correlated with psychological distress.[114,115] More educated women are consistently less likely to report hot flashes,[114,115] and cultural beliefs and expectations about menopause affect women's symptom reporting.[116]

The Prevalence of Hot Flashes After Breast Cancer

Women with breast cancer are the group most at risk for troublesome hot flashes after cancer treatment because they are advised not to use systemic estrogen replacement. No large case-control study has compared hot flashes in breast cancer survivors and other women. Carpenter and colleagues

surveyed breast cancer survivors from a tumor registry, with about a third responding (N = 69), and compared them to a convenience sample of women with no history of breast cancer but similar age. Hot flashes were more frequent, severe, and distressing for the breast cancer sample. This finding may reflect selection bias in women who chose to participate, as well as the fact that women in the breast cancer group were significantly more likely to be menopausal and less likely to be using estrogen replacement.[117] Within the breast cancer group, hot flash severity and indices of emotional distress were related, parallel to findings in the general population of postmenopausal women.[117,118]

Among 860 breast cancer survivors surveyed by Ganz and colleagues at an average of 3 years post-diagnosis, 55% reported problems with hot flashes, a higher rate than expected from similar studies in healthy postmenopausal non-users of HRT.[119] Women who are premenopausal at breast cancer diagnosis and become menopausal because of cancer treatment are at highest risk to have hot flashes.[119–121] Although women taking tamoxifen experience hot flashes, they decrease after therapy ceases if women resume menses.[122,123] When adjuvant chemotherapy causes permanent menopause, however, hot flashes, vaginal dryness, and decreased quality of life persist even at long-term follow-up.[122,124]

Menopause Symptoms After Other Malignancies

Very little information is available on the prevalence and severity of menopausal symptoms in young women treated for other malignancies with chemotherapy or pelvic radiation that causes ovarian failure, although hot flashes and vaginal dryness are classic symptoms in women who become menopausal after treatment for gynecological cancer[125,126] or after intensive chemotherapy for hematological malignancies.[127] Women whose tumors are not hormone-sensitive may be less reluctant than breast cancer survivors to use estrogen replacement,[127] although publicity about the results of the Women's Health Initiative[128] has many women questioning the benefits of estrogen to manage all but the most short-term menopausal symptoms.

Hot Flashes in Male Cancer Survivors

A final group of cancer survivors at risk for menopausal symptoms are men who have androgen ablation to treat prostate cancer or take hormonal therapy for male breast cancer. Whether prostate cancer treatment involves orchiectomy or administration of a gonadotropin-releasing-hormone (GnRH) agonist, half to three-quarters of men report troublesome hot flashes.[129] As in the literature on menopausal women, there is not convincing evidence that androgen ablation increases depression in men, although sexual dysfunction is quite common.[129] Although in the year 2002, 189,000 new cases of prostate cancer were expected compared to only 1,500 men diagnosed with breast cancer,[130] the symptoms of hot flashes and sexual dysfunction are also common when men are treated with tamoxifen for advanced breast malignancies.[131]

Managing Menopausal Symptoms in Cancer Survivors

A variety of treatments are available for menopausal symptoms, ranging from relaxation treatment to antidepressant medication or hormonal replacement therapy. Only a few have been validated in double-blind randomized trials, a crucial design given the large and enduring placebo effect observed when breast cancer survivors are presented with a credible treatment for hot flashes.[132] Most intervention studies have used breast cancer survivors, the principal group at risk because of their concern about using estrogen replacement and their high rates of hot flashes. Men on hormonal therapy for prostate cancer have been another target group.

Estrogen Replacement for Hot Flashes

Estrogen replacement has consistently been shown to reduce hot flashes in 80% to 90% of postmenopausal women.[132] Nevertheless, an estimated 56% of all American women on HRT tried to stop within the first 8 months after publication of the Women's Health Initiative findings.[133] This randomized trial not only failed to confirm health benefits of HRT[128] but showed that HRT increases the risk of breast cancer.

The literature on using estrogen replacement after treatment for breast cancer also showed clear benefits in alleviating menopausal symptoms.[134–136] Case control studies failed to find an impact on survivors' cancer recurrence or decreased survival,[134,135,137–143] including a meta-analysis comparing 717 breast cancer survivors using some form of HRT to 2,545 nonusers. The relative risk of recurrence for women on HRT was 0.72 (95% confidence interval 0.47–1.10).[144] The relative risk of death for women on HRT after breast cancer was 0.18 (95% confidence interval, 0.10–0.31).

The first randomized trial[145] to be conducted confirmed these results, but included only 56 women in the estrogen-treated group. Women who agree to participate in such a trial may be a very select sample, since most survivors of breast cancer are highly anxious about the risks of taking estrogen.[145,146] More recently, the HABITS trial of the safety of hormone replacement therapy after breast cancer was stopped after 345 women had been followed for a median of about 2 years. An excess of new breast cancer events showed up in the hormone-treated group.[147]

One alternative hormonal therapy for hot flashes is to use progestins alone. Depomedroxyprogesterone acetate was effective in reducing hot flashes in a randomized clinical trial of breast and prostate survivors, and 45% continued using the medication for up to three years, despite some side effects.[148]

Nonhormonal Therapies for Hot Flashes

Trials of nonhormonal approaches to treating hot flashes are summarized in Table 19.2, with a focus on trials that include cancer survivors. Newer antidepressants appear to be the most promising nonhormonal therapy for both breast and prostate cancer survivors with hot flashes, producing greater relief and fewer side effects than older treatments such as progestins, clonidine, or bellergal.[132] Some other widely touted remedies such as isoflavones, black cohosh, and magnetic therapy have proved disappointing when tested in placebo-controlled trials.[153–155,158,159]

TABLE 19.2. Trials of nonhormonal therapies for hot flashes.

Reference	*Year*	*Type of trial*	*Number of patients*	*Type of treatment*	*Type of patients*	*Average length of follow-up*	*Impact on hot flashes*
Pandya et al.[149]	2000	Randomized, double-blind trial	194	Oral clonidine, 0.1 mg./day	Postmenopausal women on tamoxifen for breast cancer	12 weeks	38% reduction on clonidine vs. 24% on placebo
Stearns et al.[150]	2003	Randomized, double-blind trial	165	Paroxetine, 12.5 or 25.0 mg./day	Postmenopausal women without active cancer or cancer treatment	6 weeks	62% reduction on 12.5-mg./day and 65% on 25.0 mg./day
Loprinzi et al.[151]	2000	Randomized, double-blind trial	191	Venlaxafine, 75 mg./day or 150 mg/day	Breast cancer survivors or women scared to use HRT	4 weeks	37% reduction on 75 mg./day, 49% on 150 mg./day and 27% on placebo
Quella et al.[152]	1999	Pilot trial	16	Venlaxafine, 25 mg./day	Prostate cancer patients on androgen ablation with hot flashes	4 weeks	54% reduction in hot flashes
Quella et al.[153]	2000	Randomized, double-blind trial	149	50 mg. soy isoflavone/day	Breast cancer survivors with severe hot flashes	9 weeks	24% of women had 50% reduction on soy, 36% on placebo
Tice et al.[154]	2003	Randomized, double-blind trial	246	57 mg. or 82 mg. of isoflavone/day	Recently postmenopausal with severe hot flashes	12 weeks	No significant group differences
Nikander et al.[155]	2003	Randomized, double-blind trial	62	114 mg.isoflavone/day	Postmenopausal breast cancer survivors with hot flashes	12 weeks	No significant group differences
Muñoz et al.[156]	2003	Random, open-label trial	136	20 mg. *Cimicifuga racemosa*	Premenopausal breast cancer survivors on tamoxifen	52 weeks	Treatment group improved significantly more than usual care group in number and frequency of hot flashes
Wuttke et al.[157]	2003	Randomized, double-blind placebo-controlled	62	40 mg. *Cimicifuga racemosa* vs. 6 mg. conjugated estrogens vs. placebo	Postmenopausal women	13 weeks	Herbal preparation and estrogen gave equal symptom relief and both were better than placebo
Jacobson et al.[158]	2001	Randomized placebo-controlled, stratified on tamoxifen use	69	Black cohosh	Breast cancer survivors who had completed primary treatment	8 weeks	No significant group differences
Carpenter et al.[159]	2002	Randomized, placebo-controlled crossover study	11	Magnetic device	Breast cancer survivors	3 days	Placebo group improved more than magnet group
Porzio et al.[160]	2002	Pilot trial	15	Acupuncture	Breast cancer patients on tamoxifen	26 weeks	Emotional distress and hot flashes decreased significantly

Given the magnitude of the placebo effect, promising results using herbal remedies or acupuncture must be confirmed with randomized, placebo-controlled trials. For example, acupuncture using clinically recommended points could be tested against acupuncture using sites judged inactive according to traditional Chinese medicine. The duration of therapies tested has also been quite short, particularly given the stubborn nature of hot flashes in breast and prostate cancer survivors. Since some studies focused on cancer survivors with severe symptoms while others used unselected samples, the efficacy of various treatments cannot be directly compared. Although not yet tested in cancer survivors, behavioral modalities such as relaxation training[132,161] and engaging in regular aerobic exercise[162] show promise in decreasing hot flashes in postmenopausal women unselected for cancer history.

One small, randomized trial has examined the efficacy of a brief, nursing intervention in reducing menopausal symptoms in 76 postmenopausal breast cancer survivors chosen because they had at least one severe problem of hot flashes, vaginal dryness, or urinary stress incontinence.[163] Women were randomized to receive usual care or to have a special session with a nurse practitioner to assess symptoms and apply treatment algorithms such as prescribing medication or advising on the use of vaginal lubricants and moisturizers. Telephone follow-up calls were included. All three target symptoms improved in the treated group compared to the usual care group. This type of inexpensive, brief intervention

should be replicated, and then tested in further studies to evaluate its effectiveness and dissemination into a variety of healthcare settings.

Risk Factors for Cancer-Related Sexual Dysfunction

To understand the prevalence of sexual dysfunction after cancer, it is important to realize how common these problems are in otherwise healthy adults.

Prevalence of Sexual Dysfunction in the General Population

The National Health and Social Life Survey (NHSLS) conducted in 1992 still provides the best estimates of the prevalence of sexual problems in American adults 18 to 59, because the researchers used probability sampling and achieved a high response rate (79%).[107,164] Thirty-one percent of men and 43% of women had experienced a sexual dysfunction in the past year. Factors associated with sexual problems included poor physical and mental health, aging, past sexual trauma, and relationship satisfaction.

More recently, the Pfizer Global Study of Sexual Attitudes and Behaviors has used similar interview techniques to sample over 26,000 men and women aged 40 to 80 in 28 countries around the world. Although response rates were much lower than in the NHSLS, the sheer volume of data is impressive. Again, one-third to one-half of men and women reported having sexual dysfunctions during the past year.[165] In the data subsets from the United States, Canada, Australia and New Zealand, lack of sexual desire was the most frequent female problem (29%) whereas premature ejaculation was the most common male dysfunction (26%)[166] Overall, women were twice as likely as men to experience difficulty with sexual desire, experiencing pleasure, and reaching orgasm. Most large surveys agree that erectile dysfunction (ED) increases dramatically with age and cardiovascular risk factors in men, so that by age 70, about half of men experience it.[167–168] In contrast, sexual problems in sexually active women (other than vaginal dryness) do not increase consistently with age or ill health.[107,166] Elderly women are more likely than men of the same age to be without a sexual partner, however.[169]

Risk Factors for Sexual Dysfunction After Cancer

Within groups of cancer survivors, sexual dysfunction is usually related to the impact of cancer treatment, rather than being a function of the cancer itself, with a few notable exceptions. Prostate cancer that is locally advanced may damage nerves essential for erection.[170] Women with gynecological cancer, especially cancer of the cervix, vagina, or vulva, may experience pain and bleeding with sexual activity as a presenting symptom of their malignancy.[171] Cancer survivors most at risk for treatment-related sexual dysfunction are those with pelvic tumors and/or those whose treatments damage the hormonal systems mediating sexual desire and pleasure.

Psychosocial factors are also crucial. The risk of sexual dysfunction for any individual cancer survivor is heightened by overall emotional distress, relationship conflict, and having a partner who is sexually dysfunctional. It is also important to remember that medications used to treat depression, anxiety, pain, and nausea during and after cancer treatment frequently have sexual side effects.[167–169]

Treatment-Related Sexual Problems in Men

Men treated for prostate cancer are the group at highest risk for sexual dysfunction. In a prospective study of 31,742 nonphysician health professionals aged 53 to 90, rates of ED for the 2,109 men who had been diagnosed with prostate cancer were 10 to 15 times higher than for men of comparable age.[168] Despite attempts to modify surgery or radiation therapy for prostate cancer to spare sexual function, recent large cohort studies suggest that 75% to 85% of men treated for localized disease have long-term problems with ED.[172–175] Rates of ED are similar after radical cystectomy[176] but somewhat lower with treatment for colorectal cancer.[177] Men on hormonal therapy for advanced prostate cancer have even more severe sexual dysfunction because of the impact of androgen ablation on sexual desire and arousability.[129,175]

Men treated for testicular cancer are often assumed to be at increased risk for sexual problems. Two extensive recent reviews of the literature on this topic concur that few studies of high quality are available.[178,179] Nevertheless, both reviews conclude that the only clear sexual morbidity of treatment for testicular cancer is the interference of retroperitoneal node dissection with antegrade ejaculation. When the lymph nodes are fully dissected along the bifurcation of the aorta, nerves are disrupted that control the smooth muscle contractions of the prostate and seminal vesicles during the emission phase of male orgasm. The result is that men experience the pleasure of orgasm, but with no expulsion of semen. Most retroperitoneal lymphadenectomies now spare crucial nerves by limiting the dissection, preserving normal ejaculation of semen in 75% to 90% of patients.[180,181]

Prospective data on sexual function from a very recent Norwegian randomized trial of chemotherapy for 666 men with metastatic germ cell tumors found that sexual problems rose somewhat 3 months after treatment began, but by 2-year follow-up had subsided to normal levels.[182] The quality of the sexual relationship with a partner had also not suffered. In the longer term, however, testicular cancer survivors who had higher doses of external beam radiation therapy may have an increased risk of ED with aging[178] because of the potential for reduced blood flow in an irradiated pelvic vascular bed.

Higher than expected rates of sexual dysfunction have been reported in longer-term survivors of renal cell carcinoma[183] and bone marrow transplantation.[184] Low-normal to frankly low levels of testosterone are common in young men treated with high-dose chemotherapy for lymphoma or Hodgkin's Disease, which could be a factor in loss of sexual interest and arousal.[29]

Treatment-Related Sexual Problems in Women

Breast cancer is often assumed to be the site most associated with female sexual dysfunction. Although sexual problems are present in about half of long-term survivors of breast cancer, rates are comparable to those in age-matched women who have not had cancer.[119] Frequency of sexual activity is

also similar to that of community-dwelling women of similar age.[119,123,185] Premenopausal women whose chemotherapy results in ovarian failure cancer do have unusually high rates of sexual dysfunction, however,[119,123,186] including a long-term loss of desire for sex, increased vaginal dryness, and dyspareunia. In a sample of 153 women interviewed 20 years after having chemotherapy for premenopausal breast cancer, 29% attributed current sexual problems to past cancer treatment.[187] In contrast to chemotherapy, tamoxifen is not associated with decreased desire for sex or impaired lubrication with sexual arousal.[119,186–188] Breast loss is not a crucial factor in these problems, contrary to conventional wisdom. Comparisons of women after various breast surgeries have been highly consistent in showing that breast conservation and reconstruction are not superior to mastectomy in preserving women's sexual function or satisfaction.[119,123,188,189]

Indeed, young women treated for leukemia or Hodgkin's disease are as likely as breast cancer survivors to report sexual dysfunction.[187] About a quarter to a third of women have sexual dysfunction after treatment for hematological malignancies. Although both psychosocial trauma and ovarian failure can contribute to their sexual problems,[190,191] in at least one, small randomized trial, a less gonadotoxic chemotherapy was not superior in sparing sexual function.[192]

A gender difference in sexual function seen both in unselected, healthy women[193] and in cancer survivors[119,194] is that women's sexual satisfaction is not tightly linked to physical functioning like men's, but rather to overall well-being and the quality of intimacy and affection with the sexual partner. For example, in women treated for vulvar cancer, the extent of the tissue excised is less important than relationship happiness in predicting sexual satisfaction.[194] Among breast cancer survivors, those who had found new partners after their cancer treatment had the happiest sex lives.[119]

Nevertheless, it is clear that treatment for gynecological malignancies, including cancer of the cervix, vulva, or uterus, does increase the prevalence of sexual dysfunction beyond that seen in healthy, community-dwelling peers, particularly rates of vaginal dryness and pain with sexual activity.[195] In women treated for localized cervical cancer, pelvic radiation therapy has a more negative impact than radical hysterectomy in reducing vaginal lubrication and expansion with sexual arousal, as seen in two small, but carefully monitored, prospective studies.[196,197] The literature on hysterectomy for benign disease also demonstrates no detriment of surgery to sexual function, even when the cervix is removed, as long as the woman's hormonal status remains unchanged.[198,199] The risk of painful sex and loss of erotic pleasure increases when bilateral oophorectomy is included, or if pelvic surgery affects vaginal caliber or depth, as in abdomino-perineal resection,[177] radical cystectomy,[200] or total pelvic exenteration.[201]

Management of Sexual Symptoms in Cancer Survivors

Despite increased attention in the past 20 years to sexual dysfunction as a consequence of cancer treatment, pitifully little progress has been made in developing cost-effective treatment programs to alleviate these symptoms. The entire field of behavior therapy for sexual dysfunction has seen scant innovation in techniques or new outcome research since the 1970s.[202] Although standard sex therapy programs have been modified for cancer patients,[203] prospective studies of efficacy are lacking.

In 1987, we published a retrospective chart review of detailed clinical notes on consultations in a sexual rehabilitation program within a cancer center over a 4-year period.[203] Out of 384 individuals or couples, 73% were seen only once or twice. Of the index patients seen, 308 were men and 76 were women. Male cancer patients were older, and were more likely to include a partner in their visits (56%) than were the women (28%). Seventy-nine percent of the patients had pelvic malignancies, but this probably reflected referral bias, since the program was located within a urology department and also had strong ties to gynecology. According to their retrospective reports, the prevalence of sexual dysfunctions had increased after cancer treatment in the index patients, but not in their partners. Most men sought help for ED whereas women typically had a combination of loss of desire and vaginal dryness/dyspareunia.

About half of patients were seen prior to or during cancer treatment, and half were first evaluated after treatment had been completed. Follow-up data on outcome were available for only 118 cases. The therapist rating of improvement was "somewhat to much better" for 63% of this group. Factors correlated with better outcome included having more counseling sessions, younger age, absence of depression, and absence of marital conflict.

Prospective clinical trials of sex therapy for specific types of sexual dysfunctions after cancer, using standardized outcome measures, should have followed this report. They are strikingly absent from the literature, however. The majority of people with sexual dysfunction after cancer never seek professional help. In the Pfizer Global Study of Sexuality, less than 20% of men or women unselected for health who had sexual problems consulted a physician about them, although roughly half discussed the problem with a partner, friend, or family member.[204]

Physicians are often urged to initiate discussions of sexuality with all patients, but an analysis of data from the same survey on 5,250 men aged 40 to 80 from 7 countries in Europe revealed that less than 7% had a physician who initiated an assessment of sexual function in the past year, although the majority of men believed such dialogues should be routine.[205] Medical schools in North America only devote an average of 3 to 10 hours to sexuality in the entire 4-year curriculum,[206] so that a physician who wants to counsel patients on sexual rehabilitation must be essentially self-taught. Qualitative interviews of nurses and physicians on an ovarian cancer treatment unit in England confirmed that less than a quarter ever discussed sexuality with patients,[207] despite knowing that sexual problems were prevalent.

We will discuss evidence-based management of sexual problems after cancer using the minimal empirical evidence that exists in the literature on treatment of dysfunctions in men and women unselected for health, and in the literature on sexual rehabilitation after cancer.

Modifying Cancer Treatment to Spare Male Sexual Function

One approach to managing cancer-related sexual dysfunction is to modify cancer treatment to prevent damage to

hormonal, vascular, or neurologic systems needed for a healthy sexual response.

In men, hormonal therapy for advanced prostate cancer results in a profound loss of desire for sex, as well as erectile dysfunction and difficulty reaching orgasm (see also Chapter 12).[175,208,209] Tactics to avoid this morbidity have included delaying treatment in asymptomatic men, using intermittent hormonal therapy to keep prostate specific antigen (PSA) values close to zero while allowing improved sexual function during intervals off treatment, or prescribing an androgen-blocker such as bicalutamide either alone or in combination with finasteride. Unfortunately, delayed treatment may compromise ultimate survival time,[210] and both androgen production and sexual function appear to be permanently impaired by a period of months on androgen ablation.[175,211] Bicalutamide is more promising, but considerable sexual morbidity still occurs.[212]

Perhaps the best-validated attempt to preserve sexual function after cancer is the nerve-sparing modification of radical prostatectomy, cystectomy, and colorectal cancer surgery.[213] Although avoiding damage to the nerves near the prostate and posterior urethra helps preserve penile hemodynamics and erection in some men, up to 80% do not recover erections firm enough to allow vaginal penetration on most attempts.[172–175,214] Success depends on the skill of the surgeon, the ability to spare nerves bilaterally, and younger patient age. Although nerve-sparing may not restore normal erections, it does increase the percentage of men who can effectively use oral medications such as sildenafil.[175,214] Similarly, using brachytherapy instead of external beam irradiation to treat localized prostate cancers is only slightly more successful in preserving erectile function.[175,215]

Modifying cancer surgery to conserve or reconstruct pelvic organs does appear superior in terms of impact on sexuality. For example, conserving the bladder by using a combination of transurethral resection, chemotherapy, and radiation leaves men with better sexual function compared to radical cystectomy.[216] Procedures to reconstruct a continent, internal urinary pouch combined with nerve-sparing also appear to result in better sex lives for men compared to the traditional, radical cystectomy with ileal conduit.[217,218]

Modifying Cancer Treatment to Spare Female Sexual Function

In women, the main approaches that spare hormonal function are aimed at fertility, i.e. the conservative surgical approaches to gynecologic cancers.[66,71–74] The sexual consequences of such modifications have not been examined. Likewise, researchers have not studied the sexual impact of efforts to spare ovarian function by using ovarian transposition prior to radiation therapy, or GnRH agonists during chemotherapy.

In contrast to results after radical cystectomy, women who have orthotopic bladder reconstruction with preservation of the anterior vaginal wall do not report sexual dysfunction.[176,219] Surgery for colorectal cancer that avoids creation of an ostomy also results in better quality of life and sexual satisfaction.[220] Despite some controversy about the value of vaginal reconstruction after total pelvic exenteration for cervical cancer, the majority of women stay sexually active with their neovagina[201] and the use of myocutaneous flaps helps fill in the surgical defect and promotes healing.

Unfortunately, these reports focus on small series of highly selected patients treated at academic centers. It would be virtually impossible to conduct randomized trials of more vs. less radical surgical procedures, keeping patient age, education, socioeconomic status, and tumor variables equal between groups. Yet, when several randomized trials did compare mastectomy to breast conservation, researchers were surprised to find that neither sexual variables nor quality of life differed according to the extent of breast surgery.[119,188]

Treatment of Desire Disorders

Loss of desire for sex is one of the most common sexual problems seen in both male and female cancer survivors. The efficacy of androgen in alleviating these problems is controversial. Decreased androgen levels are an important factor in men on androgen ablation, some men treated for testicular cancer, or men who have sustained gonadal damage from high-dose chemotherapy.[221] Ovarian failure in women and chronic use of opioid therapy[222] in both genders also can reduce circulating androgens and sexual desire.

Unfortunately, androgen replacement therapy remains more of an art than a science. In young men who are clearly hypogonadal, testosterone replacement restores sexual motivation and pleasure.[223,224] Only two double-blinded, randomized, placebo-controlled trials of the newer testosterone gel or patch formulations have been published, however, with contrasting outcomes.[225,226] Androgens were administered to hypogonadal men unselected for cancer history. The study showing no benefit focused on men over age 65 with testosterone in low-normal range.[225] Men in the more successful trial were more hypogonadal.[226]

In men, loss of desire for sex is often linked to frustration and low self-esteem when erectile function is impaired.[175] One research group has had success in treating ED by combining testosterone with sildenafil for men with low circulating androgen levels.[227] The same strategy was helpful to eight severely hypogonadal men who had testicular failure after bone marrow transplant.[221] Whereas testosterone replacement is a viable option for young , hypogonadal, cancer survivors, men treated for prostate cancer are obviously not candidates. Although elevated luteinizing hormone levels combined with low-normal testosterone levels are common in young men after high-dose chemotherapy, a recent trial of the testosterone patch in 35 such survivors failed to document positive changes in mood or sexual function.[228]

Loss of desire for sex is common after systemic treatment for breast cancer,[119,124,188] As reviewed in the previous section of this chapter, there is reasonable evidence for the safety of short-term estrogen replacement in breast cancer survivors, but no studies have examined the impact of androgen replacement in this population, despite suggestions that such treatment might improve women's sexual function.[229] Yet, high androgen levels are clearly associated with breast cancer risk in postmenopausal women, and have also been observed post-diagnosis.[230]

In fact, the level of androgens needed to maintain normal sexual function in women, particularly after menopause, is unknown.[231] Several methodologically sound studies have not found any correlation between endogenous androgen levels and sexual function in naturally postmenopausal

women.[232–234] The only randomized, placebo-controlled trials that have shown a sexual benefit of testosterone replacement in women have studied surgically menopausal women and have raised testosterone above the normal physiological level.[235–237] No published trials of testosterone replacement have focused on female cancer survivors, although studies of safety and efficacy would be appropriate in women in ovarian failure after treatment for tumors that are not hormone sensitive. However, female survivors of Hodgkin's disease exposed to radiation would be poor candidates because of their already elevated risk of breast cancer, which appears to be potentiated by ovarian hormones.[238]

In the future, selective androgen receptor modifiers may provide a safer modality to treat desire problems in women with abnormally low testosterone. A recent randomized, double-blind cross-over trial of tibolone vs. placebo in 44 postmenopausal women who did not have sexual complaints found in a laboratory paradigm that women taking tibolone had increased sexual desire, fantasies, and arousability, as well as improved vaginal lubrication.[239] Unfortunately, tibolone also appears to increase the risk of breast cancer in postmenopausal women.[240]

Loss of sexual desire after cancer treatment is often multifactorial, rather than a purely hormonal problem, particularly in women. Risk factors can include lingering post-treatment fatigue, pain, or nausea; perceiving oneself as less attractive after cancer; loss of sexual pleasure because of changes in skin sensitivity or genital blood flow; dreading sex because of dyspareunia; medication side effects; mild depression; and relationship conflict exacerbated by cancer treatment. Empirical studies suggest that sexual desire and arousability are linked in women, not only with each other, but with chronic mood disorders, low self-esteem, and guilt about sexuality.[241] Andersen developed a questionnaire to measure negative sexual self-image and found women's scores correlated with failure to resume sex comfortably after gynecological cancer.[242] Treating low desire in women may involve cognitive-behavioral psychotherapeutic interventions rather than a simple, pharmaceutical approach. Such treatment programs should also be evaluated in randomized, controlled trials.[243,244]

Treatment of Erectile Dysfunction (ED) After Cancer

Most efforts at sexual rehabilitation for men after cancer have had the goal of mechanically restoring erectile rigidity. Despite the revolution in treating ED in the past 20 years, yielding not only the various types of penile prosthesis, medications to inject into the penis, vacuum devices, urethral suppositories, and more recently several oral prostaglandin E5-inhibiting drugs (PDE5-inibitors), the majority of men who seek help for ED are not satisfied in the long term. In three studies of outcome in impotence clinics where men were not selected for health or the etiology of their ED, only 30% to 40% of men were sexually active and considered their problem resolved by one to five years after their initial evaluation despite trying a mean of two treatment modalities.[245–247]

Men prefer noninvasive, "natural" therapies, such as oral medication, and often will not try more invasive treatments for ED if PDE-5 inhibitors do not restore reliable, firm erections. Men's adherence even to taking a pill is limited. In two case series of men prescribed sildenafil for ED of varied etiology, over half were no longer taking it by 2-year follow-up.[248,249] In a cohort of 197 consecutive patients, the most significant correlate of discontinuing sildenafil was a history of radical prostatectomy, primarily because the drug was less effective for these men.[249] Only 56% of the men who stopped using sildenafil tried a second treatment.

The importance of encouraging men who fail a first-line treatment to try a more invasive method is reinforced by data from 89 men with ED prospectively followed over 12 months.[250] Men tried an average of two treatments for ED, and those who found an effective medical treatment for ED reported better quality of life and less emotional distress about ED. Prostate cancer survivors were more likely to report trying more than one ED treatment.

In our own retrospective cohort study of men in the prostate cancer registry at the Cleveland Clinic Foundation, half of consecutive men surveyed filled out questionnaires.[214] At an average of 4.5 years after cancer treatment, 59% of 1,188 respondents with ED had tried at least one treatment for it. Only 38% of men found a medical treatment that was at least somewhat helpful in improving their sex lives, however, and just 30% of respondents were still using an ED treatment at the time of the survey. Seventy-nine percent of men had stopped using intraurethral prostaglandin suppositories, 66% no longer used penile injections, 61% stopped taking sildenafil, 59% discarded a vacuum erection device, and 19% no longer had sex with their implanted penile prosthesis. The most important factor in men continuing to use a treatment for ED was that it worked effectively. As in the case series above, men who tried a greater number of treatments were more likely to have positive scores on the International Index of Erectile Function.

A man's motivation to progress from taking a pill to trying a more invasive therapy may be a particularly important factor in the ultimate success of sexual rehabilitation. Penile injection therapy is one of the most effective treatments for men after prostate cancer.[214,250] Other correlates of a good sexual outcome in our survey included younger age, having a sexual partner who still enjoyed sex, having a cancer treatment that was more likely to spare some erectile function (e.g., bilateral nerve-sparing prostatectomy or brachytherapy), and no historical or current use of anti-androgen therapy.[175,214]

Surgeons who perform radical prostatectomy frequently encourage men to begin attempts within 6 weeks to get an erection through use of penile injections, a vacuum device, or a PDE5-inhibitor.[251] The theory is that regular increases of blood circulating to the penis will oxygenate the tissues of the cavernous bodies, preventing fibrosis and atrophy and enhancing the chance of nerve regeneration. This popular theory is based on one very small randomized trial using early penile injection therapy after prostatectomy, published in 1997.[252] Despite a number of attempts to replicate the results using oral medication or vacuum devices, no other peer-reviewed randomized trial has been published.

Treating Female Sexual Arousal Disorder (FSAD)

Men can observe their erections, but women are often unaware of vaginal expansion and lubrication, and subjective ratings of sexual arousal do not always correlate well with

physiological measures.[253] When women complain of poor sexual arousability after cancer, they typically report a loss of desire for sex, along with a lack of subjective excitement and symptoms of vaginal dryness and tightness. Ovarian failure is a frequent medical factor.

In recent years, researchers testing pharmacological treatments for women's sexual problems have created the "diagnosis" of female sexual arousal disorder (FSAD), an isolated sexual complaint characterized by lack of genital vasocongestion. Nine randomized, placebo-controlled trials of therapies for FSAD in postmenopausal women have been published, including those reviewed above on androgen replacement.[254–257] None focus on cancer populations. Two randomized, placebo-controlled clinical trials of sildenafil for FSAD have not produced convincing results on its efficacy,[255,258] and Pfizer no longer intends to seek approval of the drug for women.[259] Another trial examined the efficacy of alprostadil cream applied to the vulva before intercourse. This is the same medication most commonly used in penile injection therapy, but no significant impact on female sexual function was observed.[256] The remaining trial compared a proprietary vulvar herbal lotion to placebo oil.[257] Only 20 women participated. The outcome measure was a sexual diary created for the study, which was conducted by the company marketing the lotion.

Thinking that FSAD might be caused by inadequate blood flow to the clitoris, researchers created a special vacuum device, the Eros, to increase clitoral engorgement.[260] In a sample of 19 women, use of the Eros over 6 weeks significantly increased reports of erotic sensation, lubrication, ability to reach orgasm, and overall sexual satisfaction, regardless of whether a woman had sexual dysfunction at baseline. The device has received FDA approval and has been shown to increase genital engorgement on repeated use.[261]

Women's subjective pleasure as well as objective changes in genital blood flow should be measured in a randomized trial comparing the Eros device to a handheld vibrator, or even to a woman's own manual self-stimulation. Although a placebo-controlled trial may not be possible, these two other conditions would presumably also induce sexual arousal and increased genital blood flow, as well as giving the woman tacit permission to enjoy genital stimulation. It is possible that these are the active components of the Eros intervention, rather than the vacuum-induced clitoral vasocongestion.

Managing Sexual Pain After Cancer Treatment

For women, pain with sexual activity is one of the most frequent problems after cancer treatment. Postmenopausal vaginal atrophy is frequently the cause. As noted in the previous section on managing menopausal symptoms, systemic or local estrogen replacement is highly effective in reversing vaginal atrophy as well as decreasing hot flashes. Although many female cancer survivors have concerns about using systemic estrogen, new forms of topical estrogen may be safer options.

The Estring® is a vaginal ring delivering a low dose of estradiol time-released over three months. It is effective in reversing vaginal atrophy with little impact on plasma estrogen levels.[262–264] In the dosage that would be used in breast cancer survivors, the Estring® may not reduce hot flashes but has been shown in randomized, placebo-controlled trials to reduce urinary incontinence in about 50% of women.[264] A higher dose could be used in women who had not had a history of hormone-sensitive tumors. Women prefer the Estring® to vaginal suppositories[265] or creams. Many can insert the Estring® themselves but others may need a medical visit to replace the ring. Women with significant vaginal prolapse may not be able to tolerate the ring. Another form of vaginal estrogen replacement that is superior to estrogen cream in patient acceptance and does not elevate plasma estradiol is the Vagifem® suppository[266] which contains 17beta-estradiol.

Trials of these localized estrogen therapies should be conducted specifically in cancer survivors. One goal would be to ascertain the safety of long-term use in women prematurely menopausal after breast cancer. Another would be to test efficacy in women whose vaginal atrophy is not just the result of estrogen deficiency, but is complicated by tissue damage from pelvic radiotherapy[267] or post-transplant graft vs. host disease.[268] These women are particularly vulnerable to dyspareunia. Recently a case report has described successful treatment of vaginal agglutination after allogeneic bone marrow transplant, using a combination of surgical dissection of adhesions, estrogen cream, and vaginal dilation.[269]

Although regular vaginal stretching by intercourse or use of a dilator has been assumed to prevent loss of depth and caliber after pelvic radiation therapy, remarkably little evidence exists to demonstrate this effect. A recent Cochrane Library review of interventions for female sexual dysfunction after pelvic radiotherapy[270] found only two references on dilators. Both were retrospective case series, although they presented evidence that dilators could help maintain or restore vaginal patency. The most recent reference was published in 1999. Furthermore, most women are probably not adherent with the classic recommendation to have sexual intercourse or use a dilator three times weekly. In one small study, 32 cervical cancer survivors were randomized to one session of counseling plus a booklet on sex and cancer, or to a 3-hour psychoeducational group designed to increase adherence to vaginal dilation.[271] Group participation increased the percentage of women under age 41 who met the criterion of dilator/intercourse use from 6% to 44%. About half of the older women met the criterion, whether they were in the intervention or control group. For all women, rates of dilation decreased over the year of the study. Since the fibrosis after radiation therapy continues to progress for several years,[267] long-term adherence to vaginal stretching would be necessary to ensure continued ability to enjoy sexual intercourse and to allow adequate pelvic examinations—assuming that vaginal stretching is indeed physiologically effective.

Perhaps the simplest and most conservative intervention for dyspareunia after cancer is instruction on the use of water-based lubricants during sexual activity. Yet, the only study that evaluates the outcome of giving advice on lubricants is Ganz' nursing intervention, which did reduce vaginal pain and dryness.[163] This trial and several others also included the use of Replens®, a polycarbophil-based vaginal moisturizer that adheres to the vaginal mucosa and is designed to be used three times weekly, independent of any sexual activity. One double-blind, crossover, randomized clinical trial compared 4 weeks of Replens® to a "placebo" water-based lubricant[272] in 45 postmenopausal breast cancer survivors. Although both preparations relieved vaginal dryness, Replens® was signifi-

TABLE 19.3. Treatment algorithms for common reproductive problems after cancer.

Level of intervention	*Hot flashes*	*Loss of sexual desire*	*Erectile dysfunction*	*Vaginal dryness/dyspareunia*
Written pamphlet, video, internet, or nurse	Education about diet, dress, sleep, hygiene	Assessment of depression, fatigue, and medications with sexual side effects	Education about impact of cancer treatment and availability of medical treatments	Education on use of water-based lubricants and vaginal moisturizers[280]
Peer counseling or counseling by a mental health professional	Stress management with focus on relaxation training	Promote positive body image, permission to have sexual fantasies, activities that increase desire, and erotic material such as stories or films[280]	Intervention to enhance couple's sexual communication, improve partner's sexual satisfaction[280]	Education on positioning, Kegel exercises to gain voluntary control over circumvaginal muscles[280]
Intervention by a physician	Prescription of antidepressant medication, and consideration of risk/benefit ratio of using estrogen replacement	Change medications that may be interfering with desire; Consideration of androgen replacement, but only if survivor's levels are in the clinically hypogonadal range and the survivor is not at high risk for breast or prostate cancer as a recurrence or second primary tumor	Try medical treatments that are acceptable to both partners, starting with least invasive[281]	Prescription of graduated vaginal dilators with instructions on use to maximize control over vaginal muscles[280]; Prescription of local vaginal estrogen replacement if appropriate; Consideration of vaginal reconstructive surgery in rare cases

cantly more effective in reducing dyspareunia scores. In two open-label studies of women unselected for cancer history, Replens® was just as effective as estrogen cream in treating vaginal atrophy and dyspareunia.[273,274]

In women with chronic pelvic pain and dyspareunia unrelated to a history of cancer treatment, successful comprehensive treatment programs have combined sexual counseling with specific biofeedback and physical therapy modalities designed to increase awareness of and control over muscle tension in the pelvic floor.[275] Trials applying these techniques are needed with women who have dyspareunia related to surgical adhesions or anatomic changes, radiation damage to the vagina, or vaginal complications of graft vs. host disease.

Similar treatments have been helpful in a pilot study of men with chronic pelvic pain.[276] Pelvic pain has been reported to be more common than usual after treatment for testicular cancer[277] or after radical prostatectomy.[175,278] This type of pain is very recalcitrant to treatment and may include aching in the testes or groin, and/or urethral pain exacerbated by urination or ejaculation. Non-steroidal anti-inflammatory or alpha-blocking drugs, low-dose antidepressants, and nerve blocks are occasionally helpful, but more extreme surgical procedures do not produce results that justify routine use.[279] Randomized trials of treatments for male pelvic pain have not been published.

Table 19.3 presents treatment algorithms for the most common reproductive symptoms seen in cancer survivors: hot flashes, loss of sexual desire, erectile dysfunction, and vaginal dryness/dyspareunia. The first level of intervention involves giving patient education materials in written, video, or interactive computerized format. If more help is needed, brief counseling can be provided either by a trained peer counselor or by a member of the oncology team, such as a nurse clinician or social worker. At the third level, a health care provider specialist is consulted. Many brief counseling interventions can be found in a self-help format[280] and algorithms for treating ED are also available.[281]

Conclusions

Reproductive health problems, including sexual dysfunction, menopausal symptoms, and infertility are common, long-term consequences of cancer treatment for both men and women. Until targeted cancer therapies are more common, systemic chemotherapy is likely to entail considerable gonadal toxicity. Efforts to modify pelvic surgery and radiation therapy to spare the reproductive system are ongoing, but remain limited in applicability and efficacy. Because sexuality and childbearing are such sensitive issues, psychosocial counseling and education may increase the efficacy of purely physiological interventions As this review highlights, very little evidence-based knowledge is available to guide oncology clinicians in remediating reproductive health issues. For many problems, pilot studies of efficacy of innovative treatments are needed before randomized trials can be justified. Hopefully our increasing knowledge about the prevalence, causes, and impact on quality of life of reproductive health problems will soon generate more research.

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