Demographics of Cancer in the Reproductive Age Female

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Abbreviations

ART	Assisted reproductive technology
BRCA	BReast CAncer susceptibility gene
CDC	Centers for disease control
ER	Estrogen receptor
FIGO	International Federation of Gynecology and Obstetrics
GnRH	Gonadotropin-releasing hormone
Gy	Gray (SI unit for ionizing radiation)
HER2	Human epidermal growth factor 2
HPV	Human papilloma virus
NSMLC	Non-small cell lung cancer
PR	Progesterone receptor
SCLC	Small cell lung cancer
TNM	Tumor node metastases
WHO	World Health Organization

Introduction

Cancer in reproductive age women represents a significant source of morbidity and mortality. The treatment of cancer in this age group whether it entails chemotherapy, radiotherapy, or surgical resection often results in survivors with impaired or absent reproductive potential without assisted reproductive technologies (ART).

Although primary treatment goals are swift diagnosis, treatment, and follow-up of the primary malignancy, a strong factor in long-term emotional well-being of cancer survivors is the ability to parent a child [1]. Despite this, only about 50 % of cancer survivors report receiving counseling regarding the cancer treatment's impact on their fertility and future options for childbearing [2, 3]. To do this appropriately requires a working knowledge of common malignancies faced in this age group, their treatments at various stages of disease, the treatment's impact on fertility, and the therapeutic options available to patients for fertility preservation and restoration [1]. Ultimately, a collaborative, multidisciplinary team approach will provide optimal management.

Risk of Infertility in Cancer Survivors

Impaired reproductive function can be caused by a number of things related to cancer and its treatment including type of cancer and stage of

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disease; chemotherapeutic agent and cumulative dose of drug; location of radiation and cumulative dose; surgical treatment, which often includes removal of reproductive organs; the disease process itself which can impair both fertility and general health.

Pretreatment counseling is an important part of long-term patient satisfaction. Poor prognostic factors in cancer treatment have been derived from large sibling cohort studies of female cancer survivors. Factors conferring a poor prognosis for future fertility include hypothalamic and pituitary radiation ≥30 Gray (Gy), ovarian and uterine radiation >5 Gy, high cumulative dose of alkylating chemotherapeutic agents, and treatment with lomustine of cyclophosphamide [4].

Several options are available to mitigate risks for infertility in female cancer survivors and are discussed in detail in Chaps. 11, 15 and 16. Briefly, they entail approaches with established efficacy in widespread use, primarily, oocyte, or embryo cryopreservation prior to treatment [5]. Other paradigms, such as ovarian tissue preservation, are offered in primary research settings [6]. Finally, several treatments exist, such as ovarian suppression with gonadotropin releasing hormone analog (GnRH), which have mixed success and are utilized when other more established treatment options are not feasible [7]. The use of gestational carriers can be offered when the reproductive tract was damaged by the cancer or removed as part of its treatment. All available options should be discussed and can be offered alone or in combination.

Female Cancer Demographics

This chapter focuses on the most common malignancies faced by reproductive-aged women and their most common treatments. This overview serves as a foundation for the subsequent chapters and places the subsequent options for fertility preservation in context. First, breast cancer, lung cancer, and cancer of the gastrointestinal tract are reviewed. The incidence and mortality rates among women of all races in all ages are seen in Table 2.1. Data on percent of cases seen in reproductive-aged women from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program from 2007 to 2011 are noted in Table 2.2.

Table 2.1 Most common causes of cancers among women and most common causes of cancer deaths according to the Centers for Disease Control (CDC) [8]

Malignancy	Rate per 100,000 (all races)
Most common cancer among women	
Breast cancer	122.0
Lung cancer	52.0
Colorectal cancer	34.9
Leading causes of cancer deaths among women	
Lung cancer	37.0
Breast cancer	21.5
Colorectal cancer	12.8

Table 2.2 Percentage of new cases in female patients of reproductive age according to the National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER] Program from 2007 to 2011

Cancer among reproductive age women (% of total cases diagnosed)			
Malignancy	<20 (years)	20–34 (years)	35–44 (years)
Breast cancer (%)	0.0	1.8	9.3
Lung cancer (%)	0.0	0.3	1.3
Colorectal cancer (%)	0.1	1.2	4.1
Ovarian cancer (%)	1.2	3.7	7.2
Uterine cancer (%)	0.0	1.6	5.6
Cervical cancer (%)	0.1	13.6	24.9

Breast cancer is commonly seen in patients of reproductive age. Lung cancer and colorectal cancer are seen more commonly in older patients, but occur with high frequency overall and have a number of cases which occur in younger women. Cancers of the female reproductive tract, particularly carcinoma of the cervix, are also seen in women of reproductive age. In the chapter, we review breast carcinoma and hereditary breast carcinoma, cervical carcinoma, uterine carcinoma, and ovarian/primary peritoneal carcinomas.

Breast Cancer

Breast cancer represents the most commonly diagnosed malignancy with over one million cases per year and is the leading cancer-related cause of death worldwide. In the United States, breast cancer is the second leading cause of death in women and the leading cause of death in women ages 20–59 [9]. According to the NCI's SEER database from 2007 to 2011, patients under 20 years of age represent 0.0 % of new cases, those aged 20–34 represented 1.8 % of new cases while patients aged 35–44 represented 9.3 % of new cases, resulting in a total number of 292,297 new cases. A number of risk factors contribute to an increased risk of breast cancer and include: age, ethnicity, history of benign breast disease, personal or family history of breast cancer, use of reproductive hormones, exposure to ionizing radiation, and environmental factors.

Treatment can include surgery, chemotherapy, and radiation therapy and is guided by the histologic subtype and stage according to the tumor node metastases (TNM) staging system. The most common histologic subtypes include:

- Infiltrating ductal carcinoma—accounts for 70–80 % of invasive cancers
- Infiltrating lobular carcinoma—accounts for 8 % of invasive cancers
- Mixed ductal/lobular carcinoma—accounts for 7 % of invasive cancers

Breast cancer is also classified by the presence or absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor 2 receptors (HER2) which guide subsequent adjuvant treatment.

Definitive TNM staging is accomplished during surgery and ultimately given a classification of Stage I–IV which helps to guide subsequent treatment. Stage I–II represents disease confined to the breast while Stage III–IV represents metastatic disease. The stage at diagnosis confers general prognosis, which declines substantially in later stages (Table 2.3). The vast majority of cancers diagnosed in the United States are early stage or locally advanced cancers, corresponding to Stage I–III disease.

Table 2.3 Breast cancer 5-year survival by stage at presentation [10]

Tumor node metastasis (TNM) stage	5-year survival (%)
Stage I	95
Stage II	
IIA	85
IIB	70
Stage III	
IIIA	52
IIIB	48
Stage IV	18

Treatment

As discussed above, the treatment is guided by the staging and molecular characteristics of the breast cancer. In general, early-stage breast cancers undergo primary surgery, either lumpectomy or mastectomy with regional lymph node removal, with radiation therapy after surgery reserved for those at a high risk for local recurrence. Subsequent adjuvant treatment is guided by TNM stage and the presence/absence of ER/PR receptors which may be amenable to endocrine therapy and/or expression of HER2 which may be amenable to HER2-directed treatment such as trastuzumab. For patients with locally advanced breast cancer, neoadjuvant systemic therapy utilizing chemotherapeutic agents, with HER2-directed agents in appropriate patients, is often employed prior to breast surgery and subsequent radiation therapy.

Fertility preservation in women with breast cancer presents the additional challenge of these cancers being hormonally responsive in certain circumstances. Involvement of a reproductive endocrinologist at the outset may allow for safe ovarian stimulation and oocyte retrieval prior to gonadotoxic chemotherapy. Because estrogen levels can rise tenfold more during ovarian stimulation when compared to the natural menstrual cycle, an approach with attempts to minimize systemic exposure should be utilized. Often agents such as letrozole, an aromatase inhibitor, and tamoxifen, a selective estrogen modulator with antiestrogenic actions in breast tissue, are employed during the ovarian stimulation process [11].

Hereditary Cancer Syndromes: BRCA 1/2

Although most breast and ovarian cancers occur sporadically, approximately 10 % of breast cancers and 15 % of ovarian cancers are associated with germ line mutations in tumor suppressor genes [12]. The most common mutations associated with these syndromes in the breast and ovaries are the breast cancer type 1 and 2 susceptibility genes (BRCA1 and BRCA2). Both mutations are inherited in an autosomal dominant fashion with high penetrance.

BRCA1 mutations are associated with cancers of the cervix, uterus, pancreas, esophagus, and stomach as well as breast and ovary. BRCA2 mutations are associated with cancers of the pancreas and possibly the stomach, biliary system, esophagus, and skin as well as breast and ovary. Women who carry the BRCA1 mutation have a 57 % cumulative risk of breast cancer by age 70 and a 40 % risk of ovarian cancer. For those with a BRCA2 mutation, this cumulative risk is 49 % for breast cancer and 18 % for ovarian cancer [13].

Women who are carriers of the BRCA1 or 2 mutations may elect to employ breast and ovarian cancer-reducing screening and/or treatment measures. Risk-reducing surgery for breast cancer involves a double mastectomy which can reduce the risk of breast cancer by as much as 90 %. Risk-reducing bilateral salpingo-oophorectomy decreases ovarian and fallopian tube cancers by approximately 80 % and also serves to decrease the risk of breast cancer by removing the primary endogenous source of estrogen. This is typically done at age 35–40 once childbearing is complete but can be done earlier.

Lung Cancer

Historically, lung cancer had a low prevalence with a death rate similar to that of pancreatic cancer. With the widespread smoking epidemic seen in the twentieth century, it became the leading cause of death first in men in 1963 and then in women in 1985. With anti-smoking campaigns in the United States, lung cancer death rates have begun to decline in both men and women [14]. Although most lung cancers occur after menopause, they still impact women of reproductive age in 3 % of cases [15]. According to the NCI's SEER database from 2007 to 2011, female patients <20 years of age represent 0.0 % of new cases, those aged 20–34 represented 0.3 % of new cases while patients in the 35–44 age group represented 1.4 % of new cases, with total number of new cases at 120,808.

There are four major histologic cell types of lung cancer according to the World Health Organization (WHO):

- Adenocarcinoma—accounts for 38 % of cases
- Squamous cell carcinoma—accounts for 20 % of cases
- Large cell carcinoma—accounts for 5 % of cases
- Small cell carcinoma—account for 13 % of cases

The remainder of the 24 % of cases cannot be fully characterized histologically. The majority of lung cancers present at very advanced stages given the lack of symptoms until that time.

The initial evaluation stage involves determining whether the patient has non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) as this will guide treatment. The staging of NSCLC follows the TNM staging system while the staging of SCLC utilizes either the Veterans Administration Lung Study Group designation (limited or extensive) or the TNM staging system.

Treatment

For patients who have NSCLC, treatment is guided by the stage of disease and involves surgical resection for early disease and chemoradiation therapy for those with extensive disease. For those with advanced disease, treatment options are limited and primarily involve palliative care.

In cases where SCLC is identified, systemic chemotherapy is the primary modality of treatment as SCLC is disseminated in nearly all cases.

Often thoracic radiation is used in combination with chemotherapy. Of importance when discussing pituitary and hypothalamic radiation, prophylactic cranial irradiation is often employed to decrease the incidence of metastasis to the head.

Cancer of the Gastrointestinal Tract

Cancer of the gastrointestinal tract, in particular colorectal cancer, is the third leading cause of death due to cancer in women. While the majority of cases occur after age 50, 11 % of cases of colon cancer, and 18 % of rectal cancers occur prior to age 50 and the incidence rates among young women have been increasing [16]. According to the NCI's SEER database from 2007 to 2011, female patients under 20 years of age represent 0.1 % of new cases, those aged 20–34 represented 1.2 % of new cases while patients aged 35–44 represented 4.1 % of new cases, where the total number of new cases was 91,411. Approximately 20 % of the cases of young-onset colorectal cancers occur as part of a familial syndrome such as hereditary nonpolyposis colorectal cancer or Lynch syndrome.

Diagnosis is achieved with tissue biopsy, typically obtained during a colonoscopy. The majority of colorectal cancers are characterized histologically as adenocarcinomas. Once the diagnosis is made, staging is accomplished utilizing the TNM staging system and guides surgical resection and chemotherapy.

Treatment

Surgical resection is the mainstay of curative therapy for locally confined colorectal cancer. In patients that have Stage III disease in which lymph nodes are positive, chemotherapy, typically with an alkylating platinum-based analogs, is recommended. In patients with more advanced Stage IV disease, surgery is not helpful and these patients are treated primarily with chemotherapy.

Cancer of the Female Reproductive Tract

Malignancies which affect the female reproductive tract, primarily cervical, uterine, and ovarian/primary peritoneal cancers present unique challenges for fertility preservation. They often occur in women of reproductive age and their therapy may result in the removal of reproductive organs and/or chemoradiation therapy, which is focused on the pelvis. Their demographics are summarized in Figs. 2.1 and 2.2 and the treatments are discussed below.

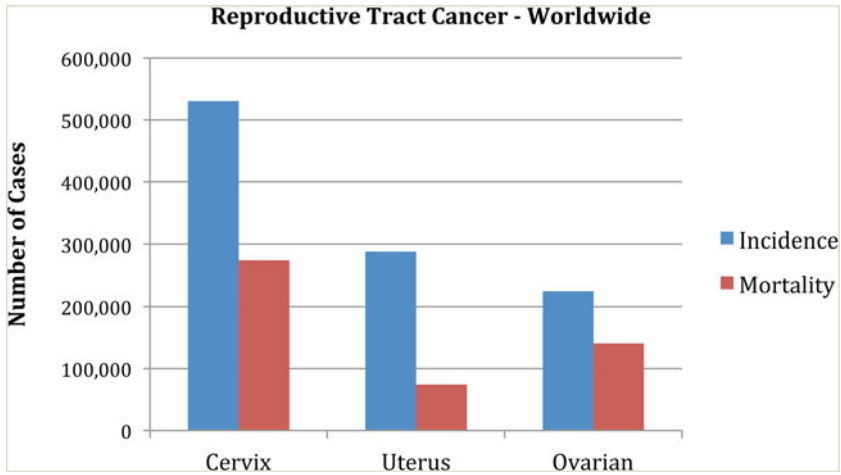

Fig. 2.1 The incidence and mortality of cancer of the reproductive tract worldwide for women of all ages [17]

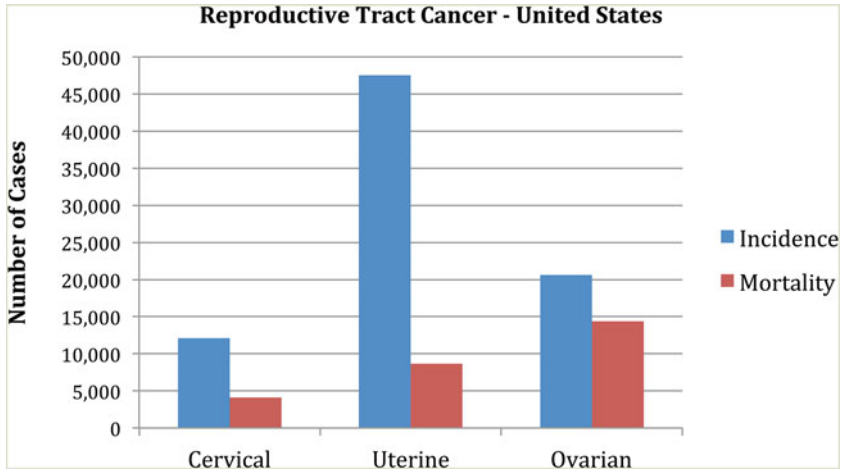

Fig. 2.2 The incidence and mortality of cancer of the reproductive tract in the United States for women of all ages [8]

Cervical Carcinoma

Cancer of the cervix represents the third most common cause of gynecologic cancers both in terms of incidence and mortality in the United States (Fig 2.2). This is not the case in underdeveloped countries of the world that lack robust screening and prevention programs. In these countries, cervical cancer remains the most common type of cancer and the most common cause of cancer deaths among gynecologic cancers (Fig. 2.1).

Although it is the third most common overall, cervical cancer represents the most significant disease burden of female reproductive tract cancers in reproductive age women. According to the NCI's SEER database from 2007 to 2011, patients under 20 years of age represent 0.1 % of new cases, those aged 20–34 represented 13.8 % of new cases while patients aged 35–44 represented 24.9 % of new cases, where total number of new cases was 17,223.

The human papilloma virus (HPV) is detected in nearly all cases of cervical cancer and squamous cell cancer and adenocarcinoma represent the majority of the histologic subtypes [18]. This represents a unique area in cancer prevention given the advent of the HPV vaccination which provides increased immunity to the most common causes of cervical cancer, namely HPV subtypes 16 and 18. It is expected that there will be a further decline in cervical cancer incidence and mortality with some regions with high vaccine utilization showing a decline in the incidence of high-grade dysplasia by 38 % [19].

Treatment

Treatment of cervical cancer depends upon the staging of the disease and extent of invasion. Cervical cancer staging is done according to the International Federation of Gynecology and Obstetrics (FIGO) classification system and takes into consideration clinical findings as well as pathology.

For women with early-stage disease, which represents microinvasive or minimally invasive disease on the FIGO system, women have several options for therapy. Treatment may include definitive therapy with surgery in the form of a modified radical hysterectomy in which the cervix, uterus, upper portion of the vagina, and the tissues closely surrounding these organs. Other options include fertility sparing surgery in which the uterus is preserved and the cancer is resected via cold knife conization or trachelectomy (removal of the cervix). Primary radiation therapy for early-stage disease is reserved for women who are not optimal surgical candidates.

Patients who have locally invasive cervical cancer, FIGO grades which comprise invasive

disease to the cervix, uterus, pelvic sidewalls, bladder, rectum, and outside of the true pelvis, treatment entail primary chemotherapy and radiation therapy. Surgery or radiation therapy alone is not as effective as combined treatment modalities. Chemotherapy is typically undertaken with an alkylating platinum-based analog (commonly cisplatin) which is sometimes combined with an irreversible inhibitor of thymidylate synthase (5-fluorouracil).

Uterine Carcinoma

Uterine cancer represents the most commonly diagnosed gynecologic malignancy in the United States. According to the NCI's SEER database from 2007 to 2011, patients under 20 years of age represent 0.0 % of new cases, those aged 20–34 represented 1.6 % of new cases while patients aged 35–44 represented 5.6 % of new cases, where total number of new cases was 57,667. Because abnormal uterine bleeding is the primary symptom associated with uterine cancer and it is seen in as many as 90 % of women with the disease, the diagnosis is made early by comparison to other gynecologic malignancies and mortality rate when compared to the incidence is quite low [20]. Nearly 70 % of cases are confined to the uterus at the time of diagnosis which confers a 5-year survival rate over 95 %.

While uterine cancers occur most commonly in postmenopausal women, it can occur in women of reproductive age. The majority of uterine cancers are adenocarcinomas which often develop in the setting of unopposed estrogen exposure. Thus, younger women at risk for uterine cancers include those who are obese and those who have chronic anovulation, such as women with polycystic ovarian syndrome. Women who have familial cancer syndromes, such as hereditary nonpolyposis colorectal cancer or Lynch syndrome, are also at an increased risk of uterine cancer.

Treatment

Treatment is guided by endometrial cancer FIGO staging as well as histologic type. Endometrial cancers are classified as Type I or Type II. Type I or endometrioid carcinomas are the most common type, are estrogen responsive, and typically carry a relatively favorable prognosis. Type II carcinomas include carcinosarcomas, serous, and clear cell cancers and have a poorer prognosis.

Surgical treatment alone is typically curative for those with early-stage Type I disease. This entails the removal of the cervix, uterus, fallopian tubes, ovaries, and adjacent lymph nodes. In patients who have higher risk for recurrence, more advanced cancers, or high-grade histopathologic subtypes, adjuvant therapy in the form of chemotherapy and/or radiation therapy is optimal.

Fertility and uterine sparing options exist for a special subset of patients who have low-risk, localized endometrial carcinoma. These patients can be treated with high-dose continuous progestin therapy, either megesterol acetate orally or with the levonorgestrel intrauterine device, with regular close follow-up.

Ovarian/Primary Peritoneal Carcinoma

Ovarian cancer is the second most common cause of gynecologic malignancy in the United States and represents the most common cause of deaths related to gynecologic cancers. According to the NCI's SEER database from 2007 to 2011, patients under 20 years of age represent 1.2 % of new cases, those aged 20–34 represented 3.7 % of new cases while patients aged 35–44 represented 7.2 % of new cases, where total number of new cases was 29,010. The reason for the high mortality relates to the lack of symptoms and late stage of presentation as opposed to that seen with uterine cancer as discussed above.

The majority of ovarian malignancies is derived from the epithelial cells of the ovary and is classified histopathologically as serous, mucinous, endometrioid, clear cell, and transitional cell tumors. These tumors, which comprise 95 % of ovarian cancers, occur most commonly in older patients. The other two layers of the ovary, the stroma and the germ cells, represent the other

cells of origin for ovarian tumors and occur more commonly in younger, reproductive-aged women. Stromal tumors include granulosa cell, thecoma, fibroma, Sertoli cell, and Sertoli–Leydig. The germ cell tumors include dysgerminomas, yolk sac, embryonal, choriocarcinoma, and teratomas. Serous epithelial carcinomas, fallopian tube carcinoma, and primary peritoneal carcinomas are thought to have a similar or common origin and behave and are treated similarly.

Treatment

Treatment of ovarian cancer is guided by histopathology and staging as determined by FIGO. There are many benign subsets of ovarian tumors which require only resection of the ovarian cyst, as is the case with benign teratomas. In other cases, conservative therapy by removal of only one ovary with close follow-up is sufficient, as is the case for many germ cell tumors. For tumors of epithelial origin, treatment involves full surgical staging which includes removal of the cervix, uterus, fallopian tubes, ovaries, surrounding lymph nodes, the omentum, and directed biopsies of lesions on the peritoneum. The goal of these surgeries is optimal cytoreduction and debulking to remove all signs of tumor >1 cm in size.

Treatment after surgery is guided based upon stage and most often includes multi-agent chemotherapy. Chemotherapy is typically undertaken with an alkylating platinum-based analog (commonly carboplatin) which is combined with a taxane that interferes with normal microtubule breakdown during cell division (such as paclitaxel).

Conclusion

The most common cancers in women are breast, lung, and colorectal cancers. Cancers of the gynecologic tract, namely cervical, uterine, and ovarian, are also common in reproductive age women. The treatment of all of these cancers, whether surgical or with chemotherapy and/or radiation therapy, have the ability to impact a women's ultimate reproductive potential.

The epidemiology of these cancers and common treatment paradigms have been discussed here. There are a number of options available to mitigate risks for infertility in female cancer survivors and these are discussed in detail in Chaps. 11, 15 and 16.

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