
PROGRAM CHAIR
Jubilee Brown, MD

Lisa Amacker-North, MS Eugenio Solima, MD Yukio Sonoda, MD

Jubilee Brown, Chair
Faculty: Lisa Amacker-North, Eugenio Solima, Yukio Sonoda

This session provides practical guidance for the gynecologist and gynecologic oncologist on genetic testing, screening for hereditary gynecologic cancers, interpretation of results, surgical techniques, and implementation of a successful program. Over ten percent of gynecologic cancers are preventable with the detection of genetic mutations and timely intervention, which incorporates minimally invasive surgical techniques. As this topic is increasingly covered in the lay media, patients desire sophisticated answers to their questions. Who should be screened? What do the results mean? When should screening and surgery take place? How should surgical techniques be performed and what else must patients do to protect themselves from related cancers? These topics will be addressed by experts in the field, along with practical guidelines for providing state-of-the-art care for your patients to eliminate preventable cancers.

Learning Objectives: At the conclusion of this course, the clinician will be able to: 1) Counsel patients on the most current recommendations for genetic testing, screening, and risk-reducing surgery to prevent hereditary gynecologic cancers.

Course Outline

12:10 Welcome, Introductions and Course Overview J. Brown
12:15 Impact of Hereditary Cancer Prevention - Essential for Every Practitioner Y. Sonoda
12:20 Genetic Testing, Program Implementation, and Telegenetics L. Amacker-North
12:25 Appropriate Techniques for Risk-Reducing Surgery in Gynecology E. Solima
12:30 Current Recommendations for Screening, Surgery, and Hormone Replacement Y. Sonoda
12:35 Panel Discussion All Faculty
1:10 Adjourn
PLANNER DISCLOSURE
The following members of AAGL have been involved in the educational planning of this workshop (listed in alphabetical order by last name).
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FACULTY DISCLOSURE
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Lisa Amacker-North*
Jubilee Brown*
Eugenio Solima*
Yukio Sonoda*
Content Reviewer has no relationships.
Asterisk (*) denotes no financial relationships to disclose.
Hereditary Cancers in Gynecologic Oncology: What the MIS Surgeon Should Know About Genetic Testing, Screening, and Risk Reducing Surgery

Jubilee Brown, M.D.
Professor and Associate Director
Department of Gynecologic Oncology
Levine Cancer Institute
Carolinas HealthCare System
Charlotte, NC

Disclosures

- I have no financial relationships to disclose

Objective

- Participants will be able to counsel patients on the most current recommendations for genetic testing, screening, and risk-reducing surgery to prevent hereditary gynecologic cancers

The Panel

- Yukio Sonoda, MD
  Surgeon, Gynecology Service
  Memorial Sloan-Kettering Cancer Center

The Panel

- Lisa Amacker-North
  Senior Genetic Counselor
  Levine Cancer Institute, Carolinas HealthCare System

The Panel

- Eugenio Solima, MD
  Surgeon, Gynecologic Oncology
  Fatebenefratelli-Macedonio Melloni Hospital, Milan, Italy
The Line-Up

• WHY?
Impact of Hereditary Cancer Prevention - Essential for Every Practitioner

• WHAT?
Genetic Testing, Program Implementation, and Telegenetics

• HOW?
Appropriate Techniques for Risk-Reducing Surgery in Gynecology

• WHO and WHEN?
Current Recommendations for Screening, Surgery, and Hormone Replacement

• Panel Discussion
Impact of Hereditary Cancer Prevention - Essential for Every Practitioner

Yukio Sonoda, MD, FACOG, FACS
Attending Surgeon
Gynecology Service
Department of Surgery
Memorial Sloan Kettering Cancer Center

Disclosures
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Objective
• Discuss effectiveness of early identification and prevention of gynecologic cancers, including family history assessment and risk reducing surgery.

Gynecologic Cancers – Estimated New Cases in 2016

- Uterine Cervix: 12,990
- Uterine Corpus: 60,050
- Ovary: 22,280
- Vulva: 5,950
- Vagina and other: 4,620


Gynecologic Cancer – Estimated Deaths in 2016

- Uterine Cervix: 4,120
- Uterine Corpus: 10,470
- Ovary: 24,790
- Vulva: 1,110
- Vagina and other: 950


Causes of Hereditary Susceptibility to Ovarian Cancer

- Sporadic
- Hereditary (~10-20%)
- HNPCC (~2%)
- Other single genes (~5%)
- BRCA1 (~70-75%)
- BRCA2 (~20%)

~4,000 cases of ovarian cancer could be prevented if we could identify all predisposing mutations
Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer)

- Lynch (HNPCC) syndrome is the most common form of both hereditary endometrial and hereditary colon cancer accounting for approximately 5% of each of these diseases.
- It is vastly under-recognized.
- Identification of individuals at risk allows application of proven risk-reduction strategies for synchronous/metachronous cancers in probands as well as family members.
- ~3,000 cases of uterine cancer could be prevented if we could identify predisposing mutations associated with Lynch Syndrome.

Assessing Family History

- Family history screen for first visit:
  - "Does anyone in your family; parents, grandparents, siblings, aunts, uncles or first cousins; have breast, ovary, uterine or colon cancer?"
- Family history screen for subsequent visits:
  - Details:
    - Lineage
    - Age of onset
  - Red Flags:
    - Ovarian cancer
    - Uterine Cancer
    - Colon Cancer
    - Early breast breast cancer
    - Male breast cancer
    - Multiple primary (es biliated) breast cancers
    - Many relatives affected over multiple generations
    - Breast and ovarian cancers
    - Ashkenazi descent

Risk-Reducing Salpingo-Oophorectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N (RRSO)</th>
<th>Ovarian Cancer</th>
<th>Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauff, et al.</td>
<td>Prospective</td>
<td>98</td>
<td>HR = 0.15 (95% CI: 0.02-1.31)</td>
<td>HR = 0.32 (95% CI: 0.08-1.20)</td>
</tr>
<tr>
<td>Rebbeck, et al.</td>
<td>Retrospective</td>
<td>259</td>
<td>HR = 0.04 (95% CI: 0.01-0.16)</td>
<td>HR = 0.53 (95% CI: 0.33-0.84)</td>
</tr>
<tr>
<td>Finch, et al.</td>
<td>Combined</td>
<td>1045</td>
<td>HR = 0.22 (95% CI: 0.07-0.58)</td>
<td></td>
</tr>
<tr>
<td>Kauff, et al.</td>
<td>Prospective</td>
<td>881</td>
<td>HR = 0.12 (95% CI: 0.03-0.41)</td>
<td>HR = 0.53 (95% CI: 0.29-0.96)</td>
</tr>
</tbody>
</table>

Prophylactic Hysterectomy/BSO in Lynch

  - Retrospective case-control study of documented MMR mutation carriers
    - No endometrial cancers in 61 women following hysterectomy vs. 69 endometrial cancers in 210 women who did not undergo hysterectomy
    - 3 unsuspected endometrial cancers detected at surgery
    - No ovarian cancers in 47 women following BSO vs. 12 ovarian cancers in 223 women who did not undergo BSO.

Impact of Risk-Reducing Hysterectomy in Lynch

Conclusions

- A significant number of gynecologic cancers can be prevented if these patients can be identified early.
- Hereditary cancer prevention starts with family history assessment.
- Risk reducing surgery is effective.

References


Thank You
Genetic Testing, Program Implementation, and Telegenetics

Lisa Amacker North, MS, CGC
Levine Cancer Institute
Charlotte, NC

Disclosures
I have no financial relationships to disclose.

Objective
Counsel patients on current recommendations for genetic testing

SGO Clinical Practice Statements
- Genetic Testing for Ovarian Cancer, October 2014
  Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of a family history.
- Screening for Lynch Syndrome in Endometrial Cancer, March 2014
  All women diagnosed with endometrial carcinoma should undergo systematic clinical screening (review of personal and family history) and/or molecular screening for Lynch syndrome, a hereditary cancer syndrome.
  Endometrial carcinomas can be screened for Lynch syndrome using immunohistochemistry (IHC) for the four mismatch repair proteins (MLH1, MSH2, MSH6, PMS2), microsatellite instability (MSI) analysis, and MLH1 hypermethylation testing.

Germline vs. Somatic Testing
- Multiple tumor typing tests are available (i.e. Caris, FoundationOne, etc.)
- MSI/IHC screening of Colon and Endometrial tumors fall in this category
- These tests look for alterations within the TUMOR DNA, not the GERMLINE DNA to help determine which, if any, chemotherapy will be effective.
- These results are NOT representative of the patient’s GERMLINE DNA.
  - Can sometimes detect germline mutations, but these would need to be confirmed through additional genetic testing.

Cancer Germline Testing History
- 1994/1995 BRCA1/2 – 30% +variant rate in 90’s, now 3%
- 2007 BART – BRCA large rearrangement test (also called Del/Dup)
- May 2013- US Supreme Court overturned Myriad Patent of BRCA1/2 genes
- Next Gen Sequencing panels 2016 # oncology genes
  - Ambry – January 2013 55
  - GenedX – August 2013 61
  - Myriad – November 2013 28
  - Invitae - 2014 94
- Future: Whole exome (Now Pediatrics) Whole genome (2-5 years)
Program Implementation

- **CoC Standard 2.3**: Cancer risk assessment, genetic counseling, and genetic testing services are provided to patients either on-site or by referral to a qualified genetics professional.

- **LCI approach**: Increase Genetic Counselors from 1 to 8, offer services regionally via 6 in-person clinics and by telemedicine at 5 sites.

- **Impact**: increase referrals of women with ovarian cancer to genetics from 40% to 96% with 19% of those tested having germline mutations identified.

References
Appropriate techniques for Risk-Reducing Surgery in Gynecology

Eugenio Solima, MD
Gynecology Oncology Director
Obstetrics and Gynecology Dept
University of Milan
Milan Italy

Disclosure
I have no financial relationships to disclose

Objectives
• Assess the best approach to RRS
• Explain rationale for different surgical techniques
• Improve patient counseling

Prophylactic salpingo oophorectomy: The most proven method for the prevention of ovarian cancer in BRCA mutation Carriers
- 70-85% reduction in ovarian cancer
- Reduction in cancer-related mortality and overall mortality
  - Domchek Jama 2010

Risk-Reducing Surgery
Salpingo-Oophorectomy
- Laparoscopic Approach
- Inspection of all peritoneal surfaces
- Cytology collection
- Resection of entire ovary (retroperitoneal in case of adhesions) resection of tube as close as possible to uterus, Lap bag

Alternative RR surgery in BRCA mutation carriers: Salpingectomy after childbearing completion
Preserve IP and UO ligaments
Resection of the tubes at the uterus
Remove all fimbriae
Wedge of ov capsule where fimbriae are attached
Specimen removal through lap sac
Subsequent ovariectomy +/- hysterectomy
Bilateral salpingo-oophorectomy offers the greatest risk reduction for breast and ovarian cancer among BRCA mutation carriers. However, when considering quality-adjusted life expectancy, bilateral salpingectomy with delayed oophorectomy is a cost-effective strategy and may be an acceptable alternative for those unwilling to undergo bilateral salpingo-oophorectomy.

Concerns

- No study has currently shown the impact of salpingectomy in BRCA mutation carriers
- No randomized study of RRS Vs RRSO
- No data for a 2-stage procedure
- Women undergoing interval salpingectomy may will never decide to undergo oophorectomy

References

Current Recommendations for Screening, Surgery, and Hormone Replacement

Yukio Sonoda, MD, FACOG, FACS
Attending Surgeon
Gynecology Service
Department of Surgery
Memorial Sloan Kettering Cancer Center

Disclosures
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Objectives
• Discuss current recommendations for screening, surgery, and hormone replacement therapy

UKCTOCS Trial
• Randomized trial to establish the effect of early detection by screening on ovarian cancer mortality
• 202,638 women, June 2001-Oct 2005, aged 50-74
  – Multimodal screening (MMS) vs annual TV US (USS) vs no screening
  – Died from Ovarian Cancer
    • MMS: 0.29%
    • USS: 0.6%
    • NS: 0.6%
  – No significant mortality reduction
  Jacobs et al. Lancet 2006

Screening for Ovarian Cancer
• High risk women have traditionally been recommended to undergo TVUS and serum CA125 measurements q6 months starting ~age 30
• FDA Statement 9/7/2016
  – Recommendation AGAINST using currently offered tests to screen for ovarian cancer for all women, including those at increased risk

Extended mortality results for ovarian cancer screening in the PLCO trial with median 15 years follow-up
Paul J. Fabszy II, Kelly Koo, Barrett S. Everson, Annabela B. Marx, Saundra S. Reis, Edward Partridge, John Galsky, 2, Christopher Berg, 1, Philip C. Picus 2

• Randomized trial, age 55-75 y/o, from 1993-2001
• 39,105 (Annual TVUS and Ca 125) vs 39,111 Usual Care
• Median f/u: 14.7yrs
• Deaths from Ovarian Cancer
  • 187 (screened) vs 176 (usual care)
  • Rate Ratio 1.06 (95% CI: 0.86-1.31)
• Conclusion: Extended f/u did not reveal a mortality benefit
Efficacy of Endometrial Biopsies for Endometrial Cancer Screening in Women with Lynch

  - 175 documented mutation carriers followed for 4.3 years.
  - 503 Surveillance visits during 759 person-years at risk
  - TV Ultrasound – 94% of visits
  - Endometrial Biopsy – 74% of visits
  - 11 of 14 endometrial cancers diagnosed by surveillance
    - 9 diagnosed by endo bx (2 with abnormal u/s, 6 with normal u/s, 1 u/s not done)
    - 2 diagnosed by u/s [1 with normal endo biopsy, 1 biopsy not done]
  - 14 (8%) of women had endometrial hyperplasia detected

Lynch Syndrome Screening

- Lynch Syndrome

Risk of Breast and Ovarian Cancer with BRCA 1&2

Sentinel Cancer in Women with HNPCC
(N = 101 excluding synchronous cases)

Risk Reducing Surgery for HNPCC

- Increase in endocrine and sexual symptomatology is common following RRSO.1
  - Sexual symptomatology is the single biggest predictor of satisfaction with RRSO.2
  - RRSO with short term HRT was still associated with a profound reduction in breast cancer risk in carriers of BRCA1 and BRCA2 mutations.
    - HR = 0.37 (95% CI, 0.14-0.96)

Conclusions

• No apparent role for Ovarian Cancer Screening
• Annual Endometrial Bx may be considered for HNPPC patients
• Prophylactic surgery involves a long discussion
• Short term HRT seems reasonable

References


Thank You
Cultural and Linguistic Competency

Governor Arnold Schwarzenegger signed into law **AB 1195** (eff. 7/1/06) requiring local CME providers, such as the AAGL, to assist in enhancing the cultural and linguistic competency of California's physicians (researchers and doctors without patient contact are exempt). This mandate follows the federal Civil Rights Act of 1964, Executive Order 13166 (2000) and the Dymally-Alatorre Bilingual Services Act (1973), all of which recognize, as confirmed by the US Census Bureau, that substantial numbers of patients possess limited English proficiency (LEP).

California Business & Professions Code **§2190.1(c)(3)** requires a review and explanation of the laws identified above so as to fulfill AAGL’s obligations pursuant to California law. Additional guidance is provided by the Institute for Medical Quality at [http://www.imq.org](http://www.imq.org).

Title VI of the Civil Rights Act of 1964 prohibits recipients of federal financial assistance from discriminating against or otherwise excluding individuals on the basis of race, color, or national origin in any of their activities. In 1974, the US Supreme Court recognized LEP individuals as potential victims of national origin discrimination. In all situations, federal agencies are required to assess the number or proportion of LEP individuals in the eligible service population, the frequency with which they come into contact with the program, the importance of the services, and the resources available to the recipient, including the mix of oral and written language services. Additional details may be found in the Department of Justice Policy Guidance Document: Enforcement of Title VI of the Civil Rights Act of 1964 [http://www.usdoj.gov/crt/cor/pubs.htm](http://www.usdoj.gov/crt/cor/pubs.htm).

Executive Order 13166,”Improving Access to Services for Persons with Limited English Proficiency”, signed by the President on August 11, 2000 [http://www.usdoj.gov/crt/cor/13166.htm](http://www.usdoj.gov/crt/cor/13166.htm) was the genesis of the Guidance Document mentioned above. The Executive Order requires all federal agencies, including those which provide federal financial assistance, to examine the services they provide, identify any need for services to LEP individuals, and develop and implement a system to provide those services so LEP persons can have meaningful access.

Dymally-Alatorre Bilingual Services Act (California Government Code §7290 et seq.) requires every California state agency which either provides information to, or has contact with, the public to provide bilingual interpreters as well as translated materials explaining those services whenever the local agency serves LEP members of a group whose numbers exceed 5% of the general population.

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