Ovarian Cancer and Primary Care
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Introductions:

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Ovarian Cancer Overview for Primary Care
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2014

The Abdomen and the Ovary
The American Cancer Society's most recent estimates for ovarian cancer in the United States for 2014:
- About 21,980 women will receive a new diagnosis of ovarian cancer
- About 14,270 women will die from ovarian cancer

Ovarian cancer is the 9th most common cancer among women, excluding non-melanoma skin cancers. It ranks fifth in cancer deaths among women, with more deaths than any other cancer of the female reproductive system. 3% of all cancers in women.

Life time risk of getting ovarian cancer:
- 1 in 72

Life time chance of dying:
- 1/100

Median age at diagnosis is 63.

More common in white women than blacks.

Why is ovary cancer so bad?
- There are no valid screening tests
- 75% of women present with advanced disease
- The symptoms are so non-specific and the disease sufficiently uncommon, that they are often wrongly ignored by:
  - Women
  - Health care providers

Are there any symptoms unique to ovary cancer?

Sadly no…

But there are some that are statistically more common…
Symptoms

Women with ovarian cancer report
- Symptoms that are persistent
- Represent a change from normal for their bodies
- On average lasting for approximately six months to one year in many instances

Statistically shown to be more common in ovary cancer

Ovarian Cancer Symptoms Consensus Statement (gynecologic cancer foundation 2007)
- Unusual bloating
- Urinary symptoms (urgency or frequency)
- Abdominal or pelvic pain
- Difficulty eating or feeling full quickly

Ovarian Cancer Symptoms Consensus
Statement (gynecologic cancer foundation 2007)

Symptoms

- Women who have these symptoms almost daily for more than a few weeks should see their doctor
- Preferably a gynecologist

Types of Ovarian Neoplasms

- Epithelial
  - Benign and malignant
  - Invasive
    - Peak age 63
    - Borderline
    - Peak at age 38-49
    - Make up 20-30% of ovary cancers in women and girls < 25 years old
    - Mean age 14
- Germ cell
  - Mature teratoma and malignant
  - Peak at age 20
- Sex cord stromal
  - Benign and malignant
  - Many before age of 40
  - Often associated with abnormal hormone production

Types of Ovarian Cancer

- Epithelial ovarian cancers
- Uncommon below the age of 40
- 16/100,000 age 40-44
- 57/100,000 age 70-74
- Serous > mucinous > endometroid > clear cell > transitional

Papillary Serous Ovarian Cancer
Types of Ovarian Cancer

- Papillary serous histologies

Types of Ovarian Cancer

- Mucinous adenocarcinoma histology

Risk factors for epithelial ovary cancer

- White race
- Increasing age
- Residence in North America and northern Europe
- No history of breast feeding
- Clomiphene use for > 12 cycles (2-3x)
- Low parity
- Unopposed estrogen use
- Genetic predisposition

Protective factors for epithelial ovarian cancer

- History of breast feeding
- Prophylactic BSO
  - Estimated to prevent 1000 cases per year
- Tubal ligation
  - RR 0.33-0.5
- Hysterectomy
  - RR 0.67
- Oral contraceptive use
  - 5-10 plus years
- High parity
  - > 3 pregnancies is protective

Protective factors for epithelial ovarian cancer

- OCP’s
  - Multiple epidemiologic studies show reduced risk
  - 40-60% risk reduction in normal risk women with >5 years OC use
  - Also probably active in high risk populations
  - Risk reduction appears to last for >30 years
  - Proposed mechanism of oral contraceptive use
    - Reduced ovulation
    - FSH levels
    - Progesterone effect on apoptosis

Mucinous Epithelial Ovarian Cancer

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Ovarian Cancer

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OVARIAN CANCER
Risk and genetic factors

- Overall risk 1.6%
- Positive family history
  - Increases risk
- Single affected member 4-5%
- Two or more members 7%
- Two or more first degree relatives 25-50%

SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer (March 2014)

- Nearly 1/3 of women with hereditary ovarian carcinoma have no close relatives with cancer
- 35% of women with hereditary ovarian carcinoma are > 60 years at diagnosis
- All women diagnosed with ovarian, fallopian tube or peritoneal carcinoma, regardless of age or family history, should receive genetic counseling with consideration of genetic testing
Reasons why it is potentially useful to have genetic susceptibility information

- Allows for identification of cancer risk in other organs
- Potentially valuable to inform other family members about their cancer risk
  - Personalized prevention to high risk individuals
  - Family members found not to carry the mutation may also receive reassurance and avoid unnecessary screening and interventions
- New therapies such as PARP inhibitors are currently being tested for the treatment of ovarian carcinoma associated with mutations in BRCA1 and BRCA2
  - A protein involved in repairing damaged DNA = poly(ADP ribose) polymerase

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HNPCC and ovary cancer

- Lynch 2 syndrome
- Represents approx. 2% genetic ovary cancer
- Proximal colon cancers
- Early age onset of colon cancer
- Mutations in DNA mismatch repair enzymes
- Risk of ovary cancer
  - 5-10%
  - Highest with mutation in MSH2 (4-24%)

Lynch 2 syndrome represents approx. 2% genetic ovary cancer. Proximal colon cancers are associated with early age onset of colon cancer and mutations in DNA mismatch repair enzymes. The risk of ovary cancer is 5-10%, and it is highest with a mutation in MSH2 (4-24%).

Germline BRCA1 and BRCA2 mutations

- Account for approximately:
  - 15% of invasive ovarian carcinomas
  - And a somewhat higher proportion of fallopian tube or peritoneal carcinomas

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HNPCC and ovary cancer

- Autosomal dominant inheritance
- Mismatch repair genes: MLH1, MSH2, PMS1, PMS2
  - Loss of function -> genomic instability, microsatellite instability
- Amsterdam criteria
  - At least three relatives must have a cancer associated with LS (colorectal, cancer of endometrium, ovary, small bowel, ureter, or renal-pelvis)
  - At least two of the following criteria should be present:
    - One must be a first-degree relative of the other two
    - At least two successive generations must be affected
    - At least one relative with cancer associated with LS should be diagnosed before age 50 years
    - FAP (Familial adenomatous polyposis) should be excluded in the CRC case(s) (if any)
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    - FAP (Familial adenomatous polyposis) should be excluded in the CRC case(s) (if any)
    - Tumors should be verified whenever possible.

Germline BRCA1 and BRCA2 mutations

- LMP or borderline ovarian neoplasms
  - Not associated with mutations in BRCA1 and BRCA2

Germline BRCA1 and BRCA2 mutations account for:
- LMP or borderline ovarian neoplasms, not associated with mutations in BRCA1 and BRCA2.

http://www.ncan.org/professionals/physician_group/ genetics colon.pdf

HNPCC and ovary cancer

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Germline BRCA 1 and BRCA 2 mutations

- Lead to a 15-50% lifetime risk of ovarian carcinoma
- BRCA 1
  - Increased risk and earlier onset as compared to BRCA 2 mutations
  - Median age of onset 48 years

BRCA options for prevention

- Many serous carcinomas of the pelvis
  - Site of origin may be the fallopian tube
  - Fimbriated end
- We have also recommended for a long time, surgical removal of the fallopian tubes and ovaries
  - Because it has been demonstrated to reduce the risk of developing, and dying from, ovarian cancer
- Risk of primary peritoneal cancer still remains
  - Approximately 3.5%

BSO

- Kauff et al. NEJM 346, 1609 (2002)
- Prospective study of 170 BRCA+ women
- Women chose surveillance or BSO
- 3.1% incidence of occult stage 1 tumors
- 85% risk reduction for ovarian cancer
- 68% risk reduction for breast cancer

Reebek et al. NEJM 346,1616 (2002)
- Case control study of 500 BRCA+ women followed for mean of 8 years
- 3.1% incidence of occult cancers
- 96% reduction in ovarian epithelial cancers
- 53% reduction in breast cancer in BSO group
- HRT use did not abolish beneficial effect of BSO
BRCA options for prevention

OCP’s

- Narod et al. *NEJM* 1998
- Case-control study of 207 women with hereditary ovarian cancer (BRCA+) compared to 161 unaffected sisters
- 6 or more years of OC use associated with 60% reduction in risk

Modan et al. *NEJM* 2001
- Population-based case-control study of 840 Israeli Jewish women with ovarian cancer and 2397 controls
- 29% of ov ca pts and 1.7% of controls BRCA +
- Increasing parity and OC use decreased risk among all patients
- No risk reduction with OC use among BRCA+ patients

Women who have BRCA1 or BRCA2 germline mutations should be counseled regarding bilateral salpingo-oophorectomy, after completion of childbearing
- It is the best strategy for reducing their risk of developing ovarian cancer
- If they opt to delay or forego risk-reducing bilateral salpingo-oophorectomy
  - They should be counseled regarding risk-reducing salpingectomy when childbearing is complete followed by oophorectomy in the future
  - The safety of this approach has not been studied.

Approximately 30% of women who are BRCA 1/2 mutation carriers choose:
- not to undergo risk-reducing salpingo-oophorectomy
- to delay this surgery
- avoid the quality of life and health risks associated with premature menopause
- Should discuss salpingectomy with them

Concerns for risk-reducing salpingectomy alone:
- Women remain at risk for developing ovarian cancer
- Women who opt to delay oophorectomy will not benefit from the 50 percent reduction in breast cancer provided through premenopausal oophorectomy

Disease with a significant prevalence
- A significant cause of mortality
- Preclinical phase evident
- Disease amenable to therapy
- High Specificity, Sensitivity, and PPV
- Cost Effectiveness
OVARIAN CANCER
SCREENING TESTS

- Not much progress
- CA-125
- Pelvic examination
- Transvaginal ultrasound (+/- Color Doppler)

Screening for ovarian cancer in an unselected population has not been shown to reduce mortality

OVARIAN CANCER
SCREENING TESTS

CA 125

- < 1% of non-pregnant females have levels >35 u/ml
- Elevated in 80-85% of advanced ovary cancers
- Only elevated in 30-50% early ovary cancers
- In post menopausal women with level > 65 u/ml
  - 97% sensitive for ovary cancer
  - 75% specific for ovary cancer
- In pre menopausal women
  - High false positive rate for a single elevated value

Screening tests—NIH consensus panel 1994

- No evidence to support routine screening in women with no family history or one 1st degree relative
- Women with stronger family history (2 or more 1st degree relatives) should be offered genetic counseling

Screening tests--NCCN 2014 Practice Guidelines for HBOC

- For those women who have not elected risk-reducing salpingo-oophorectomy
  - consider concurrent transvaginal ultrasound (preferably day 1-10 of menstrual cycle in premenopausal women) + CA-125 (preferably after day 5 of menstrual cycle in premenopausal women)
  - every 6 mo starting at age 30 y or 5-10 y before the earliest age of first diagnosis of ovarian cancer in the family
- Consider chemoprevention
  - Ocp’s

The Role of the Generalist in the Early Detection of Epithelial Ovarian Cancer

- Your patient presents with symptoms of more than a few weeks duration that are non-specific, but abdominal or pelvic in origin…
Women with persistent and progressive symptoms, such as an increase in bloating, pelvic or abdominal pain, or difficulty eating or feeling full quickly should be evaluated—ovarian cancer being included in the differential diagnosis.

Evaluation of the symptomatic patient includes:
- Physical examination
- May include transvaginal ultrasound and measurement of levels of the serum tumor marker CA 125—use sparingly in premenopausal women.

When physical examination and imaging techniques have detected the presence of a pelvic mass that is suspicious for a malignant ovarian neoplasm, the presence of at least one of the following indicators warrants consideration of referral to or consultation with a physician trained to appropriately stage and debulk ovarian cancer, such as a gynecologic oncologist:
- Postmenopausal women: elevated CA 125 level, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasis.
- Premenopausal women: very elevated CA 125 level, ascites, or evidence of abdominal or distant metastasis.

Obtain family history and refer for genetic counseling if indicated.

- Abdominal/pelvic exam
- Ultrasound and/or abdominal/pelvic CT scan
- Chest imaging
- GI evaluation if indicated
- CA 125 or other tumor markers as clinically indicated
  - Use CA 125 sparingly in premenopausal women
- Complete blood count and serum chemistries with liver function tests.

Pre menopausal
- < 5% malignant
- < 8 cm likely to regress spontaneously

Premenarchal and postmenopausal
- More likely to be malignant.

The role of the recto-vaginal exam is important during reproductive years, palpable during reproductive years, abnormal during premenopausal years.

Determines extent and spread of disease
Guides treatment decision-making
Offers general prognostic information

IS A SURGICAL DECISION
**Surgical stages of ovary cancer**

- **Stage 1**: ovary/ovaries
- **Stage 2**: involves the pelvis
- **Stage 3**: upper abdomen, omentum, retroperitoneal LN
- **Stage 4**: liver/spleen/distant mets

**5 year survival by stage**

- **Stage 1**: 90% (60-80)
- **Stage 2**: 80%
- **Stage 3**: 15-20% (50)
- **Stage 4**: 15%

Women with a mass having a significant risk of malignancy should be given the opportunity to have their surgery performed by a gynecologic oncologist. There is published data that supports that primary evaluation and surgery by a gynecologic oncologist confers a survival advantage:

- Associated with debulking surgery
- Before neoadjuvant chemotherapy

**McGowan et al.**

**Role of Debulking surgery**

- < 1 cm residual disease
- Optimal debulking
- 39 month median survival vs 17 months
- Can debulk:
  - 52% (17-88) stage 3 disease
  - 30-40% stage 4 disease
- Interval debulking is valid
- Overall increase in OS and PFS

**Other staging realities**

- 46% inadequately staged overall
- 97% adequate staging gyn oncologist
- 52% adequate staging general OB/GYN
- 35% adequate staging general surgeon


- 81 cohorts (stage III/IV)
- N = 6,885 patients

Results:

- Expert centers have high optimal rates
- Optimal vs. not: 11 mos (50% increase)
- Each 10% increase in cytoreduction = 5.5% increase in survival
- Platinum intensity = NS

Bristow et al 2002
Chemotherapy is standard treatment
- A platinum and a taxane
- IP/IV for advanced optimally debulked disease
- 6 month improvement in OS
- 6 month improvement in PFS
- Armstrong et al, NEJM, 2006
- Goal is to improve quality and quantity of life
- Chemotherapy only benefits patients that can tolerate it
- Must understand potential benefits and risks
- Clinical trials are a good option

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Use of Hormone Replacement Therapy
- Appears to be acceptable
- Should be based on QOL issues
- Mixed data regarding usage
- Discuss increased risk of Breast cancer and stroke (WHI info)
- Suggestion that Pg induces apoptosis in ovary cancer cells

No survival benefit to early institution of treatment
- 25.7 vs 27 months median OS in early vs delayed
- Quality of Life superior in the late treatment arm
  - First deterioration of QOL score occurred at
    - 3.2 mo for early treatment
    - 5.8 mo for late treatment
- NCCN Guideline suggests discussion of possible utility of following CA125 levels with our patients
- Society of Gynecologic Oncologists’ (SGO) Position statement also suggests discussion

Possible limitations of the study include:
- the possible role of secondary cytoreduction in recurrent cases
- participants were not stratified for residual disease after cytoreduction.
- remission was not consistently confirmed by imaging
- treatment regimens at relapse were not standardized.
OVARIAN CANCER SUMMARY

- Not a very common disease
- Some types of early-stage cancers are treatable with surgery +/- chemotherapy
- Advanced invasive ovary cancer is difficult to cure, but women are living longer with disease
- Chemotherapy can improve overall survival
- Women with ovarian (especially serous) cancers should be offered genetic counseling, regardless of family history
- Molecularly targeted therapy can improve progression-free survival
- We need a screening test and better treatment for platinum-resistant disease

Deanna Cosens – Stage IIIc PPC

Woman with suspicious symptoms: what now?
- Many women report they’ve seen multiple providers, delaying diagnosis
- Refer ASAP!
- Best: refer to Gynecologic Oncologist
- Gynecologic Oncologists in Michigan, by county (updated annually)

Paying for follow-up care
- Private Pay (a costly option)
- Insurance available through Health Marketplace; may have a large deductible and/or have large co-pays for diagnostic services
- As of April 1, 2014, Healthy Michigan Plan: people <140% FPL eligible to enroll. Will pay for diagnostic services and treatment www.michigan.gov/mibridges or 1-855-789-5610 (or local DHS office)

Other resources
- CDC: Inside Knowledge (reproductive cancers)
  - www.CDC.gov/cancer/knowledge
- Michigan Cancer Consortium: Ovarian Cancer Resources
  - www.michigancancer.org Resources>Health Professionals> Cancer Type> Ovarian
- Fact sheet available:
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