Cancer is often considered a disease of aging, and many times it is, as the risk of malignancy increases with age. In fact, according to the American Cancer Society, 77% of all cancers are diagnosed in patients older than age 55 [1]. However, it is not a disease isolated to the older population alone. Any person can develop cancer; it targets children and young adults, and it does not discriminate by gender, race, socioeconomic status, political belief, or religious affiliation. Data collected from the National Cancer Institute (NCI) registry of cancer patients estimated that there were 10,500,000 survivors of cancer in 2003 and roughly 1,440,000 new cancer cases are expected to be diagnosed in 2007 (see Fig. 16.1). Among survivors, 5% are between 20 and 39 years old, resulting in at least 525,000 young survivors of cancer, a number that increases every year. More than 200,000 men and women under the age of 45 are diagnosed with cancer annually. Moreover, 25% of breast cancer patients are younger than 40 years of age. Though over 12,400 children and adolescents (less than 19 years old) are diagnosed with cancer each year, the cure rate for all childhood cancers has reached 80% [2]. While this is a remarkable statistic, the improvement in survival reflects progress in earlier detection of certain malignancies and the extraordinary rise in cancer curing therapies.

Cancer is now a disease with a variety of treatment options that are leading survivors to live longer and more productive lives. With the advent of improved cancer treatments and the subsequent rise in survival, a host of new health care and quality-of-life issues has emerged for young cancer patients. Many of these issues were not anticipated at the time of diagnosis. While advances in radiation and chemotherapy have improved survival rates, these therapeutic agents may also permanently impact the reproductive capacity of cancer survivors. Systemic chemotherapy, although targeted at a specific cancer cell, can have detrimental effects on the reproductive axis at the level of the hypothalamus, pituitary gland, or the gonads. Pelvic radiation and alkylating agents are two known causes of induced sterility in cancer patients [3–6]. Consequently, the survivor may face immediate infertility or premature loss of reproductive function due to the toxic damage. For example, men may experience decreased hormone production and its sequelae, including decreased or lost spermatogenesis or increased sperm abnormalities. In women, treatment-induced premature ovarian failure results in a hormonal milieu similar to the natural menopause.
However, not all treatments result in acute gonadal failure. Instead, some treatments cause subfertility, which reduces sperm count in men and causes an accelerated loss of follicles in women. Young cancer patients are particularly susceptible to the gonadotoxic effects of certain anti-cancer agents. Beyond their role in reproduction, the gonads produce steroid hormones that impact other physiologic processes, such as bone growth and maintenance, cardiovascular health, and the development of secondary sex characteristics. For young cancer survivors, the prepubertal loss of gonadal function requires hormonal intervention to recover the beneficial effects of sex steroids as well as provide a sense of normalcy. With hormone replacement therapy, the young cancer survivor will regain these benefits and will reach the same developmental milestones as her peers; however, she may not recover the ability to conceive her own.

**Infertility: An Unmet Clinical Need for Young Cancer Patients**

Approximately 270,000 Americans are childhood cancer survivors, and by 2015, the NCI reports that 1 in every 250 adults will be living with a history of childhood cancer [2,7,8]. Great strides in medical therapy have improved survival rates for childhood cancers, which have risen from 20% to almost 80% [9,10]. Due to the increase in the number of survivors, the early and late effects of treatment are beginning to garner increased attention for survivors, their families, and their medical providers [11–13]. Infertility is one of the most common chronic medical problems reported by childhood cancer survivors and can be of primary concern, particularly among female survivors [14,15]. Additionally, the loss of fertility is identified as the most important concern after mortality by newly diagnosed cancer patients. Unlike other late effects, such as complications in cardiovascular or liver function, female infertility has biological and psychosocial implications that can neither be narrowly defined nor easily addressed given the number of ethical and legal questions surrounding fertility preservation [16–20]. Therefore, the hurdles associated with fertility preservation often result in the lack of meaningful discussions of the reproductive consequences of cancer therapy and the options available to women at the time of cancer diagnosis. Despite physicians’ reservations, women attest that fertility is a focal point
in their lives and information about fertility preservation options is a key expectation women have as part of their recovery process.

As cancer survivorship increases, the preservation of fertility in women and girls with malignancies has become an increasingly relevant unmet need. Fertility preservation for men has long been an option; post-pubertal boys and men are offered a simple process of semen cryopreservation. Although women and girls faced with a devastating cancer diagnosis have the same hope for recovery, they lack the fertility preservation options that their male counterparts are afforded. That there are fewer options for women, particularly for prepubescent girls diagnosed with cancer, holds back many medical oncologists from discussing the potential threat of cancer or its treatment to their female patients’ fertility. Even more troublesome is that some physicians will not discuss options with sick women, but will talk with men [21]. For instance, seven-time Tour de France winner Lance Armstrong recalls that his oncologist recommended sperm cryopreservation at the time of his diagnosis despite facing life-threatening metastatic testicular cancer. Clearly, expanding the current menu of viable fertility-conserving options for women is necessary. However, this must be linked to a shift in a physicians’ attitude about fertility and a subsequent shift in clinical practice to include future fertility as an integral part of the discussion of quality-of-life issues in the cancer remission period. Certainly, patients are vocalizing their desire to discuss fertility as a survivorship issue. In a 2000-person survey of patients at the Moore Comprehensive Cancer Center at the University of California, San Diego, fertility was of greatest concern second only to mortality, and men and women were equally concerned with how cancer treatment would impact their future ability to have children. This landmark study emphasized the importance of fertility for younger people facing cancer (see Loscalzo and Clark, this volume). Its findings underscore the urgency with which clinical centers must begin providing patients with comprehensive information regarding the potential fertility threat that cancer treatment poses and to ensure that health care professionals provide adequate fertility-conserving options for their patients. Given this unmet need, new approaches to understanding the interplay between age of diagnosis and cancer treatment and their influence on fertility outcomes are essential. It is expected that as the number of young cancer survivors increases, there will be a corresponding increase in the need for clinicians trained to meet their needs.

To further understand the barriers between patients’ needs and what they are offered, a close inspection of the existing obstacles is essential. There are three main gaps that create the unmet need in fertility preservation for women and girls with cancer: the information gap, the data gap, and the option gap (see Fig. 16.2). The first gap is an information gap. In many cases, the treatment will not affect the ovaries. However, in some cases, the impact of particular treatments on fertility is not known because valid studies have not been performed on the survivors. Certainly, the ability to advise patients about the impact of a particular treatment on fertility is important. The information gap underscores the importance of the psychosocial consequences of infertility and the vital role that physicians play in allaying the concerns of cancer patients and helping them to make informed choices.

Patients are gaining appreciation that cancer treatment poses a significant fertility threat, in part due to advocacy groups such as Fertile Hope, which are dedicated to promoting fertility awareness in light of a cancer diagnosis. In response, the American Society of Reproductive
Medicine offered a committee report, which outlines the pertinent issues surrounding reproduction in cancer patients for both cancer and reproductive specialists [22]. Furthermore, the America Society of Clinical Oncology published a review of the current literature pertaining to fertility preservation options to guide oncologists as they encounter patients of reproductive age [3]. Both organizations advocate that physicians include a discussion of the possible reproductive consequences of cancer therapy as part of the patient education and counseling prior to treatment. In order to present the full menu of options, these conversations should be initiated early in the cancer management plan. While many physicians treating young cancer patients are gaining awareness about long-term survivorship issues, oncologists traditionally have focused efforts on providing the best treatments available to improve survival. The information delivery gap still remains because many physicians are not aware of the direct correlation between the best therapies and reproductive outcomes; thus they do not discuss the possibility of treatment-induced infertility with patients [3]. Therefore, the emergence of a new scholar, one who can directly interface with practitioners and cancer patients about their fertility needs, will be necessary to meet the unique needs of cancer survivors.

Despite the best efforts of researchers, there still exists a paucity of data on the precise gonadotoxicity of cancer drugs (the data gap). Medical and surgical oncologists treat sick cancer patients. On the other hand, reproductive endocrinologists often work with healthy patients that are infertile. These two patient cohorts are dramatically different and the strategies for fertility management have not been thoroughly developed in cancer patients. The new supra-specialty of “oncofertility” exists at the intersection of these two medical arenas, and an emerging
An oncofertility scholar will serve to bridge this gap. This gap must be addressed by bringing the two medical disciplines together to rigorously assess the endocrinology of the cancer patient before, during, and after treatment, as well as during the remission period. Data acquisition is complicated by the fact that patients are treated at different ages and with different drug regimens. These variables make studies of gonadotoxicity more challenging and require knowledge of the treatment schedule, changes in drug regimen, and a long-term commitment to this new field. Moreover, new drugs are introduced frequently and their fertility threat must be quickly evaluated. The new oncofertility specialist will be uniquely qualified to fill this data gap.

Fundamentally, fertility preservation for men and women revolves around the common themes of gamete storage and later utilization. However, the currently available reproductive options for female survivors, as compared with their male counterparts, offer a very different prospect for future fertility (the option gap). Whereas men possess the proven success of semen cryopreservation and intracytoplasmic sperm injection (ICSI), female survivors have few established options. Options traditionally available to women, such as ovarian transposition, embryo cryopreservation, and mature oocyte cryopreservation, present unique limitations when applied to cancer patients, particularly childhood cancer patients. The promise for some female survivors lies in the strides made toward ovarian transplantation and in vitro follicle maturation (see Agarwal and Chang, this volume). The emerging scholar will fill the option gap with concrete and diverse alternatives that will result in the ability to provide authoritative answers to many of the fundamental clinical questions of oncofertility: (1) Which patients are at risk of premature loss of gonadal function? (2) Which patients should be offered fertility preserving options? and (3) Which options can provide true hope for fertility conservation?

**Oncofertility and the Oncofertility Scholar**

Oncofertility stems from the medical subspecialties of oncology and reproductive endocrinology and infertility (REI). With the evolution of this new complementary medical discipline comes the emergence of a new medical scholar. The purpose of the discipline of oncofertility is to address the issue of fertility preservation after cancer treatment with medical experts specifically trained to advise and treat their patients with new and emerging technologies. The long-term success of this ambitious initiative requires the well orchestrated and focused development of a physician–scientist global workforce that will implement research and clinical goals. Ultimately, the clinical investigator will spearhead the expansion and development of this new interdisciplinary field. The uncertain event horizon for the patient, the immense amount of decision-making that must occur at the time of treatment, the paucity of data about treatment-related fertility threats, and the rapidity with which an action plan must be enacted are the major clinical obstacles that must be addressed by the new oncofertility specialist.

In order to prepare this new scholar, a specialized training program will need to be created to meet the goals of the discipline. The intent of the oncofertility training program is to train and educate the first generation of new scholars and open the pipeline for the development of academic specialists in the new interdisciplinary field of oncofertility. Such education and training will provide the foundation for further development of this discipline, which exists at the intersection of oncology, pediatrics, reproductive science and medicine, biomechanics, materials science, mathematics, social science, bioethics, religion, policy research, reproductive health
law, and cognitive and learning science. The goal of this training program is to prepare talented academic clinicians from the ranks of reproductive endocrinologists for investigative careers that focus on the unique reproductive and fertility needs of the female cancer patient and cancer survivor. Research will be based on molecular, cell biology, biomaterials, cryobiology and non-human primate physiology, as well as interdisciplinary training in medical oncology, bioethics, and health law or communication studies. Each of these disciplines places particular emphasis on basic and translational interdisciplinary research in order to prepare physician investigators to meet the challenges of the care of the female cancer patients and survivors.

Reproductive Endocrinology and Infertility as the Springboard to a New Oncofertility Scholar

Reproductive endocrinology and infertility is one of four subspecialty fellowships for advanced training after completion of a residency in Obstetrics and Gynecology. Formal certification for this advanced training in reproductive medicine is under the aegis of the Division of Reproductive Endocrinology and Infertility of the American Board of Obstetrics and Gynecology, Inc. (ABOG). This board awards certificates of special competence for the practice of REI to individuals after completion of an accredited training program and subsequent passing of written and oral examinations. At present, there are over 900 REI Board certified specialists in the United States.

Training in REI has had an impressive evolution during the past three decades. This training had pursued an unstructured pathway prior to the introduction of ABOG approved training programs initiated in 1974. The American Board of Obstetrics and Gynecology, Inc. is responsible for administration and oversight of fellowship programs. There are currently 37 approved three-year national fellowship programs, with 68 fellows in training. The majority of the programs support one fellow per year with some programs having one fellow every other year and only four programs approved for two fellows per year.

When REI fellowship programs began to proliferate in the late 1970s, two years was deemed adequate to expose fellows to state-of-the-art clinical management principles in infertility and endocrinology. The successful in vitro conception of Louise Brown in 1978 forever changed the field. An explosion in technology followed, and the clinical applicability of in vitro fertilization (IVF) and embryo transfer has expanded and remains largely within the province of the reproductive endocrinologist. Sophisticated technical advances in assisted reproductive technologies are now acquired during fellowship. This increase in required clinical competencies and the explosion in knowledge and scientific advances in molecular biology and genetics prompted ABOG to extend the required fellowship training period from two to three years, effective in 1998, by expanding the length of required research training from a minimum of 6 months to a minimum of 18 months. This additional requirement for research training by ABOG emphasizes the need and commitment for clinically trained individuals to experience an immersion in the laboratory, gain exposure to cutting edge basic research using molecular and cellular biology techniques, and complete successfully the thesis requirement. This research time also represents the opportunity to identify those fellows who are interested in reproductive research as a life-long pursuit.
Initially, the specialty was oriented towards attaining clinical competency in the field of reproductive medicine. However, research competency has always been a feature of REI training and a formal thesis requirement was instituted in 1974, concurrent with the first oral examination in the subspecialty. The thesis requirement enforces the need for exposure to scientific methods of inquiry. Fellows are required to perform and publish a study that demonstrates adequate hypothesis testing and to further defend a thesis at the time of oral examination to attain certification in the subspecialty. The Division of Reproductive Endocrinology of ABOG closely monitors the publication of this research work in peer-reviewed journals as it considers each fellowship program for continued accreditation. Formal progress reports and reviews of each program take place yearly, and formal re-accreditation reviews, which include site visits, occur at three to five year intervals.

The American Society of Reproductive Medicine (ASRM) is a multidisciplinary organization devoted to the advancement of knowledge and expertise in reproductive medicine and biology. With over 9,000 members, it is one of the premier professional associations for reproductive endocrinologists and infertility specialists. Included in its mission statement is “…a comprehensive educational program comprised of educational activities which serve to maintain, develop, or increase the knowledge, skills, and professional performance and relationships that a physician uses to provide reproductive medicine services for patients, the public and the profession” [23]. A similar mission statement can be proposed for the emerging oncofertility specialist: to provide service to the patient, to the public, and to the profession of oncofertility. The oncofertility specialist serves as the liaison between the patient and his/her options, between the medical disciplines of reproductive endocrinology and oncology, and between the scientific advances at the laboratory bench and the practical applications at the bedside.

It is expected that as the number of young cancer survivors increases, there will be a corresponding increase in the need for clinicians trained in oncofertility to meet their needs. One of the primary functions of the oncofertility specialist is to assume the role of patient advocate. In this role, the physician must acquire the most up-to-date, authoritative information and convey that information effectively to allow the patient to make a fully informed decision. The specialist must also convey authoritative information to fellow medical colleagues. Second, the emerging scholar will serve the patient as well as the public as a clinical investigator. A number of areas for investigative research, both in the basic sciences and the clinical realm, are proposed below. For instance, a greater understanding of ovarian physiology, structure, and function may help solve the complex puzzle of human in vitro follicle maturation. In addition, the direct impact of cancer treatments on reproductive capacity remains unanswered. Advancements at the bench can be translated to bedside as new technologies for fertility preservation are developed. Thus, the new scholar will contribute greatly to the field of reproductive medicine while contributing to the expansion of fertility conservation options for the public. Lastly, the oncofertility specialist will provide service to the profession of oncofertility, reproductive medicine, and oncology. As the emerging scholar, the new oncofertility specialist functions as the vanguard, thus inaugurating the discipline. It is the charge of the original scholars to create the scope of the discipline, to help shape the future directions, and to serve as mentors to the next generation. The new scholarship will expand the training of selected REI specialists into the new discipline of oncofertility through a rigorous educational, laboratory, and research curriculum (see Fig. 16.3). Reproductive endocrinology and infertility is a relatively new subspecialty, begun in the mid 1980s soon after
the birth of Louise Brown and in response to the human need for fertility options. The development of the oncofertility specialist represents the next major paradigm shift for the discipline and one that will be embraced by research scientists, clinicians, and teachers of the next generation.

Research Directions

Research is a central feature of REI fellowship programs and of subsequent academic careers. The scope of research spans both basic and clinical inquiries and covers an array of topics within reproductive medicine (see Fig. 16.4). Board-approved REI training programs are academically rigorous and require a major commitment of time to research. This is the only formalized time during the training of Obstetrician/Gynecologists that such a rigorous commitment to an academic research exercise is required. More importantly, the fellowship years represent a unique time when physicians in training have the opportunity to develop a lasting interest in, and hopefully a passion for, research. In this way, the REI fellowship programs serve as a pipeline for the development of academic reproductive medicine specialists.

Future Directions

It is anticipated that in the future other physicians who develop an interest in oncofertility, such as medical and pediatric oncologists or medical endocrinologists, will be able to participate in this or similar training programs. Moreover, a number of other diseases and surgical procedures
that impact female fertility could be addressed using methodology developed through oncofertility research and clinical activities. For example, fertility is reduced after restorative proctocolectomy with ileal–anal anastomosis [24]. Restorative proctocolectomy is the gold standard operative therapy for patients with mucosal ulcerative colitis and familial adenomatous polyposis, which results in 69% infertility rates in women. In patients who receive intraoperative blood transfusions [24] a further decrease in fertility rates has been observed. The pelvic pouch procedure tends to be performed in young women. Little work has been done on linking gastroenterologists with fertility specialists, but the threefold increased risk of becoming sterile when treating inflammatory bowel diseases suggests that this interaction should occur. Women with autoimmune diseases such as lupus, scleroderma, and rheumatoid arthritis also have an enhanced risk of infertility, not from the disease, but from the drug cyclophosphamide, a powerful immunosuppressive drug. Women treated with cyclophosphamide after age 30 are 66% more likely to become infertile [25]. Women with chronic renal disease also have impaired fertility that can be rectified by kidney transplant [26]. Smoking, abnormal nutritional status (either morbid obesity or anorexia), and excessive exercise are known to contribute to infertility and these links are usually addressed by behavior modification and IVF [27]. In vitro fertilization is not successful in all cases. For instance, IVF does not efficiently produce viable offspring in women older than 42 years of age, in women resistant to exogenous hormone therapy, or in women who fail to produce viable embryos after multiple cycles. In addition, women with polycystic ovarian disease and type II diabetes represent a subset of candidates likely to fail IVF [28]. Methods to intervene in failed cases have not been well developed and new technologies could provide hope to those who face infertility after attempted IVF [29]. Indeed, if the technology works, a role may emerge for ovarian tissue banking by young women prior to entry into professional tracks, ensuring that eggs of good quality will be available at any time she is ready to have a family. As more drugs are introduced to the cancer and wider-health care markets, the impact on fertility may not be the first parameter tested. The point of this work is not to limit the access of women to vital drugs, rather, to provide health care providers and patients with information about the fertility implications of treatment and the ability to conceive and bear a pregnancy after treatment. Helping physicians understand what secondary effects treatment will have on their patients and the options available will substantially improve health care delivery.

Conclusion

Since the late 1970s, treatments for infertility have undergone a tremendous change that is as substantial as the rise in the number of cancer survivors. Not all cancer treatments cause the acute loss of ovarian function and infertility; thus, patients must be informed that their treatment may not significantly impact fertility. However, for some patients, life-saving cancer treatment may permanently influence their reproductive capacity. Therefore, the oncofertility specialist must be present to help patients and health care providers consider fertility conservation at the time of initial diagnosis. Frank discussions about fertility impairment as a consequence of treatment have not been a priority for the medical oncologist. There are a number of reasons for this. First, the main goal of the oncologist and the patient is to eliminate the cancer with the use of the best available therapies. This scenario provides a unique niche for the new oncofertility specialist to apply their unique knowledge and training. Second, the impact of the improving and constantly changing landscape of cancer drugs on fertility has not been directly assessed.
Therefore, it is difficult for the oncologist to know what to advise their patients. It is the role of the new oncofertility specialist to examine this question and provide a means for informed dialogue with the patient. Finally, for women, there have been so few viable options to preserve fertility that patients may not be able to find a fertility specialist until it is too late.

The current method of coordination and implementation of fertility care in women with cancer consists of a series of communications between a cancer specialist with limited knowledge of reproductive biology and a reproductive specialist who has little understanding of how cancer treatment impacts oocyte health. Therefore, a comprehensive approach to provide patients and their families with a full overview of reproductive options is necessary. Moreover, there is no single specialty in physiology or medicine that can provide all the elements of such a service. The emerging oncofertility training program will directly address this void by providing reproductive specialists with the necessary knowledge and skills to fulfill this unmet need. To that end, the curriculum is broad and highly focused in selected areas. In particular, there is a heavy emphasis on research, not only to learn more about the impact of cancer treatment on follicle and oocyte health, but also for the purpose of conveying the latest information to patients and their health care providers. In addition, it will provide the budding oncofertility specialist the opportunity to become familiar with emerging technologies for in vitro follicular growth and for cryopreservation of ovarian tissue, follicles, and oocytes. Moreover, this research experience will provide a springboard for fellows to pursue an academic career in this specialty. The comprehensive nature of the training will introduce bio-psychosocial, ethical, and policy considerations that arise during an emotionally difficult time for patients and their families, which will improve the ability of health care providers to give counsel.

Infertility is one condition that transgresses the realm of pure science and medicine into the social sciences. It causes significant emotional and financial stress for those it affects. Thus, attempts to prevent iatrogenic infertility require an approach that involves the social sciences as well as the physical and medical sciences. Infertility resulting from cancer therapy in women is particularly complex due to the limited options for its prevention. It requires understanding how to maintain the life potential of the female gamete in its immature state and how to harness that potential when the time is appropriate. It also requires an understanding of the social and emotional impact of cancer therapy on affected individuals, as well as on society, in the face of uncertainty. Overcoming such a complex challenge necessitates the interaction of many individuals with varying expertise.

Oncofertility recognizes that fertility and cancer combine to create a unique set of issues to be addressed. Oncofertility is not a multidisciplinary field allowing for scholarship on a problem from different perspectives, rather it is an interdisciplinary field that brings together scholars from diverse fields to collaboratively ask new questions and develop new measures and research paradigms, resulting in a new way of looking at the problem of cancer and infertility. This involves more than identifying a generic menu of reproductive options that may be applied to all cancer patients. Rather, the aim is to develop novel technologies that take into account the unique circumstances of cancer patients and to bring together insights from a broad range fields including gynecology, oncology, and endocrinology into a new area of scholarship. Moreover, education, ethics, and the social sciences are constitutive parts of oncofertility because understanding the social dynamics that envelop emerging technologies are not secondary.
research issues but require careful empirical inquiry as well. This comprehensive and interdisciplinary approach will ensure that the medical discoveries of oncofertility are both robust in their scientific base but also that these technologies can be moved from the bench to the bedside. The newly trained oncofertility scholar will therefore have unparallel opportunities that will contribute to solving the gaps in fertility preservation for women and girls facing a cancer diagnosis. The aim of this interdisciplinary approach is to fill in the “gaps” in our current knowledge and promote understanding of the intersection between fertility and cancer. Filling in these gaps in information exchange (e.g., how do physicians learn about the latest oncofertility techniques?) and data (e.g., what is the precise gonadotoxicity of cancer drugs?) will ultimately result in the ability to provide new fertility-preserving options for women diagnosed with cancer so they can take proactive steps to help safeguard their future ability to have biological children.

Although malignancy remains a critical health concern, significant medical advances in cancer detection and treatment have improved survival rates for patients. As patients live longer, the immediate and long-term consequences of cancer management are assuming greater importance for survivors, their families, and their providers. Traditionally, cancer patients had few choices for fertility preservation. However, recent advances employing a three-dimensional alginate scaffold system for the in vitro maturation of murine follicles provides a promising new technology that may one day be applied clinically to the maturation of human ovarian follicles (see Xu, Woodruff, and Shea, this volume). Restoration of fertility and hormonal function would substantially improve the quality of life for women of reproductive age after surviving cancer and the exposure to potentially gonadotoxic cancer therapies. The oncofertility training program is vital to the goals of this pursuit by ensuring the creation of a new generation of specialists who will help to merge fertility-conserving options into conventional cancer care.

References

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