

Evolving Paradigms in Gynecologic Cancer: Introduction

In the past decade, there has been a rapid increase in the understanding of how various cancers develop and progress. This new knowledge has led to the advance of novel and more targeted strategies for the prevention, diagnosis, and treatment of many malignancies, including gynecologic cancers.

Gynecologic cancers include 5 main cancers occurring in the female reproductive system: cervical, ovarian, uterine, vaginal, and vulvar. Malignancies in each of these sites can be of multiple histological types, so that the group of diseases encompassed by the term “gynecologic cancers” is large and heterogenous. Collectively, these cancers had an estimated incidence in 2014 of 95,000 new cases in the United States and nearly 29,000 deaths. Uterine cancer is the most commonly diagnosed gynecologic cancer, accounting for over 55% of new diagnoses in 2014, while ovarian cancer is the most lethal, comprising nearly 50% of deaths from gynecologic malignancies (**Figure 1**).¹

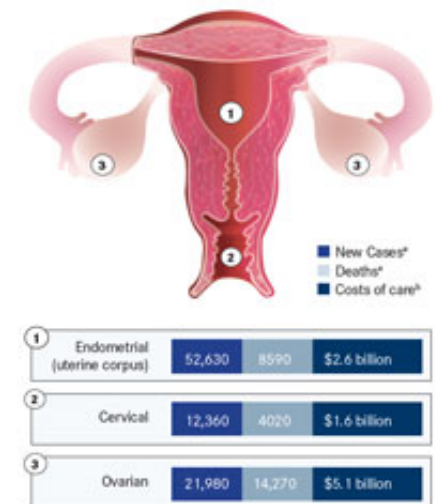
Because of newer methods that enable the early detection and prevention of cervical cancer, both the incidence and mortality rates for this disease declined by about 50% between 1975 and 2011. In contrast, reductions in the incidence and mortality for uterine and ovarian cancer have been much more modest, due in large part to incremental improvements in care rather than drastic shifts in treatment paradigms,^{3,4} while incidence and mortality rates of the much more rare vaginal and vulvar cancers have remained largely static for the past 30 years.

OVERVIEW

Ovarian Cancer

Ovarian cancer is the most deadly gynecologic neoplasm and is the fifth leading cause of cancer death in women in the United States.⁵ The majority of malignancies that arise from the ovaries tend to be epithelial cancers (90%). Fallopian tube cancers and primary

FIGURE 1. The annual impacts of the 3 major gynecologic cancers are shown in terms of incidence, mortality, and health care cost.³ Numbers for new cases and deaths are estimates for 2014¹; costs are estimates for 2010.²



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^aNew cases and deaths are estimates for 2014.

^bCosts are estimates of national expenditures in 2010.

peritoneal cancers are uncommon gynecologic cancers that are also epithelial in nature and are addressed with the same therapeutic strategies as epithelial ovarian cancer (EOC). The histopathologies of the remaining 10% of cases of ovarian cancer are ovarian low malignant potential tumors (also known as borderline epithelial ovarian tumors), malignant germ cell neoplasms, carcinosarcomas, and malignant sex cord-stromal tumors.

Uterine Cancer

The majority of uterine malignancies are adenocarcinomas, which are also referred to as endometrial cancer. Endometrial cancer is the most common cancer of the female genital organs in the US.⁶ Other less common types of uterine cancer include uterine serous adenocarcinomas, clear cell adenocarcinomas, sarcomas, and epithelial tumors, which are more aggressive and are managed differently from adenocarcinomas.

Cervical Cancer

The most important factor driving the development of cervical cancer is infection by the human papilloma virus (HPV). This fact is demonstrated by the correlation observed between the rate of HPV infection and the incidence of cervical cancer across different countries and geographical areas.⁷ While the incidence of cervical cancer has decreased significantly in countries with screening and vaccination programs in place, it remains a major cause of mortality in women in developing countries.

Approximately 80% of all cervical cancers are squamous cell carcinomas, while the remaining 20% are mainly adenocarcinomas.⁸ Tumors of the vagina that involve the cervix of women with an intact uterus are also usually classified as cervical cancers.

The bulk of the decline in the incidence of cervical cancer overall is accounted for by a decline in squamous cell carcinoma; however, cases of cervical adenocarcinoma have increased in recent years, possibly due to a failure of cytological screening methods to detect adenocarcinoma. The recent implementation of HPV-based testing and vaccination may correct this imbalance due to their respective abilities to effectively detect and prevent both types of cervical cancers.

Vaginal Cancer

Vaginal neoplasms are fairly uncommon, representing only about 1% of all cases of

gynecologic cancers, and they are also frequently curable if identified at an early stage.⁹ About 85% of vaginal cancers are squamous cell carcinomas, while 5% to 10% are adenocarcinomas. Squamous cell carcinoma of the vagina is associated with HPV infection and shares many risk factors in common with squamous cell carcinoma of the cervix. Additional rare types of vaginal neoplasms are melanomas, sarcomas, and small-cell carcinomas.

Vulvar Cancer

Cancer of the vulva accounts for approximately 5% of all cases of gynecologic cancer in the US, and about 90% of vulvar neoplasms are squamous cell carcinomas. Approximately 50% of vulvar tumors involve the labia majora, and the labia minora are the site of 15% to 20% of vulvar cancers.¹⁰ As in the case of cervical and vaginal cancers, HPV infection is strongly associated with the development of vulvar cancer.

Table 1. Risk Factors for Gynecologic Cancer

Ovarian Cancer (EOC) ⁵	Uterine Cancer ⁶	Cervical Cancer ⁸	Vaginal Cancer ¹¹	Vulvar Cancer ¹²
BRCA1/2 mutations	Increased estrogen levels	HPV infection	HPV infection	HPV infection
Lynch syndrome	Lynch syndrome	Oral contraceptive use	HIV infection	HIV infection
>35 years old at first pregnancy/birth	Late age at menopause	Early age of onset of coitus	Prenatal diethylstilbestrol (DES) exposure	Lichen sclerosus
Nulliparity	Nulliparity	Autoimmune disease		Melanoma or atypical moles
Postmenopausal hormone therapy	Early age at menarche	Chronic immunosuppression		

The main variable affecting the survival rate for vulvar cancer is whether or not it has spread to the lymph nodes. If not, the overall survival (OS) is reported to be 90%; however, if there is involvement of nearby lymph nodes, the 5-year survival rate drops to less than 60%. Overall, approximately 30% of cases have lymph node involvement at diagnosis.

RISK FACTORS

Various overlapping genetic and lifestyle characteristics can increase the odds of developing gynecologic cancer for certain individuals. The most important known risk factors for each type of cancer are listed in **Table 1**. The factors listed, such as estrogen levels or infection by HPV, tend to be specifically associated with gynecologic malignancies. Other more general cancer risk factors, including advanced age, obesity, and smoking, are risk factors for gynecologic cancers as well.

Lynch Syndrome

Lynch syndrome is a dominantly inherited disease of dysfunction in the cellular DNA mismatch repair system. This syndrome predisposes patients to develop several types of cancer, the most common being colorectal, endometrial, and ovarian.¹³ National Comprehensive Cancer Network (NCCN) guidelines recommend screening endometrial tumors for mismatch repair defects with immunohistochemistry and microsatellite instability to identify patients who should be tested for genetic mutations that cause Lynch syndrome, especially for patients under 50 years of age.⁶

More from this project will be coming soon.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014;64(1):9-29.
2. National Cancer Institute. Costs of Cancer Care. Cancer Trends Progress Report – 2011/2012 Update. 2012; http://progressreport.cancer.gov/doc_detail.asp?pid=1&did=2011&chid=105&coid=1026&mid=. Accessed December 4, 2014.
3. Herzog TJ, Armstrong DK, Brady MF, et al. Ovarian cancer clinical trial endpoints: Society of Gynecologic Oncology white paper. *Gynecol Oncol.* 2014;132(1):8-17.
4. Tan W, Stehman FB, Carter RL. Mortality rates due to gynecologic cancers in New York state by demographic factors and proximity to a Gynecologic Oncology Group member treatment center: 1979-2001. *Gynecol Oncol.* 2009;114(2):346-352.
5. National Comprehensive Cancer Network. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 3.2014). 2014; http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed November 7, 2014.
6. National Comprehensive Cancer Network. Uterine Neoplasms (Version 1.2015). 2014; http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed November 7, 2014.
7. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55(2):74-108.
8. National Comprehensive Cancer Network. Cervical Cancer (Version 2.2015). 2014; http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed November 7, 2014.
9. National Cancer Institute. PDQ® Vaginal Cancer Treatment. PDQ Cancer Information

Summaries

<http://cancer.gov/cancertopics/pdq/treatment/vaginal/HealthProfessional>. Accessed November 8, 2014.

10. National Cancer Institute. PDQ® Vulvar Cancer Treatment. PDQ Cancer Information Summaries <http://cancer.gov/cancertopics/pdq/treatment/vulvar/HealthProfessional>. Accessed November 8, 2014.
11. American Cancer Society. What are the risk factors for vaginal cancer? <http://www.cancer.org/cancer/vaginalcancer/detailedguide/vaginal-cancer-risk-factors>. Accessed November 25, 2014.
12. American Cancer Society. What are the risk factors for vulvar cancer? <http://www.cancer.org/cancer/vulvarcancer/detailedguide/vulvar-cancer-risk-factors>. Accessed November 25, 2014.
13. Cohen SA, Leininger A. The genetic basis of Lynch syndrome and its implications for clinical practice and risk management. *Appl Clin Genet*. 2014;7:147-158.