Chapter 1

The Emergence of a New Interdiscipline: Oncofertility
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Oncofertility: The New Offensive in the War on Cancer

In 1971, the National Cancer Act was signed, providing funds to the newly established National Cancer Institute (NCI) to coordinate research and new medical advances to detect, diagnose, and treat cancer. Since then, there has been a steady increase in the number of cancer survivors, reaching 3.5% of the domestic population in 2003. The rise in the number of survivors is due to earlier detection of disease, aggressive radiation therapy, and new chemotherapeutics. Thus, while the suffering and death associated with cancer have not been eliminated, cancer has been converted, in some cases, from an acute death sentence to a disease that many people survive and live with for an extended period of time.

The war on cancer has been an aggressive one and successful treatment is associated with significant complications. These complications include a physical toll on the cardiovascular system, bone biology, movement of lymph in the appendages, and the loss of organ function. Complications can also involve psychological issues such as depression, anxiety, uncertainty, isolation, and an altered body image. The survivor can also face social and existential crises such as a fear of engaging in interpersonal relationships, problems with health and life insurance, job loss, problems with school and finances, an altered sense of purpose, and a different appreciation of life. One of the main complications of modern cancer treatment, particularly for young men, women and children is the impact of cancer treatment on future fertility.

It is the purpose of this book to review the factors impacting fertility caused by the treatment of cancer. In so doing, we will provide chapters on state-of-the-art research, clinical practice, and training that happens at the intersection of oncology, pediatrics, reproductive science and medicine, biomechanics, material science, mathematics, social science, bioethics, religion, policy research, reproductive health law, cognitive, and learning science. Taken together, this book will describe the emergence of a new discipline called “oncofertility” (Fig. 1.1).

Secondary Effects of Treatment on the Health and Quality of Life of Young Survivors of Cancer

Many people think of cancer as a disease of aging, and in many cases it is. But cancer does not impact older people alone; it also targets children and young adults, and it affects men and women of all races, socioeconomic status, political persuasions, and religious leanings. It is a disease that does not discriminate. Data collected from the NCI registry of cancer patients reports that there are 10,500,000 survivors of cancer, and 5% are between 20 and 39 years old. This means there are at least 630,000 young survivors of cancer and the number increases every year.
Moreover, 25% of breast cancer patients are younger than 40 years of age. Over 12,400 children and adolescents (younger than 19 years) are diagnosed with cancer each year and the cure rate for all childhood cancers has reached 75%. In fact, the NCI reports that 1 out of every 250 adults will be a survivor of childhood cancer by 2015. This is a staggering statistic and reflects both the ability of children to survive cancer treatment and the extraordinary rise in cancer curing drugs.

**Fig. 1.1** Oncofertility is a new interdisciplinary approach to address the reproductive future of young men, women, and children facing a life-preserving but fertility threatening cancer diagnosis

Therefore, the age of many cancer patients and the aggressive nature of the treatments they survive create a variety of new health care and quality-of-life problems for the young survivor, many of which were not anticipated at the time of diagnosis. The secondary effects of cancer treatment are exaggerated in this patient cohort because of their young age and greater life expectancy compared with the older cancer survivor. Thus, a secondary effect can become a long-term chronic issue that requires additional medical intervention. For example, patients may experience chronic pain, cognitive dysfunction, fatigue, peripheral neuropathies, cardiovascular and bone disease, or incontinence as a consequence of cancer or its treatment. The young survivor may still be in school, recently become independent, but not yet achieved the economic footing they will have later in life, or be a young parent. A cancer diagnosis can create a further tailspin because time away from education, jobs, and family for primary or ancillary treatment
can derail pursuit of a degree or career advancement and can place strain on a new marriage. Moreover, access to health care coverage may be limited due to the previous cancer diagnosis. The future needs of a young cancer patient must be considered at the time of diagnosis and treatment. However, balancing survivorship and quality-of-life issues are sometimes difficult. This book details many of the questions and a roadmap toward the solution. Clearly, much more research and scholarship is needed to provide definitive answers to patients and providers. This book is the first comprehensive assessment of the field and is a call to more research and scholarship on the topic of oncofertility.

Fertility Threats Due to Cancer Treatment

While advances in radiation and chemotherapy have improved survival rates, these therapeutic options may also permanently impact the reproductive capacity of cancer survivors. For instance, systemic chemotherapy, although targeted at a specific cancer cell line, can direct toxic effects at the gonads. Consequently, the survivor may encounter immediate infertility or premature loss of reproductive function due to sublethal damage. In women, induced infertility results in a hormonal milieu similar to that seen in the natural menopause. Furthermore, pelvic radiation and alkylating agents are two known causes of induced-sterility in cancer patients. Young cancer patients are particularly susceptible to the gonadotoxic effects of these agents. However, not all treatments result in acute gonadal failure. Instead, some treatments cause subfertility, which reduces the sperm count in men and causes an accelerated loss of follicles in women. Besides their role in reproduction, the gonads produce steroid hormones that contribute signals to affect other physiologic systems, 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, young cancer survivors can achieve the same developmental milestones as their peers. In order to manage the child’s transition through puberty and to ensure good bone health and cardiovascular function, boys are given the testosterone patch while girls use oral contraceptive pills to create a normal cyclic hormonal profile. However, these treatments do not restore fertility. The primary goal of treatment is to eradicate the disease, and clinicians have a full armamentarium of cancer therapies to ensure the best opportunity for survival. But even as these strategies improve survivorship, patients are now shifting their focus to understanding and managing the long-term sequelae of their cancer treatment, particularly the effect on reproductive function. Given this unmet need, new approaches to understanding the interplay between age of diagnosis and cancer treatment and its influence on fertility outcomes are essential.

Fertility threats to young women, men, children, and their families are often just as difficult to assimilate as the cancer diagnosis itself. Indeed, in a 2,000 person survey of patients at the Moores University of California – San Diego (UCSD) Cancer Center, fertility was of greatest concern, second only to mortality, and men and women were equally concerned with how cancer treatment may impact their future ability to have children (see Loscalzo and Clark, this volume). This ongoing landmark study emphasizes the importance of fertility for younger people facing cancer and its findings underscore the urgency for clinical centers to begin to provide patients with comprehensive information regarding the fertility-threat their cancer treatment poses and to ensure they provide adequate fertility-conserving options for their patients.
Moreover, post-cancer fertility is also a potential source of health disparity among cancer survivors. For example, racial and ethnic differences in access to medical care, time of cancer diagnosis, and quality of treatment have led to different outcomes across racial/ethnic lines in terms of morbidity and quality-of-life post-cancer. According to the UCSD survey, African–American patients were more concerned about fertility than other racial/ethnic groups and were also more likely to want to discuss the issue with a health care staff member, suggesting that they were less likely to discuss the issue prior to treatment. This finding is distressing because a lack of information regarding possible infertility and treatment options is the major deterrent to cancer patients not taking steps (such as sperm banking) to help safeguard their future fertility. Further research is needed on how information regarding fertility is shared with patients by health care practitioners and institutions because of the implications for later health inequities in terms of which survivors are able to meet desired parenting and family goals.

An Emerging Urgent Unmet Need for Young Cancer Patients: Balancing Life-Preserving but Fertility-Threatening Cancer Treatments

Fertility preservation for men has long been an option. The most famous person who has publicized his fertility preservation and family after cancer is Lance Armstrong, the bicyclist and seven-time winner of the Tour de France. The following excerpt describes his initial realization of the impact his cancer treatment could have on future fertility:

“I’ve decided Lance needs to move up his first chemotherapy treatment. He starts Monday at one o’clock. “Why?” my mother asked. … The cancer was not just spreading, it was galloping, and Youman no longer thought I could afford to wait a week for chemo. I should begin treatment directly, because if the cancer was moving that quickly, every day might count. I hung up the phone…I would have one chance and one chance only to go to the sperm bank in San Antonio: that very afternoon. … I was depressed and falling apart emotionally from the shock of the diagnosis. I wanted to be a father – quite badly – but I had always assumed it would happen when I was in love. I had no choice; I closed my eyes and did what I had to do.” From: ‘It’s Not About the Bike: My Journey back to Life’, Lance Armstrong with Sally Jenkins, 2000, Berkeley Books

At least Lance had an option. Women who face a similarly devastating diagnosis do not have the same options that men have to easily preserve fertility. This reality, which is particularly unfortunate for prepubescent girls diagnosed with cancer, means most medical oncologists do not discuss potential threats to fertility with female patients. Even more worrisome is that some physicians are less likely to discuss options with women than with men. Lance Armstrong had a very grim disease, yet he was offered the hope of a future. Clearly, good choices for fertility preservation are necessary for women, and this must be coupled with a change in physician attitudes about fertility as a part of the patient’s quality of life and her expectations of a cancer-free future.

In 2002, the Lance Armstrong Foundation, the Robert H. Lurie Comprehensive Cancer Center and the Chicago chapter of Gilda’s Club co-hosted an evening called Families After Cancer (Fig. 1.2). Nearly 600 cancer survivors attended the event. Lance and Kristin Armstrong answered questions about their experiences with a devastating cancer diagnosis and the simultaneous recommendation to bank sperm, their fertility treatments, and their hopes that women might one day have the options men have to preserve their fertility. Dr. Woodruff was part of a panel
including a patient advocate (Lindsay Nohr-Beck, Founder and Executive Director of Fertile Hope) and a leading reproductive endocrinologist (Zeev Rosenwaks, MD, Cornell Medical School). The group addressed the need for more basic science at the intersection of a variety of disciplines to solve a previously intractable problem, namely, in vitro follicle growth and oocyte maturation.

There are three main gaps that create the unmet need for preserving fertility in patients with cancer: the information gap, the data gap, and the option gap. Addressing these unmet needs is the goal of many research scientists, clinical investigators, and scholars, and has become the guiding principle behind the newly created Oncofertility Research Program at the Robert H. Lurie Comprehensive Cancer Center at the Feinberg School of Medicine, Northwestern University. The problem requires a comprehensive interdisciplinary approach that will result in a new supra-disciplinary medical specialist in oncofertility and a new research discipline that addresses questions of reproductive function and conservation.

Fig. 1.2 In 2002, the Lance Armstrong Foundation, the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and the Chicago chapter of Gilda’s Club co-hosted an evening called Families After Cancer. Nearly 600 cancer survivors attended the event. Lance and Kristin Armstrong answered questions about their experiences with a devastating cancer diagnosis and the simultaneous recommendation to bank sperm, their fertility treatments and their hopes that women might one day have the options men have to preserve their fertility.
**Information GAP**

The first gap is an information gap. Indeed, in many cases, cancer treatment will not affect the ovaries or testes and therefore doctors could relieve one of the uncertainties about the future by simply conveying this fact to the patient. In other cases, the impact on fertility is not known because valid studies have not been performed on the survivors of particular treatments. This lack of fundamental knowledge about the fertility threat of treatment is partly due to the inconsistency with which patients are treated within and between cancer centers and the need to evaluate ovarian function over an extended period of time. Clearly, the ability to advise patients about the impact of a particular treatment on fertility is important and the programs are needed to gather the data necessary to provide authoritative information to physicians and patients alike. Perhaps more problematic than the information gap is the intellectual problem medical oncologists face: a belief that there ‘are no good options to offer, so why bring up the subject.’

Due to the work of Lance Armstrong and the Lance Armstrong Foundation and Lindsay Beck founder of Fertile Hope, an advocacy group dedicated to promoting fertility awareness at the time of a cancer diagnosis, patients are now, more than ever, aware that cancer treatment poses a fertility risk. Both the American Society for Reproductive Medicine (ASRM) and American Society of Clinical Oncologists (ASCO) have published guidelines that suggest that doctors talk to patients about the fertility implications of cancer treatment (guidelines published in 2005 and 2006; Brannigan, this volume and updated guidelines by Backhus et al., this volume). Nevertheless, the information delivery gap still exists because medical oncologists are not aware of the precise reproductive threats of their treatments on reproductive outcomes and clinical reproductive endocrinologists do not routinely treat cancer patients. Moreover, new drugs and multi-drug treatments pose a particular problem to clear information exchange. Therefore, it is important that we meet the need of creating new oncofertility specialists who can directly interface with practitioners and cancer patients about their fertility needs. Since it will take time for oncofertility programs to develop and train oncofertility specialists, we are simultaneously developing comprehensive, authoritative educational and outreach information that gives the traditionally trained medical oncologists badly needed information so they can confidently advise patients about the fertility threats posed by their treatment plan. If no threat is posed, cancer patients can confidently move forward with treatment. Where fertility is threatened, a new cadre of oncofertility specialists will be able to provide up-to-the-minute information on traditional and newly introduced cancer drugs on fertility. Finally, the information gap creates a tremendous amount of anxiety for a patient and his or her families and partners about choices for treatment. Understanding the needs of the patient, providing information in a way that can be understood at a time of remarkable stress, and creating corridors for support is the third way an oncofertility program will fill the information gap. Knowing that information must be packaged appropriately or the gap will remain, navigation tools for oncofertility programs must be developed, providing a means for unique scholarly inquiry about how medical information is communicated (see Kondapalli, this volume), as well as understanding the perspective of the family cluster in medical decision-making (see Clayman et al., this volume). These scholarly activities will provide the oncofertility specialist with primary information to ensure that information delivery is appropriate to the need.
**Data GAP**

Despite the best intentions of medical oncologists and reproductive endocrinologists, there exists a paucity of data on the precise gonadotoxicity of cancer drugs. This gap must be addressed by once again bringing the two medical disciplines together to rigorously assess the endocrinology of the cancer patient before and after treatment and during follow up. Complicating the data acquisition is that patients are treated at different ages and with different drug regimens. These variables make the studies more challenging and require knowledge of the treatment schedules, changes in drug routine, and a long-term commitment to this new field. Moreover, new drugs are introduced frequently and the fertility threat must be immediately evaluated. Traditional hormone tests over time must be conducted, and more rapid bioassays that assess risk factors used in a sophisticated way to address this problem. The new oncofertility specialist will be uniquely qualified to fill the data gap.

**Option GAP**

The option gap is most important to women with cancer. Recent breakthroughs in tissue cryopreservation, in vitro follicle growth, and ovarian transplants provide important new ideas that must be developed in a collective manner to ensure that these new concepts are tested in primates and are real solutions to the problem rather than simply proof-of-principle observations. In order to accomplish this goal, basic scientists, clinical investigators, and clinicians-in-practice from a variety of fields must not just collaborate, but must become fully integrated across traditional disciplinary borders representing biomedical discovery, advanced medical practice and application, and scholarship in the humanities and social science (Fig. 1.3 and see Kondapalli, Snyder, Clayman et al., Kinahan et al., this volume). This interaction is the first step in becoming interdisciplinary. Importantly, the new field of oncofertility biology must use non-human primate models and human tissue to appropriately move the ideas from the bench to the bedside. To do this, basic and clinical science must work together in ways that each group can understand the terms and concepts of the respective disciplines as well as understand patient needs and limitations. To ensure patient needs are primary, clinical coordinators and navigators trained at the intersection of disciplines will be engaged at all level of activity.
Fig. 1.3 Oncofertility represents a new interdisciplinary program that will span the known gaps and address the needs of patients with cancer by encouraging new work by newly envisioned oncofertility scientists, specialists, and scholars.

**Conclusion**

This book and the oncofertility effort are aimed at an emerging health care crisis faced by nearly one million young people. Ironically, we coined the word “oncofertility” in February 2006 as part of a grant submission process. Clearly, the need existed for this new discipline, but to fill the need required something much larger, more comprehensive, and interdisciplinary. The term oncofertility has now entered the public sphere and we believe it has already reached a “tipping point” in public consciousness. Indeed, two years ago we were barely able to get any traction on the idea, but, now, every clinical practice we talk to is not just interested but committed to the concept. The goal of oncofertility is to meet an emerging urgent unmet need for young cancer patients: balancing life-preserving treatments with fertility-preserving options. To meet this challenge successfully, we must develop new oncofertility specialists, scientists, and scholars who will develop the tools and approaches that can best achieve this goal. Importantly, this is a
problem that can be solved using a interdisciplinary approach and simply cannot be achieved in isolation.

It is hoped that future books in this series will report on significant new advances in the oncofertility field and provide new hope to those young people impacted by cancer.