Gorlin’s syndrome (Basal cell nevus syndrome)

The syndrome: Gorlin syndrome affects 1:57,000 live births. It is a hereditary syndrome transmitted as an autosomal dominant. Affected individuals have facial and skeletal abnormalities and basal cell carcinomas. Less than 1% of basal cell carcinomas are attributed to Gorlin syndrome.

The gene: The gene responsible is the patched (PTCH) gene in the Hedgehog signaling pathway. PTCH encodes a receptor protein and functions as a tumor suppressor.

The ovarian tumor: The entity that is associated with Gorlin’s syndrome is an ovarian fibroma.

When to suspect Gorlin’s syndrome: Fibromas of individuals with Gorlin syndrome are more likely to be 1) seen in children and young women, 2) bilateral (75%), 3) multinodular and 4) calcified. The fibromas are more likely to be calcified.

References:
Tsuji T, Catasus L, Prat J. Is loss of heterozygosity at 9q22.3 (PTCH gene) and 19p13.3 (STK11 gene) involved in the pathogenesis of ovarian stromal tumors? Hum Pathol. 2005;36:792-6

Peutz-Jeghers Syndrome

The syndrome: This syndrome affects from 1:25,000 to 1:300,000 newborns. It is transmitted in an autosomal dominant pattern. These individuals have intestinal hamartomatous polyps and a 80 and 520-fold relative risk of colonic and small intestinal cancer respectively. However, there is increased risk in multiple organs and the cumulative risk of any cancer by age 64 is 93%.

The gene: STK11/LKB1 tumor suppressor gene with variable penetrance.
The ovarian tumor: Individuals with the PJS have a 27-fold higher relative risk of an ovarian tumor. The principal types are Sertoli cell tumors and sex cord tumors with annular tubules.

When to suspect Peutz-Jegher’s syndrome: The precise frequency of SCTATs associated with P-JS is unknown but estimated at about one third of cases. In the largest study, Young et al reported P-JS in 27 of 74 cases (36%). Distinguishing features in the SCAT include 1) slightly younger mean age (27 vs 34 years), 2) bilaterality and 3) small nodules rather than a single tumor mass.

References:
Young RH, Welch WR, Dickersin GR, Scully RE. Ovarian sex cord tumor with annular tubules: review of 74 cases including 27 with Peutz-Jeghers syndrome and four with adenoma malignum of the cervix. Cancer. 1982;50:1384-402

Hereditary non-polyposis colorectal cancer (HNPCC)
The syndrome: HNPCC (Lynch Syndrome) is a defect in mismatch repair that results in microsatellite instability. It confers an 80% lifetime risk of both colon and endometrial cancer. The cumulative risk of ovarian cancer in HNPCC individuals exceeds 12%. One meta-analysis of 650 patients and nearly 2200 years at risk identified a single advanced ovarian cancer. Estimated cumulative risk for ovarian cancer with mutations in MLH1, MSH2 and MSH6 have been estimated at 20, 24 and 1% respectively. The actual frequency of these mutations in tumors diagnosed (17, 49, 33 %) does not parallel this figure. Estimated cumulative risk of cancer by age 40 is less than 1%.

The ovarian tumor: The tumor is typically an endometrioid (35%) or clear cell adenocarcinoma (17%), with serous under-represented relative to the population (25%). However, cases of primary peritoneal cancer have been detected in women following risk reduction surgery. Tumors are typically low stage (47%). Tumors are missing the relevant MMR protein in over 90%.
When to suspect HNPCC: Younger age (<50 yrs) or synchronous tumors of the ovary and endometrium increase risk. MMR studies should be based principally on accepted risk assessment criteria for this disease.

References:

Hereditary breast cancer associated (BRCA+) pelvic-ovarian cancer

The syndrome: Germline mutations in the BRCA1 or BRCA2 tumor suppressor gene. Mutations in either are present in 0.1-0.6% of the general population and 2.3% of women of Jewish descent. Approximately 60% of affected individuals will develop breast cancer without intervention; 20-40 per cent will develop pelvic cancer without intervention, mostly high-grade (serous or endometrioid). Risk-reducing salpingo-oophorectomy of asymptomatic women will uncover an early malignancy in about 8%, but this is probably dependent on the age and increases in frequency the older the mean age at which the procedure is performed. Interestingly the mean age of women with symptomatic cancer in our experience is around 50 years, whih is similar to the mean age of women with early malignancy. Up to 80% of early malignancies are actually found in the distal fallopian tube in the form of a serous tubal intraepithelial carcinoma (S)TIC. Interestingly, in women with symptomatic (advanced) malignancies the frequency of (S)TIC is similar to that of women without germ-line mutations, around 40%. The risk of recurrent cancer following removal of uncomplicated (S)TICs is unknown but based on limited studies is low. The overall risk of a de novo pelvic cancer after a presumably normal RRSO is approximately 6%. Thus women with these mutations must be counseled that their risk is not baseline but approximately 4-fold higher compared to the general population.

The “ovarian” tumor: The typical pelvic carcinoma in a BRCA+ woman is high grade and usually serous in appearance. About 20% may appear endometrioid, including cases with an origin in the fallopian tube. Studies of the early cancers (S)TICS) have verified p53 mutations and many have verified inactivation of the BRCA1 or BRCA2 gene.
The precursors: Analysis of fallopian tubes of BRCA+ women have verified differences in transcriptome as well as a higher baseline proliferative activity. A putative precursor – the p53 signature – has been described in benign secretory cells with strong intranuclear (and sometime none in “null” mutations) p53 accumulation. P53 signatures have been found in continuity with (S)TICs suggesting they play a role as an immediate precursor. However, like all precursors, p53 signature are common, reported in up to 70% of BRCA+ tubes and 50% of controls.

When to suspect BRCA+: Two parameters of note in BRCA+ cancers include the following:

1) High frequency of oviductal involvement in RRSOs. About 10-15% of high-grade serous cancers are BRCA+. Earlier reports noted a similar frequency of BRCA+ in ovarian and tubal carcinomas. This figure is complicated by the difficulties in determining the precise origin of advanced pelvic cancers. Two studies have reported that from 30-40% of cases presenting with (S)TIC are BRCA+, a figure that will require further support.

2) Distinct histologic features. Some recent studies suggest that BRCA+ carcinomas are more likely to manifest with certain histologic features. Soslow et al reported a) (pseudo)endometrioid or transitional histology, b) necrosis c) higher mitotic index and d) tumor infiltrating lymphocytes. Fujiwara noted a) serous/undifferentiated histology, b) marked nuclear atypia c) high mitotic index, d) giant, bizarre nuclei and d) prominent intraepithelial lymphocytes.

Should either of the above parameters (STIC or histologic features) be used to triage women for BRCA1 or BRCA2 gene testing who have a pelvic cancer? One study surveyed the records of 3765 women and found that 23.8% fulfilled the criteria for high risk based on family history. However, only 12% had been referred for genetic counseling. Another study subdivided women into four groups including a) reference group with no testing, b) personal history of breast cancer, family history of breast/ovarian cancer, or Ashkenazi Jewish ancestry; c) serous histology and d) all non mucinous histologies. The highest cost-effective approach was based on history. In the paper by Soslow et al, Solid, pseudoEndometrioid and Transitional features (SET) were combined with necrosis and mitotic index produced a sensitivity, specificity and positive predictive value of 1, .57 and .60. However given the relatively small number of cases (43) and controls (12), larger studies will be required to assess the role of histologic subclassification.

References:


http://www.genome.gov/10000940

Mika Fujiwara, Anna Felberg, Alice S Whittemore, Valerie M McGuire, Teri A Longacre
Germline BRCA1 Mutation Positive Ovarian Cancer Exhibits a Distinctive Highly Specific Phenotype. (abstract 1043 USCAP 2011)


Kwon JS, Daniels MS, Sun CC, Lu KH. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. J Clin Oncol. 2010;28:675-82

Tone AA, Virtanen C, Shaw PA, Brown TJ. Decreased progesterone receptor isoform expression in luteal phase fallopian tube epithelium and high-grade serous carcinoma. Endocr Relat Cancer. 2011;18:221-34

Mehra KK, Chang MC, Folkins AK, Raho CJ, Lima JF, Yuan L, Mehrad M, Tworoger SS, Crum CP, Saleemuddin A. The impact of tissue block sampling on the detection of p53 signatures in fallopian tubes from women with BRCA 1 or 2 mutations (BRCA+) and controls. Mod Pathol. 2011;24:152-6

Outline

• Gorlin Syndrome
• Peutz-Jeghers Syndrome
• HNPCC
• BRCA1 and BRCA2
Gorlin Syndrome

- Basal cell nevus syndrome
- 1:57,000 live births
- PTCH gene
Ovarian Fibromas in Gorlin Syndrome

- Younger age group
- Bilateral (75%)
- Multinodular
- Calcified
Peutz Jeghers Syndrome

- STK11/LKB1 gene
- 1:25,000+ live births
- 80-520 fold higher risk of intestinal tumors
- 27-fold higher risk of ovarian tumors
- SCTAT and SLCT
- 50% have an affected parent and 50% have no family history (Pagon 2001)
- STK11(LKB1) mutations found in both populations
SCTAT in P-JS

- Slightly younger mean age (27 vs 34)
- Often bilateral
- No discrete mass
SCTAT
HNPCC (Lynch syndrome)

- Mismatch repair defect
- 80% lifetime risk of colon/endometrial cancer
- Cumulative risk of ovarian cancer approximately 12%
- Cumulative risk of ovarian cancer by age 40 estimated at 1%
Ovarian Cancer in HNPCC

• Link to allele
  – MLH1 – 20%
  – MSH2 – 24%
  – MSH6 - 1%

– JAMA. 2011 Jun 8;305(22):2304-10
Ovarian Cancer in HNPCC

• Characteristics (63 cases)
  – Mean age of 48 years (30-79)
  – 47% FIGO stage I
  – 35% endometrioid, 25% serous, 17% clear cell
  – MSH2 – 24%, MSH6 33%, MLH1 17%
  – Loss of MMR protein in 92%
When to think HNPCC

• Synchronous endometrial and ovarian tumors
  – 102 women
  – 2 patients met the Amsterdam criteria
  – 5 patients had the MSH (medium risk)
  – All low risk patients negative
  – Suggested screening if both synchronous primaries and suggestive family history

Soliman et al
Hereditary Breast and Ovarian Cancer Syndrome (BRCA)

- BRCA1 and BRCA2 Tumor suppressor genes
- 0.1-0.6% of the general population
- 2.3% of Jewish women
- 60% risk of breast cancer
- 20-40% risk of pelvic (serous) cancer
- 10-15% of all pelvic cancers
High Grade Serous Carcinoma
Early pelvic cancer in asymptomatic BRCA+ women

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<th>Number</th>
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<th>Tubal involvement(%)</th>
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<td>Hirst (2009)</td>
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<tr>
<td>Total</td>
<td>490</td>
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SEE-FIM Protocol

• Sectioning and extensively examining the fimbriated end

• Based on the hypothesis that the fimbriated end is unique and susceptible to tubal neoplasia

Medeiros et al 2006
Pathogenesis in BRCA+ Women

• 85+% of carcinomas detected early in BRCA+ women originate in the distal fallopian tube.

• The distal fallopian tube is the preferred site for all tubal carcinomas, irrespective of BRCA status

Early serous carcinoma
Serous Tubal Intraepithelial Carcinoma (STIC)

A common early serous carcinoma detected in ~ 5% of BSOs from BRCA+ Women
Carlson et al, Int J Gynecol Pathol 2010
TIC – loss of polarity

TIC – intra-epithelial fractures
Some molding but not TIC

Nuclear enlargement but not TIC
Not TIC – preservation of polarity and cilia
Criteria for tubal intraepithelial carcinoma

• In increasing order of importance
  – High N/C ratio
  – Variable thickness
  – Prominent nucleoli
  – Nuclear enlargement and molding
  – Loss of polarity
  – Exfoliation, intraepithelial fractures
Criteria for tubal intraepithelial carcinoma

• Immunohistochemical
  – Diffuse or completely absent p53 staining
  – High (>70% in at least some foci) MiB-1 index
  – Diffuse Cyclin E, p16 staining
Systematic Approach

• Focus on loss of polarity, high n/c ratio
• Second opinion
• Stain additional no-waste sections
• Immunostains will help but I never depend on them entirely
• Always caution the clinicia/patient that there is an increased risk of recurrence relative to controls (4X) no matter what you find
STIC from Patient Previously Treated for Breast CA

p53

Mib-1
Practical Issues

• Of the few TICs reported in isolation, most have not had adverse outcomes
• However, some are treated with chemotherapy
• Therefor: Use extreme care in making the diagnosis and get help if not sure.
### Outcome (Stage 0 (STIC))

<table>
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<tr>
<th>Au</th>
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<th>Chemo</th>
<th>FU</th>
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Early ovarian carcinoma in a BRCA+ Woman
Early BRCA+ endometrioid carcinoma
Immuno-localization of p53 protein (associated with mutation) can be found in both early serous carcinomas and benign tubal mucosa (p53 signatures).
HE

P53

Mib-1

p53Sig

p53

TIC

MIB1

1004delG (codon 335)
The Tubal “p53 Signature” is a Precursor to Pelvic Serous Carcinoma

• In this model, the proposed precursor (p53 signature) shares the following with serous carcinoma:
  – Involves secretory cells (BCL-2+, HMFG2+)
  – Predominates in the distal fallopian tube (fimbria)
  – Exhibits evidence of DNA damage (γ-H2AX)
  – Frequent p53 mutations by LCM and direct sequencing
  – Evidence of transition lesions (TILTs)
  – Seen in continuity with STIC.
  – Similar epidemiologic profile as ovarian cancer

Lee, Miron, et al 2007
Summary

BRCA1-haploinsufficient histologically normal fallopian tube

Increased Ki-67
Increased proliferation

Mutation in TP53

p53 focus

Downregulation of p27

Decreased p27 within p53 focus

Intraepithelial neoplasia

BRCA1-deficient histologically abnormal fallopian tube

Loss of wildtype BRCA1 allele

Invasion +/- metastasis

Carcinoma

Norquist et al 2010
What is the role of the ovary?

• One half of tumors classified as ovarian or peritoneal carcinomas were associated with an early carcinoma (TIC) in the fimbria.

• Approximately the same frequency is found in symptomatic BRCA+ women

• Two populations of “ovarian” cancer?

Pelvic Carcinoma in BRCA+ Women

Symptomatic vs Asymptomatic

Two pathways for the development of ovarian serous carcinoma

1. Fimbria
   - Endosalpingiosis
   - Mullerian metaplasia
   - Endometrial transport

2. Ovary or Peritoneum
   - Exfoliated tumor cells from TIC or invasive carcinoma
   - Surface or invasive carcinoma

- Mullerian inclusions
- Precursor condition
- Carcinoma

TIC Invasion
The Pelvic Ovarian Cancer Interception Project
Why examine the fimbria in women undergoing surgery for benign disease

- Rarely, a TIC or early serous carcinoma will be detected
- Depending on family history, further work up for a BRCA mutation may be indicated
- Implications for other family members