Progress Review Groups

Report of the Gynecologic Cancers Progress Review Group

November 2001

NATIONAL® CANCER INSTITUTE

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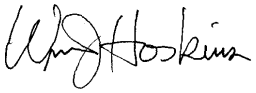
From the Leadership

It is a great pleasure to submit this Report of the Gynecologic Cancers Progress Review Group (GYN PRG) to the Acting Director and Advisory Committee to the Director of the National Cancer Institute (NCI). At the beginning of 2001, the GYN PRG accepted the charge of NCI Director Dr. Richard Klausner to develop a national plan for the next 5 years of gynecologic cancer research. The expertise of the GYN PRG members and the clinical, research, industrial and advocacy community participants of the GYN PRG Roundtable Meeting met that charge with this report. It reflects innovative research strategies that represent the next steps toward preventing, diagnosing and treating gynecologic cancers. We look forward to discussing these priorities with the leadership of the NCI.



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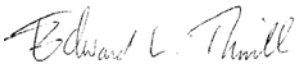

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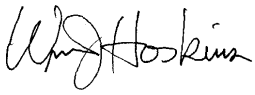
We the undersigned members of the Gynecologic Cancers Progress Review Group concur with the enclosed report.



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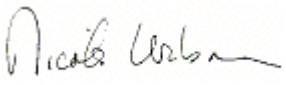

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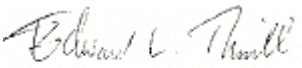

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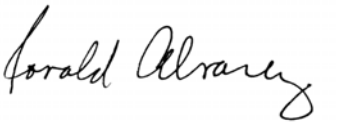
R 

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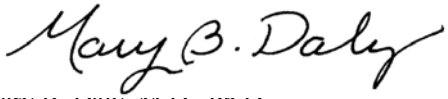

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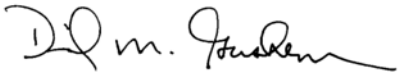
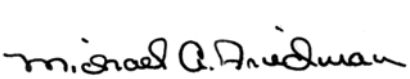
D 



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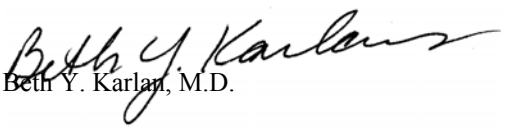

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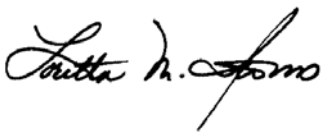
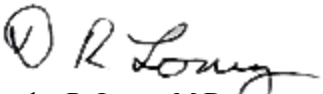
L 



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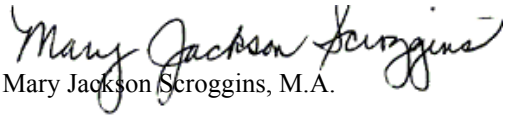

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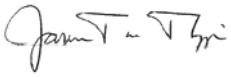

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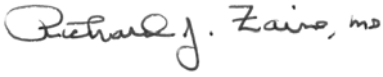

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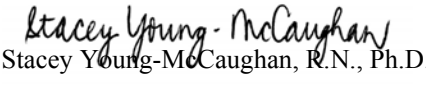

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Acknowledgments

This report is the product of 11 months of intense work that drew on the combined expertise and efforts of many individuals. The Progress Review Group (PRG) particularly acknowledges the contributions of:

- The many scientists, clinicians, and advocates across the country, who gave of their time and knowledge and were an integral part of making this report a successful document that should help advance research in gynecologic cancers.
- Staff of the NCI Office of Science Planning and Assessment (OSPA), under the leadership of Cherie Nichols, who provided ongoing guidance and technical support throughout the PRG process—in particular, Deborah Duran and Anna T. Levy, who coordinated the PRG, as well as Kevin Callahan, James Corrigan, and Annabelle Uy.
- A group of experienced science writers, who provided excellent writing support both during the Roundtable Meeting and the subsequent development of the PRG report: Deborah Shuman, Nancy Volkers, Randi Henderson, Alice Lium, Cheryl Pellerin, Barbara Shapiro, and Cheryl Ulmer.
- Josette James, Audrey Thomas, and their colleagues at Palladian Partners, Inc., who provided excellent logistical support to the PRG.
- David N. Louis, Co-Chair of the Brain Tumor Progress Review Group, for his presentation to Roundtable participants.

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Priorities of the Gynecologic Cancers Progress Review Group

INTRODUCTION

BACKGROUND

Cervical, endometrial, and ovarian cancers represent 95 percent of gynecologic cancers and collectively rank fourth in both incidence and mortality among cancers that affect women. It is estimated that 80,300 women in the United States will be diagnosed with a gynecologic cancer (cancers of the cervix uteri, corpus uteri, and ovary) in 2001 and an estimated 26,300 will die of these diseases. Thus, gynecologic cancers will account for 14 percent of all solid tumors in women and 11 percent of deaths from them. Worldwide, gynecologic cancers account for an even larger share of cancer mortality in women. In non-industrialized countries, cervical cancer screening is minimal; consequently, this disease is a major cause of cancer deaths, second only to breast cancer in incidence and mortality. These three cancers have in common their origin in the organs of the female reproductive system, but they differ dramatically in most other ways.

As with all solid tumors, the key to the control of gynecologic cancers lies in understanding their biology. If we can identify the genes, proteins, and environmental agents that drive their initiation and progression, we can make significant progress in improving outcomes for women at risk for these malignancies.

We understand, and therefore control, cervical cancer best. Our recognition of precursor lesions in cervical cancer, and our use for nearly 50 years of the Pap test to detect them, has all but eradicated invasive cervical cancer in developed countries of the world. Our more recent discovery that infection by the human papillomavirus (HPV) is a necessary condition for the development of most if not all of cervical cancer provides an unprecedented opportunity. By developing vaccines against HPV infection and/or cervical cancer development among those exposed to HPV infection, there is the potential to control cervical cancer throughout the world. Although we do not understand endometrial cancer well, we do know the precursor lesion for the most common type of disease, and can usually detect and diagnose it early enough to treat it successfully. However, there is an aggressive form of endometrial cancer, type II, that, like ovarian cancer, is very poorly understood. Ovarian cancer, by far the most lethal of the gynecologic cancers in developed countries, has presented a challenge to researchers because it is not symptomatic until late in the disease process. Tumors are not easily identified using current methods of early detection. Research on biomarkers for early detection of ovarian cancer has resulted in at least one marker (CA-125) for ovarian cancer. CA-125 is currently being tested in randomized controlled trials along with an imaging method, transvaginal sonography, for early detection. In addition, recent applications of proteomic techniques have shown promise in identifying unique markers of ovarian cancer. Nevertheless, much work remains to be done in both ovarian and type II endometrial cancer if they are to be controlled within the next few decades.

PROCESS

The Gynecologic Cancer Progress Review Group (GYN PRG) was charged with identifying and prioritizing areas of research to advance progress against these cancers. In this process, we attempted to maintain a global perspective, and our recommendations reflect priorities that will benefit women throughout the world.

At a Planning Meeting held in February 2001, the GYN PRG organized a Roundtable to consider progress and identify needs across the continuum of gynecologic cancer research. Topics were selected for breakout sessions and experts were nominated to participate in the Roundtable. PRG members served as co-chairs for the breakout sessions.

The GYN PRG Roundtable of approximately 120 participants met June 18–20, 2001, in Herndon, Virginia. Participants were assigned to 1 of 14 scientifically focused breakout groups and asked to identify top priorities for gynecologic cancer research in these areas over the next 5 years.

Scientific Breakout Groups at the GYN PRG Roundtable Meeting

- Angiogenesis, Metastasis, and Growth Signaling
- Defining Signatures of Cancer Cells, Genomics, Proteomics, and Informatics
- Clinical and Molecular Genetics
- Early Detection, Screening, and Prevention
- Genes and Environment
- Health Disparities, Communication, Education, and Quality of Care
- Health Related Quality of Life and Survivorship
- Imaging
- Immunology
- Laboratory and Clinical Models
- Radiobiology
- Treatment, Clinical Trials, Gene Therapy, Staging, and Surgery
- Treatment and Drug Discovery
- Tumor Biology, Hormone Receptors, Epithelial-Stromal Interactions, and Early Activation

In support of the priority-setting process, the Roundtable participants were provided with analysis of NCI's gynecologic cancer research portfolio and extensive information about ongoing NCI initiatives and activities that might address some of the needs of the field.

Following the scientific breakout sessions, Roundtable members were convened in three groups to consider the specific gynecologic tumor types—cancer of the cervix, endometrium (uterine corpus), and ovary. These groups were asked to identify gaps in knowledge and barriers to progress, drawing

on the reports of the scientific breakout groups. Groups were to recommend four to six priorities for research in each specific disease type, as well as any recommendations relevant to all three disease sites. Finally, the groups were asked to define an action plan to achieve the research goals. The full reports of the 14 scientific breakout groups and the 3 groups addressing specific gynecologic tumor types are provided in Appendix C.

OVERVIEW OF PRIORITIES

Following the Roundtable, the PRG leadership used the recommendations of the scientific breakout groups and tumor-specific groups to identify an *Essential Priority,* the Virtual Shared Specimen Resource (VSSR), an initiative considered absolutely necessary for advancing the detection, classification, and treatment of gynecologic cancer. Three *High-Impact Priorities* provide opportunities to expedite progress in our knowledge and understanding of gynecologic cancers and thus make significant impacts to reduce the burden of disease. Thematically, these priorities address either broad, cross-cutting research areas or focus on a specific gynecologic cancers. Finally, six *Scientific Opportunities* to expedite progress in translational research of gynecologic cancers were identified.

ESSENTIAL RESEARCH PRIORITY	HIGH-IMPACT PRIORITIES	SCIENTIFIC OPPORTUNITIES
Develop and make available to the cancer research community a Virtual Shared Specimen Resource (VSSR) to support gynecologic cancer research. There was consensus among members of the Roundtable that progress in gynecologic cancer research requires timely access to high quality samples of human tissue and body fluids. The VSSR will enable the research community to exploit emerging genomics, proteomics and informatics technologies to identify gynecologic cancers early in the disease process and to discover new targets for their prevention and treatment.	(1) Identify precursor lesions, markers of risk and early detection, molecular disease classifications, prognostic indicators, and new targets for prevention and treatment. (2) Develop effective human papillomavirus (HPV) vaccines to prevent biotransmission and development of neoplasia. (3) Conduct research to (a) understand and improve the quality of life of gynecologic cancer patients and (b) reduce or eliminate disparities related to care among patients with gynecologic cancers.	(1) Characterize the hormonal, immunologic, and epithelial-stromal interactions that result in the development of gynecologic cancers. (2) Develop imaging techniques to evaluate tumor biology, molecular signatures, and therapeutic response. (3) Develop preclinical models for gynecologic cancers. (4) Find ways to overcome resistance to chemotherapy and radiotherapy. (5) Develop individualized, optimized radiation therapy techniques in conjunction with other treatment modalities. (6) Encourage increased participation in clinical trials in gynecologic cancer.

As in all types of cancer, the promise of exciting new technologies is that we may be able to classify gynecologic cancers at the molecular level so that we can detect them early and diagnose them in ways that guide treatment decisions. The establishment of a Virtual Shared Specimen Resource (VSSR) would enable the gynecologic cancers research community to realize the potential of the emerging technologies that require human

tissue samples. A cooperative effort of this kind, facilitated by the NCI, will speed progress in the type of research needed to control ovarian and endometrial cancer. The time is right for such an initiative. The NCI has already begun an important effort to work with the research community to define the Common Data Elements (CDE's) that describe such specimens. Sharing of specimens will enable investigators to collaborate across disciplines and institutions to answer the most important research questions.

The GYN PRG has formulated the priorities and opportunities described in this report to stimulate multi-disciplinary research that will significantly advance progress against these diseases. Implementation of these priorities can ultimately lead to discoveries that will ameliorate the significant impact of the gynecologic cancers on the health and lives of American women.

ESSENTIAL RESEARCH PRIORITY

THE VIRTUAL SHARED SPECIMEN RESOURCE

Priority: *Develop and make available to the cancer research community a Virtual Shared Specimen Resource (VSSR) to support gynecologic cancer research.*

To make significant progress, the gynecological cancer research community needs to exploit emerging genomics, proteomics and informatics technologies to identify precursor lesions, markers of risk and early detection, molecular disease classifications, prognostic indicators, and new targets for prevention and treatment. Despite a wealth of opportunities, progress is impeded by the dearth of high-quality, fresh-frozen, annotated specimens available to the gynecologic research community. In part because technologies are developing so rapidly, cutting-edge research requires specimens that are obtained at critical points in the disease process, processed and stored in evolving ways, and associated with high-quality clinical and follow-up data.

The VSSR will allow us to perform molecular profiling to identify the molecular signatures of gynecologic cancers. It will facilitate the discovery of markers of gynecologic cancer risk, premalignant and malignant disease, and new approaches of preventing and treating progressive disease. Specifically, it will enable us to achieve answers to the following questions, which have been elusive in the past:

- How can women at high risk for gynecologic cancers be identified?
- How can ovarian and endometrial cancers be detected early?
- What strategies can be developed to prevent gynecologic cancers?
- What new approaches can be developed to better treat gynecologic cancers?

Various tissue collection initiatives have been proposed and many exist, but they are limited in their usefulness for one or more of the following reasons:

- Banked specimens were not processed or stored appropriately for current scientific needs.
- Banked specimens were not obtained at the appropriate time in the course of disease, or do not represent the needed tissue types.
- Informed consent obtained from tissue donors was not adequate for current scientific needs.

- Specimens were not linked to adequate clinical data, including demographics, risk factors, therapy, and follow-up.

- Lack of incentives to share specimens inhibits widespread use.

As a result, specimens are not currently available in a timely fashion to a large group of researchers addressing the critical scientific questions in gynecologic cancer research.

Nearly every GYN PRG breakout group cited the critical need for quality samples of tissue and body fluids for research in gynecologic cancer. The groups also pointed out that these specimens must be collected in a manner to allow adequate preservation of DNA and RNA for research use. They further listed the need for these specimens to be linked to adequate patient data, including demographics, risk factors, therapy, and follow-up. Where possible, these specimens should be serially collected: before treatment, during treatment, and at any recurrence. Specimens from women without gynecologic cancer are needed as well, including women with benign gynecologic conditions and women with no evidence of gynecologic or malignant disease. Finally, these specimens and their associated clinical data must be collected with appropriate informed consent to allow for their use in all future research, including techniques yet to be developed and questions yet to be asked.

The VSSR will enable the gynecologic cancer research community to realize the promise of exciting new technologies to identify gynecologic cancers early in the disease process and to discover new targets for their prevention and treatment. To make significant progress, a cooperative effort is needed to ensure that the best scientists have access to the right specimens. Although the scientific community has made efforts to this end, it is very difficult. NCI has an opportunity to facilitate the scientific community efforts and in fact, have already begun the process through the definition of common data elements to describe the specimens.

Features of the VSSR would include specific scientific goals, a coordinating center, and an advisory committee to ensure efficiency, equity, quality, and inventory control in specimen collection, management, and distribution. The VSSR is "virtual" in the sense that although information describing the specimens is managed centrally, the specimens themselves reside in various institutions.

The VSSR will surmount existing barriers to effective specimen banking and distribution in the following ways:

- Its virtual design will overcome the reluctance of institutions that collect specimens to have their specimens stored centrally.

- Its central coordination will provide equitable access to banked specimens as well as providing a means of prospective collection of specimens when banked specimens are inadequate.

- Its scientific oversight will ensure that appropriate policies are developed regarding consortia members' rights and responsibilities, with attention to structuring incentives to promote collaboration.

Recommended Actions

- The National Cancer Institute (NCI) should provide the resources needed to facilitate development of a VSSR for gynecologic cancer research.

- An advisory committee composed of leaders, including advocates, in

gynecologic cancer research, such as members of the GYN PRG, should monitor and oversee the progress of the resource and the research it supports.

- Multiple institutions should collaborate in the development and use of the VSSR, with a long-term goal of serving the specimen needs of the larger gynecologic cancer research community.

Resources

The VSSR would probably involve multi-institutional consortia addressing one or more of the critical scientific questions identified by the GYN PRG, including identification of precursor lesions; biomarkers of risk, early-stage disease, and prognosis; molecular signatures of malignant and premalignant lesions; and targets for prevention and therapy. Each consortium would develop a specimen repository to support its own research needs as well as those of the larger gynecologic research community.

Fresh tissue and fluids would be obtained at critical points in the disease process from large numbers of women (hundreds to thousands, depending on the research focus), including those with and without gynecologic cancer. Rates of specimen accrual for rare types of gynecologic cancer (such as type II endometrial, stage I serous ovarian, and invasive cervical cancers) and other conditions of interest (such as prophylactic oophorectomy and precursor lesions) would be important in selecting consortia.

Also important would be quality control of collection, processing, storage, and characterization, as well as the ability to collect data on risk factors, clinical aspects, follow-up, and outcome by using common data elements (CDEs) agreed upon by the major NCI networks (Cancer Therapy Evaluation Program, Specialized Programs Of Research Excellence [SPOREs], Early Detection Research Network, etc.). Plans for specimen collection and processing would be based on the specific research questions to be addressed, as well as on the development of a more generally useful repository. Expertise in genomics, proteomics, and/or informatics would be needed within each consortium to support specific research goals. Consortia would provide access to banked specimens in the virtual repository and would initiate prospective specimen collection to meet the specific goals of new studies for which banked specimens were unavailable or inadequate.

The VSSR coordinating center would:

- Facilitate specimen access by the greater research community
- Manage specimen inventory and data
- Develop policies and systems to provide equitable access to the resource, as well as a plan for managing specimen inventory, including rapid prospective collection of tissue to meet research needs for which banked specimens are inadequate
- Coordinate the work of the collection sites across consortia so that the "spigot" can be turned on as needed to collect specimens of a particular type, to be appropriately processed and characterized to maintain inventory and/or to meet specific scientific objectives
- Monitor and control the inventory of banked specimens to ensure the adequate availability of banked specimens to meet the needs of the research community
- Oversee a Specimen Allocation Committee, composed of investigators at the collection sites, which would approve applications for prospective collection of unique specimens to meet particular

scientific research objectives, as well as the use of stored specimens

- Ensure the appropriate involvement of patient advocate groups as resources
- Provide data collection forms and a specimen inventory control and tracking system (such as the Biological Specimen Inventory), to ensure the use of CDEs, facilitate specimen and data sharing, and avoid unnecessary investment in computer systems at each institution and consortium site
- Provide a website (clearinghouse) to support communication with the greater research community regarding the ability of collection sites to accrue numbers of specimens of different types within a year, and availability of specimens banked already in the repository

While the GYN PRG hopes that all or many of the priorities in this report will be addressed, we also believe that there can be little progress in gynecologic cancer research unless this essential priority is implemented. The absence of a dedicated specimen resource will preclude timely scientific progress in gynecologic cancer research. Human specimen resources are required to meet the critical scientific needs identified in the 2002 NCI Plans and Priorities for Cancer Research (http://www.planning.cancer.gov), as well as those identified in this report. If successful, the VSSR could become a model for a resource that covers tumor types beyond gynecologic cancers.

HIGH-IMPACT RESEARCH PRIORITIES

Drawing on the discussions of Roundtable participants, the PRG leadership identified three areas of research:

- Identification of markers of risk, early detection, and targets for treatment
- Development of human papillomavirus vaccines
- Research to improve patients' quality of life and to reduce disparities related to care

These areas were selected because of their importance to the science of gynecologic oncology in terms of both the state of the science today and the potential for benefit over the next 5 years. Two of these priorities are relevant to all three gynecologic tumor types and encompass areas of the science of oncology that also apply to other types of cancer. The other priority (HPV vaccines) is included as a high-impact priority because it has the potential to nearly or completely eliminate cervical cancer and thus would have a major effect on women's health throughout the world.

Within each of the three areas, cross-cutting priorities for research were culled and consolidated from the lists of priorities developed by the breakout groups. This section presents background information, descriptions, and justifications for each of these areas.

MOLECULAR PROFILING FOR MARKERS OF RISK, EARLY DETECTION, AND TREATMENT

Priority: *Identify precursor lesions, markers of risk and early detection, molecular disease classifications, prognostic indicators, and new targets for prevention and treatment.*

Cancer control strategies will be most effective and economically feasible if potentially lethal cancers can be identified and treated before they become invasive, and if treatment can be appropriately targeted. Emerging new technologies offer

unprecedented opportunities. However, the use of these technologies to translate new discoveries for patients' benefits will require access to high-quality annotated human specimens.

Although early detection and prevention offer the best hope for reducing mortality from gynecologic cancers and improving the quality of life of cancer survivors, we do not have effective screening strategies for ovarian cancer or endometrial cancer. Identification of cervical intraepithelial neoplasia type III (CIN III) as a precursor lesion for cervical cancer has allowed us to develop effective screening strategies for those cancers, but the precursor lesions for ovarian cancer and for type II endometrial cancer are unknown.

We also have only limited means of identifying women at high risk for these diseases. A model of cancer risk—such as the Gail model for breast cancer enhanced with the addition of biomarkers—is needed for the gynecologic cancers. To develop risk models and define risk groups for ovarian and endometrial cancer, we need epidemiologic studies conducted in large populations. Such models should incorporate markers and address long-term risk (i.e., over the lifetime) as well as short-term risk (i.e., within the next 1 to 5 years). Proteomic approaches will make possible the development of new markers to identify individuals with early-stage cancer or at high risk of developing cancer.

To identify *in situ* and precursor lesions, a two-pronged approach will be needed. In addition to research on basic tumor biology, including novel ways to understand benign but abnormal biology in the pelvis and its progression to malignancy, new technologies such as genomics and proteomics should be used to identify precursor lesions and provide their molecular signatures. Well-designed molecular profiling studies are needed to identify the precursor lesions and discover their markers.

Once cancer has been diagnosed, treatment recommendations are made on the basis of histology and extent of disease, as they have been for the past 50 years, yet response to treatment varies widely among women with the same histologic and clinical features. Many women now run the risk of over-treatment with adjuvant therapy, which can potentially incur unnecessary expense and morbidity. The availability of new techniques to identify molecular and genetic characteristics of tumors should be combined with clinical follow-up data so that molecular markers of risk can be incorporated into the staging system for gynecologic cancers. Molecular and proteomic signatures are needed to supplement or replace the role of histology and extent of disease in treatment decisions, to provide accurate prognostic markers, and targets for new therapeutic and preventive agents. Partnerships with industry will facilitate the development of new chemical and biologic therapies directed toward the targets identified by molecular profiling investigations.

To advance knowledge in all these areas—screening, risk, treatment, and prognosis—we must identify molecular markers associated with cervical, endometrial, and ovarian cancers. Markers for early detection and risk will help diagnose cancer in its earliest stages, increasing the chances for successful treatment with minimal effects on quality of life. Molecular targets for treatment can lead to more individualized and less toxic therapies. Markers for response to therapy and prognosis will also help tailor therapies according to the molecular profile of each woman's cancer.

Achieving this priority would allow us to begin to answer the following questions:

- What are the precursor lesions associated with epithelial ovarian cancer and high-risk endometrial cancer?

- What biomarkers, measurable in easily accessible fluids, are associated with these precursor lesions?

- What biomarkers, measurable in easily accessible fluids, are associated with invasive gynecologic cancers, especially ovarian and high-risk endometrial cancer?

- What biomarkers, measurable in easily accessible fluids, are associated with response or non-response to therapy?

- What models of risk, incorporating biomarkers as well as family history, environmental exposures, and reproductive history, can predict future development of epithelial ovarian cancer and endometrial cancer?

- What new approaches can be identified for prevention of the gynecologic cancers?

- What is a clinically relevant molecular classification and staging system for invasive gynecologic cancers?

- What new targets can be identified for which directed therapies can be developed to improve survival from the gynecologic cancers?

Recommended Actions

The NCI is already sponsoring a variety of initiatives and projects relevant to the molecular profiling of cancers, including the Director's Challenge, the Cancer Genome Anatomy Project, and various investigator-initiated grants. The SPOREs now include ovarian cancer and will be expanded to include endometrial and cervical cancers. However, it will not be possible to make progress in comparative genomics and proteomics, or in molecular profiling of the gynecologic cancers, without an efficient and equitable means of ensuring the availability of appropriate human specimens. Specimens must be accompanied by associated clinical information, including medical and family history, risk factors, therapeutic interventions, response to intervention, and long-term follow-up.

Resources

The PRG recommends that NCI sponsor a mechanism to ensure the availability of three types of resources:

1. Expansion of existing efforts in tumor banking is needed to ensure collection of a variety of specimens from primary surgery, including appropriately processed tissue from malignant and benign tumors; normal tissue; and urine, blood products, and other body fluids obtained at the time of diagnosis and serially throughout the disease process. Of particular importance is the collection of samples from patients with potential precursor lesions, early-stage cancers, and no gynecologic cancer. Samples of tissue and body fluids must be accompanied by associated clinical information, including medical and family history, epidemiological risk factors, therapeutic interventions, and long-term follow-up. This resource—which we have referred to as the VSSR—is an essential research priority.

2. Large, well-documented specimen repositories are needed to allow for the development and validation of early detection and risk models that incorporate markers measured in fluids. Of particular interest are repositories that include serial specimens from women without cancer at entry and with good follow-up data for cancer endpoints, such as the Prostate,

Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial resource. Criteria for access to very valuable specimens, such as these, need to be developed.

3. The large randomized controlled trials that will eventually be needed to test the efficacy of new strategies for gynecologic cancer detection and prevention are so expensive that we can afford to perform a limited number. A statistical and bioinformatics infrastructure must be developed to allow for adequate analysis and interpretation of the findings from molecular and validation studies to ensure that the best strategies are selected for testing in trials.

HUMAN PAPILLOMAVIRUS VACCINES

Priority: *Develop effective human papillomavirus (HPV) vaccines to prevent biotransmission and development of neoplasia.*

Cervical cancer remains one of the leading causes of cancer deaths among women throughout the world; according to the World Health Organization, more than 230,000 women around the world die each year from the disease. Research has made clear the primary role of HPV in the development of cervical neoplasia; the development and implementation of effective HPV prophylactic and therapeutic vaccines has the potential to nearly eradicate cervical cancer. In addition, each year in the United States, more than 1,250,000 women are diagnosed with potentially precancerous changes on Pap smear. The cost to evaluate and treat women with abnormal Pap smears has been estimated at $6 billion annually. Development of effective prophylactic and therapeutic vaccines could dramatically reduce the cost of screening for cervical cancer.

Although HPV vaccine research has been under way for some time, no effective prophylactic or therapeutic HPV vaccine has been identified. Key issues to be addressed include:

- Role of mucosal and humoral immunity in HPV infection
- Impact of endogenous and exogenous factors on the risk of developing cervical neoplasia
- Most efficacious vaccine strategies
- Immunologic biomarkers that might be used to clinically evaluate resulting vaccines

Investigators at the NCI, universities, and industry have begun work to develop both prophylactic and therapeutic HPV vaccines. To date, however, progress has been limited. A variety of vaccine strategies have been proposed, targeting virus-like particles, protein, naked DNA, and bacteria. We lack a framework, however, for comprehensive clinical evaluation of vaccine combinations, adjuvants, and cytokines. Many vaccine products are still in preclinical development and only a handful has reached clinical evaluation. Clinical trials have also been hampered by fragmentation of efforts, and few partnerships exist between industry and government. At present, no effective HPV vaccine has been identified for any clinical setting, and none has been approved for use anywhere in the world.

Achieving this priority would allow us to begin to answer the following questions, among others:

- What are the roles of endogenous (e.g., hormones) and exogenous (e.g., other pathogens and smoking) factors in immunity?

- What are the differences between immune responses at the systemic level and at the mucosal surface or the site of neoplasia?

- How does immune response differ between a virus-infected cell and a cancer cell?

- What are the differences between HPV-specific immunity and cervical cancer–specific immunity?

- What are the immunologic profiles at the cellular and molecular levels in women who develop chronic HPV infection and those in whom it is eradicated?

- Is HPV a sufficient target or are other tumor antigens involved in malignant transformation?

- What are the laboratory and biologic correlates for vaccine response?

Recommended Actions

Although activity has begun for the development of vaccines both for prevention and for therapy, gaps in knowledge remain. A 'world-wide' broad-based effort should be undertaken to create a network of scientists from NCI, industry, the Clinical Trials Cooperative Groups, NCI-designated Cancer Centers, and individual institutions to address existing gaps. Research toward an HPV vaccine would be enhanced by:

1. Encouraging studies to improve our basic understanding of mucosal immunity in the cervix.

    - Prioritize the understanding of both endogenous factors (e.g., influences of hormones) and exogenous factors (e.g., smoking and other pathogens) and their role in influencing mucosal immune responses.

    - Define the differences between systemic immunity and the immune responses at the mucosal surface or site of neoplasia.

2. Understanding the initiation of effective mucosal immunity.

    - Define effective anti-viral (HPV) and anti-tumor immune responses.

    - Validate laboratory and biologic correlates for clinical response.

    - Determine a vaccine strategy that will differentiate between the immune response to a virally infected cell and to a cancer cell.

    - Understand the differences between HPV-specific immunity and cervical cancer-specific immunity including the antigenic repertoire as well as the phenotype of both T cell and humoral immunity generated at the site of disease.

3. Researching who develops chronic HPV infection and in whom it can be eradicated.

    - Obtain immunologic profiles of women with cervical cancer.

    - Evaluate profiles at both the cellular and molecular levels.

    - Include population and epidemiologic evaluation in studies to link immune defects with other potential environmental concerns.

    - Stimulate biologically relevant anti-viral and/or anti-tumor immunity, including whether HPV is a sufficient target or whether other tumor antigens involved in malignant transformation are needed for tumor eradication.

- Define the immunologic problems in the development of prophylactic versus therapeutic vaccines.

Resources

To facilitate the research efforts needed to develop effective prophylactic and therapeutic vaccines, enhancement of existing resources and development of new ones in the following areas are critical:

- Core laboratories for viral and immunologic evaluation of specimens from clinical trials.
- A "world-wide" network of clinical centers to conduct HPV vaccine studies in individuals at risk for HPV infection, those infected with HPV, and those with cervical neoplasia.
- An expanded cadre of individuals with expertise in clinical trials and HPV immunology to conduct future studies.
- Effective partnerships between industry and government to facilitate rapid evaluation of new vaccines and vaccine combinations and strategies, including cytokines and adjuvants.
- The integration of research efforts world wide to ensure that promising new efforts receive rapid evaluation and that the interventions developed are acceptable to women around the world.

QUALITY OF LIFE: DISPARITIES RELATED TO CARE

Priority: *Conduct research to (1) understand and improve quality of life, and (2) reduce or eliminate disparities related to care among patients with gynecologic cancers.*

Much is unknown about how to ensure that all women with gynecologic cancers experience optimal health-related quality of life. Disparities in the care of some patients may lead to vastly different outcomes. Significant research support is needed to understand and to develop interventions that will improve quality of life for all women; and to understand and overcome the underlying factors that result in disparities in care.

Understand and improve quality of life. Little is known about how to ensure high quality of life of gynecologic cancer patients before, during and after treatment. Women diagnosed with gynecologic cancers often experience fatigue, decreased cognitive function, skin and hair changes, sexual dysfunction, psychosocial problems, and other problems that can persist for months to years after primary treatment.

Women in the United States are not routinely screened for these symptoms at diagnosis or follow-up. There are no effective interventions for many of these symptoms, and other aspects of these women's lives have not been well studied: for example, we do not know the effect of chemotherapy on fertility or the risks of hormone replacement therapy after treatment for a gynecologic cancer.

With nearly 20 percent of cancer survivors comprised of women who have had cervical, endometrial or ovarian cancer, our understanding of their short- and long-term quality-of-life issues—and discovering ways to address them—is crucial to providing the complete scope of cancer care. Despite the scope of the problem, this area remains understudied and under-supported. Additional research is badly needed to address questions of quality of life and to devise interventions for cancer-related and treatment-related symptoms.

Reduce or eliminate disparities in care. Medical science has given us the means to effectively treat the majority of gynecologic cancers; currently, we cure approximately 72 percent of cervical cancers, 50 percent of ovarian cancers, and 86 percent of cancers of the uterine corpus. Nevertheless, studies suggest that many U.S. women with gynecologic cancer—particularly those with ovarian or cervical cancer—do not receive optimal care, and that outcomes of care may vary widely across populations.

For example, there are striking disparities in stage at diagnosis and in mortality by race and socioeconomic status. Black, Asian, American Indian, and Hispanic women have higher mortality rates from cervical cancer than do white women (black women's rates are the highest by far—more than double those of white women). Black women also have much higher mortality rates from endometrial cancer than do whites. In ovarian cancer, white women have the highest mortality rates, followed by blacks and then Hispanics.

Barriers to receiving optimal screening and treatment—whether age-related, educational, cultural, geographic, social, or some other type—may explain some of the disparities, but research has not elucidated which barriers are most important or how to overcome them. Many women diagnosed with gynecologic cancer are not referred to doctors with expertise in the management of gynecologic cancer. Specialists who treat gynecologic cancers may make assumptions based on race, education, or socioeconomic status about a woman's ability to tolerate or comply with more aggressive treatment, and these assumptions may lead to differences in type of treatment offered and, ultimately, differences in outcome.

Screening disparities also exist; older women and women in certain areas of the United States are less likely to be screened, or screened regularly, for cervical cancer. This frequently translates into later disease stage at diagnosis and worse outcome, even if the best care is provided. We need focused research to determine how to ensure that all women diagnosed with gynecologic cancer in the United States receive optimal care. Such research must include collaborations among investigators with expertise in gynecologic oncology, epidemiology, health services research, health communication, and health psychology.

Achieving this priority will help answer the following questions, among others:

- What are the short- and long-term outcomes among women with gynecologic cancers?
- Are there differences in population outcomes related to disparities in detection and diagnosis? If so, what can be done to eliminate the disparities?
- What interventions can maintain and enhance health-related quality of life among women with gynecologic cancers?

Recommended Actions

1. We propose large observational cohort studies of patients with newly and previously diagnosed gynecologic cancer. These studies should do the following:
    - Investigate the impact of targeted interventions on patient-centered outcomes
    - Identify the influence of modifiable risk factors on gynecologic cancers
    - Discover options to eliminate disparities in the delivery of high-quality cancer care

We recommend that these studies be conducted through the newly created, NCI-sponsored Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) initiative. However, it is essential that the studies look across the disease continuum, from diagnosis through treatment to survivorship and end-of-life care, and include sites with sufficient representation of disadvantaged populations to enable examination of health disparities in treatment and outcomes.

2. We propose intensive research to develop and evaluate interventions to maintain and enhance health-related quality of life in women with gynecologic cancers. These efforts would build on the ongoing health-related quality of life observational research currently conducted by the Clinical Trials Cooperative Groups, Cancer Centers, and individual investigators. It is critical that state-of-the-science therapies are translated into practice.

Resources

To conduct the large observational studies required to evaluate quality of care and survivorship issues in gynecologic cancers, new research mechanisms will be needed. These mechanisms should include the following:

- Development of collaborative projects and consortia to conduct large cohort studies in patients with gynecologic cancer
- Collaboration among investigators with expertise in gynecologic oncology, epidemiology, health services research, heath communication, and health psychology
- Development of a cadre of new and existing investigators in the fields of communication, health psychology, health-related quality of life, and health services research related to gynecologic cancers

SCIENTIFIC OPPORTUNITIES

In addition to identifying high-impact priorities, we have identified six Scientific Opportunities that should also be an important part of the National Cancer Institute's research plan for gynecologic cancer. The individual breakout reports (see Appendix C) that cited the need for each priority are given in parentheses.

1. **Characterize the hormonal, immunologic, and epithelial-stromal interactions that result in the development of gynecologic cancers.** (Breakouts: Tumor Biology, Ovarian Cancer)

   The endometrium, ovary, and cervix are all hormone-responsive sites. We do not fully understand the etiologic events that transform normal epithelial cells into hormone-dependent tumors, nor can we identify the molecular events in hormone-independent tumors arising in the reproductive tract. We do not understand the molecular mechanisms that facilitate the interactions and synergy between hormones and growth factors and their corresponding receptors in both the epithelium and the stroma. We do not know how aging, race/ethnicity, body mass index, puberty, pregnancy, menopause, oral contraceptives, hormone replacement therapy, or selective estrogen receptor modulators influence these interactions.

2. **Develop imaging techniques to evaluate tumor biology, molecular signatures, and therapeutic response.** (Breakouts: Imaging, Endometrial Cancer, Cervical Cancer)

Because we can directly visualize the transformation zone of the cervix, where most neoplasia begins, we have made major strides in screening for cervical cancer and in deepening our understanding of the biology of preinvasive cervical lesions. At present, however, we are not able to obtain reliable images of precancerous lesions in the endometrium or ovary. Although ultrasound and magnetic resonance imaging can provide information on abnormal structures in the adnexa and uterus, no currently available imaging modality provides effective screening for ovarian endometrial cancer or effective biologic characterization of cervical, ovarian, or endometrial cancer.

3. **Develop relevant preclinical models for gynecologic cancers.** (Breakouts: Genes and Environment, Models, Treatment, Endometrial Cancer)

   Gynecologic cancers are characterized by unique genetic, physiologic, and environmental processes that lead to carcinogenesis. Within each gynecologic cancer are multiple, heterogeneous histologic subtypes. Each gynecologic cancer also has a range of biologic behaviors, including different patterns of growth and metastasis and different responses to therapy. Although a variety of gynecologic cancer models are in development, no models as yet recapitulate the human cancer for which they were designed.

4. **Find ways to overcome resistance to chemotherapy and radiotherapy.** (Breakouts: Radiobiology, Treatment, Cervical Cancer)

   In general, gynecologic cancers are initially sensitive to chemotherapy and radiation therapy. Nonetheless, in most cases, resistant clones develop, resulting in death. For example, more than 80 percent of women with advanced ovarian cancer experience a complete clinical response to platinum-taxane–based chemotherapy after initial surgery, but only 25 percent of women with stage III/IV ovarian cancer are alive at 5 years. More than 80 percent of women with locally advanced cervical cancer experience a complete clinical response to platinum-based chemoradiation, but only 30 percent of women with stage III/IV cervical cancer are alive at 5 years. Identification of the mechanisms by which gynecologic cancers develop resistance would help us improve current treatment and cure more women with gynecologic cancer.

5. **Develop individualized and optimized radiation therapy techniques in conjunction with other treatment modalities.** (Breakouts: Radiobiology, Endometrial Cancer, Ovarian Cancer)

   Radiation therapy remains a mainstay of treatment for cervical and endometrial cancers. Several studies suggest that radiation therapy also has great potential in the treatment of ovarian cancer. Much of the progress to date has been empirical, based on patterns of recurrence and toxicity. To make further progress, we must gain a better understanding of the interaction between therapeutic radiation and gynecologic cancer, and how radiation therapy can be optimized in its combination with other treatment modalities, such as chemotherapy.

6. **Encourage increased participation in clinical trials in gynecologic cancer.** (Breakouts: Treatment and Drug Discovery, Ovarian Cancer)

   Despite the establishment of a subspecialty that is devoted to gyneco logic cancer, as well as effective

multidisciplinary collaboration in clinical cancer research, less than 2.5 percent of women with gynecologic cancers are enrolled in prospective treatment trials. This figure is in marked contrast to the 50 percent of children with cancer who are entered in clinical trials. A variety of new approaches, including chemotherapy, biologic therapy, immunologic therapy, radiation therapy, and hormonal therapy, need evaluation in women with gynecologic cancer. Progress depends on effective communication to women and health care providers about the importance of clinical trials, and an effective clinical trials network with adequate funding for translational research.

CONCLUSION

The report of the GYN PRG identifies one Essential Priority, three High-impact Priorities, and six Scientific Opportunities. We consider the implementation of these 10 priorities to be essential if in the next 5 years we are to show significant progress toward the cure of gynecologic cancer. We encourage the reader to study in detail the individual reports of the 14 breakout groups and the 3 tumor-type groups, which are provided in Appendix C. These individual reports expand further on the 10 priorities and offer additional direction for the research community. The material in these reports represents the careful considerations of all participants at the Roundtable.

Appendix A

About the National Cancer Institute's
Progress Review Groups

Appendix A: About the National Cancer Institute's Progress Review Groups

The National Cancer Institute (NCI) supports basic, clinical, and population-based research to elucidate the biology, etiology, early detection, prevention, and treatment of cancers of various organ sites. These research efforts have produced a substantial base of knowledge that, while providing a wealth of new scientific opportunities that can further advance our knowledge and progress against these diseases, also requires that the Institute determine the best uses for its resources.

To help ensure the wise use of resources, NCI has established Progress Review Groups (PRGs) to assist in assessing the state of knowledge, reviewing the Institute's research portfolio, and identifying scientific priorities and needs for its large, site-specific research programs.

CHARGE TO THE PRGs

Each PRG is charged to:

- Identify and prioritize scientific research opportunities and needs to advance medical progress against the cancer(s) under review.
- Define the scientific resources needed to address these opportunities and needs.
- Compare and contrast these priorities with the current NCI research portfolio.
- Prepare a written report that describes findings and recommendations.
- Discuss a plan of action with NCI leaders to ensure that the priority areas are addressed.

The following section details the process used to execute these charges.

THE PRG PROCESS

PRG members are selected from among prominent members of the scientific, medical, and advocacy communities and from industry to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's cancer research agenda. The membership is also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

The leadership of each PRG finalizes an agenda and process for a PRG Planning Meeting. At the Planning Meeting, participants are identified to take part in a subsequent Roundtable meeting. Topics are identified for Roundtable breakout sessions to which participants will be assigned and for which the PRG members will serve as co-chairs.

A PRG Roundtable brings together in an open forum approximately 100–180 leading members of the relevant cancer research, medical, industry, and advocacy communities to formulate key scientific questions and priorities for the next 5–10 years of research on specific cancers. As part of the process, the NCI provides the PRG Roundtable with an analysis of its portfolio of cancer research in the relevant organ site. This analysis is intended to enable the Roundtable to compare and contrast identified scientific priorities with the research currently being done under the Institute's auspices. Input from the

Roundtable is used by the PRG in delineating and prioritizing recommendations for research, related scientific questions, and resource and infrastructure needs. At its discretion, the PRG may solicit additional input from the research and advocacy communities through workshops, ad hoc groups, or by other means. The PRG also may consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

THE PRG REPORT

After the Roundtable, the PRG's recommendations are documented in a draft report, multiple iterations of which are reviewed by the PRG leadership and PRG members. The final draft report is then submitted for deliberation and acceptance by the NCI Advisory Committee to the Director. After the report is accepted, the PRG meets with the NCI Director to discuss the Institute's response to the report, which is widely disseminated and integrated into the Institute's planning activities. At this meeting, the PRG and the NCI identify the research priorities that ongoing NCI initiatives and projects do not address. Then the PRG and NCI discuss a plan for implementing the highest research priorities of the PRG. This plan becomes a blueprint for tracking and hastening progress against the relevant cancer.

PRG reports on breast cancer, prostate cancer, colorectal cancer, pancreatic cancer, lung cancer, brain tumors, and leukemia, lymphoma, and myeloma, in addition to this PRG report on gynecologic cancers, are available online at http://osp.nci.nih.gov. Other PRG reports currently in development or planned include reports on kidney and bladder cancers and on stomach and esophageal cancers.

Appendix B

Gynecologic Cancers PRG
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Gynecologic Cancers PRG
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Appendix C

Gynecologic Cancers PRG
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Appendix D

Reports of the Gynecologic Cancers PRG
Roundtable Breakout Groups

Health-Related Quality of Life and Survivorship

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BACKGROUND: STATE OF THE SCIENCE

Improved therapies and supportive care measures are improving survival rates and durations for women with both primary and recurrent gynecologic cancers. Accordingly, issues concerning health-related quality of life and survivorship are becoming a more urgent concern. Of the approximately 3.9 million women alive today with a history of any type of cancer, nearly 20 percent (656,108) have been diagnosed with a gynecologic cancer. Yet only 3 percent of the survivorship research funded by the National Institutes of Health and the Department of Defense (DoD) addresses the concerns of women with gynecologic cancers.

The collective research portfolio of the National Cancer Institute (NCI), the Gynecologic Oncology Group (GOG), the DoD, and the American Cancer Society contains fewer than 25 studies on health-related quality of life and survivorship among patients with gynecologic cancer. These studies are primarily investigator-initiated, descriptive studies of women with ovarian or cervical cancer or are drug intervention studies funded by the GOG in which quality of life is added as an outcome measure. Four intervention studies examined psychologic interventions, interventions for sexual dysfunction, and an exercise intervention. Several of the studies dealt with a relatively small proportion of the population of women with gynecologic cancers, such as those with germ cell tumors or *BRCA1* mutations.

Health-related quality of life and survivorship studies can be reviewed by at least five NCI study sections (Social Sciences, Nursing, Epidemiology, and Methods; Nursing Research; Biobehavioral and Behavioral Processes; Prevention and Health Behavior; or a special study section) and can be funded by at least three NCI divisions (Cancer Treatment and Diagnosis, Cancer Prevention, and Cancer Control and Population Sciences). Thus, investigators are often confused as to potential NCI program officers or where to send their proposals for review and funding. The DoD does not have any special funding mechanisms for health-related quality of life or survivorship proposals, instead requiring investigators to submit their best ideas under more generic award mechanisms. Very few proposals having to do with health-related quality of life have been submitted or funded by the DoD.

Issues related to health-related quality of life and survivorship for the gynecologic cancers include the following:

All Gynecologic Cancers (cervical, endometrial, ovarian)

- Study is needed to ascertain the role and optimal administration of hormone replacement therapy in the care of women who are at risk for, as well as those diagnosed with, gynecologic cancers.
- There is a need for longitudinal, descriptive studies in most areas of research on health-related quality of life and survivorship as a basis for thoughtfully designed intervention studies. In particular, virtually nothing is known of the quality of life of women who have survived endometrial cancer, although it has the highest overall survival rate of the gynecologic cancers.
- Areas needing assessment include symptom experience and intensity, skin and hair changes, memory loss, and aging. No additional descriptive studies of sexual dysfunction are needed, as the sexual sequelae to the diagnosis and treatment of gynecologic cancers have been carefully documented and validated.
- There is a need for a description of the effects of secondary and tertiary treatments, as well as those of chronic treatment for recurrent cancer.
- There is a need for a description of the long-term effects of chemotherapy and radiation therapy.
- Population-based documentation of patterns of care is also needed.

Cervical Cancer

- Sexuality and reproductive concerns
- Quality of life, especially as it relates to the social stigma and socioeconomic status associated with the disease
- Communication with health professionals
- Cultural sensitivity to age, race, ethnicity, and environment
- Access to care

Endometrial Cancer

- Care of women with comorbid conditions, such as obesity and diabetes
- Sense of well-being and body image
- Physical functioning
- Dietary and exercise interventions
- Connections with other cancers, such as colon cancer
- Well-woman care and health-seeking behavior

Ovarian Cancer

- Fear of recurrence
- Treatment decision-making
- Social support interventions
- Supportive and palliative care
- End-of-life care
- Education and communication
- Insurance issues

RESEARCH PRIORITIES

Priority 1: *Intervention research addressing sexuality and fertility outcomes in women with gynecologic cancers.*

Rationale

Longitudinal research has documented that as many as 50 percent of patients with gynecologic cancer experience significant sexual difficulties after diagnosis and treatment. Difficulties arise during the immediate post-treatment period; if left untreated, they do not resolve and may worsen with time. When sexual difficulties are studied in the context of other major life areas (e.g., mood, social adjustment, employment), they remain an island of disruption in an otherwise generally positive survivorship scenario. Thus, with a substantial research basis of descriptive efforts, it is now appropriate to begin intervention research to prevent or remediate these difficulties. This effort will be facilitated by the availability of efficacious treatments for the treatment of female sexual dysfunctions.

Complementary concerns for many young cancer patients are the effects of cancer therapy on fertility, as well as the availability of therapies to treat symptoms of menopause. The risk/benefit study of hormone replacement therapy in women with gynecologic cancers is of particular interest.

Barriers

Sexuality and fertility issues often are not easily discussed, either between partners or with health care professionals. This reticence makes it difficult to study interventions that address sexuality and fertility outcomes.

Resources Needed

Trained professionals are needed to broach sexuality and fertility issues and to design appropriate intervention studies. With professional encouragement and adequate funding for research, investigators will be more likely to devote their careers to the study of gynecologic cancers.

Priority 2: *Research on quality-of-life issues surrounding the late effects of treatment and long-term survival.*

Rationale

Advances in gynecologic care and treatment have lengthened disease-free intervals and have improved survival rates. Survival advances have been achieved through the effective use of combination therapies (e.g., chemoradiation for cervical cancer), lengthy treatment regimens, and the use of multi-agent chemotherapy regimens. Thus, most gynecologic cancer patients reach 5-year survival periods (and longer) and cope with the accompanying changes that may have occurred in their quality of life. Knowledge is needed regarding the scope and magnitude of psychosocial difficulties confronting these long-term survivors, including predictors, magnitude, and course of psychosocial responses and outcomes. These issues are particularly important for patients receiving multiple therapies or therapies with late effects, as well as for those who have medical comorbidities or limited socioeconomic resources at the time of their diagnoses.

Barriers

Although gynecologic tumors account for 14 percent of annual cancer cases in women and nearly 20 percent of female cancer survivors, minimal attention and study have focused on the quality-of-life and survivor concerns of

these women. This absence of research, though driven in part by lack of funding, is also due to the absence of a cadre of trained investigators devoting their careers to the study of health-related quality-of-life issues among patients with and survivors of gynecologic cancers.

Resources Needed

To better describe quality-of-life issues surrounding the late effects of treatment and long-term survival, a Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) award or similar mechanism for the gynecologic cancers is needed. This mechanism should focus on patient-centered outcomes, investigating the dissemination of state-of-the-science therapies into community practice, examining the influence of modifiable risk factors, and analyzing disparities in the delivery of quality cancer care.

Furthermore, funding mechanisms are needed to bring new investigators into the field, provide training resources to senior investigators for mentorship, and induce psychosocial investigators to focus research programs on gynecologic tumors. In turn, these new investigators and more senior investigators can serve as mentors for future researchers.

Clinical and Molecular Genetics

Co-Chairs: Mary B. Daly and Judy Garber

Participants:

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Richard Buller	Samuel Mok	Joellen Schildkraut

BACKGROUND: STATE OF THE SCIENCE

Emerging technologies in molecular biology and genetics are providing new and powerful tools with which to explore gynecologic malignancies and describe tumor heterogeneity. Despite the sophistication of these new technologies, their clinical application to the prevention, early detection, and treatment of ovarian, endometrial, and cervical cancers is lagging. Progress in molecular genetics has the potential to elucidate the basic mechanisms of tumor initiation, growth, and invasion; identify molecular targets for prevention, screening, and treatment; and explore gene-gene and gene-environment interactions. A systematic approach to exploit this potential has not been initiated, however. Clinical assays can now identify individuals with germline mutations who face a significantly increased risk for ovarian or endometrial cancer, yet clinicians caring for these individuals have very little to offer beyond surgical preventive strategies. Furthermore, the clinical phenotypes of hereditary cancers are not well defined and optimal treatment strategies are lacking. Larger societal issues of public and professional education and ethical concerns in the protection of privacy and confidentiality must also be addressed.

In this area, attention must be paid to the following:

- Novel and powerful technologies that can potentially characterize the molecular evolution of gynecologic malignancies have recently become widely available. These tools permit the identification of points of molecular commonality across cancers and have tremendous potential for translational research.

- The molecular heterogeneity observed in gynecologic tumors may provide important clues to the role of genetic and environmental exposures and may help define gene-gene and gene-environment interactions.

- A concerted effort is needed to translate important molecular discoveries into clinical applications. However, a significant gap in the knowledge and appreciation of the promise of genetics within the medical community hinders the incorporation of these findings into clinical care.

- Complex ethical, cultural, and societal barriers to the conduct of genetic research must be addressed. These barriers include fear of genetic discrimination, concerns

about privacy and confidentiality, and fragmentation of the regulatory bodies that oversee research.

- Markers of inherited risk for ovarian and endometrial cancers are now available in the clinical setting and are being utilized by clinicians. A better understanding of these inherited cancers will provide insights into the carcinogenic pathways in sporadic as well as inherited cancers. There is, however, a profound lack of information about strategies for early detection, the role of chemoprevention, the risks and benefits of prophylactic surgeries, and the importance of the traditional risk factors in these individuals.

- There is some evidence that inherited cancers are different from their sporadic counterparts. For example, *BRCA1/2*-associated ovarian cancers appear to have a better prognosis than do sporadic ovarian cancers. The details of any biologic differences between hereditary and sporadic gynecologic cancers must be defined to permit assessment of the extent to which hereditary cancers can serve as models for early detection, prevention, and treatment interventions that can be generalized to the larger population, as well as to individualize treatment options to match the biologic characteristics of the tumors.

RESEARCH PRIORITIES

Priority 1: *New and emerging molecular technologies must be applied to gynecologic cancers, where the need for effective therapies is critical. We must characterize the molecular features of gynecologic cancers for the identification of intermediate biomarkers for prevention, molecular targets for early detection and treatment, and factors with prognostic and predictive significance.*

Priority 2: *Populations at risk for inherited cancers are an ideal group for pilot studies of etiology and prevention. It is critical to study genetically high-risk individuals and their cancers to identify genetic and environmental determinants of penetrance, to compare and contrast hereditary and sporadic cancers, to address issues of clinical management, and to extend this knowledge to the field of pharmacogenetics.*

Priority 3: *Genetic identification of individuals at high risk is possible for all three common gynecologic cancers. Modifier genes and genetic polymorphisms are also being identified that increase susceptibility. In other malignancies, there exist effective therapeutic interventions directed against molecular targets. Research must emphasize the translation of genetic and molecular paradigms into clinical applications and define effective strategies to prepare the public and medical communities to embrace these revolutionary approaches. New models will affect risk assessment, targeted surveillance, prevention, and treatment.*

BARRIERS

Despite progress in federal and state privacy legislation, concerns about genetic discrimination remain significant for many individuals who would otherwise participate in informative research. Additional efforts to ensure protection from discrimination in health insurance, employment, and other opportunities on the basis of genetic information remain critically important to permit ongoing research in the genetics of gynecologic malignancies.

Protection of the rights of research participants and their family members to privacy and confidentiality is the charge of Institutional Review Boards and the Office of Human Research Protection. These bodies must be educated and supported as they devise systems to protect participants without

hindering research that depends on access to critical human blood and tissue specimens and, sometimes, on ongoing contact with participants. These systems must balance the rights to individual privacy against the burden of "overconsenting" and must consider the special issues raised by genetic studies, which may have implications for family members.

Genetic testing for hereditary susceptibility to cancer is limited by financial and sociocultural factors. Despite increasing coverage of genetic testing by health insurance companies, access to genetic tests for individuals without health insurance or with less comprehensive policies—more than 12 million Americans annually—is not available. Sociocultural barriers to genetic testing are also important to issues of access and utilization. These must be addressed both practically and as appropriate topics for research.

RESOURCES

- For the goals described herein, meticulously collected and verified clinical treatment and outcome data are critical. Coordinated access to existing resources must also be addressed.

- A resource of germline and malignant tumor material with associated clinical data from individuals with hereditary predisposition to cancer would greatly facilitate the elucidation of the proposed research goals. Such collection might be facilitated through the Cancer Family Registries, the Cancer Genetics Network, or other programs.

- Mechanisms must be developed to facilitate funding for and conduct of correlative science investigations in gynecologic malignancies within the cooperative treatment groups from their existing and developing characterized tissue repositories.

- Special mechanisms must be developed with which to attract young investigators to molecular biologic and translational research in gynecologic malignancies.

- Mechanisms to foster collaborative research and encourage interaction across disciplines must be emphasized.

Defining Signatures of Cancer Cells, Genomics, Proteomics, and Informatics

Co-Chairs: Ruedi Aebersold, Garnet L. Anderson, and Mark Boguski

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BACKGROUND: STATE OF THE SCIENCE

The availability of the complete human genomic sequence and emerging technologies for the systematic and quantitative measurement of the genes (genomics) and proteins (proteomics) expressed by a cell or tissue provide new opportunities to define molecular signatures of cancer. Such signatures are expected to have an impact on essentially any type of cancer and on topics of cancer research, such as the study of the molecular mechanisms of cancer, early detection, diagnosis, discovery of new treatment targets, and assessment of treatment outcome.

The generation of biologically and clinically relevant signatures in gynecologic cancers via genomic and proteomic tools critically depends on the availability of high-quality, well-annotated samples. Furthermore, the detection of signatures consisting of multiple elements requires the analysis of relatively large numbers of samples to make the signatures statistically significant.

Although genomic and proteomic technologies are still rapidly evolving, their initial application has indicated that the development of meaningful molecular signatures requires the development of new study designs, integrated databases, advanced computational tools, and centers for high-throughput data generation. Technology centers subject to these recommendations are expected to significantly accelerate the access of cancer biologists to state-of-the-art analytical facilities and to provide an urgently needed pool of researchers trained in emerging technologies.

RESEARCH PRIORITIES

Priority 1: *Develop a national resource for the collection and distribution of clinical samples.*

- The resource will contain high-quality, well-annotated specimens including normal, benign, and pre-malignant lesions; all histologies and stages; and specimens from various risk groups. The number of specimens will be sufficiently high to support studies leading to statistically significant conclusions.

- The specimen resource will ideally include matched (tissue and blood) and serial samples from the same patient.

- Specimens will be annotated with clinical, pathologic, epidemiologic, and molecular signatures specific for each tumor type.

Barriers

Although a number of tissue collection initiatives exist, the following factors have limited usefulness for defining signatures of cancer:

- Lack of standardized protocols for the collection and annotation of high-quality specimens
- Lack of sufficiently large matched sample sets to support studies yielding statistically significant conclusions
- Lack of appropriately trained personnel
- Lack of infrastructure for the decentralized collection of specimens representing the whole population
- Lack of standardized criteria to provide access to rare specimens
- Privacy and informed consent policies that constrain the use of specimens for unanticipated studies

Resources

- Existing specimen banks such as the Gynecologic Oncology Group, the Early Detection Research Network, the Cancer Genetics Network, Ovarian Specialized Program of Research Excellence, and private-sector programs
- Patient advocate groups as resources for raising patient participation in donor programs and for addressing constraining privacy and informed consent policies

Priority 2: *Develop optimal study design and data analysis methods. These methods will define appropriate sample sizes and comparison groups to achieve statistical significance and will be informed by biologic and experimental variability.*

Barriers

- Lack of data and high-quality samples to assess biologic and experimental variation
- Lack of a mathematical paradigm for interpreting high-dimensional data analysis

Resources

- Rich source of analytical tools developed for other scientific disciplines that are adaptable to this setting

Priority 3: *Establish Centers of Excellence to apply leading-edge technologies to discover and validate signatures of cancer. These centers will provide the following:*

- Cost-efficient access to integrated technology platforms
- Training and education in the use of these technologies
- Access to advanced computing resources for data management and analysis

Barriers

The definition of molecular signatures by the systematic analysis of gene expression requires integrated facilities consisting of trained personnel, instrumentation for data generation, and computational infrastructure for data management and analysis. The following factors limit the ability to generate molecular signatures of cancer:

- Lack of databases and software tools for integrating large, diverse, and complex data sets
- Lack of availability of specialized advanced computing resources
- Lack of standardized open-source tools for data representation and query languages

- Lack of trained personnel at all levels
- Lack of awareness of the requirements and the potential of the technologies by cancer biologists

Resources

- Targeted programs for development of innovative technologies by the National Cancer Institute
- Potential for private/public sector partnerships

Treatment and Drug Discovery

Co-Chairs: Peter J. O'Dwyer and Branimir I. Sikic

Participants:

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BACKGROUND: STATE OF THE SCIENCE

The three major gynecologic cancers differ appreciably in their biologic and clinical characteristics and treatment approaches. Ovarian cancer is considered moderately responsive to many cytotoxic agents, particularly platinum drugs and taxanes. Although the large majority of patients respond favorably to initial therapy, only 20 to 30 percent of patients with stage III disease are cured. Thus, drug resistance is still a dominant feature in this disease. Cancers of the cervix and endometrium are less responsive to cytotoxins than are ovarian epithelial cancers. Cancers of the cervix are characterized by a human papillomavirus etiology, the availability of a screening test to detect early stages, and the recent demonstration of major clinical benefit from combining chemotherapy and radiation therapy in localized but bulky tumors. Endometrial cancers arise in a much older population of women, and their etiology involves hormonal mechanisms.

Considerable current research in the pharmaceutical industry has focused on developing new or improved cytotoxic agents. Examples include analogs of platinums and taxanes with improved toxicity and antitumor activity profiles, and the development of epothilones as non-cross-resistant antitubulin drugs. Some of these cytotoxins are likely to prove beneficial for patients with gynecologic cancers because of increased antitumor activity and/or lower toxicity than current agents.

The past year in cancer therapy has been noteworthy for the approval of one of the first drugs that inhibits tyrosine kinase growth signaling. Gleevec, or STI-571, is a splendid example of how knowledge about the molecular pathogenesis of a cancer can lead to the identification of a therapeutic target, synthesis of a potent small-molecule inhibitor of the target, preclinical validation, and demonstration of remarkable clinical benefits.

Progress in the treatment of gynecologic cancers is likely to result from the introduction of novel drugs against specific molecular targets that are implicated in the growth and malignant behavior of cancer cells. Many such drugs are currently in various stages of development. The targets include growth signaling tyrosine kinases, cell cycle regulation, angiogenesis, apoptosis, and others. In setting priorities for therapeutic development, the members of the breakout group made two assumptions. First, all of the important targets for cancer treatment have not yet been discovered, which presents a great opportunity. Second, efficient clinical

testing for the hundreds of expected agents against known and future targets repre sents a major challenge to the oncology community.

RESEARCH PRIORITIES

The two major priorities in drug discovery and development for gynecologic cancers are relevant to all three major gynecologic cancers. Special opportunities exist in cervical and ovarian cancer research to serially sample specimens to define molecular targets and genetic determinants of response to therapies.

Priority 1: *Identify and validate key molecular targets for therapies.*

a. Support for national resources for tissue acquisition and banking should be markedly increased.

Rationale

Recent technologic developments permit analysis of all the expressed genes in tumor cells. It is widely believed that the pattern of gene expression in a particular tumor determines its aggressiveness, likelihood of metastasis, response to therapies, and potential to be cured. Fresh tissue is required for gene expression analysis. Currently, only one-third to one-half of specimens in the Cooperative Human Tissue Network sponsored by the National Cancer Institute (NCI) are suitable for studies requiring intact RNA. Furthermore, only a very small percentage of tumor specimens are obtained from patients who are currently entering clinical trials and for whom there are clinical data associated with the tissue samples.

Specific Recommendations

- More and better tissues should be acquired, appropriately stored, and annotated. This will require funding of key personnel at the centers that are the major contributors of tissues to the network.
- Serial sampling of specimens should be supported in clinical trials for evaluation of molecular factors contributing to response and resistance.

b. Preclinical models of gynecologic cancers should be developed for validation of targets and testing of therapeutic agents.

Rationale

Currently there are very few animal models for gynecologic cancers, and none that recapitulate the behavior of the human diseases. Such models might enable genetic manipulations for validation of targets and testing of new targeted therapeutic agents.

Specific Recommendations

Major incremental funding should be provided to establish models of gynecologic cancers. These models might include murine syngeneic tumors, orthotopic and non-orthotopic human xenografts, transgenic mice, and other systems. They should be representative of the diversity of these diseases and should be suitable for validation of therapeutic targets and new drugs.

c. Gene expression profiling of RNA and proteins (genomics and proteomics) should be systematically applied in

clinical specimens and tumor models of gynecologic cancers.

Rationale

Data from recent and ongoing clinical trials in ovarian cancer should reveal genes or clusters of genes that are related to more malignant behavior, pathologic subtypes, and drug sensitivity versus resistance. Localized cancers of the cervix are anatomically accessible with minimally invasive procedures and thus represent a suitable clinical model for serial sampling of tumors during therapies. Ovarian cancers often provide an opportunity to obtain serial samples of tumor at diagnosis and subsequent surgeries, although "second-look" operations are not usually performed as standard procedures.

Specific Recommendations

- Funding mechanisms should be introduced for translational studies in clinical trials that do not require—as they currently do—a grant review and implementation process of 8 months or longer.

- Trials should be solicited of serial tumor sampling of locally advanced cervical cancer in the context of new therapeutic development.

Priority 2: *Optimize therapeutic clinical trials in gynecologic cancers.*

This priority presents a major challenge because of the large and increasing number of drugs available for development and the relatively limited number of participants in clinical trials. Optimization of therapeutic clinical trials in gynecologic cancers will be furthered by the approaches discussed next.

a. Develop and implement surrogate markers for drug efficacy in clinical trials of new and existing agents.

Rationale

Large numbers of targeted therapies will be emerging in the next 5 years. The lack of reliable models requires efficient clinical testing. We must be able to rapidly address these questions: Is the drug getting to the target? Is it affecting the target as planned? Is the target interaction producing the desired effect?

Specific Recommendations

- Increase support for translational endpoints in clinical trials. Such support may include tumor tissue profiles, serum markers, and novel imaging technologies. The NCI should focus on barriers to these trials: patient accrual, physician reluctance, regulatory burdens, infrastructure support. The real costs of acquiring tissues and performing assays should be covered.

- Spearhead research efforts in discovery and implementation of intermediate endpoints of effects of (often cytostatic) targeted interventions.

- Foster broader use of pharmacokinetic and pharmacodynamic analyses in both early and late clinical trials through modeling with limited sampling techniques, quantitative and validated imaging, and genomic signatures of drug effect.

b. Facilitate patient and physician participation in clinical trials of new drugs.

Rationale

Only 2 to 3 percent of patients with gynecologic malignancies enter clinical trials. Even in Cancer Cooperative Groups, the bulk of accrual is accounted for by a small proportion of the physician membership. Barriers include lack of information to patients, lack of interest and information on the part of practicing physicians, economic disincentives to physician participation, lack of infrastructure support, consent requirements which go beyond those essential to informing patients of risks, benefits, and procedures.

Specific Recommendations

- Increase direct marketing of clinical trials to patients and physicians through a targeted public education effort with the participation of physician and patient advocate groups.

- Increase physician education on clinical trials through engagement of physician organizations.

- Direct funds to infrastructure support for physician participation in clinical trials.

- Address regulatory obstacles through central institutional review boards and simplified consent procedures and reporting requirements.

c. Develop pharmacogenomic approaches to predict drug response and toxicity.

Rationale

Variability in patients' responses to therapy reflects differences in genetic make-up as expressed in quantitative and qualitative differences in gene products. These differences may be detected at the level of DNA, RNA, or protein through the application of novel technologies. Currently the purview of select academic and commercial sites, these powerful analyses have the potential to identify patients at risk of toxicity, patients in whom the intervention may work, and even the doses that are likely to be needed for efficacy.

Specific Recommendations

- Support (rapidly and without burdens of paperwork) the application of these techniques to samples obtained in clinical trials.

- Limit the increasing consent burden that is a growing deterrent to such studies.

d. Make new drugs available to patients with gynecologic cancers.

Rationale

The testing of new agents in gynecologic cancers is often delayed because these cancers are less prevalent than some other cancer types. The early clinical trials step will be a barrier to the investigation of promising targeted therapies in coming years. The large number of promising candidate molecules demands that a reevaluation of this system be undertaken. In parallel, growing numbers of patients who are aware of opportunities to participate in clinical trials will create a widespread demand for clinical trials. This demand should be met by increasing access to novel treatments for patients with gynecologic malignancies.

Specific Recommendations

- Make the evaluation of novel agents in gynecologic cancers a priority early in

the course of development of new drugs.

- Implement physician and patient education to ensure enrollment in clinical trials early in the course of the disease (first, second, or third line), rather than referral after the failure of numerous marginally effective therapies.

Immunology

Co-Chairs: Peggy A. Crowley-Nowick, Mary (Nora) Disis, and Douglas R. Lowy

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Cornelia Trimble
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BACKGROUND: STATE OF THE SCIENCE

The immune system plays a role in modulating the growth of tumors in animal models. Ovarian, cervical, and endometrial cancers can serve as model tumor systems to evaluate immunologic questions that may be translatable to other tumor types.

For example, the peritoneum of ovarian cancer patients is extraordinarily immunologically active. Ascitic fluid is rich in both lymphocytes and antigen-presenting cells. However, cancer cells grow despite this rich immune environment. Ovarian cancer offers an optimal model system for investigating immunosuppressive factors induced by the tumor or even by immune cells.

Cervical cancer also offers a model immunologic system. Human papillomavirus (HPV) infection is the main etiologic factor in cervical cancer. Cervical cancer is a primary model for assessing the development of mucosal immunity. The initiation and maintenance of antigen-specific immune responses at the mucosal surface is necessary for the eradication of precursor and progressive cervical lesions. Principles defined in the generation and evaluation of mucosal immunity in the development of cervical cancer could be directly applied to other mucosal-based malignancies, such as oral cancer or colon cancer.

Finally, hormonal influences may affect the immune response. The endometrial cancer model offers a system for evaluating the role of estrogen and progesterone in influencing the immune microenvironment. Studies performed in this area could have direct application to hormone-driven tumors such as breast and prostate cancers. Thus, evaluation of immunity in gynecologic tumors will not only advance the development of new therapies for the treatment of these diseases, but will also establish paradigms of immune evaluation applicable to other human malignancies.

Patients with gynecologic cancers are being treated with immune-based therapies with mixed clinical results. Immunologic treatment will play a major role in the clinical treatment of gynecologic cancers. Effective translation of immune-based therapy can occur only if the underlying mechanisms of the immune response are better understood and defined.

Clearly, all the components needed to stimulate immune responses—for example, APC and T cells—are present in the peritoneum of ovarian cancer patients. However, T cells specific for ovarian cancer cells in the peritoneum are detectable at only very low precursor frequencies. Preliminary studies demonstrate that both tumor and immune system cells may be involved in limiting the cancer-specific immune response;

however, the relative role of each remains poorly defined. In addition, no ovarian cancer-specific tumor antigens have been defined to allow specific laboratory assessment of the immune response.

Cervical cancer may have the potential to be eradicated via the development and implementation of effective HPV vaccines. However, the steps required for the initiation of an effective immune response at the mucosal surface are not yet defined. Definition of vaccine strategies that would stimulate effective T cell and humoral immunity must be developed and rapidly tested.

Finally, the uterus is an immunologically active organ. Other benign conditions such as endometriosis and pregnancy are present, in part, due to modulation of immunity. The effect of hormones on the initiation or augmentation of immunity has not been studied systematically. In addition, principles defined in related disorders are not being applied to the study of endometrial cancer and could rapidly advance our knowledge base.

In summary, it is critical to study the endogenous immune response that occurs in patients with gynecologic malignancies. First, ovarian, cervical, and endometrial cancers each present unique immunologic problems and represent model systems for establishing principles that may be applied to other malignancies. These tumors are models because human material is easily accessible, both systemically and at the site of tumors (ascites and cervical washings). Second, immune-based therapies have proven utility in the treatment and prevention of disease, particularly the use of HPV vaccines in cervical cancer. Finally, effective treatments for advanced-stage ovarian, cervical, and endometrial cancers are not available. Harnessing the immune system for treatment offers a new translational modality for gynecologic cancer therapeutics.

QUESTIONS AND CHALLENGES

OVARIAN

Which components of the immune and tumor microenvironments initiate regulatory effects on the tumor-specific immune response?

- Define the immune components in the peritoneum of patients with ovarian cancer and determine the functional defects as compared with components in the periphery and in non-tumor-bearing hosts.
- Determine tumor antigens involved in ovarian cancer to provide a model for evaluation and dissection of the endogenous immune response.
- Determine the role ascitic fluid plays in modulation of immune response.

CERVICAL

What are the steps in the initiation of effective mucosal immunity, based on the phenotype and clinical efficacy of the generated immune response?

- Define an effective anti-viral (HPV) immune response.
- Define an effective anti-tumor immune response.
- Determine a vaccine strategy that would stimulate biologically relevant anti-viral and/or anti-tumor immunity.
- What are the immunologic problems in the development of prophylactic versus therapeutic vaccines?

- Is HPV a sufficient target or are other tumor antigens involved in the malignant transformation needed for tumor eradication?

ENDOMETRIAL

What is the regulatory role of steroid hormones in influencing the generation of immunity to endometrial cancer?

- Define differences in local immunity between the hyperplastic and atrophic uterus.

- Characterize the hormonal influence in local cytokine production and regulation of immunostimulatory molecules on APC and immune effector cells.

- Identify immunogenic proteins in endometrial cancer and determine whether hormone environment effects their expression.

RESEARCH PRIORITIES

Priority 1: *Focus on the characterization and function of the immune micro-environment in the genital tract.*

Ovarian: Immunosuppressive effects of the tumor and regulation of immune effectors

Cervical: Influences on the generation of effective mucosal immunity

Endometrial: Role of the hormone environment in regulating immunity

Priority 2: *Advance the clinical translation of immune-based therapies to both target specific antigens and correct or overcome defined immune modulating defects. Clinical trials must be designed to evaluate biologic endpoints as a primary result. In addition, trials must seamlessly integrate laboratory evaluation. Human clinical trials can serve as the primary model for the evaluation of immune-based therapies.*

Priority 3: *Define and expand the repertoire of tumor antigens for each of the gynecologic cancers.*

TUMOR-SPECIFIC PRIORITIES

OVARIAN

Priority 1: *Increase basic science studies to determine the role of the peritoneal micro-environment in modulating the immune response at different stages of disease. Focus basic studies on discerning the differences in peripheral immune response versus local immune response in both ascites and at the tumor site. Define immune dampening factors secreted not only by the tumor but also the very cells stimulating the immune response.*

Priority 2: *Define immunogenic proteins (i.e., tumor antigens in ovarian cancer). Target tumor antigens will provide some model systems for monitoring immune responses and defining immunogenic defects. The critical assessment of specific antigens through the ovarian disease process may minimize the need for the development of animal models for evaluation of immunity.*

Priority 3: *Prioritize human clinical translational studies of immunologic agents in trials that have a strong correlative aspect. The human studies must be designed to answer basic biologic questions as a priority. These clinical trials may be intercalated into standard therapies to improve recruitment for novel therapies.*

CERVICAL

Priority 1: *Encourage studies to improve our basic understanding of mucosal immunity in the cervix. Prioritize the understanding of both endogenous factors (e.g., influences of hormones) and exogenous factors (e.g.,*

smoking and other pathogens) and their role in influencing mucosal immune responses. Define the differences between systemic immunity and the immune responses at the mucosal surface or site of neoplasia.

Priority 2: *Develop prophylactic and therapeutic vaccines and validate laboratory and biologic correlates for clinical response.*

Priority 3: *Differentiate between the immune response to a virally infected cell and to a cancer cell. What are the differences between HPV-specific immunity and cervical cancer–specific immunity (temporal phenotype)? These differences include the antigenic repertoire as well as the phenotype of both T cell and humoral immunity generated at the site of disease. Studies would include the basics of immune responses needed for prophylactic versus therapeutic vaccines.*

Priority 4: *Obtain immunologic profiles of women with cervical cancer to discern in whom chronic HPV infection develops and in whom it is eradicated. Profiling should be evaluated at both the cellular and the molecular levels. Studies should include population and epidemiologically based evaluation to link immune defects with other potential environmental concerns.*

ENDOMETRIAL

Priority 1: *Discern the effects of hormones on the immune system and the cytokine environment of the endometrium. Evaluate the differences in the immune microenvironment of atrophic and hyperplastic endometrium. Determine tumor antigens present in endometrial cancer and how hormones regulate them.*

Priority 2: *Develop phase I clinical trials of immune-based therapies for the treatment of endometrial cancer.*

BARRIERS

Numerous barriers impede the progress of elucidating tumor-specific immunity in gynecologic cancers, as well as our ability to develop new and effective immune-based therapies:

- Unavailability of biologically relevant animal models for the evaluation of immunity in gynecologic cancers
- Lack of emphasis on the translation of clinical strategies from other cancer therapies into gynecologic disease
- Lack of defined immunologic endpoints for the readout and interpretation of clinical trials
- Insufficient "cross-talk" between critical disciplines involved in the evaluation of immunity, such as basic immunologists, biologists, and gynecologic oncologists
- Deficiency in the education of the community concerning the effects of HPV infection on health maintenance and the development of cervical cancer, limiting study accrual
- Lesser incentive of patients with preinvasive disease, as compared with cancer patients, to participate in clinical trials
- Lack of defined immunologic targets (i.e., tumor antigens) in gynecologic malignancies

RESOURCES

- Request for Application (RFA)-based P01 mechanisms to fund groups of multidisciplinary investigators focused on the priority research topics

- Increased funding for development and validation of immunoassays to establish correlates of clinical response
- Support to fund extensive longitudinal analysis of baseline immune responses to tumor antigens and to assess immunologic memory or persistence of immune responses in patients undergoing immunomodulatory therapy
- Infrastructure for community education, recruitment, and retention of patients with precancerous lesions in clinical trials for HPV vaccines
- A standardized and validated system for the collection and storage of peripheral blood lymphocytes, sera, tissue, and genital tract secretions for the evaluation of tumor-specific immune response as the field develops and antigens are identified
- Molecular target assessment and evaluation initiatives for gynecologic tumor antigens and programs to link scientists working on cell biology and array technology with immunologists to assist in the identification of potential target antigens
- Immunologic advisory committee within the Cancer Cooperative Group system to aid in the rapid translation of biologically based therapies into phase II studies

Radiobiology

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OVERVIEW AND STATE OF THE SCIENCE

Radiation therapy plays an important role in the management of many patients with gynecologic malignancies, particularly cervical, endometrial, vaginal, and vulvar cancers. Although at present the role of radiation therapy in ovarian cancer is limited, this has not always been the case and should not be assumed to remain so.

Because radiation therapy is a local treatment modality (although extended fields are feasible), it is worthwhile to recognize that failure to cure can result from either the inability of radiation therapy to produce local control or systemic failure outside the radiation-treated volume. In some cases, both patterns of failure are seen, and some data suggest that failure to control local disease can itself lead to systemic failure by providing clonogens for dissemination.

Many questions remain regarding the determinants of intrinsic radiosensitivity. One therapeutic strategy would be to measure radiosensitivity at the initiation of radiation therapy, using this information to individualize a prescription that would favorably affect radiosensitivity, such as chemotherapy, specific chemotherapy agents, bioreductive agents, optimized radiation therapy fraction sizes, and so forth. Ultimately, correlations between gene expression and translation and intrinsic radiosensitivity are needed. Tumor heterogeneity and genomic instability are potential barriers to understanding that need to be overcome.

Measurements of intrinsic radiosensitivity would facilitate research into methods of modifying it. For example, early data suggest that Cox-2 inhibitors might favorably impact radiosensitivity. If so, the concept of dose-response relationship for microscopic disease might be found to be much more complex than currently realized. This would open broad new avenues for clinical research and would imply significant changes to currently accepted treatment methods and concepts.

Optimum management of gynecologic cancers with radiation therapy requires an understanding of normal tissue tolerance. Specifically, the structure and function of organs such as the small and large intestines, rectum, and bladder must be preserved in a large majority of patients. Otherwise, the therapeutic ratio will tilt away from the use of radiation therapy.

Attempts to ameliorate or limit radiation toxicity by using radioprotectors have been met with some success, but further research is needed. Also, clinicians have long had some qualitative understanding of the relationship between tolerance and volume of normal tissue treated. The use of three-dimensional

imaging and treatment planning techniques, quantitative analyses of dose distributions (e.g., dose-volume histograms), and special treatment techniques such as intensity-modulated radiation therapy (IMRT) has yielded an increasing understanding of these relationships. Typically, these specialized treatment techniques "spread out" dose over larger volumes, giving lower doses to organs with less tolerance to radiation. The radiobiologic implications of giving lower doses of radiation therapy to larger volumes can and must be considered quantitatively.

CERVIX

Radiation therapy is the primary therapy for patients with tumors extending beyond the cervix. Given the reasonably high doses that can be delivered safely by using brachytherapy techniques, high rates of local control and cure are reproducibly obtained. Recent clinical trials have shown that concurrent chemotherapy, generally with platinum or platinum-based regimens, can further augment these outcomes. However, even with optimum radiation therapy and chemotherapy, about one-fourth of patients with stage II cancer and up to two-thirds of those with stage III cancer still die of their disease.

Clinicians recognize a wide spectrum of individual tumor responsiveness to and curability with radiation therapy. Some trends in responsiveness and curability are seen. For example, certain histologies, such as small cell carcinoma and very poorly differentiated tumors, are generally very responsive to radiation therapy but have a significant rate of systemic dissemination, which impairs their curability. Patients with lower hemoglobins and lower tumor oxygen tensions probably have lower cure rates with radiation therapy. Patients with larger tumors fare more poorly than those with smaller tumors, such as unilateral versus bilateral stage IIB or IIIB, and stage II versus stage III. However, none of these clinically identifiable factors directly correlate with responsiveness to or curability with radiation therapy. Furthermore, only tumor oxygenation is potentially alterable after the diagnosis is made and treatment initiated.

Tumor hypoxia is an area of considerable interest. In fact, a current Gynecologic Oncology Group trial is evaluating the potential of hemoglobin maintenance above 12 g to improve outcomes compared with hemoglobin maintenance above 10 g. Both transfusions and growth factors (erythropoietin) are used in the 12-g arm of this study. However, this is a relatively crude approach because it does not directly assess for tumor hypoxia. Furthermore, hypoxia is not an all-or-none phenomenon, but a continuum. Hypoxia markers such as pimonidazole and EF5 are possible routes to a better understanding of patient-specific tumor oxygenation status.

It should be recognized that unsuccessful attempts to overcome tumor hypoxia in cervical cancers have been previously made using hypoxic cell sensitizers, carbogen and oxygen breathing, and densely ionizing radiations. At present we have a poor understanding of why these maneuvers lacked efficacy. Possibly it is simply a matter of not being able to select those patients who would benefit from these approaches, thus diluting any potential gain. More likely, it is much more complicated. For example, it is known that the tumor vasculature is abnormal both anatomically and physiologically. Therefore, it is quite possible that systemic attempts to alter the tumor microenvironment (e.g., tumor oxygenation status) will yield inconsistent and uninterpretable results. Perhaps this is an area for investigation and therapeutic intervention (e.g., nicotinamide). Also, the lack of efficacy of therapeutic strategies directed at overcoming tumor hypoxia does not necessarily imply failure of all such strategies. Therefore, the potential of bioreductive drugs

such as tirapazamine continues to be investigated.

Separate, more logistical problems with identification of hypoxic tumors (and other tumor-specific factors with therapeutic implications) concerns the invasiveness of procedures required to establish tumor oxygenation status (Eppendorf electrode) and tumor heterogeneity. Imaging tools, recognition of gene expression patterns consistent with hypoxia, or identification of endogenous factors, if validated, could be useful in individualizing therapy based on tumor-specific characteristics. Furthermore, there is some question regarding the importance of tumor oxygenation status at the time of diagnosis and/or initiation of therapy, since this variable is almost certain to change significantly over the course of fractionated radiation therapy.

Although some questions remain, recent clinical trials have shown improvement in local control and survival by combining chemotherapy with radiation therapy for most patient populations with cervical cancer. The biologic basis of this is unclear and needs further study. One possibility is that chemotherapy affects the fidelity of radiation repair through one or more mechanisms, including lesion recognition, aberrant signaling, inaccurate repair, and others. Similarly, ionizing radiation could be sensitizing tumor cells to the antiproliferative effects of the chemotherapy agents, accounting for the synergy observed clinically. Given the widely accepted clinical utility of combining chemotherapy and radiation therapy in patients with cervical cancer, it is surprising that we know so little about the mechanisms of these interactions. Such information could suggest additional, more effective ways in which to exploit the advantages of combined therapies. One potential line of investigation concerns measuring levels of DNA-cisplatin adducts and correlating these findings with clinical outcomes.

The identification of accelerated repopulation of tumor clonogens during fractionated radiation therapy has had an impact on the radiotherapeutic management of some tumor sites such as head and neck cancers. In cervical cancer, it is likely that there are similar opportunities to favorably impact outcomes using treatment strategies such as altered fractionation schemes, optimally timed treatment combinations, and others. We need a better understanding of the genetic basis of tumor growth kinetics, including factors affecting gene expression and translation. Again, for treatment alterations and concepts to have the potential to improve treatment, it will obviously be necessary to determine patient- and tumor-specific kinetic information so that appropriate patient and treatment selection can be undertaken. A significant barrier to this concept (and all radiobiologic concepts) is the phenomenon of tumor heterogeneity and genomic instability. In other words, the treatment target(s) are moving and changing between different patients and even within the same patient and her tumor. Hopefully, patterns will emerge that can be identified and exploited clinically.

ENDOMETRIAL AND OVARIAN CANCERS

Radiation therapy plays a largely adjunctive role in early-stage endometrial cancer, which fortunately makes up the vast majority of these tumors. However, treatment outcomes remain poor for most patients with advanced disease or certain high-risk tumor types. For these patients with unfavorable disease, multiple approaches with radiation therapy have been used, with only moderate success. Although radiation therapy is clearly a very active agent with demonstrably high response rates in endometrial and ovarian cancer patients with measurable disease, barriers to its successful use in unfavorable and late-

stage endometrial cancer include the propensity of this subgroup of patients to have hematogenous or peritoneal tumor dissemination and the limited normal tissue tolerances of large volumes (particularly liver and small bowel) treated with radiation therapy.

Radiation therapy has been used extensively for ovarian cancer in the past, and it is known to have significant activity and curative potential in identifiable subsets of patients. However, its use in curative management has largely been curtailed as cytotoxic agents and combinations with high response rates have been identified. Even so, high and even complete response rates with modern chemotherapy fail to cure the vast majority of women diagnosed with this disease. Given the demonstrable single-agent activity of ionizing radiation, it is reasonable to postulate that its use should be furthered studied, at least in combination with other active agents. Again, tumor biology–based predictive assays could help direct treatment and further study.

The Gynecologic Oncology Group has recently completed a direct comparison of cytotoxic chemotherapy versus whole-abdomen radiation therapy in patients with stages III and IV disease. The results of this study are not yet available, but it is clear that the majority of women are still not being cured of their disease, despite these aggressive therapies. The use of combined-modality therapy, so common and so promising in other diseases, has been only minimally studied in endometrial cancer. In the limited clinical efforts to combine systemic therapy with radiation therapy, no translational research has been undertaken to understand issues of radiosensitization and/or chemosensitization. This leads to the current situation in which only empirical approaches to combined-modality therapy can be considered.

Similarly, before the taxane era in ovarian cancer management, the Gynecologic Oncology Group conducted a combined-modality study of limited chemotherapy followed by whole-abdomen hyperfractionated radiation therapy. The results from this study suggested that outcomes in disease status were reasonably equivalent to those achieved with more prolonged chemotherapy regimens. Furthermore, this study yielded information about integrating treatments including surgery, dose-response relationships, and appropriate radiation therapy volumes and treatment delivery. As taxanes became integrated into the standard cytotoxic regimen, no further studies incorporating radiation therapy have been undertaken in ovarian cancer; however, other clinical data, particularly from Europe, strongly suggest the potential of combined-modality therapy to improve outcomes over chemotherapy alone.

Very little success has been achieved in attempts to understand the mechanisms of radioresistance and radiosensitivity in endometrial and ovarian cancers. It follows that we know very little about how to modify radiation response. It is known that the dose-response relationship for microscopic disease is a multifactorial rather than a consistent relationship, accounting for the continuum of responses and control rates observed clinically. Possible factors involved in this phenomenon include inherent clonogen radiosensitivity, the number of clonogens, tumor microenvironment, patient immunologic status, and others.

In ovarian cancer and some variants of endometrial cancer, we need to think more critically about treatment strategies in which radiation therapy is used in novel ways that might be more effective and with less toxicity. For example, one concept is to use “intermittent” radiation therapy along with cycles of chemotherapy, thinking conceptually of ionizing radiation as simply

another cytotoxic agent used in combination with other cytotoxic agents. This idea would require a change from thinking of radiation therapy as a continuous course of daily treatment. In this schema, radiation therapy would be used intermittently and at lower doses. Conceptually, this approach would allow the use of a very active single agent, avoid blind adherence to previous dose and time concepts, and entail the use of therapy that would be potentially effective at lower doses, possibly lowering toxicity rates. Well-thought-out clinical trials are needed in this area.

Another novel concept being studied in a clinical trial entails the use of intra-abdominal radionuclides and vaginal cuff brachytherapy in stages I through IIIA serous papillary endometrial carcinoma. This approach potentially treats microscopic disease within the entire abdominal cavity without the potential acute and late toxicities of whole-abdomen external-beam radiation therapy from standard doses. A next step could be the integration of chemotherapy or biologic therapies into this regimen. For example, some laboratory data suggest that combining intraperitoneal cisplatin with radioactive phosphorus-32 kills ovarian cancer cells synergistically. Early clinical work using this combination and other intraperitoneal isotopes has been promising but largely ignored.

RESEARCH PRIORITIES

Priority 1: *Use current and future technologies to gain a better understanding of tumor biology through multiple assays that are related or potentially related to the efficacy of radiation therapy, including hypoxia, intrinsic radiosensitivity, growth kinetics, gene expression/suppression, and angiogenesis.*

- Develop a computerized, integrated tumor biology database that permits sharing of information and collaboration between investigators to combat overly focused "reductionism" and promotes interaction in biologically oriented cancer and radiation biology research. Potentially, this would move us toward clinically relevant predictive assays based on best practices and, possibly in time, standardization.

- Recognize that tumor biologic parameters potentially are typically measured at only one point in time (typically at the beginning of treatment). We must discover how these parameters change with time in surviving cells, either in terms of the natural history of the disease or in response to treatment, such as fractionated radiation therapy.

- Establish tissue banks and cell lines to investigate tumor biologic markers that might function as predictive assays. This will permit both prospective research and retrospective validation of these parameters based on patient outcome (e.g., evaluate why treatment failed in some patients and not in others). Markers may also serve as molecular targets.

- Correlate laboratory-derived tumor information with noninvasive types of functional predictive assays, including endogenous markers, imaging techniques, and so forth.

- Investigate clinically relevant methods to overcome or modify radiation resistance as prospectively identified through laboratory studies of fractionation, dose rate, treatment combinations, and so forth.

Rationale

The goal is individualized and optimized therapy based on patient- and tumor-specific characteristics that can be identified at the time of diagnosis. The concept of optimized therapy might well require changes in tumor biology during treatment, raising the question of a "dynamic" and individualized approach to treatment with radiation therapy.

Discussion Points

a. Hypoxia—relationship to angiogenesis, pH, redox potential?

- Measurement—pimonidazole, EF5, HL91, and so forth
- Endogenous markers, non-invasive assessment vs. direct assessment
- VEGF, HIF-1alpha, Glut-1
- EPO, carbogen
- Blood flow alterations (e.g., nicotinamide)
- Tumor vasculature abnormal anatomically and physiologically
- Surrogate for other effects increased metastatic potential
- Promotes mutations

b. Growth kinetics

- Ki67, IUdR incorporation, PCNA
- Accelerated repopulation
- Overall treatment time
- Effects of cell cycle agents
- Importance of tissue banks and cell lines with varying proliferative characteristics

c. Intrinsic clonogen radiosensitivity

- Two ways to kill cell: alpha (single hit), beta (double hit); different effects at different dose rates and fraction sizes, different repair characteristics
- DNA arrays
- Functional assays

Priority 2: *Understand better the biologic basis of combination therapies.*

- Gain a better understanding of the mechanism(s) of action of currently used combination therapies (platinum–radiation therapy). Can they be combined more effectively? How can we capitalize on "resistance"?
- Evaluate new approaches ("new paradigm") to the use of radiation therapy in non-conventional ways. For example, radiation therapy could be used in a manner more akin to a chemotherapy agent—concurrently with a course of chemotherapy, such as every 3 weeks—instead of as a single continuous course of treatment. In addition, there has been no systematic study of the use of chemotherapy concurrently with low-dose-rate brachytherapy. This needs to be investigated because there are several potential applications in gynecologic cancers. Radiobiologic studies can potentially guide clinical investigations.
- Investigate additional ways in which to combine therapies to optimize outcomes, for example, schedule dependence, new agents, combinations of agents, and so forth. Ideally, the efficacy of combined regimens will be predictable on the basis of laboratory parameters.

- Identify tumor characteristics correlating with which tumors are most amenable to specific combinations of therapies. (This recommendation overlaps with Priority 1.) Gain an understanding of the biologic basis of multiple combination therapies.

- Investigate the potential and role of gene therapies with radiation response elements in the radiotherapeutic management of gynecologic cancers.

- Evaluate the potential of agents that alter either the dose-response relationship (equivalent response at lower dose) or dose-toxicity relationship (e.g., radioprotective agents).

Rationale

The goal is individualized and optimized therapy combinations, when appropriate, based on patient- and tumor-specific characteristics which can be identified at the time of diagnosis in order to improve outcomes.

Discussion Points

- Mechanisms of cisplatin–radiation therapy sensitization (e.g., correlation of DNA adducts with outcome, effects on fidelity repair of radiation damage, patient/tumor variability)

- Concurrent platinum-32

- Variability in response—uptake, MDR, kinetics

- Effects on normal tissue

- Sequencing/timing

Priority 3: *Develop novel radiation treatment strategies designed to improve response and control rates and decrease acute and late toxicities. This will require a paradigm shift in relation to how radiation therapy is used and combined with other therapies, as well as support from Cancer Cooperative Groups and Cancer Centers that are interested in gynecologic cancers.*

- Evaluate strategies that can favorably alter dose-response relationships. For example, if radiation in combination with another agent (e.g., Cox-2 inhibitors) can reproducibly sterilize microscopic disease at doses lower than 45 Gy, this will have major implications for the use of higher doses to smaller volumes, will make radiation therapy more efficacious at larger volumes, and so on. (This recommendation overlaps with Priority 2.)

- Study novel ways of using radiation therapy, particularly in combination with other cytotoxic or biologic therapies, sequencing/timing issues, "intermittent" radiation therapy with courses of chemotherapy, and concurrent chemotherapy with low-dose-rate brachytherapy.

- Work toward a more quantitative understanding of the relationship between treatment volume and tissue tolerance through dose-volume histogram analysis, and so forth.

- Better understand the biology of different radiation fractionation schedules, brachytherapy, radiation effects on normal tissue, and so forth. (This recommendation overlaps with Priority 1.)

- Study the potential of technological approaches to improvements in radiation therapy by more accurate definitions of target volume, use of "dose sculpting," intensity-modulated radiation therapy, and so forth.

- Strengthen education and training of health professionals in the area of gynecologic cancer treatment with radiation, with particular attention to the needs of nonindustrialized countries, research into electronic media–based instruction and testing, and movement toward a reproducibly high standard of radiation therapy capability that can be effectively communicated and implemented. Specifically, scientific and clinical partnerships with non-industrialized countries could be considered that could answer research questions in a more timely way while providing access to improved therapies to underserved populations.

Rationale

The goal is to optimize treatment selection and delivery utilizing biologic and technical advances.

Discussion Points

- HIV status
- Photodynamic therapy
- Importance of clinical trials
- Recognition of overlap between technical science and biologic science
- HPV status

BARRIERS

- Currently there is a lack of a dedicated, versatile, centralized tissue bank (associated with clinical outcomes) that will facilitate a prospective analysis of tumor biology, assessment of correlations with radiation response, and understanding of potential of combination therapies and other novel therapeutic approaches. Such a centralized resource would facilitate retrospective correlative studies designed to assess tumor characteristics associated with treatment failure. In addition, similar considerations would suggest the establishment of multiple tumor cell lines of various radiobiologic characteristics that can be shared among investigators.

- There is a huge problem with tumor heterogeneity and genomic instability. These realities are typically ignored in tumor biology research in the interest of simplicity. This suggests the need for repeated sampling of patients' tumors over the course of treatment and the course of their disease. Potential barriers include patient acceptance and the logistical difficulties of repeated sampling.

- There is a large number of disparate methods for multiple assays, for example, hypoxia. The relative lack of uniformity of approach and validation of markers and methodology is a significant barrier to progress.

- It is also very difficult to perform combined predictive assays in the same patient/tumor, since sample size can be a significant problem.

- It is possible that the relationship between the Radiation Branch of the National Cancer Institute (NCI) and the NCI, more generally, should be rethought. This would potentially increase the awareness of the need for radiobiologically oriented and technologically oriented research, foster collaborations with other scientists, and result in removal of some current barriers to research.

- The cost of methodologies, including imaging techniques, tissue bank, and cell line maintenance, are significant and operates as a barrier to progress.

RESOURCES

- A tissue bank and tumor cell lines characterized for radiation response and other relevant endpoints. Ideally, this will include sequential biopsies over the course of treatment as well as samples from recurrent tumors. Furthermore, to maximally benefit from this research material, the tissue and cell lines should be potentially linkable to patient information regarding treatment and outcomes.
- A program of basic research to define the tumor properties that have an impact on and predict radiation sensitivity, response, and outcomes (hypoxia, growth kinetics, angiogenesis, apoptosis, intrinsic radiosensitivity).
- There is a need to forge alliances between groups to work with the same tumor samples but with interests or abilities to measure different predictive endpoints.
- There is a need to better recognize and correct the serious lack of understanding of the mechanisms of action of radiation combined with chemotherapy, biological therapy, and gene therapy in the treatment of gynecologic cancers. This will require the initiation of a well-supported program of basic tumor biology research focused on this issue and will have the potential of suggesting different and better treatment combinations.
- Additional support is needed for new technologies and approaches aimed at improving dose distribution, target volume accuracy, and normal tissue tolerance in gynecologic cancers.
- Initiatives to strengthen education and training of health professionals in gynecologic cancer treatment in the United States and in developing nations should be undertaken with the goal of moving toward a reproducibly high standard of clinical radiation therapy.

Laboratory and Clinical Models

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BACKGROUND

A variety of gynecologic cancer models are in various stages of development. A critical question that needs to be addressed is the relevance of these various models to human gynecologic cancers. Unless models recapitulate the human cancer they were designed to model, results from modeling will be irrelevant to cancer prevention, detection, and treatment.

Following is a brief overview of current models for ovarian, cervical, and endometrial cancer. The strengths and weaknesses of these models are also described.

OVARIAN CANCER

Various models of ovarian cancer are under development. These include *in vitro* models that employ spontaneous and genetically transformed ovarian surface epithelial cell lines, as well as *in vivo* rodent and avian models that employ xenografts, induce spontaneous cancers, or utilize gene transfer and transgenic technology. Some models, such as transgenic *in vivo* models, have come about only in the past few years. One current strategy involves crossing two transgenic strains to produce one that has expression specific to ovarian surface epithelial cells. Another involves screening for candidate oncogenes by isolating cultures of epithelial cells, transfecting with the candidate oncogene, and reintroducing the cells into a mouse or rat.

Strengths

- Epithelial in nature
- Controlled and controllable systems
- Employ candidate genes involved with carcinogenesis

Weaknesses

- Variations in histologic subtypes not recapitulated
- Inherent differences in human ovarian biology may frustrate the study of specific interactions (lack of post-reproductive phase in mice or differences in ovulation biology in avian models)

CERVICAL CANCER

Models of cervical cancer include several that examine human papillomavirus (HPV), which has been implicated in the overwhelming majority of cervical cancers. *In vitro* model systems include a three-dimensional

organotypic culture of stratified epithelium, which allows for direct comparison with patient specimens. The cultures can also be transfected with specific HPV oncogenes and can be used to test the effects of therapeutic drugs, the interactions with other microbes, and the effect of other phenomena, such as wound healing.

Cervical cancer mouse models are also under study, including a transgenic model in mice that express the HPV genes *E6* and *E7*, which have shown to be necessary (but not sufficient) for cervical carcinogenesis. This model differs from human disease in several ways, however: it exhibits no intraepithelial lymphoid aggregates, model cancers remain microscopic and confined to the cervix, cancer development requires chronic estrogen treatment, there is no metastasis, and model cancers may regress in the absence of estrogen.

Strengths

- Histologic similarities to human disease
- Controlled and controllable systems
- Utilizes HPV genes involved with carcinogenesis

Weaknesses

- Lack of immunocompetent models
- Dependence upon hormonal manipulation

ENDOMETRIAL CANCER

Most mouse models for endometrial cancer are of endometrioid (type I) cancer, which has a significant estrogen component. There are no mouse models of serous (type II) endometrial cancer, which does not have a significant estrogen component. The two genetic models that are best developed are the phosphatase and tension homologue (*PTEN*) gene and the DNA mismatch repair models. All mouse models are limited due to the fundamental differences between the biology of the mouse and that of the human, including the estrus cycle in mice versus the menstrual cycle in humans, a limited post-reproductive anestrus period in mice compared with that of humans, and anatomical differences. A hormonal mouse model of endometrial cancer produced 100 percent penetrance but no metastatic disease; therefore, it is unclear whether the model will be useful for preclinical drug development.

Strengths

- Histologic similarities to human disease
- Controlled and controllable systems
- Similar etiology

Weaknesses

- Inbred animals may respond to genetic and environmental factors in a strain- or line-specific way (however, this may allow identification of genetic modifiers).
- Inherent differences in endometrial biology may frustrate the study of specific interactions (lack of post-reproductive phase in mice).

RESEARCH PRIORITIES

Priority 1: *Validate genetic, physiologic, and environmental pathways in current and future models.*

Rationale

Gynecologic cancers are characterized by unique genetic, physiologic, and environmental processes that lead to carcinogenesis. It will be important to determine whether models, as they are

developed, recapitulate these etiologic components.

Priority 2: *Validate histopathology in current and future models.*

Rationale

Within each gynecologic cancer are multi ple, heterogeneous histologic subtypes. It will be important to determine whether models recapitulate the histologic features of the various cancers.

Priority 3: *Validate biologic behavior in current and future models.*

Rationale

Each gynecologic cancer has a range of biologic behaviors (e.g., growth, metastasis, response to therapy); it will be important to determine whether models have similar features, especially their responses to standard-of-care treatment for individual diseases.

OTHER PRIORITIES

- Build interaction between investigators identifying molecular signatures and those developing models.
- Provide training for young investigators in the area of model development.

BARRIERS

- Resources for training of investigators in cancer models and infrastructure to support their interaction with animal scientists
- Infrastructure to provide various *in vitro* and *in vivo* models to cancer investigators
- Technology to allow for serial sampling of small tumor lesions in *in vivo* models
- Limited access to patent-protected potential preventive and therapeutic agents for testing in available models
- Resources to develop stable model systems that recapitulate human disease. For example, mice with a promotor and the *E6* and *E7* genes are not hardy and often do not live beyond 1 year, and 20 to 45 percent of K14-HPV-16 mice have problems with bladder obstruction. These models often have complications or a reduced life span that diminish their utility as models.
- Technology to allow development of difficult-to-produce transgenic animal strains. Certain models are difficult to produce. For example, a PTEN heterozygote/DNA mismatch repair model is produced in only 1 of 16 offspring from the relevant parent mice.

RESOURCES

The National Cancer Institute Mouse Model Consortium

Health Disparities, Communication, Education, and Quality of Care

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BACKGROUND: STATE OF THE SCIENCE

As a population, women with cervical cancer are characterized by striking disparities in mortality and stage at diagnosis by race and socioeconomic status. To a lesser extent, the same is true of women with endometrial cancer. Increased research in cervical cancer is needed to further define and characterize risk factors and the biologic, sociocultural, systems, and provider components for these discrepancies.

There are also discrepancies by age and geographic region in obtaining Pap smears. Older women are less likely to obtain a Pap smear, or at least to obtain one regularly, than younger women, and women in certain areas of the country (such as Appalachia, the deep South, and certain areas with large Latina populations and subsets of Asian populations) are also less likely than the general population to obtain Pap smears. Research is needed to identify the reasons for these discrepancies and to assess compliance with follow-up for abnormal Pap smears.

Discrepancies appear to exist even in the care provided by specialists to women. Some specialists appear to make assumptions based on race, education, or socioeconomic status about a woman's ability to tolerate or comply with more aggressive treatment. Research is needed to determine the factors that influence these physicians' decisions. Research is also needed on cultural preferences for certain communication styles and on interventions for improving cultural competency in the health professions. In addition, it is not clear what sources of information (such as friends or family members) patients use to make decisions about their treatment. Little research has been conducted on follow-up care and survivorship in non-white and lower-income populations.

Very little is known about whether women with gynecologic cancers are receiving appropriate quality of care. The evidence from other cancers suggests that the quality of cancer care is uneven at best. There are several reasons why the study of quality of gynecologic cancer care could be especially informative. First, many women with gynecologic cancers are treated by general surgeons or general oncologists rather than gynecologic oncologists. There is some evidence that women with gynecologic cancers receive higher-quality care and experience better survival under the care of specialists, compared with generalists. Second, the striking differences in both the incidence and outcomes of cervical cancer by race suggest that health disparities may be a particular problem in the quality of care for this disease. One particular clinical situation—the treatment of recurrent or

refractory ovarian cancer—raises all of the issues discussed above.

RESEARCH PRIORITIES

Priority 1: *Assess the quality of care and outcomes of treatment of women with gynecologic cancers.*

We propose large observational cohort studies of newly and previously diagnosed patients with gynecologic cancer, investigating the impact of targeted interventions on patient-centered outcomes, dissemination of state-of-the-science therapies into practice, the influence of modifiable risk factors, and disparities in the delivery of quality cancer care. We recommend that these studies be conducted through the newly created, National Cancer Institute (NCI)-sponsored Cancer Care Outcomes Research and Surveillance Consortium (CanCORS), with two modifications. First, it is essential that these studies look across the disease continuum, from diagnosis to treatment to survivorship and end-of-life care. Second, these studies must include sites with sufficient representation of underserved, socioeconomically diverse populations to be able to examine health disparities in treatment and outcomes.

Rationale

Little is known about quality of care and outcomes in women with gynecologic cancers. Gynecologic cancer survivors account for 17 percent of all cancer survivors, but only 3 percent of cancer research grants go toward research on survivorship. The majority of females with gynecologic cancer do not receive care from gynecologic oncologists; the impact of this on quality of care and outcomes is unknown. Because gynecologic oncologists provide multimodality oncology care, studies of quality of care and outcomes for gynecologic cancers provide a particularly informative setting in which to study specialist versus generalist care and volume-outcome relationships.

Priority 2: *Assess health disparities in cervical cancer incidence and outcomes.*

We propose a multipronged research strategy including large database studies, population-based cohort studies, and in-depth qualitative studies, including patient and provider interviews. This is necessary to determine the relative contribution of risk factors, screening (including compliance and follow-up rates), treatment (including recommendations, patient preferences, and provider expertise), and survivorship (including post-treatment surveillance) to the observed disparities in cervical cancer incidence and outcomes.

Rationale

- Marked differences exist in the incidence and outcome of cervical cancer that are attributable to multiple factors, including race, ethnicity, income, age, and education.
- There is a major emphasis among multiple cancer institutions, including the NCI, the American Cancer Society, and the Centers for Disease Control and Prevention, to eliminate this disparity over the next 10–15 years.
- To accomplish this goal, it is essential that we understand fully and completely the influence of the multiple factors underlying this disparity, including biologic, sociocultural, health care system, and provider factors. Without this information, it will be essentially impossible to design the interventions necessary to modify any or all of these factors.

Priority 3: *Study treatment choice and outcomes in patients with recurrent or refractory ovarian cancer.*

Rationale

The majority of women diagnosed with epithelial ovarian cancer die of their disease, yet the effect of second- and third-line treatments on survival, quality of life, patient satisfaction, and costs is unknown. Nonetheless, this treatment has become standard care, such that randomized trials of chemotherapy versus best supportive care are controversial. As a result, there is a need to study both the outcomes of this treatment and the decision-making process involved in choosing a treatment strategy. With careful attention to the sociocultural context in which physician-patient communication occurs, this research will be an informative case study about truth-telling, expectations, and preferences in advanced cancer.

BARRIERS

- The components of optimal-quality care have not been defined.
- Individual investigators do not have access to sufficient numbers of cases of gynecologic cancers to conduct studies.
- Health disparities are likely to involve a complicated interaction among biologic, cultural/individual, systems, and providers issues.
- Race/ethnicity is becoming more difficult to define as population migration and intermarriage increase.
- Accrual to large trials in the refractory or recurrent ovarian cancer setting may be difficult.

RESOURCES

- Consortia of investigators collecting standardized data in each of the three tumor types to provide sufficient numbers of patients
- Quality-of-care indicators
- Collaboration among investigators with expertise in gynecologic oncology, health communication, health services research, and health psychology

Genes and Environment

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BACKGROUND: STATE OF THE SCIENCE

Our understanding of the etiology of gynecologic malignancies is in its infancy. Some of the genetic and environmental factors that contribute to risk for developing endometrial, cervical, and ovarian cancer have been identified. For cervical cancer, human papillomavirus (HPV) infection is a key environmental factor. For endometrial cancer, exposure to unopposed estrogen is a major environmental factor. For ovarian carcinoma, use of oral contraceptives is protective. Some of the germline and acquired genetic factors (tumor cell–specific events) associated with tumor etiology and progression have also been delineated. However, it remains largely unknown how these genetic and environmental factors interact in tumorigenesis.

Improving our understanding of the interaction between genotype and environment will afford opportunities for the prevention, detection, diagnosis, and treatment of gynecologic malignancies. For each malignancy there are unique opportunities for investigations into the causes of cancer.

ENDOMETRIAL CANCERS

Endometrial carcinoma is the most common gynecologic malignancy in the United States: an estimated 36,000 new cases occur each year. The overall 5-year survival rate for endometrial cancer patients is excellent, due in large part to the fact that most tumors are detected at an early stage (when the cancers are confined to the uterus). Therapies for recurrent or persistent endometrial cancer, however, are largely ineffective.

Endometrial cancers are often subclassified as type I or type II disease, according to a classification system that reflects differences in histology, etiology, and behavior. Approximately 85 percent of endometrial cancer cases are type I, reflecting histology arising on a background of abnormal endometrial proliferation and carrying an excellent prognosis. Type II disease includes tumors of the uterine serous and other less common histologies that appear to arise from the atrophic (non-proliferative) endometrium.

Exposure to estrogen (both endogenous and exogenous) is a potent risk factor for the development of type I disease. Estrogenic stimulation can result in abnormal endometrial proliferation, or endometrial hyperplasia. Nearly 100,000 hysterectomies are performed each year in the United States because of abnormal endometrial proliferation (e.g., atypical endometrial hyperplasia). However, it is recognized that in as many as 75 percent of women who undergo hysterectomy because of a diagnosis of endometrial hyperplasia, the disease might not progress to

cancer. The mechanism by which estrogenic exposure increases the risk for endometrial cancer is not well understood, nor are the genetic and environmental factors that are associated with progression to cancer. Different ethnic groups show striking differences in the incidence of type I (estrogen-promoted) tumors, suggesting that there are race-specific unrecognized genetic and environmental factors that contribute to disease.

CERVICAL CANCER

Cervical cancer is the second most common cause of cancer-related death worldwide. Although the use of the Pap smear has reduced the incidence of invasive cervical cancer, the test lacks specificity and sensitivity. Millions of follow-up procedures are performed each year because of abnormal Pap smear findings, the vast majority of which are benign.

Human papillomavirus (HPV) infection is an early event in cervical carcinogenesis, but only a small fraction of women infected with HPV go on to develop cancer. Smoking and a number of other environmental factors have also been linked to the risk for cervical cancer. Genetic factors that influence risk for cervical cancer and interact with HPV have been identified, but the precise nature of these interactions has not been determined. Immune response genes and, potentially, the *TP53* tumor suppressor gene somehow interact with HPV in cervical tumorigenesis. Why certain women with HPV infection go on to develop invasive cancers and others do not is unknown.

Several histologically recognizable precursors to cervical cancer exist. There appears to be a phenotypic progression from normal to precancerous intraepithelial lesions and to invasive carcinoma. Many genetic changes associated with progression remain to be determined.

OVARIAN CANCER

Ovarian cancer is the leading cause of death from gynecologic cancer in the United States. The low overall survival rate for patients with ovarian cancer is due in large part to the fact that most cases are diagnosed at an advanced stage. Although the use of chemotherapy has improved survival rates, in most patients the disease ultimately progresses.

Ovarian cancer has four distinct histologic subtypes: mucinous, serous, endometrioid, and clear cell. Each of these appears to be associated with a distinct molecular pathway, and there may be distinct environmental risk factors for each. A variety of nonmalignant changes in ovarian carcinoma may represent premalignant precursors; these include cystic lesions and borderline ovarian tumors, endometriosis, and endosalpingosis.

Mutations in the *BRCA1* gene confer a high risk for development of ovarian cancer. Risk is also increased among *BRCA2* mutation carriers. The vast majority of women with ovarian cancer, however, do not have an obvious familial or genetic risk for the disease.

Several environmental risk factors for ovarian cancer are well established, including infertility, low parity, late menopause, prolonged ovulatory age, and increased number of spontaneous abortions. Asbestos exposure and the use of talc on the perineum has also been linked to an increased risk for ovarian cancer. The use of oral contraceptives, on the other hand, has a protective effect. Different ethnic groups show differences in incidence of ovarian cancer, pointing to the existence of as yet unrecognized genetic and environmental factors that contribute to disease.

OVERARCHING RATIONALE

To date, studies to assess the effects of genetic factors on the risk for developing cancer or how the cancer patient's genotype influences tumor progression and response to therapy have been conducted "one gene at a time." Although there has been considerable progress in identifying and characterizing the genes that confer risk for certain gynecologic cancers (e.g., *BRCA1* and *BRCA2* for ovarian carcinoma and *MSH2* and *MLH1* for endometrial carcinoma), these "major" susceptibility genes account for only a small fraction of gynecologic malignancies. Several lines of investigation suggest that inherited genetic factors modify the risk for development of gynecologic malignancies. Such "modifier genes" are likely to work in concert with other genetic and environmental factors. Common genetic variants could confer an increased risk for a specific cancer type, might have a general cancer risk effect, or could be protective. The effect of any given modifier of risk may be relatively small at the level of the individual, but because the variant forms are common, the effect at the population level could be large. Among the gynecologic malignancies, it is recognized that the risk for cervical carcinoma is determined in part by genetic variation in the immune response (*MHC*) genes, which somehow mediate patients' responses to HPV infection. Because studies to assess the effects of genetic factors have been conducted one gene at time, often in populations for which environmental risk factors are unknown or have not been considered, little is known about how genes interact with one another and with environmental risk factors.

Priority 1: *Support the development of laboratory-based research methods for the analysis of tissues and epidemiologic data, as well as enhanced collection of tissue samples obtained through National Cancer Institute (NCI)-designated Cancer Centers, Networks, and Cancer Cooperative Groups, for development of the following:*

- Tissue banks with linked clinical and standardized data on endogenous and exogenous risk factors (e.g., reproductive history, smoking, hormone use, family history, race)

- Methods for collecting tissues that preserve the biomolecules of interest (RNA, proteins, DNA) and for working with limiting (small-volume) tissue sources

- Banks of "immortalized" RNA for gene expression studies, to address the problem of limited amounts of RNA for many samples and the possibility that amplification may change expression levels

Rationale

Although there are a number of recognized risk factors for gynecologic cancers, this information typically is not linked to the research tissue specimen. Additionally, current methodologies are inadequate for the study of limited tissue resources, and there are no robust methods for analysis of pre-cancerous lesions and other very small clinical specimens.

Because information on environmental risk factors for the development of cancer is rarely obtained as part of routine clinical care, there have been few opportunities to determine the important exposures and lifestyle factors that determine risk. Too often, epidemiologic studies have been limited to "looking under the lamp post": in the case of endometrial and ovarian cancers, estrogen exposure is a known risk factor, and epidemiologic studies have focused on factors that are known to influence estrogen levels, such as contraceptive use, pregnancy, and smoking. Cancer patients, and women in general, may

be aware that estrogens might increase the risk for developing gynecologic cancers, but there is much less known about what foods, food additives, chemicals, and pollutants add to this risk. Epidemiologic studies are usually conducted independent of genetic (DNA-based) studies, and it has been difficult to merge epidemiologic and genetic data to look at how the genome and the environment interact.

A greater understanding of the important genetic and environmental factors that influence risk for gynecologic malignancies holds promise for prevention, detection, and treatment of these cancers. The identification of high-risk groups, based on genetic profiles, environmental exposures, or combinations of both, could be used to focus cancer surveillance efforts and to guide chemoprevention and intervention efforts. Understanding what genes and pathways contribute to tumor development affords opportunities for new treatments and prevention strategies.

Priority 2: *Understand the genetic influences on environmental factors in the development of gynecologic cancers (e.g., oral contraceptives in ovarian cancer, HPV infection in cervical cancer, and use of unopposed estrogen in endometrial cancer) through the following:*

- Developing *in vivo* and *in vitro* models of genotype-environment interactions
- Identifying and characterizing single-nucleoside polymorphisms (SNPs), in candidate genes and across the genome, for use in studies of gynecologic cancer etiology, progression, and treatment response or prognosis
- Developing novel study design and analysis methods that can accommodate the complex genomic and genotype-environment interaction data required to understand these diseases

Rationale

Genotype-environment interaction studies are in their infancy. The substantial characterization of SNPs and the functional significance of potential interactions hold promise in identifying individuals and populations at risk and in developing strategies for prevention and risk reduction.

In vivo and *in vitro* models are needed to elucidate the biologic mechanism of genotype-environment interactions identified by epidemiologic approaches and to help direct epidemiologic studies that translate information from *in vivo* or *in vitro* models to human populations. Available mouse models for gynecologic cancers are inadequate or have not been appropriately validated. Additional models for these cancers are urgently required. Organotypic or new cell culture systems in which the cell genotype can be manipulated are needed to assess the interactions between cellular environment and genotype.

A systematic characterization of SNPs and other polymorphic variants in both candidate genes and novel variants found by the Human Genome Project should include a definition of allele frequencies in defined ethnic groups (focusing on the major U.S. ethnic groups) and the functional significance of SNPs. Other high-throughput technologies could be used in large-scale molecular epidemiologic studies. For example, SNP chips could be developed for the evaluation of variants in genes of specific metabolic pathways. This information is required for the success of molecular epidemiologic studies of cancer risk, progression, prognosis, and natural history.

Novel study design and statistical analytic methods are needed to identify patterns fusing

large data sets (i.e., many genotypes and epidemiologic risk factors on large numbers of individuals) and evaluate the complex interactions of these factors in epidemiologic studies. Novel methods for data mining, for the purposes of genera ting hypotheses and distilling large data sets to identify relevant factors that can be evaluated in traditional hypothesis-testing approaches, need to be translated into studies of genotype-environment interactions.

Priority 3: *Define the environmentally related molecular profile (e.g., altered gene expression or DNA damage after exposure to a carcinogen) of gynecologic tumors to identify the following:*

- Heterogeneity in disease that can be used to focus studies of genotype-environment interactions
- Homogeneous subtypes of disease for improved assessment and clinical outcome
- Patterns of disease progression

Rationale

Gene expression profiling studies in breast cancers from women with *BRCA1* or *BRCA2* mutations have proven that distinct molecular pathways exist in histologically indistinguishable tumors. It has become evident that there is a need to classify tumors with a resolution that is greater than that possible using conventional histo-pathology. By subclassifying gynecologic tumors, it should be possible to understand the interaction between specific gene or environmental effects and tumor behavior. Furthermore, elucidation of the genotypic progression that underlies phenotypic progression will provide opportunities for the development of new diagnostics and approaches to treatment.

BARRIERS

Most early endometrial and cervical carcinomas are treated by general-practice gynecologists. As a consequence, key tissue resources for the study of both genetic and environmental factors contributing to cancer risk cannot easily be acquired for investigation. Methods for fixation of tissues that can be used in a routine clinical setting are lacking. Furthermore, key epidemiologic data are unlikely to be collected in the generalist's practice.

Available approaches are limited for appropriate study design and statistical analysis of complex genotype-environment interaction data. In addition, there has been little support for methodologic research to address these issues in gynecologic cancers.

RESOURCES CURRENTLY AVAILABLE

Genomic Resources

The draft sequence of the Human Genome and the wealth of information on polymorphism provide opportunities for unraveling how the genome and environment interact in tumorigenesis. Methods for detecting genetic variations among individuals, tumor cells, and populations are evolving rapidly. Targeted resequencing of moderate-to-large–sized genomic intervals of interest is likely to become feasible in the near future.

Methods for Genetic Epidemiology Studies

Genetic epidemiology methods are being developed that take into consideration both genetic and environmental factors. The science of data mining for the purposes of generating hypotheses (artificial intelligence, neural network, and other novel analytic approaches) is evolving rapidly. Expression

array studies have already distilled large data sets to identify relevant factors that can be evaluated in traditional hypothesis-testing approaches.

PATIENT SPECIMENS AND MODELS FOR INVESTIGATION OF GENOME-ENVIRONMENT INTERACTIONS

Several existing *in vivo* and *in vitro* models for gynecologic malignancies can be exploited to further our understanding of how the environment and genome interact in tumorigenesis. Mouse HPV models (transgenic and cell culture) for cervical carcinoma have been devised, as have a variety of other cell culture systems. Endometrial cancer models for genetic factors contributing to disease risk have already been developed (phosphatase and tension homologue [*PTEN*] gene and DNA mismatch repair knockouts), as have hormonal models (estrogenic tumor promotion). A wide variety of ovarian cancer cell lines have been established and extensively characterized. Mouse models of ovarian carcinoma are being developed through the NCI-funded Mouse Models for Cancer Consortium. Systems for culture and manipulation of primary ovarian epithelium are well established.

The human tissues available for investigation represent a major resource for studies to determine how environmental and genetic factors interact in tumor initiation and progression. Histologically recognizable precancerous precursors for endometrial and cervical carcinoma are accessible for study. These provide unique opportunities to define the earliest signatures of cancer and the molecular fingerprints that the environment leaves on the cell. Populations of women with cancers are already being assembled by Cancer Cooperative Groups such as the NCI-sponsored Gynecologic Oncology Group.

RESOURCES NEEDED

To maximize the potential for success of the recommended research priorities, a number of resources should be put in place. In addition to the resources specified in Priorities 1 and 2, collaborative research groups or consortia are needed to allow the substantive interaction of genetic and environmental epidemiologists in studies of genotype-environment interactions in the etiology of gynecologic cancers.

OPPORTUNITIES

Several unique research opportunities exist in gynecologic malignancies. In cervical and endometrial cancer, there are recognized potent environmental risk factors, such as HPV in cervical cancer and estrogenic exposure in endometrial cancer. In both cervical and endometrial cancer, there are histologically recognizable precancerous lesions. These early lesions progress to cancer in only a fraction of women. Identifying and characterizing the factors that are associated with disease progression will provide insights into early events in tumorigenesis. With this understanding will come opportunities to prevent disease, halt progression, and identify those women who will benefit most from interventions and those for whom minimal intervention is required. The ability to distinguish high- and low-risk precancerous changes will translate to a reduction in costs for continued follow-up and care and reduce the burden of "cancer concerns" for women who have abnormal Pap smears, abnormal uterine bleeding, or other potential indications of cancerous or precancerous changes.

Several opportunities also exist for synergy in gynecologic cancer research. The histologic and biologic similarities in endometrioid ovarian and endometrial cancers and in serous ovarian and endometrial cancers suggest disruption of common pathways.

Access to precancerous endometrial and cervical lesions presents a unique opportunity for progress in understanding the interaction between genetic and environmental factors in the genesis of solid tumors.

Imaging

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BACKGROUND: STATE OF THE SCIENCE

Over the last two decades, the imaging sciences have made remarkable advances in technology for visualizing tissue structure and function. Novel imaging paradigms are being developed to provide noninvasive assessments of tissue (tumor) at cellular or molecular levels. Imaging modalities of the future are centered on the molecular differences between cancer cells and normal cells.

These new approaches will facilitate early cancer detection and allow anatomic and biologic cancer staging. It will assist in the goal to design and implement evidence-based, risk-adjusted, and patient-specific therapy. These developments also will provide new and exciting opportunities to assess signal transduction pathways targeted by specific antitumor drugs. For example, patients may be selected for a particular drug therapy on the basis of imaging prior to drug administration, and drug effects could be monitored by measuring specific protein-protein interactions, signal transduction, or metabolic pathways. In this way, new end-points for monitoring drug response could be developed.

Physicians and scientists could benefit from quantitative methods for identifying partial and complete response. These would serve as endpoints to act as a credible surrogate for survival in clinical trials. Another aspect of the molecular imaging effort is the ability to use reporter constructs to monitor gene therapy. For example, it is now possible to monitor the distribution, concentration, and persistence of viral vectors and the level of therapeutic transgene expression by using reporter constructs and noninvasive imaging techniques. We therefore have an opportunity to develop nomograms for specific patient-based individual therapies.

In imaging, as elsewhere in cancer research, animal models of cancer are making it possible to perform certain kinds of studies that are difficult if not impossible to perform in humans. In addition to learning more about cancer and development of animal tumor models, research with animal models will facilitate improvements and developments in imaging technology that eventually can be applied to clinical cancer care.

A distinct advantage of noninvasive imaging in animal models of cancer is the ability to perform repetitive, noninvasive observa tions of the biologic processes underlying cancer growth and development without sacrificing the animal. Furthermore, the level of resolution with small-animal-imaging modalities is now approaching the size of individual cells. Imaging in animals can also help assess the effectiveness of new instruments and therapeutic technologies, such as radiation therapy and directed drug therapies. Animal models are critical in

providing insights that cannot be obtained from humans because of practical or ethical considerations. Imaging provides a parallel modality (in conjunction with biopsy and tissue assay) for obtaining information from human subjects and animal models, and this dual approach can be rigorously applied. Based on the current potential in imaging, and in synergy with cancer research developments, two research priorities for dramatic differences in cancer are put forward: imaging tumor biology and genetics, and developing imaging biomarkers for prediction and assessment of treatment response, and even toxicity.

RESEARCH PRIORITIES

Priority 1: *Imaging of tumor biology and genetic signatures.*

Rationale

Using imaging, it is possible to define a signature of cancer cells. Parameters that can be quantified include angiogenesis, hypoxia, apoptosis, receptors, tumor growth kinetics, and pharmacokinetics. Imaging can also define the phenotypic heterogeneity of tumors.

Site-specific techniques for cancers of the ovary, cervix, and endometrium must be developed. These advances will allow the early detection and characterization of tumors. Surrogate markers that are important in the development of treatment regimens will be evaluated for proof of principle, proof of biologic target, toxicity, and tumor response. An example of functional imaging of gynecologic cancers involves steroid hormone receptors. Estrogen and progesterone receptors are overexpressed in many endometrial and cervical cancers. Positron emission tomography (PET) imaging with ^{18}F-labeled estradiol has been studied in breast cancer and holds great promise in endometrial cancer for tumor detection and to guide appropriate therapy. PET will permit the determination of receptor status of all disease, rather than the limited tissue available by biopsy. Similar agents to quantify levels of various growth factors are under development.

Priority 2: *Imaging biomarkers for predicting and assessing therapeutic response.*

Rationale

The technologies developed and validated under Priority 2 can be used in planning individual patient treatment protocols as well as in clinical trials involving new drugs. The latter will involve both agents aimed at the biologic target as well as surrogate markers. These technologies will allow the determination of endpoints in a very short time in all areas discussed. Specifically, imaging will assist in the following:

- Design of individual treatment
- Early assessment of treatment efficacy
- Implementation of surrogate endpoints in clinical trials
- Drug development and response

BARRIERS

Modern molecular imaging involves interdisciplinary science. It depends on building and sustaining a strong research infrastructure. It should promote and practice science without the traditional specialty-driven walls of medicine. A lack of trained imaging scientists in key scientific areas (e.g., physician scientists, cellular and molecular biologists, chemists, physicists, mathematicians, and engineers) is a major barrier to the widespread application of modern molecular imaging technology.

Imaging discoveries and developments are driven by both technology and biology. Technology of modern imaging (nuclear magnetic resonance, ultrasound, and optical) is rapidly developing. Cancer-specific contrast media are emerging as well. Understanding the potentials and limitations of each technology is essential for their proper utilization. Furthermore, the lack of standardization in the evaluation of modern imaging techniques is yet another barrier. All new techniques must be validated and standardized prior to their widespread implementation and dissemination.

RESOURCES

An infrastructure including facilities, equipment, and personnel in imaging science is needed. We recommend the following:

- Establish imaging centers of excellence for laboratory and clinical research.
- Ensure supplemental funding for translational research in imaging.
- Train new generations of imaging scientists knowledgeable in the biology and technology of imaging.
- *Bioinformatics*—Develop and support research-oriented PACS (patient archiving and communication system) for image data management, analysis, and application of new computer-driven technical advances such as image fusion to allow "biological tumor volume," three-dimensional assessment of tumor extent, and automatic tumor volume measurement for monitoring treatment response.

Tumor Biology, Hormone Receptors, Epithelial-Stromal Interactions, and Early Activation

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BACKGROUND: STATE OF THE SCIENCE

The endometrium, ovary, and cervix are hormone-responsive sites within the female reproductive tract. The link between estrogen-induced proliferation and progesterone-induced differentiation is well established in the malignant and non-malignant endometrium. Newer findings relating to the protective effects of oral contraceptives on the risk of developing ovarian cancer suggest that progesterone may inhibit carcinogenesis, and provocative but preliminary studies in cervical cancer support a role for hormones in the regulation of human papillomavirus (HPV). Although hormonal regulation is initiated via ligand binding to specific receptors that have been appropriately assembled, it is the subsequent interaction with coregulators and the transcriptional machinery that results in the desired corresponding hormone effect.

The microenvironment within which malignant transformation occurs is complex and poorly understood. When significant alterations occur, a preneoplastic lesion or malignant transformation results. Our understanding of the etiologic processes resulting in transformation within all gynecologic tissue sites is limited, and studies to address this scarcity are urgently needed.

Although the majority of endometrial cancers are hormone dependent, some become resistant, and our current knowledge regarding their uncontrolled growth, invasion, and metastasis is incomplete. Evidence from breast cancer research suggests that alterations in hormone receptor isoform expression, assembly, modulation, and/or degradation may be predisposing etiologic factors. Furthermore, the altered hormonal milieu appears to activate growth factor pathways.

In contrast, hormone-independent tumors appear to harbor constitutively activated growth factor pathways. Our knowledge of the molecular interactions, or "cross-talk," among hormones, specific growth factors, hormone and/or growth factor receptors, coregulators, and other modulators of the physiologic processes requires expansion. The complexity of the interactions in both hormone-dependent and -independent tumors is magnified by the important, but poorly understood, interdependence of the stroma and the epithelium. The origin of the abnormal over- or under-expression of hormones and/or growth factor in the microenvironment is presumed to be the

result of epithelial-stromal interactions. For example, in the endometrium, abnormalities in the surrounding stroma are associated with endometriosis and possibly with early events in epithelial carcinogenesis, but this is an area of tumor biology that is essentially unexplored.

Challenges and questions include the following:

- What are the etiologic events that result in the transformation of hormone-dependent tumors?
- What are the identifiable molecular events in hormone-independent tumors?
- What are the molecular mechanisms facilitating the interactions and synergy between hormones and growth factors and their corresponding receptors?
- What are the etiologic and maintenance factors that are localized to the various histologic compartments and their specific roles in carcinogenesis in the female reproductive tract?
- What are the alterations in the hormone receptors, growth factors and their respective receptors, and epithelial-stromal interactions as a function of aging, ethnicity, body mass index, and tissue variables, as well as biologic processes including puberty, pregnancy, and menopause and exposures to commonly used pharmacologic agents, including oral contraceptives, hormone replacement therapy (HRT), and selective estrogen receptor modulators (SERMs)?

RESEARCH PRIORITIES

Priority 1: *Elucidate the role of stromal-epithelial interactions in transformation, tumor growth, and invasion.*

- Evaluate the activity of enzymes such as aromatases, 17-beta-HSD (hydroxysteriod dehydrogenase), and sulfatases that potentially influence the hormone levels in the microenvironment.
- Address the stromal versus epithelial regulatory influence on growth, invasion, and metastasis by growth factors including members of the epidermal growth factor, tumor growth factor-alpha, and insulin-like growth factor families as well as angiogenic factors and proteases.
- Evaluate the effects of selective hormone modulators (selective estrogen receptor modulators, selective progesterone receptor modulators [SPRMs], etc.), as well as hormones used for oral contraception or HRT, on the epithelium as well as the stroma.

Rationale

The interactions between the hormonally responsive stroma and epithelium in the uterus, ovary, and cervix are not well understood. The stroma may be a major target of hormones and may in turn affect the epithelium. Previous studies have examined tumors and/or cells in isolation without considering the microenvironment. New data suggest that an abnormal microenvironment may predispose to transformation, uncontrolled growth, and invasion. Information in this area will illuminate the etiology of reproductive tumors and will ultimately contribute to novel chemoprevention and early detection strategies.

Aromatase inhibitors, growth factors, proteases, and angiogenic factors must all be examined in the context of stromal-epithelial interactions. Questions to be answered include the following:

- Are there ethnic differences in expression?

- What are the differences between normal and malignant tissue expression?

- What are the effects of aging?

Priority 2: *Understand hormone receptor expression, assembly, degradation, and modulation.*

- Evaluate the expression of hormone receptors and their isoforms in malignant and non-malignant reproductive tissues, including tumor subtypes such as endometrioid, papillary serous, and clear cell.

- Address hormone receptor induction and down-regulation by multiple mechanisms, including transcriptional regulation, translation, and post-translational modification and degradation.

- Determine the effects of hormone receptor co-modulators on receptor function.

- Evaluate the genes induced by hormones through their receptors and receptor isoforms.

- Investigate receptor complex assembly on DNA and chromatin remodeling in response to hormone agonists and antagonists.

Rationale

Tumors of the female reproductive tract are hormonally regulated, and steroid hormones act through receptors. Despite much research in breast cancer, little is known about hormone receptor expression, assembly, degradation, and modulation in response to co-activators, co-repressors, or hormone agonists and antagonists. The understanding of receptor isoforms is key to this priority.

Priority 3: *Improve understanding of the interactions among hormones, hormone receptors, growth factors, and growth factor receptors.*

- Integrate multiple pathways to cell growth: determine the points of cross-talk between steroid hormones and their receptors and other pathways to cell growth, including growth factors and growth factor receptors.

- Determine links between hormones and factors that promote tissue invasion by stimulating angiogenesis and cancer cell morphogenesis.

- Investigate the link between constitutive activation of growth factors and the development of hormone-independent tumor growth.

- Study the clinical as well as the basic science aspects of new therapeutic agents to block growth factor receptors on cell growth and tumor hormone dependence.

Rationale

Multiple pathways drive tumor cell growth. Hormone-dependent tumors rely on hormones to drive growth, which in turn activate growth factor pathways. Hormone-independent tumors may be characterized by the constitutive activation of one or more components of a growth factor pathway, such as her-2-neu or epidermal growth factor receptors. New data suggest that the loss of hormone receptors and growth factor activation may be linked. Cross-talk between these pathways should be studied to provide a more complete understanding of cancer cell growth. In addition, the availability of new molecules to block growth factor pathways may have relevance for the management of gynecologic tumors. This area of research may lead to the use of molecules such as

tyrosine kinase inhibitors to restore hormone dependence and facilitate treatment.

BARRIERS

- *Tissue resources:* Lack of tissue for use in tumor biology studies, specifically normal and adequate tumor specimens. With regard to the latter, the availability of the less common tumor types (e.g., clear cell, serous, tamoxifen-associated) is critical.

- *Informed consent:* The increasing difficulty in securing informed consent resulting from extramural mandates is an ever-increasing challenge in accessing specimens for biomedical research.

- *Challenges regarding patient accrual to clinical/translational trials:* Only a small proportion of women with gynecologic malignancies participates in clinical trials. This may be due to resistance on the part of the patient or the referring physician or to the lack of dissemination of information on the availability of experimental therapies.

- There are limitations pertaining to the availability of reliable tools for assaying receptor isoforms, phosphorylation sites, etc.

- Challenges regarding technology and methods for the investigation of the epithelial and stromal interactions and the validation of these investigation tools.

- Appropriate reagents, and protocols for their application, to identify hormone receptor isoforms and other molecules of interest should be rigorously tested and standardized for widespread research and clinical use. For example, the currently available antibodies purported to recognize receptor isoforms may be nonspecific.

- The rapid institution of exploratory clinical trials in gynecologic malignancy is hampered by the lack of multi-center consortiums that (1) have an interest in novel therapies and translational investigations and (2) can act quickly to institute studies.

RESOURCES

- Advocates are a key resource to help educate the patient community about the importance of entering clinical trials and donating surgical tissue for future research. They may also help to increase acceptance of new methods of treatment in clinical trials, such as the need for serial biopsies.

- Multi-center groups, such as the Gynecologic Oncology Group (GOG), are important resources that allow clinical trials to be carried out in patients with relatively infrequent tumor types. In addition, new consortium groups should be established to promote multi-center trials using novel or exploratory therapies that do not fall within the purview of GOG.

- Existing tissue collection facilities within the GOG and the National Cancer Institute are useful but should be expanded.

Angiogenesis, Metastasis, and Growth Signaling

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ANGIOGENESIS

BACKGROUND

The process of angiogenesis is critical to tumor formation and metastatic spread. In addition, angiogenic growth factors contribute to the unique biology of gynecologic cancers (e.g. ascites development). New blood vessel formation is required as the primary tumor grows and spreads. The molecular definition of angiogenesis is evolving, with new targets identified and agents characterized that can interact with them. Unfortunately, the heterogeneity of vessels, the complexity of the process, and all of the targets have yet to be defined.

ANGIOGENESIS RESEARCH PRIORITIES

Priority 1: *Develop better* in vivo *and* in vitro *models that will demonstrate all elements of angiogenesis in use in preclinical drug development.*

Relevant Questions

- Which angiogenic regulators are important in gynecologic tumors?
- Can *in vivo* and *in vitro* models be used to prioritize known anti-angiogenic compounds for clinical trials?

Rationale

Angiogenesis is a critical process in the oncogenesis of gynecologic cancers. It provides a unique target for agents that would be non-cross-resistant with traditional drugs. The development, validation, and widespread availability of models in which to test these agents would facilitate drug development and prioritization.

Priority 2: *Characterize vessel biology and delineate the molecular basis for vessel heterogeneity. Identify and characterize novel angiogenesis genes.*

Relevant Questions

- What is the normal state of vessel biology and how is it hormonally regulated?
- What dictates vessel heterogeneity and regional differences in vessels? What is the functional/biologic significance of these differences?
- What is the effect of the microenvironment on vessel growth and development?
- Can genomics/proteomics approaches be used to identify and characterize novel angiogenesis genes and delineate the molecular basis for vessel heterogeneity?

Rationale

The basic biology of tumor versus that of normal blood vessels remains unknown. To effectively identify and use new anti-angiogenesis agents, we need to better understand the overall biology of angiogenesis. Emerging data have demonstrated a surprising amount of vessel heterogeneity. This finding has dramatic implications for the role of blood vessels in tumor formation and the development anti-angiogenesis agents. Further, an understanding of this heterogeneity will be important for predicting response.

Priority 3: *Develop better methodologies for the clinical analysis and prioritization of anti-angiogenesis agents.*

Relevant Questions

- How can we encourage the use of angiogenesis inhibitors in phase I trials of gynecologic cancers?
- Can we take advantage of new imaging technologies to assess endpoints?

Rationale

Angiogenesis provides a unique target for agents that would be non-cross-resistant with traditional drugs. However, among the major problems in the field of anti-angiogenesis are the large numbers of emerging agents, the small numbers of patients, and the limited ways in which these can be prioritized. More extensive preclinical testing and better biologic endpoints in clinical trials would assist in prioritizing these agents.

RESOURCES

- Appropriate animal models to explore the basic science of angiogenesis and to screen for agents that inhibit this process
- Carefully obtained and processed normal and malignant tissues to characterize the process of angiogenesis
- Validated biomarkers for each molecular element involved within the process of angiogenesis

BARRIERS

- A lack of understanding of the basic biology of anti-angiogenesis
- Limited resources to make clinical-grade materials
- Minimal preclinical models and clinical trials with relevant biologic endpoints to prioritize new agents

METASTASIS

BACKGROUND

The subject of this Progress Review Group is three very distinct organ sites, each with unique aspects. This discussion focuses primarily on general problems in metastasis research in gynecologic malignancies. The vast majority of patient mortality is attributed to metastatic disease. Therefore, a more detailed understanding of the factors that initiate, promote, or ultimately prevent metastasis will have an immediate and significant clinical impact.

A major goal of metastasis research is to elucidate key factors of tumor biology and their relationship to metastatic progression and dissemination. This approach may ultimately yield new treatments for metastatic disease. Cancer of the endometrium and of the cervix each account for 6 percent of all cancers in women in the United States. Most cervical cancers are associated with HPV infection, and the majority (> 90 percent) can be detected through use of the Pap smear.

In contrast, ovarian carcinoma, the fifth most frequent cause of cancer death in women, is so resistant to early detection that the majority of patients are diagnosed with advanced disease. This results in a mortality rate that is approximately 65 percent of the incidence rate.

Mechanisms of metastasis are likely to differ in ovarian cancer, in which metastatic dissemination is commonly via local shedding into the peritoneum, followed by peritoneal implantation, invasion, and growth.

METASTASIS RESEARCH PRIORITIES

Priority 1: *Develop and validate model systems to promote understanding of metastatic disease. Develop, validate, and widely disseminate cell culture, co-culture, and organ culture models as well as transgenic and knock-out animal models.*

Relevant Questions

- Can we develop and validate whole-animal model systems that more accurately mimic tumor biology? Does tumor biology differ in the context of the affected tissue? To answer these questions requires orthotopic models.

- Can the appropriate and specific promoters be identified for use in a transgenic approach to induce organ-specific expression (or lack thereof) of specific genes thought to be relevant in metastasis?

- Can these models be exploited for testing the efficacy of novel therapeutic agents?

- Can cell lines be generated from normal, premalignant, and cancerous gynecologic tumors and widely disseminated for study in multiple laboratories?

- What are the appropriate organ-specific co-culture or organ culture systems? How can these be validated?

Rationale

The vast majority of patient mortality from gynecologic cancer is attributable to metastatic dissemination, yet we currently possess a limited understanding of the molecular, cellular, tissue, and organ level of the factors that initiate, promote, and ultimately prevent metastasis. This knowledge is essential for the develop ment of novel therapeutic approaches for treatment and prevention of metastatic disease. Although early detection of gynecologic cancer is a priority area, in the absence of effective early detection strategies, effective treatments for metastatic disease will ultimately impact favorably on patient mortality.

Priority 2: *Characterize the basic biology of normal, cancerous, and metastatic tissues.*

Relevant Questions

- What biochemical and molecular interactions are important for normal tissue development during organogenesis, morphogenesis, and differentiation? What genes control this process and how does transcriptional/translational activation of these genes differ in the primary tumor and metastases? Relevant animal models that accurately recapitulate the disease process are essential here.

- What is the basic cell and molecular biology of the normal organ, with particular emphasis on events that induce or control neoplastic progression to the malignant and ultimately metastatic phenotype? Is there a defined precursor lesion? Relevant animal models that accurately recapitulate the disease process are essential here.

- Do the molecules that participate in epithelial-stromal interactions vary in the normal organ relative to the primary tumor or metastatic lesion? Does this cause differential activation of specific and identifiable signaling pathways?

- How can emerging technologies in genomics and proteomics be best applied to the problem of metastatic disease? Are the appropriate normal, primary, and metastatic tissue specimens widely available? Is there sufficient bioinformatics support?

Rationale

In gynecologic cancer our understanding of tumor biology is limited in large measure by a lack of detailed information about normal tissue development, organogenesis, morphogenesis, and differentiation. This in turn hampers efforts to identify aspects of aberrant patterns of growth in tumors and metastatic lesions. Evaluation of cell signaling and loss of growth control, normal epithelial-stromal interactions, develop ment of cancerous lesions (i.e., whether there is a defined precursor), and genomics/ proteomics-based analysis of normal, pre-malignant, and malignant cells should be encouraged.

Priority 3: *Identify and characterize molecular targets unique to metastatic cells.*

Relevant Questions

- What specific molecules or groups of molecules control localized invasion, migration, and metastasis? Relevant animal and culture models are essential here.

- How do cell-matrix and cell-cell (epithelial-epithelial, epithelial-stromal, or epithelialendothelial) interactions contribute to metastasis? What are the relevant signaling pathways activated by these interactions and how do they differ from those in normal cells?

- How are metastatic cells disseminated? Addressing this question requires consideration of intravasation as well as lymph node metastasis. Ovarian cancer is unique here in that dissemination takes place predominantly via direct extension into the peritoneal cavity, indicating a distinct set of problems to address.

- Are there specific changes in cytoskeletal architecture that enhance the "flexibility" or "deformability" of tumor cells relative to normal epithelium? This question requires investigators with experience in cellular biophysics to apply their expertise to gynecologic malignancies.

- How does proteolytic activity contribute to migration and invasion? What are the target substrates in the stroma and on the cell surface?

Rationale

Metastatic cells represent a distinct sub-population of tumor cells with the ability to escape the primary tumor and establish a secondary lesion. The cellular properties that distinguish metastatically competent cells from other cells in the tumor must be identified. These attributes may represent novel targets for therapeutic intervention. It should be re-emphasized that the majority of deaths from gynecological malignancies are directly attributable to metastatic disease, such that identification of molecular targets unique to metastatic cells may have immediate therapeutic impact.

BARRIERS

Based on 1999 statistics from the National Cancer Institute (NCI) and the American Cancer Society, more than 75,000 gynecologic cancers were diagnosed in 1999 and over 25,000 women died from these diseases. The majority of these deaths are directly attributable to metastatic disease. However, a significant barrier to progress in this area becomes apparent upon analysis of the NCI Cancer Research Portfolio (researchportfolio.cancer.gov). These data demonstrate that less than 3 percent of the total funding allocated to the study of gynecologic cancers is used directly for metastasis research.

Cancer Type	No. of Funded Projects	No. of Metastasis Projects[a]
Cervical	455	7[b]
Endometrial	207	3[c]
Ovarian	575	16[d]

[a]Obtained from a search combining the terms *cancer type* and *metastasis*
[b]Two R01 and five P30 Center Grants
[c]Three P30 grants
[d]Six R01, six P30, and two Z01 grants

RESOURCES

- A review of the Glossary of Select NCI Initiatives indicates that funding mechanisms are in place to support animal model development and genomics/proteomics. A pool of these funds should be earmarked specifically for development of relevant metastasis models for gynecologic cancers, and investigators should be encouraged to apply to these mechanisms for studies of gynecologic malignancies.

- There are no apparent funding mechanisms specifically for metastasis research. The NCI is strongly encouraged to supply targeted funding for metastasis research in general and for gynecologic malignancies specifically.

- New funding mechanisms should be added to promote cross-disciplinary research and to attract new investigators in other important areas of biology (e.g., developmental biology/organogenesis, cellular biophysics) to focus on these gynecologic cancer models. In particular, an increased understanding of the cell, molecular, and developmental biology of the normal organ is a necessary prerequisite for comparative studies of malignant and metastatic tissues.

GROWTH SIGNALING

BACKGROUND

Three decades of molecular biologic discovery culminating in the recent genomic revolution has identified a complex network of signal transduction pathways, which are critical for the growth, differentiation, and survival of normal and malignant cells. These pathways involve a myriad of proteins, including growth factor receptors and their ligands, intracellular signal transduction molecules such as kinases and phosphatases, and downstream transcription factors. These signaling pathways are most certainly tissue and tumor specific and are modulated by both micro- and macro-environmental influences such as the stroma and treatment modalities. This complex, dynamic signaling network will provide clues to the etiologies of cancer, sensitivity to treatment modalities, and malignant aggressiveness. Further, understanding these pathways will provide an outstanding opportunity for the identification of novel target molecules, which can be then utilized for the development of unique therapeutic agents.

Unfortunately, signaling pathways in gynecologic cancers and their normal

tissue counterpart remain essentially uncharacterized. Many pathways that have been well characterized in other tumors have not been investigated in gynecologic cancers. Further, the potential for unique signaling pathways within gynecologic cancers remains a real possibility.

GROWTH SIGNALING PRIORITIES

Priority 1: *Define signaling pathways that regulate growth and survival in normal and malignant gynecologic tissues and validate them in appropriate animal models.*

Rationale

The signal transduction pathways in gynecologic cancers remain essentially unknown. Their elucidation and characterization will provide the following:

- Outstanding targets for small molecules, which can modulate their activity. These agents will be ideal potential chemotherapeutic and chemopreventive drugs.
- Provide important information concerning the etiology of these cancers.

Priority 2: *Redesign each early clinical trial to efficiently assess a large number of small molecules in a limited pool of patients.*

Rationale

Many small molecules that affect signal transduction pathways will become available in the near future. It is reasonable to predict that these new agents will rapidly overwhelm the present preclinical and clinical trial design. To assess their clinical efficacy, a streamlined trial design will be needed to rapidly and efficiently determine the activity of these agents.

Priority 3: *Identify the molecular signatures of specific signaling pathways that have been shown to be dysregulated in gynecologic cancer.*

Rationale

To determine the precise elements of a signaling pathway, laboratory-based approaches will be required to manipulate a single pathway in a controlled fashion and examine its downstream effects by use of genomic analysis. This cataloguing of pathways in different gynecologic tissues will be a powerful database that will serve to further identify potential molecular targets, create potential screening assays for drug development, and help interpret genomic analyses of gynecologic tissues.

BARRIERS

- Scarcity of data concerning the signaling networks within gynecologic cancers
- A complete lack of knowledge of signaling pathways in normal gynecologic tissues
- Inadequate supplies of appropriate tissue specimens
- Lack of smooth and efficient transfer of knowledge and reagents between industry and academics
- Lack of appropriate *in vitro* and *in vivo* (animal) models

RESOURCES

- Tissue banks utilizing appropriate tissue processing. There is a need for carefully selected, removed, and frozen specimens, which can be used for phosphoprotein, enzymatic, and protein analysis.

- Appropriate *in vivo* and *in vitro* models for screening and validation of pathways and small molecule inhibitors
- Strong and close industrial-academic collaborations will be needed to efficiently develop effective drugs for newly identified molecular targets.
- Redesigned clinical trials would allow for the testing of large numbers of small molecules in small numbers of patients with biologic endpoints.
- Well-tested, validated, and broadly applicable genomic techniques.

Early Detection, Screening, and Prevention

Co-Chairs: Andrew Berchuck and Beth Y. Karlan

Participants:

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BACKGROUND

Both screening/early detection and prevention approaches were successfully employed to reduce cancer mortality in the 20th century. Most cancers for which screening has an impact on mortality (e.g., cervical and colorectal cancers) are relatively common and have a well-defined preinvasive lesion, and screening efforts focus on detection and eradication of these precursors. Easy accessibility of the target organ is another characteristic of cancers (e.g., cervical and breast cancers) in which screening and early detection programs have been successful, as this facilitates identification of preinvasive and early invasive changes. Pap smear screening has dramatically reduced cervical cancer mortality and serves as a paradigm for the potential efficacy of this approach.

The enormous potential impact of preventive approaches in controlling cancer mortality also has been clearly demonstrated. Elimination of nitrates as food preservatives with the introduction of refrigeration in this country led to a large decrease in the incidence of stomach cancer. Likewise, the striking relationship between tobacco use and lung, head, and neck cancers is now well known. In these cancers prevention can be accomplished by avoidance of identifiable exogenous carcinogens.

The potential for development or improvement of screening/early detection or prevention strategies for gynecologic cancers is discussed in the following sections.

OVARIAN CANCER

In 2001, about 23,400 new cases of ovarian cancer will be diagnosed in the United States, and about 13,900 of affected women will die of their disease. Some ovarian cancers are detected at an early stage, when cures are easily achieved, but too often these cancers do not produce alarming symptoms while still confined to the ovaries, and extensive intraperitoneal metastases are found at diagnosis. Although debulking surgery and platin-paclitaxel chemotherapy substantially increase median survival, few women with advanced disease are cured. Active new cytotoxic agents may further extend survival, but treatment of these cancers at the point when there is an enormous tumor burden may not be the most effective approach to decreasing ovarian cancer mortality.

Screening and early detection represents a promising strategy for decreasing ovarian cancer mortality, because 90 percent of ovarian cancers confined to the ovary can be

cured. Significant obstacles to early detection exist, however. The ovaries are small, relatively inaccessible organs that lie in the peritoneal cavity, and most masses that arise in the ovaries are not malignant or even premalignant. The preinvasive lesion that precedes the development of ovarian cancer remains unknown. Transvaginal ultrasound and the CA-125 blood test have been explored as potential tests for the early detection of ovarian cancer, but both suffer from less than acceptable sensitivity and specificity. For example, most ovarian masses detected by ultrasound are not malignant, and about 3 percent of healthy postmenopausal women have an elevated CA-125 level. Although the ability of these tests to decrease ovarian cancer mortality is under evaluation in large population-based studies, existing data suggest that further refinement will be needed to create a cost-effective screening procedure. Because the disease is uncommon, a cost-effective program will require either a very accurate screening method or a method of triaging women by risk or both. Further research efforts on both aspects are needed. In particular, gene arrays and other techniques that allow global analyses of expression patterns have the potential to identify markers of stage I disease that could greatly facilitate early detection. A Gail-type model for ovarian cancer could be useful for both efficient trial designs and implementation of screening programs.

In view of the formidable obstacles to treatment and early detection, prevention of ovarian cancer should be seriously considered as a means of decreasing mortality. Epidemiologic studies have shown that oral contraceptive use and pregnancy are associated with marked decreases in ovarian cancer incidence. Use of the pill for 5 years or having 3 children reduces the risk of ovarian cancer by about 50 percent. This may be attributable to reduction of the numbers of lifetime ovulatory cycles, but there is also evidence that the progestagenic milieu of oral contraceptives and pregnancy may have a direct preventive effect by inducing apoptosis in the ovarian epithelium. This suggests the potential for development of chemo-prevention strategies that could have a significant impact on ovarian cancer mortality. In addition, tubal ligation and hysterectomy significantly reduce risk, perhaps due to interruption of access of potential carcinogens via the genital tract, and this also presents an opportunity for risk reduction. Again, the low ovarian cancer incidence rates make direct assessment of prevention strategies difficult and costly. The lack of surrogate endpoints and well-characterized animal models represent significant barriers for intermediate testing of these approaches.

ENDOMETRIAL CANCER

About 35,000 new cases of endometrial cancer are diagnosed annually in the United States, and most are confined to the uterus and can be cured surgically. About 5 percent of endometrial cancers have a hereditary basis and occur due to inherited mutations in one of the DNA mismatch repair genes in the context of hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Sporadic endometrial cancers have been characterized as type I or type II based on etiologic, pathologic, and, more recently, molecular features. Type I cancers are more frequent, particularly in whites, and arise due to unopposed estrogenic stimulation of the endometrium. Endometrial hyperplasia has been shown to represent a precursor of type I endometrial cancers, and these premalignant lesions can be targeted for screening (tissue biopsy) and prevention (progestin) strategies. The source of un-opposed estrogen in type I cases may be endogenous (obesity, nulliparity) or exogenous (hormone replacement, tamoxifen). These cancers usually are

well-differentiated, diploid, endometrioid, early-stage lesions that frequently exhibit mutations in the phosphatase and tension homologue (*PTEN*) tumor suppressor gene. Type II cancers are not associated with unopposed estrogen and usually are poorly differentiated, aneuploid, and non-endometrioid (serous, clear cell); have alterations in genes associated with virulent behavior (*p53*, *HER-2*/*neu*); and often present at an advanced stage. African Americans more often have type II cancers, and their survival is significantly worse than that of whites.

Most endometrial cancers occur in postmenopausal women and are heralded by vaginal bleeding, which leads to early diagnosis by endometrial biopsy. It has been demonstrated that combination oral contraceptives and the addition of progestins to postmenopausal estrogen replacement therapy reduce risk, and this approach could be exploited to further reduce mortality of type I estrogen-dependent cancers. Further improvements in early detection, particularly for type II cancers, could be facilitated by the ease of access to the endometrial cavity if early markers of malignant transformation were identified.

CERVICAL CANCER

Cervical cancer previously was one of the leading causes of cancer deaths in women in the United States, and this remains the case in most nonindustrialized countries. The peak incidence of cervical cancer occurs at about 40 years, and women who die of this disease often leave behind dependent children. Sexually transmitted high-risk strains of human papillomavirus (HPV) have been shown to represent the etiologic agents that are mainly responsible for the development of these cancers; however, other cofactors, such as smoking and immune function, also have been identified. In industrialized nations, Pap smear screening has dramatically reduced cervical cancer mortality. The ease of accessibility of the cervix and the ability to diagnose and ablate preinvasive lesions have been critical factors in the success of cervical cancer screening. Most of the residual burden of cervical cancer mortality in the United States is attributable to women who are not screened, but in some cases conventional Pap smears fail to detect disease at a preinvasive or early invasive stage. A number of new approaches are emerging that could further decrease cervical cancer deaths, including HPV testing, thin-layer Pap smear cytology, new cervical imaging methods, chemopreventive agents, and vaccines. A major challenge will be to determine the most effective means of employing these new approaches to reach the goal of eradicating cervical cancer. These methods could also be used to address more economically the management of women with low-grade cervical intraepithelial neoplasia (CIN) and atypical squamous cells of undetermined significance (ASCUS).

RESEARCH PRIORITIES

Priority 1: *Define populations at high risk for all gynecologic cancers in which screening and prevention can be focused.*

Rationale

Development of the most effective screening, early detection, and prevention strategies for all gynecologic cancers would be facilitated by an improved ability to define subsets of women who are at increased risk. This is particularly germane to ovarian and endometrial cancers, which have a relatively low incidence and are responsible for only a small fraction of all cancer deaths. Screening for and prevention of these cancers would be most cost-effective if these strategies could be directed toward populations at increased risk. Some of the epidemiologic risk factors (e.g.,

reproductive events, estrogen exposure) and genetic risk factors (e.g., *BRCA1/2*, DNA repair genes) for these cancers have been identified, but more work is needed to extend this knowledge to the point where we can identify workable high-risk populations in which to target screening and prevention. Areas of investigation that have the potential to augment our knowledge in this area include the role of common genetic polymorphisms and factors that modify genetic susceptibility. Although highly effective screening methods exist for cervical cancer, new technologies abound and a major issue now is how to best focus these in the most cost-effective manner. One possibility is to stratify women into different screening and/or prevention algorithms on the basis of their risk of cervical cancer. A better understanding of the genetic factors (e.g., polymorphisms) and environmental exposures (HPV, smoking) that are involved in the development of cervical cancer is needed to achieve this goal.

Priority 2: *Identify molecular pathways and/or surrogate endpoints that can be targeted in developing and implementing screening and prevention strategies for all gynecologic tumor types.*

Rationale

Understanding the molecular etiologies and pathways involved in gynecologic carcinogenesis can provide a rational basis for directing screening and prevention strategies and resources. Although cytologic and viral biomarkers exist for cervical cancer risk, more specific molecular markers of disease progression are vitally needed to refine the large population of women with mild dysplasia or HPV infection and to focus interventions. Similarly, histologic precursors for type I endometrial cancer have been identified; however, the rising death rate, racial disparities, and risks associated with current endometrial cancer screening modalities drive the need to identify biomarkers for endometrial carcinogenesis. Furthermore, endometrial cancer provides a model system with which to study the molecular pathogenesis of estrogen-responsive tumors. There is an urgent need for an effective screening test that can identify stage I ovarian cancer. The lack of specific symptoms and late stage at diagnosis of ovarian cancer have hampered our understanding of the precursors of this disease. High-throughput and other new technologies are poised to help identify a panel of biomarkers for the detection of ovarian cancer. Further research into the functional role of these molecules may allow them to serve as surrogate endpoint biomarkers of ovarian cancer progression or as targets for preventive strategies. These surrogate endpoint biomarkers will be vital to the analysis of prevention trials, such as those based on epidemiologic observations of ovarian cancer risks and risk reduction strategies. The striking protection against ovarian cancer that appears to be provided by oral contraceptives and pregnancy suggests that prevention may be a feasible approach to decreasing mortality, but the lack of surrogate endpoints and well-validated animal models represent significant obstacles to their evaluation.

Priority 3: *Identify the most effective and economical means of eradicating the residual burden of cervical cancer deaths.*

Rationale

Conventional Pap smear screening has been widely adopted in the United States and other industrialized countries, and this has translated into a striking decline in cervical cancer mortality. A number of new approaches are emerging that could further decrease cervical cancer deaths, including HPV testing, thin-layer Pap smear cytology, new cervical imaging methods, chemopreventive agents, and vaccines. We may be

about to witness a major paradigm shift in which some or all of these approaches are incorporated into the prevention, detection, and management of preinvasive cervical disease. Perhaps the most significant challenge in the next decade will be to determine the most effective and economical means of employing these new approaches to reach the goal of eradicating cervical cancer deaths in the United States. It is conceivable that the optimal approach may vary between rural and urban environments or between various racial and ethnic groups. Hopefully, lessons learned in the United States will be useful in addressing the enormous worldwide burden of cervical cancer.

BARRIERS

Difficulties in achieving the goals outlined here include the following:

- The current composition of many National Institutes of Health (NIH) study sections does not provide the expertise needed to knowledgeably evaluate proposals on screening and prevention.

- There is a need for increased funding and dedicated funds for screening and prevention studies.

- Primary care physicians and health maintenance organization leaders need to be better educated about current screening and prevention guidelines and ongoing research needs. Because most early cancers are diagnosed by primary practitioners in the community, as opposed to in academic medical centers, targeting these caregivers may allow increased access to early cancers.

RESOURCES

Existing funding mechanisms and study resources could be better harnessed to focus efforts on the screening and prevention of gynecologic cancers:

- Specialized Program of Research Excellence (SPORE) grants (in ovarian and gynecologic cancers) and the Early Detection Research Network could intensify their efforts on all gynecologic cancers.

- The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial, the Women's Health Initiative, and the Nurses' Health Study represent large ongoing studies that already have large serum banks that may be useful for testing and validating new biomarkers. Improving access to these valuable resources is important to advancing the field.

- The Gynecologic Oncology Group may be able to provide access to patients to help validate new markers if funding to collect these specimens are made available.

- Career development awards or other funding mechanisms are required to attract young investigators into the field. To retain these investigators in the screening and prevention fields will require additional and dedicated funding for studies that address these issues.

- The field would also be enhanced by improved mechanisms to encourage collaborations with physical scientists, including engineers, chemists, and physicists, who can bring a different skill set and knowledge base to this area.

- Quality tissues (enhanced with early-stage tumor tissues), serum banks (with serial samples in both diseased and nondiseased individuals), and linked epidemiologic and clinical data are much-needed resources. Increased funding to encourage quality banking of these samples is critical. Likewise, for the development of chemoprevention strategies.

- Patient advocates are passionate about the importance of early detection and prevention. Their energies and voices are important resources to increasing funding and awareness for these studies.

Treatment, Clinical Trials, Gene Therapy, Staging, and Surgery

Co-Chairs: Richard Barakat, Loretta Itri, and James Tate Thigpen

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BACKGROUND: STATE OF THE SCIENCE

Large clinical trials have established the current standard of care for the three most common gynecologic cancers: epithelial carcinoma of the ovary, carcinoma of the cervix, and endometrial carcinoma. From 1976 through 2000, a series of large staging studies and large phase III trials of the Gynecologic Oncology Group have defined patient populations for study and have demonstrated incremental improvements in the management of these cancers. The large staging studies represented concerted efforts to systematically assess the surgical-pathological staging of patients with carcinomas of the ovary, cervix, and endometrium. Data obtained from uniform surgical assessments and carefully reviewed pathologic analysis formed the basis for categorization of patients into groups of similar prognoses that were amenable to similar therapies. Phase III trials in each of these groups then identified optimal therapeutic approaches for each group.

In ovarian carcinoma, phase III trials have focused on three major groups of patients: those with bulky, advanced disease; those with minimal residual, advanced disease; and those with high-risk, limited disease. In bulky, advanced disease, trials have shown that the addition of first the platinum compounds and then the taxanes to front-line therapy resulted in successive 30 percent reductions in mortality. After further refinement of the regimen of choice with additional phase III trials, the current standard of care is a combination of paclitaxel plus carboplatin given every 3 weeks for 6 cycles. In minimal residual, advanced disease, the same regimen is considered the current standard of care after appropriate assessment of options such as intraperitoneal therapy. In patients with high-risk, limited disease, phase III trials have finally established the value of platinum-based adjuvant chemotherapy.

In carcinoma of the cervix, four distinct groups of patients have been identified: those with early disease (preinvasive and early invasive disease; stages 0 and IA); those with lower-volume stage IB disease; those with stage IB bulky through stage IVA disease; and those with stage IVB and recurrent disease. Relatively few trials of early invasive disease have been pursued because of the high cure rates that have been achieved with surgical resection. Radical hysterectomy remains the standard of care in patients with stage IB disease amenable to surgical resection, although ongoing trials are evaluating neoadjuvant chemotherapy. Significant improvement in survival has resulted from at least five major phase III trials of the use of concurrent chemoradiation in stages IB–IVA disease. Although trials continue to assess systemic approaches for patients with stage IVB or recurrent disease,

progress in this group has been slow because of prior radiation in most of these patients.

In endometrial carcinoma, surgical staging studies identified four distinct groups of patients for trials: those with low-risk stage IA disease; those with intermediate-risk stage IB–II disease; those with high-risk stage III–IVA disease; and those with stage IVB or recurrent disease. Major phase III trials have established a standard of care that dictates surgery alone for the low-risk patient population, surgery followed by pelvic irradiation for the intermediate-risk group, and systemic therapy for those with stage IVB or recurrent disease. Studies continue in the high-risk group with no consensus at present.

In each of these areas, clear progress has been made over the last 25 years. The basis for this progress has been knowledge about the appropriate populations for study within each tumor type. The large surgical-pathological staging studies thus have provided invaluable guidance over that 25-year period of clinical investigation.

In the last decade, however, information about the biology of these cancers has virtually exploded. It is no longer reasonable to base potential therapeutic investigation solely on surgical-pathologic staging that fails to take into account the impact of biologic information on the selection of study populations. Two potential solutions present themselves. Biologic markers can be incorporated into the staging system on the basis of collected information from a number of small trials, but such information suffers from inconsistent collection of crucial information about the biology of the lesions under study. The second solution offers a much better alternative. Large staging studies evaluating not only the anatomic extent of disease but also the biologic characteristics that have been identified as potential prognostic markers should provide valuable information collected in a consistent fashion in a uniformly assessed group of patients. Such information will allow for the development of a "molecular staging" system that will allow better definition of patient populations for targeted, biologically based therapy. With biologic information integrated appropriately into the definition of patient populations, the development of appropriate treatment trials should follow in a logical fashion.

In the interim, while such staging studies are evolving new molecular staging systems, priorities for clinical trials that will further improve current therapy should be addressed. The following recommendations are divided into primary recommendations, which have broad implications for the field of gynecologic cancer, and secondary recommendations, which focus on specific tumor types and important current clinical questions.

RESEARCH PRIORITIES

PRIMARY RECOMMENDATIONS

Priority 1: *Perform large staging trials in each of the three major gynecologic cancers for the purposes of evaluating current molecular markers as integral features of staging ("molecular staging") and of storing specimens for evaluation of future molecular markers.*

Rationale

The accurate definition of patient populations for specific interventions is critical to the proper use of biologically targeted therapy, which is likely to be the mainstay of future treatment approaches. Current anatomic staging systems do not define patient populations in a way that is consistent with the application of targeted therapies. Refinement and revision of current staging systems to take into account molecular markers is crucial and will require new, large

staging studies to collect specimens from patients with clinical outcome information so that proper clinical correlation can be done. The information from these trials will form the basis for molecular staging and appropriate design of trials to evaluate biologically targeted interventions.

Barriers

Availability of a tissue bank capable of storage and quality assessment of specimens for adequacy for studies of DNA, RNA, protein, and microenvironment

Resources

- Funding for patient accrual and tissue acquisition
- Funding for laboratory studies of appropriate biologic markers
- Funding for tissue bank
- Biologic knowledge to identify appropriate biologic markers to study

Priority 2: *Develop, through appropriate randomized trials, imaging techniques that can replace more invasive staging techniques and provide precise staging information.*

Rationale

Accurate staging is crucial to the proper evaluation of patients to be entered into clinical trials. The process currently requires invasive approaches to the assessment of the extent of disease. Replacement of invasive procedures with accurate imaging techniques can substantially reduce patient morbidity and, in some instances, mortality. A further advantage of staging that does not require major invasive procedures is an increase in accrual to clinical trials. Many patients are currently lost because they are referred to the investigative center only after surgery that is inadequate for staging purposes. It is much easier ethically to recommend imaging studies to establish stage than to advocate additional surgery solely for staging purposes.

Barriers

- Equipment
- Knowledge of appropriate target molecules

Resources

- Access to surgically staged patients
- Equipment and personnel to perform required imaging

Priority 3: *The National Cancer Institute (NCI) should provide to Cancer Cooperative Group chairs discretionary funds to permit funding of tissue acquisition and translational research studies as an integral part of multi-institutional clinical trials.*

Rationale

The true test of a translational research idea is a phase III trial. The only setting in which this can be done expeditiously and on a sufficiently large scale to allow the detection of reasonable differences is in a multi-institutional trial. The translational research must proceed concurrently with the clinical aspects of the trial; hence, appropriate funding must be available on a timely basis. The current NCI grant mechanism leads to delays and often loss of the translational endpoint. A discretionary fund appropriately administered by the Cooperative Group chair (a process that could easily be reviewed by the NCI) is the only way to ensure that the translational study will proceed.

Barriers

Willingness of NCI to assign adequate funds

Resources

- Appropriate merit review process within each cooperative group
- Necessary discretionary funds

SECONDARY RECOMMENDATIONS

These recommendations include more specific suggestions about studies of each tumor type and about the method of funding clinical investigations on a multi-institutional level. Each recommendation, other than the funding recommendation, represents a special opportunity within a specific tumor type and pertains only to the indicated tumor type.

Ovarian Carcinoma

Recommendation 1: In advanced disease, treatment trials should focus on two areas of potential improvement in outcome: development of better primary therapy and identification of effective consolidation strategies. Although primary therapy has improved with the addition of, first, the platinum compounds and, then, the taxanes, expected pathologically complete response rates are only 50 percent in minimal residual disease and 25 percent in bulky disease. With the marked increase in new active agents, it is reasonable to expect further improvement in primary therapy. At the same time, because over half of patients who achieve a pathologically complete response eventually relapse, there is a need for effective consolidation strategies. So that consolidation trials will not interfere with the interpretation of front-line studies, patients for consolidation trials should be drawn from those who receive front-line therapy outside of clinical trials and present for further recommendations after achieving a clinically complete response.

Recommendation 2: In limited disease, better definition of the high-risk patient population represents the most urgent need in order to identify those patients most likely to benefit from adjuvant therapy. A large study of the role of molecular markers in identifying such a population is thus a high priority.

Recommendation 3: The rapid assessment of new biologic (non-cytotoxic) agents as potential elements in front-line therapy requires the identification of a population of patients who are appropriate for phase II trials of combinations of these agents with platinum-based chemotherapy. Platinum-sensitive patients with long treatment-free intervals (> 12 months) afford an opportunity for such studies. The development of such studies within the Cooperative Group context should be a priority.

Cervical Carcinoma

Recommendation 1: Emphasis in clinical research should be placed on further enhancement of efforts to prevent cervical cancer. These efforts should include studies of barriers to screening in underserved populations. The rationale for this recommendation is simply that this disease is potentially completely preventable.

Recommendation 2: In recognition of the fact that some patients will fail to seek appropriate screening, trials to build on the success of concurrent chemoradiation in patients with locally advanced disease should be a priority. Reasonable approaches in this area include efforts to develop more effective chemotherapy regimens to employ with radiation, as well as studies of the potential role of non-cytotoxic agents in combination with chemoradiation.

Recommendation 3: Patients at high risk for the development of carcinoma of the cervix should be the focus for studies of vaccines directed against human papillomavirus. Carcinoma of the cervix represents an ideal tumor for such studies because of the availability of target molecules to which vaccine can be directed.

Recommendation 4: Recent retrospective data suggest that maintaining an adequate hemoglobin level through the combined use of transfusion and erythropoietin results in a further 25 percent reduction in mortality with the use of concurrent chemoradiation. Studies should be undertaken to ascertain the factors that account for this improvement and to validate these observations in prospective randomized trials.

Endometrial Carcinoma

Recommendation 1: Studies should focus on patients with aggressive forms of endometrial carcinoma rather than on those with common, low-grade, endometrioid endometrial carcinomas. Such aggressive lesions include papillary serous carcinomas, clear cell carcinomas, and all grade 3 carcinomas. The rationale for this recommendation is that these lesions account for a disproportionately higher number of deaths than do the more common lesions.

Recommendation 2: Current active systemic agents include a limited number of drugs: the anthracyclines, the platinum compounds, paclitaxel, and progestins. The development of effective systemic therapy for both advanced disease and the aggressive forms of limited disease requires more active agents; hence, the assessment of new drugs, both cytotoxics and non-cytotoxics, is a high priority.

Recommendation 3: Recent retrospective data suggest that maintaining an adequate hemoglobin level through the combined use of transfusion and erythropoietin results in a further improvement in outcome with the use of both chemotherapy and concurrent chemoradiation. Studies to ascertain the factors that account for this improvement and to validate these observations in prospective randomized trials should be undertaken in women with endometrial carcinoma as well as carcinoma of the cervix.

CLINICAL TRIALS FUNDING ISSUES

Recommendation: Accrual to studies is the single most important issue in large phase III trials. At present, less than 10 percent of patients with gynecologic cancers actually enter clinical studies. The experience of the Gynecologic Oncology Group suggests that funding of patient acquisition through a per-capita payment rather than a grant mechanism results in significant increases in accrual through the incentive to offer trials to more patients. The NCI should explore a per-capita funding mechanism for all Cancer Cooperative Group trials as a means to increase further accrual to studies.

Cervical Cancer

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BACKGROUND

Despite the dramatic decline in the incidence of and mortality from cervical cancer over the last 30 to 40 years, the disease remains a significant burden, both worldwide and in certain U.S. populations. We lack a full understanding of the molecular biology of human papillomavirus (HPV) and of the role of local and systemic immune responses in controlling the development of truly preneoplastic lesions. This has led to significant over-evaluation and over-treatment of women who probably have a reversible infectious process rather than an irreversible preneoplastic condition. It is thus essential to improve our understanding of the process of carcinogenesis. This knowledge will lead to more selective therapy and the development of preventive vaccines.

HPV testing has demonstrated excellent sensitivity for detecting cervical intra-epithelial neoplasia (CIN) II and III lesions. Its role in cost-effective screening and evaluation of women must continue to be examined in the United States and worldwide.

The marked differences in the incidence and outcome of cervical cancer are attributable to multiple factors, including race, ethnicity, income, age, and education. These disparities must be fully and completely studied (within the context of biologic, sociocultural, health systems, and health provider factors) in order to design the interventions necessary to eliminate the gaps.

Significant advances have recently been made in the treatment of locally advanced cervical cancer with the addition of chemotherapeutic agents and radiosensitizers. A full under-standing of the radiobiology and molecular events that have led to this improvement could further advance our knowledge and the potential to cure more advanced disease.

Although the dramatic reduction in incidence and mortality for cervical cancer is a true success story, the viral etiology of this disease, the accessibility of the organ for study, the rapid development of molecular biology, and the recognition that more must be done to screen certain populations present a tremendous opportunity to eliminate this disease in the United States and perhaps worldwide.

RESEARCH PRIORITIES

Priority 1: *Conduct population-based studies of quality of care and short- and long-term outcomes, with a special emphasis on health disparities.*

Rationale

Little is known about quality of care and outcomes in women with gynecologic cancers. Seventeen percent of all cancer survivors have had a gynecologic cancer, but only 3 percent of cancer survivorship research grants focus on gynecologic cancers. The majority of women with a gynecologic cancer receive their care not from gynecologic oncologists, but from general gynecologists or general surgeons. Therefore, studies of quality and outcomes of gynecologic cancer care would provide a particularly informative setting in which to study the relationships between specialist versus generalist care and between volumes and outcomes.

We propose large observational cohort studies of newly and previously diagnosed gynecologic cancer patients. These studies would investigate the impact of targeted interventions on patient-centered outcomes, the dissemination of state-of-the-science therapies into practice, the influence of modifiable risk factors, and disparities in the delivery of high-quality cancer care. We recommend that these studies be conducted through the newly created Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) initiative sponsored by the National Cancer Institute (NCI), with two modifications. First, it is essential that these studies look across the disease continuum, from diagnosis through treatment to survivorship and end-of-life care. Second, these studies must include sites with sufficient representation of disadvantaged populations to be able to examine health disparities in treatment and outcomes.

Priority 2: *Conduct research on tumor biology and genetic/molecular imaging.*

The results of this research could be used to:

- Predict and assess treatment response
- Customize therapy

Rationale

The critically important task of accurately staging cervical cancer currently requires invasive approaches. Noninvasive, biologically based strategies have the potential to spare patients the morbidity and, in some instances, mortality associated with current staging strategies. Furthermore, optimal treatment for cervical cancer would be individualized based on patient- and tumor-specific characteristics identified at the time of diagnosis. Finally, the ability to detect changes in tumor biology that occur during treatment would allow a dynamic, individualized approach to treatment with radiation therapy.

Priority 3: *Characterize the molecular features of gynecologic cancers and identify the molecular pathways and surrogate biomarkers involved in gynecologic cancers, including those relevant to HPV and its role in cervical carcinogenesis.*

Rationale

Understanding the molecular etiologies and pathways involved in gynecologic carcinogenesis can provide a rational basis for directing screening and prevention strategies and resources. Although cytologic and viral biomarkers exist for cervical cancer, more specific molecular markers of progression are needed to refine the large

population of women with mild dysplasia or HPV infection and to focus interventions. High-throughput and other technologies can help identify a panel of biomarkers for cancer detection, progression, and response to therapy. Such surrogate endpoint biomarkers will be vital to the analysis of prevention trials such as those based on observation of risks and risk-reduction strategies.

Priority 4: *Develop vaccines for both prevention and treatment of cervical cancer.*

Such vaccines will require:

- Research to better understand the immune microenvironment in the genital tract
- Clinical translation of immune-based therapies
- Targeting of specific tumor antigens

Rationale

Vaccine development is underway in cervical cancer, but a thorough understanding of immunity as it relates to cervical carcinogenesis is necessary. The understanding of the role of endogenous factors (such as hormones) and exogenous factors (such as other pathogens and smoking) on immunity is also needed. It will be important to examine both systemic immunity and immune responses at the mucosal surface or the site of neoplasia.

Vaccine research should include the development of laboratory and biologic correlates for vaccine response; a differentiation of immune response to a virally infected cell and a cancer cell; differences between HPV-specific immunity and cervical-cancer–specific immunity; and immunologic profiling at cellular and molecular levels to discern which women develop chronic HPV infection. Finally, research should determine whether HPV is a sufficient target or whether other tumor antigens are involved in malignant transformation.

Priority 5: *Develop and test screening and prevention strategies for use in high-risk populations.*

Rationale

Although highly effective screening methods already exist for cervical cancer, the abundance of new technologies raises the major issue of how to focus these emerging methods in the most cost-effective manner. Development of more effective screening tests, as well as early detection and prevention strategies, would be facilitated by an improved ability to define subsets of high-risk women. We need a better understanding of the genetic factors and environmental exposures (e.g., HPV and smoking) that are involved in the development of cancer.

Priority 6: *Assess health disparities in cervical cancer incidence and outcomes.*

Research should include database studies, population-based cohort studies, and in-depth qualitative studies, including patient and provider interviews. Such research would determine the relative contributions of risk factors, screening, treatment, and survivorship.

Rationale

Several institutions, including NCI, the American Cancer Society, and the Centers for Disease Control and Prevention have placed a major emphasis on eliminating the marked disparities in the incidence and outcome of cervical cancer over the next 10–15 years. To accomplish this, we must understand the influence of factors underlying these disparities.

Priority 7: *Conduct intervention research to decrease sexual dysfunction and to improve fertility outcomes.*

Rationale

Longitudinal research has documented that as many as 50 percent of patients with gynecologic cancer experience significant sexual dysfunction after diagnosis and treatment. Difficulties arise during the immediate post-treatment period and, if left untreated, these problems do not resolve and may worsen over time. When sexual difficulties are studied in the context of other life areas (e.g., mood, social adjustment, employment), they remain an "island" of disruption in an otherwise generally positive survivorship environment. With a substantial research base of descriptive efforts on such outcomes, it is now appropriate to begin intervention studies to prevent or ameliorate these difficulties. Of additional concern for many young cancer patients are issues surrounding fertility after treatment; this area should also be explored through intervention research.

Priority 8: *Understand the mechanisms of effective combination therapies.*

Combining chemotherapy and radiation therapy has recently been shown to improve outcomes in patients with advanced cervical cancer. To capitalize on this progress, we must better understand the mechanisms behind the effectiveness of this therapy combination, as well as others. To that end, future research should:

- Select the optimal techniques for quantifying the biology and genetics of cervical cancer radioresistance and modify individualized treatments to target their dominant mechanisms
- Evaluate new approaches to the use of radiation therapy in non-conventional ways
- Investigate additional ways to combine therapies to optimize outcomes
- Identify tumor characteristics that correlate with which tumors are most amenable to specific combinations of therapies

Rationale

This research could lead to individualized therapy when appropriate, based on patient- and tumor-specific characteristics.

BARRIERS

The following key areas were identified as barriers or challenges to achieving the priorities:

- Funding principles that discourage collaboration
- Inconsistent and restrictive policies concerning informed consent
- Professional and public ignorance regarding cancer genetics research, epidemiologic studies, and clinical trials
- Economic disincentives
- Unfunded mandates to collect specimens
- Availability and access to high-quality tissue specimens
- Incomplete and inconsistent phenotypic data associated with specimens
- Small study populations and geographic variability in cancer incidence requiring national collaborations

- Geographic inconsistencies in the quality of tumor registry data

RESOURCES

The following resources are needed to advance cervical cancer priorities:

- Validated preclinical models (*in vitro* and *in vivo*)
- Biological specimen repositories for the collection, storage, and distribution of well-characterized clinical samples
- Cross-disciplinary training and support for individuals with commitment to research in gynecologic cancers

Endometrial Cancer

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BACKGROUND AND STATE OF THE SCIENCE

The American Cancer Society estimates that approximately 38,000 new cases and 6,600 deaths will accrue from endometrial cancer during calendar year 2001. The link between estrogen-induced proliferation and progesterone-induced differentiation is well established in normal endometrium. Whereas hormonal regulation is initiated via receptor assembly, ligand binding, and interactions with coregulators and the transcriptional machinery, the functional identifiable hormone response incorporates complex interactions with a multiplicity of growth factors that reside in both the epithelium and the stroma.

Our understanding of the etiologic processes that predispose to malignant transformation in the endometrium is very limited. Although the majority of endometrial cancers are hormone dependent, the normal control mechanisms are nonetheless lost, allowing uncontrolled growth, invasion, and metastasis. Evidence from breast carcinoma suggests that alterations in hormone receptors and changes in the hormonal milieu in the microenvironment result in the activation of various growth factor pathways. In contrast, hormone-independent tumors constitutively appear to activate growth factor pathways. These tumors account for a minority of the endometrial cancers but constitute a more aggressive histologic subtype and a decrease response to treatment. Our knowledge of the molecular biology in this subset, particularly the understanding of the "cross-talk" among hormones, specific growth factors, hormone and/or growth factor receptors, and other modulations, is very limited. Furthermore, these molecular processes are influenced by interactions within both the epithelium and the stroma.

The expansion of knowledge and an understanding of how to manipulate the molecular indices of endometrial cancer will be facilitated by directed resources investigating alterations in oncogene/tumor suppressor gene regulation, hormone receptors, growth factors, growth factor receptors, and other modulators of transformation, invasion, and metastasis. At present, the investigative community is hampered by limited tissue availability with accompanying detailed epidemiologic and clinical data. Furthermore, animal models with validated genetic, histopathologic, and behavioral features resembling human endometrial carcinoma are not available.

Prevention, early detection, and treatment of endometrial cancer will be predicated on our understanding of the molecular signatures of the various histologic subtypes. The process of securing this critical fund of molecular information will necessitate the design and maturation of clinical trials with priorities that include clinical staging, long-term follow-up, and meticulous collection and storage of tissue specimens and the analysis and correlation of molecular indices with clinicopathologic parameters. These efforts will likewise facilitate further clinically relevant diagnostic and therapeutic approaches.

RESEARCH PRIORITIES

Priority 1: *Establish a specimen bank as an enduring national resource.*

- To provide an efficient, orderly framework to evaluate the biologic and clinical features of endometrial cancer representing large numbers of clearly evaluated subjects
- To foster evaluation of new tests and techniques for tissue acquisition and storage that allow for more precise tests on smaller amounts of tissue (e.g., immortalized RNA banks for gene expression studies to address limited RNA in samples)
- To identify prognostic and predictive markers for treatment efficacy (CT, RT, surgery, biologic therapy) and toxicity, using populations of patients consistently evaluated, treated, and followed
- To compare normal endometrium, endometriosis, and endometrioid and other histologic types of malignancies
- To access other relevant specimens (e.g., blood, serum, lymphocytes)
- To link to endogenous and exogenous risk factors (e.g., reproductive history, smoking, and hormone use)

Currently no such comprehensive resource exists. Specific issues for a specimen bank include the following:

- The provision of a long-term, comprehensive national repository will be expensive and must be properly funded.
- Currently there are numerous disincentives to specimen collection—surgeons, pathologists, and the like must be engaged.
- Far more patient/subject specimens would be needed to provide appropriate statistical power and robustness.
- Legal/ethical concerns for subject protection, institution/individual indemnification, and commercial rights may require legislation or executive clarification.
- There needs to be a "societal will" to make this bank a success—patient advocates, learned societies, and care providers (and their associations) must be committed to its success.
- Correlative clinical data as to staging, therapy, and outcomes must be of high quality (accuracy). In addition, follow-up specimens should be captured where feasible.
- Normal specimens that are appropriately matched (epidemiologic) would be highly valuable.
- Provision of specimens should be made for fair, equitable distribution of specimens to interested investigators based on objective criteria.

- New assays, hypotheses, and techniques to be tested would likewise be evaluated and prioritized in a fair, transparent way.

- Comprehensive information management would be needed to allow for powerful correlations, comparisons, and analyses.

Priority 2: *Define endometrial tumor biology with special attention to unique opportunities and features.*

- Understand steroid hormone receptor expression, assembly, degradation, and modulation in normal and malignant states. Understand interactions between steroid and polypeptide hormones, growth factors, and various receptors (cross-talk).

- Understand epithelial-stromal interactions for tumor growth and invasion (including aromatases, dehydrogenases, sulfatases, growth factors).

- Take advantage of the knowledge of cycling endometrium and characterize blood vessel biology for normal and tumor vessels. There are clinically exploitable interventions and specific molecular probes with which to evaluate VEGF, PDGF, FGF, integrin, and MMPI mechanisms.

- Characterize the immunologic microenvironment for endometrial cancer and endometriosis.

Priority 3: *Develop relevant, validated animal models for endometrial cancer, as none currently exist.*

- Study genetic, physiologic, and environmental pathways, correlating histopathology, biologic behavior, and molecular features.

- Study steroid hormone receptors, other growth factor receptors, genetic features, stromal-epithelial interactions, and angiogenic and metastasis mechanisms that provide insight into human disease.

- Provide correlates and leads for imaging research efforts.

Priority 4: *Develop imaging methods that provide more sensitive, dynamic, and functional information in both animal models and among women patients.*

- Define the molecular signatures of endometrial cancer cells (such as hormone receptor, growth factor receptor, or p53 imaging).

- Define the physiologic characteristics of tumors (e.g., angiogenesis, apoptosis, hypoxia, pharmacodynamics of therapy).

- Identify surrogate markers for:

  —Proof of target studies (e.g., tyrosine kinase phosphorylation)

  —Proof of principle (e.g., change in angiogenesis)

  —Proof of efficacy (e.g., tumor shrinkage)

- Evaluate all modalities, including:

  —Radiotracers

  —Scintigraphy/SPECT/PET

  —Magnetic resonance imaging and magnetic resonance spectroscopy

  —Optical (bioluminescence, optical coherence tomography, spectroscopy, confocal microscopy)

  —Ultrasound (contrast, microscopy, elastography, 3-D)

- Conduct intertechnique comparisons, standardization, and correlation with surgery for the technologies.
- Implement multidisciplinary collaboration among physicians, biologists, chemists, engineers, and biostatisticians to provide important insights.
- Develop techniques for screening appropriate populations for early diagnosis and prevention studies.
- Provide accurate, noninvasive staging, reevaluation, and response assessment information.

Priority 5: *Create a natural history database for molecular and clinical correlation.*

- Obtain large databases of endometrial cancer patients consistently evaluated, surgically-pathologically staged, further treated as needed, and sufficiently followed to provide comprehensive disease overview.
- Utilize a tissue bank (Priority 1) to perform molecular biologic characterizations so that biologic features and clinical outcome can be meaningfully related.
- Correlate, if need be, sensitivity to, resistance to, and toxicity of chemotherapy, biologic therapy, and radiation therapy.

Priority 6: *Conduct early detection and prevention clinical studies.*

- Conduct specific (hypothesis-based) prevention studies conducted on characterized higher risk populations.
- Identify molecular pathways/surrogate markers that can be targeted for screening and prevention studies.
- Develop valid surrogate markers of clinical outcomes to ease regulatory barriers and compress time and investment needed to determine benefit.

BARRIERS

The following key areas were identified as barriers or challenges to achieve the priorities:

- *Tissue resources:* Lack of tissues for use in assessing the molecular signatures of endometrial cancer. Tissue procurement to date has not included normal, proliferative, hyperplastic and various histologic subtypes of endometrial cancers. In addition, the accompanying clinical data for correlative studies is not readily available. A variety of regulatory barriers exist that impede accrual in trials securing tissues will need to be addressed.
- *Animal models:* Currently no validated animal models exist that demonstrate genetic, histopathologic and behavioral characteristics of the human model.
- *Uniform technology/reagents:* There exists a lack of readily available reagents with sufficient sensitivity and specificity with regard to antibodies, imaging probes, etc. There exists a need for the development of appropriate surrogates in imaging, early detection and other diagnostic and treatment areas.
- *Technology/equipment:* Currently noninvasive staging is limited by the sensitivity of imaging reagents and equipment.
- *Patient accrual:* Clinical trials for early detection, prevention and treatment have failed to accrue patients with appropriate ethnic, economic and geographic diversity. Likewise, epidemiologic studies involving patients with the high-risk histologic subtypes are not available.

RESOURCES

The following resources were identified in order to achieve the priorities:

- Leverage NIH and other public health organizations and initiatives to better address endometrial cancer priorities; for example:

  — Link to NICHD to co-fund, share information, and collaborate on studies of normal endometrium, implantation (placental) biology, endometriosis, etc.

  — Link to the Office of Women's Health, NIAMS, NHLBI, NIDDK, and Indian Health Service to study populations of overweight, older women with special reference to osteoarthritis, hypertension, diabetes, and endometrial cancer

- Robust commercial interest in diagnostic, therapeutic and prevention products and techniques of relevance

- Tissue accessible relatively easily and repeatedly; organ extirpation relatively frequent, which permits biopsy–intervention–resection studies

- Opportunity to leverage insights from breast and prostate cancer biology

Ovarian Cancer

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BACKGROUND: STATE OF THE SCIENCE

Ovarian cancer is the second most common gynecologic malignancy, accounting for 23,400 new cases and 13,900 deaths annually. It is the fifth most common cancer in women in the United States. Although incremental improvement in survival has occurred in the past three decades, the 5-year survival for all stages of the disease is only about 40 percent. This low survival rate reflects the lack of an effective prevention strategy, the failure to detect ovarian cancer in early stages, and the inability to cure advanced stage disease. Significant improvement in survival rates will require identification of new strategies for early detection and prevention of ovarian cancer.

Although the etiology of ovarian carcinoma is unknown, epidemiological studies have demonstrated the protective effects of oral contraceptive use and tubal ligation. Approximately 10 percent of ovarian cancers are hereditary and the remaining 90 percent are sporadic.

Ovarian cancer represents a heterogeneous group of tumors with varying biologic behaviors. Relatively little is known about growth signaling pathways, response to hormonal influences, mechanisms of peritoneal spread, and epithelial-stromal interactions in this disease. In contrast to carcinomas of the cervix and endometrium, no well-defined precursor lesion has been identified thus far. Since no effective screening method exists, over 70 percent of cases are detected after cancer has spread beyond the ovary.

Comprehensive surgical staging has enabled us to more precisely define prognosis. However, because most women are not operated on by gynecologic oncologists, incomplete surgical staging remains a major problem in the year 2001.

For stage I low-grade tumors, surgery alone provides effective therapy in a majority of cases. For all other stages and grades, standard treatment consists of primary surgery, followed by platinum-based chemotherapy. Although metastatic ovarian

cancer is moderately sensitive to chemotherapy, there is a high rate of relapse. The introduction of taxanes into the therapeutic armamentarium has not improved long-term survival as much as anticipated.

Secondary therapy for refractory disease is generally ineffective, thus providing an important incentive for new drug discovery. Since most women with recurrent ovarian carcinoma are not cured of their disease, the quality as well as duration of survival is a critical issue.

RESEARCH PRIORITIES

Priority 1: *Develop strategies for early detection and prevention of ovarian cancer.*

- Define the populations at increased risk, due to either hereditary or environmental factors, for which screening and prevention research should be focused.
- Develop the most effective screening and prevention strategies.
- Elucidate the genetic influences on environmental factors in the development of ovarian cancer.
- Identify the pathways involved in the development of both hereditary and sporadic cancers. This would include characterization of molecular, immunologic, and histologic pathways. Points along these pathways might serve as surrogate endpoints in future clinical studies.
- Identify biomarkers and develop imaging techniques to detect early-stage disease.

Priority 2: *Develop high-throughput approaches to characterize gene expression and function using genomic and proteomic technology.*

- Define molecular signatures of ovarian carcinoma characterized by histologic type and surgical stage.
- Develop a molecular classification system for ovarian cancer. This classification system should be independent of cell type or histologic grade and be predictive of response to therapy and survival.
- Identify potential molecular targets for therapy.
- Identify markers of sensitivity and resistance to therapeutic agents.

Priority 3: *Elucidate mechanisms responsible for tumor progression and the regulation of metastasis.*

- Understand the interactions of stromal and epithelial cells in the normal ovary and in the development of ovarian carcinoma.
- Study the response of both epithelial and stromal cells to hormonal stimulation.
- Elucidate the growth signaling pathways responsible for tumor progression and metastasis.
- Determine the role of angiogenesis in tumor progression and metastasis.
- Determine the role of the peritoneal microenvironment in modulating the immune response at different stages of disease.
- Define the immunogenic proteins in ovarian cancer.

Priority 4: *Determine how ovarian cancer and its therapy influence quality of life and survivorship.*

- Study quality of life in ovarian cancer patients, including acute effects of

therapy, sexuality, fertility, psychosocial health, and late effects of therapy.

- Study how to provide optimal supportive care at the end of life.
- Study the safety and quality of life associated with hormone replacement therapy in ovarian cancer survivors.
- Investigate disparities in access to care, quality of care, and outcomes in various populations, including underserved populations.

Priority 5: *Optimize efficiency of clinical trials.*

- Prioritize the study of and ensure access to new agents and combination strategies.
- Develop surrogate markers and imaging techniques of treatment efficacy.
- Enhance patient and physician participation in clinical trials.
- Develop pharmacogenomic approaches to predict drug response and toxicity.

BARRIERS

- Inconsistent and restrictive policies concerning informed consent
- Issues of privacy, confidentiality, access, and discrimination for employability and insurability
- Restrictive research regulatory environment for clinical trials and drug evaluation
- Inefficient and lengthy protocol review process
- Professional and public lack of knowledge regarding cancer genetics, epi demiologic, and clinical trials research
- Economic disincentives regarding referral by community physicians to academic medical centers for patient care are clinical trials
- Lack of funding directed toward ovarian cancer research
- Absence of timely funding for translational research linked to clinical trials
- Limited availability and access to high quality tissue specimens
- Limited access to novel investigational agents or combinations of agents developed by pharmaceutical firms
- Inequities in access of underserved populations to clinical trials

RESOURCES

- High-quality tissue, epidemiologic data, follow-up information, early-stage samples, and serial samples
- Generation and validation of models
- Innovative study design (biostatistical, laboratory-based endpoints, epidemiologic, etc.)
- Career development (outcomes, quality of life, clinical trials, laboratory-based) in ovarian cancer research
- Professional and public educational programs
- Centers of excellence in proteomics, genomics, and bioinformatics
- Professional and public education related to health disparities
- Supplemental funding for translational research linked to clinical trials