Case 1

On January 29, 1951, Henrietta Lacks went to Johns Hopkins Hospital. She went there because she felt a lump inside her. It all started when she asked her cousins to feel her belly, asking if they felt the lump that she did. Her cousins assumed correctly that she was pregnant. But, after giving birth to her fifth child, Henrietta started bleeding and it wasn’t menstrual. She told Day, was then taken to the local doctor, tested for syphilis, which came back negative, and then referred to Johns Hopkins Hospital.

Johns Hopkins was their only choice for a hospital, since it was the only one in a close proximity to them that treated black patients. Howard Jones, her new doctor, examined Henrietta and the lump in her cervix. It was nothing he had ever seen before. He cut off a small part of the tumor and sent it to the pathology lab. Soon after, Jones discovered she had a cervical cancer Stage 1.

Lacks was treated with radium tube inserts, which were sewn in place. After several days in place, the tubes were removed and she was released from Johns Hopkins with instructions to return for X-ray treatments as a follow up. During her radiation treatments for the tumor, a small part of Henrietta’s cervix was taken off—a healthy part and a cancerous part—without her permission. The cells from her cervix were given to Dr. George Otto Gey. These cells would eventually become the HeLa immortal cell line.

In significant pain and without improvement, Lacks returned to Hopkins demanding to be admitted on August 8 and remained until her death. Though she received treatment and blood transfusions, she died of uremic poisoning on October 4, 1951, at the age of thirty-one. A subsequent partial autopsy showed that the cancer had metastasized throughout her body.
HPV is the cause of cervical cancer

The human papillomaviruses (HPV) are small viruses with double stranded DNA that have a particular tropism for the epithelium, inducing its proliferation. It is believed that the HPV enters the body after slight trauma to the epithelium and needs terminally differentiated epithelial cells for replication. HPV causes epithelial lesions of varying severity. Over 100 different HPV types have been identified and each is associated with a different type of lesion. HPV type 1 causes verrucas, HPV type 2 causes common warts and HPV11 causes genital warts. Certain HPV types, such as HPV16 and HPV18, infect cervical epithelium and cause lesions that can progress through different grades of cervical intraepithelial neoplasia to cancer. These viruses are known as 'high-risk' papillomaviruses. Most 'high-risk' HPV infections are successfully resolved by the host immune system and do not become life-threatening. In a small number of cases, however, lesions caused by 'high-risk' HPV types can persist and can develop into cancer.

Low-grade lesion
High-grade lesion

Myometrium
Leiomyoma
Leiomyosarcoma
Adenomyosis
Case 2
Ms. Smith is a 42 years old school teacher and suffered from pelvic pain which is aggravated during menstruation (sick days off). Attempts to become pregnant have failed. Pelvic examination revealed a pelvic mass which was confirmed by imaging.

Endometrium

Endometritis
Atrophy endometrium (cause postmenopausal bleeding)
Endometrial hyperplasia (precursor of carcinoma)
Endometrial carcinoma (endometrioid and serous type)

Leiomyoma, the most common benign uterine tumor in women

Leiomyosarcoma

Endometriosis

Atrophy endometrium

Hyperplastic endometrium
Case 3

Ms. Smith with BMI 38 is a 64 years old presented with heavy vaginal bleeding. No other symptoms were noted. Endometrial biopsy was performed. Imaging study was followed to determine the extent of the disease.
Case 4

Ms. Smith is a 19 y/o college student. She presented with acute abdominal pain, admitted to ER in the early morning. She did not show signs of infection. BP drops and HR increases in ER. B-hCG test is positive. She was operated.

Ectopic Pregnancy

- Epidemiology:
  - ~20 per 1000 pregnancies
  - Strongly associated with PID
  - 98% occur in fallopian tube
- Symptoms:
  - Abdominal pain
  - Vaginal bleeding
- Exam findings:
  - Adnexal mass on bimanual exam
- Imaging Findings:
  - No evidence of intrauterine pregnancy
  - Presence of pregnancy outside of uterus
- Diagnosis:
  - Based on physical exam findings
  - Imaging
  - Presence of pregnancy
- Treatment:
  - Surgery or methotrexate

Acute and chronic salpingitis

- Epidemiology:
  - Caused by pelvic inflammatory disease (PID)
  - Pathogens include Chlamydia trachomatis, Neisseria gonorrhoeae, bacteria that comprise the vaginal flora (e.g. anaerobes, G. vaginalis, H. influenzae, enteric gram negative rods, S. agalactiae)
- Symptoms:
  - Abdominal/pelvic pain, worse with coitus, shortly following menses
  - Vaginal discharge
  - Abnormal vaginal bleeding
- Exam findings:
  - Diffuse abdominal tenderness
  - Cervical, adnexal, and pelvic tenderness
  - Purulent endocervical discharge
- Diagnosis:
  - Based on physical exam findings
  - Imaging
  - Presence of pregnancy
  - Serologic tests for PID
  - Treatment:
  - Antibiotics for patient and her sexual partner

The Fallopian Tube: Physiology

- Fimbriated end catches oocyte
- Ciliated columnar epithelium and muscularis sweep oocyte to ampulla
- In ampulla, fertilization of oocyte typically occurs
- Cilia and muscularis sweep fertilized oocyte (zygote) to uterus
- Action of hormones on tube:
  - Estrogen stimulates cilia
  - Estrogen enhances secretory activity of Peg cells
  - Progesterone stimulates Peg cell production

Pyosalpinx

- Hydrosalpinx

Chronic salpingitis and hydrosalpinx
Acute pelvic inflammatory disease (pyosalpinx)
Tubal pregnancy
Tubal serous carcinoma

Fallopian tube
Tubal serous carcinoma

Ovary

Endometriotic cyst
Benign cysts (corpus luteum cyst, serous cyst, etc.)
Ovarian neoplasm

Ovarian cancers include:

Case 5
Ms. Smith is a 48 y/o housewife. She has been healthy in the past. Routine Gyn annual check-up reveals a possible adnexal mass, which appears benign by sonogram and CA125 is not elevated. She decides to be operated.

Mature Cystic Teratoma

- Epidemiology:
  - Also known as a dermoid cyst
  - Most common germ cell tumor
  - Accounts for 95% of teratomas and is benign
  - Most common ovarian tumor in the 2nd and 3rd decades of life
  - Contains mature tissue of ectodermal, mesodermal, and endodermal origin
- Symptoms:
  - Usually asymptomatic, but can cause pain if torsion or rupture
- Exam findings:
  - Adnexal mass on bimanual exam
- Imaging Findings:
  - Characteristic ultrasound appearance
  - Ultrasound = 98-100% sensitive
- Diagnosis:
  - Based on ultrasound
- Treatment:
  - Surgery to remove cyst (ovarian cystectomy)
The fact of ovarian cancer

- Ovarian carcinoma is the major disease of cancer mortality in women (22,430 new cases, 15,280 new deaths in 2007)
- Molecular etiology is poorly understood
- Patients are usually on death roll if tumors recur
- A peritoneal disease, ideal for i.p. therapy

Adnexal Masses

- Ovarian masses
  - Physiologic cysts (also known as functional cysts)
    - Simple vs. complex
      - Simple cysts: follicular cyst
      - Complex cysts: hemorrhagic cyst, corpus luteum cyst, theca lutein cyst
  - Neoplasms
    - Benign: endometrioma, cystadenoma, teratoma
    - Borderline
    - Malignant: epithelial ovarian cancer, germ cell tumors, sex cord stromal tumors
  - Metastatic: from cancer of breast, colon, endometrium

Adnexal Masses: Differential Diagnosis

- Variables to consider
  - Age
  - Medical history
  - Symptoms
  - Physical exam
  - Objective findings

Adnexal Masses: Age

- <15 years old
  - high percentage of ovarian masses are malignant

- Premenopausal women
  - 6-11% risk of ovarian malignancy

- Postmenopausal women
  - 29-35% risk of ovarian malignancy

Adnexal Masses: History

- Personal history of breast cancer
  - Increased risk for an ovarian malignancy

- Family history of breast, ovarian, colon cancer
  - Increased risk of ovarian malignancy

Adnexal Masses cont’d

- Tubal masses
  - Paratubal cyst
  - Ectopic pregnancy
  - Hydrosalpinx
  - Tuboovarian abscess (TOA)
  - Fallopian tube cancer

- Adnexal masses not involving the ovary or fallopian tube
  - Peritoneal inclusion cyst
  - Pedunculated fibroid
  - Diverticular abscess
  - Appendiceal abscess or tumor
  - Inflammatory or malignant bowel disease
  - Pelvic kidney
Adnexal Masses: Symptoms
- Mid-cycle pain in premenopausal women → physiologic cyst
- Pain immediately following intercourse → ruptured cyst
- Pain, fever, purulent cervical discharge → TOA
- Dysmenorrhea, dyspareunia → endometrioma
- Chronic abdominopelvic pain, bloating → ovarian neoplasm or fibroid
- Pain, postmenopausal bleeding, watery vaginal discharge → fallopian tube cancer

Adnexal Masses: Physical Exam
- Pelvic exam
  - Look at cervix
  - Perform Pap if needed
  - Consider endometrial biopsy if abnormal bleeding
- Bimanual exam: assess uterus, assess adnexa for size, location, consistency, mobility, and tenderness
- Rectal exam
  - Assess posterior uterus, assess for stool in rectum and uterosacral nodularity
- Abdominal exam
  - Assess for fluid shift consistent with ascites
- Breast exam
  - Assess for masses

Adnexal masses: Blood tests
- Pregnancy test
  - Positive: ectopic pregnancy, theca lutein cyst
- Complete blood count
  - Elevated white blood cell count: TOA, appendicitis, diverticulitis
- Tumor Markers
  - CA 125: serum glycoprotein that is elevated in ovarian cancer, endometrial cancer, pancreatic cancer, endometriosis, uterine fibroids, pelvic inflammatory disease, heart failure, and abdominal surgery in young women
    - Sensitivity for predicting ovarian malignancy
      - Premenopausal women: 50-74%
      - Postmenopausal: 60-87%
    - Specificity for predicting ovarian malignancy
      - Premenopausal: 26-92%
      - Postmenopausal: 81-100%
    - Positive predictive value for ovarian malignancy
      - Premenopausal: 5-67%
      - Postmenopausal: 75-100%
- HE4: protein expressed in ovarian cancer tissue
  - Not elevated in women with endometriosis
  - Approved by FDA in 2008 for monitoring patients with ovarian cancer for disease progression or recurrence
- AFP, LDH, HCG: measured when germ cell tumor is suspected
- CA19-9, CEA: measured to assess for GI malignancy involving the adnexa

Adnexal Masses: Imaging
- Pelvic ultrasound
  - Most valuable imaging test to evaluate the adnexa
  - Performed using transducer transabdominally and/or transvaginally
- Ultrasound findings:
  - Malignancy
    - Solid component
    - Nodular or papillary excrescences
    - Thick septations
    - Blood flow in the solid component
    - Presence of ascites
    - Peritoneal masses, enlarged nodes, or matted bowel
  - Functional cyst: solitary, thin walled, unilocular, < 8 to 10 cm in diameter
  - Dermoid cysts: varying densities due to the presence of sebaceous material, bone, adipose tissue, and/or hair
  - Endometriomas: homogeneous low to medium level echoes, thick walled
  - Serous cysts: anechoic
  - Mucinous cysts: echogenic
- Pelvic MRI
  - Can be useful when ultrasound does not provide adequate information

Polycystic Ovarian Syndrome (PCOS)
- Definition:
  - Menstrual irregularity + signs of hyperandrogenism
  - Menstrual irregularity = oligo or amenorrhea
  - Hyperandrogenism = hirsutism, severe acne, and/or pattern alopecia
- Associated with:
  - Infertility
  - Type 2 diabetes mellitus
  - Obesity
  - Cardiovascular disease
  - Endometrial carcinoma
- Imaging finding:
  - 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume on ultrasound
- Treatment:
  - Oral contraceptives or cyclic progestrone

Serous Borderline Tumor
- Epidemiology:
  - Account for 10-20% of epithelial ovarian tumors
  - Average age at diagnosis = 40-60 years
- Symptoms:
  - Usually asymptomatic, but may cause pain
- Exam findings:
  - Adnexal mass on bimanual exam
- Imaging Findings:
  - No sonographic features highly suggestive of a borderline tumor
- Diagnosis:
  - Diagnosis made based on histology once ovary removed
- Treatment:
  - Surgery to remove ovary (oophorectomy)
Serous carcinoma

**Epidemiology:**
- Serous carcinoma of the ovary is an epithelial ovarian cancer.
- 90% of ovarian cancer from ovary is epithelial in origin.
- Most common primary site of metastasis, stomach, lung, peritoneum.
- Second most common cause of death among women with gyn malignancy.
- Average age of diagnosis = 50-60 years.

- Average age of diagnosis = 65-70 years.

**Symptoms:**
- Vague and ill-defined: bloating, early satiety, increased abdominal size, pelvic/abdominal pain, urinary urgency/frequency.

**Exam Findings:**
- Solid, fixed, irregular mass noted on bimanual exam.
- Ascites noted on abdominal exam.

**Imaging Findings:**
- Solid component: nodular or papillary excrescences.
- Thick septations.
- Blood flow in the solid component.
- Presence of ascites.
- Peritoneal masses, enlarged nodes, or matted bowel.

**Diagnosis:**
- Ultrasound.
- CA 125.
- CT scan.
- Surgery.

**Treatment:**
- Gyn oncologist: removal of uterus and cervix (total abdominal hysterectomy), removal of tubes and ovaries (bilateral salpingo-oophorectomy), staging.

**Mutation:**

- **HG** LG CCEM MU
- TP53
- BRCA1/2
- KRAS
- BRAFT
- PIK3CA
- PTP
- CTNNB1
- ARID1A
- PPP2R1A

**HG** LG CCEM MU

- Mutation
- 10%-30%
- 5%-15%
- 0%<1%

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**Ovarian cancer - not a single disease...**

**Ovarian endometrioid carcinoma (Type I)**

- Endometriosis
- Endometrioid borderline tumor
- Endometrioid carcinoma
Case 6

Ms. Smith is a 65 y/o retired pharmacist. She never gave a birth and has been healthy in the past until recently she complains for abdominal fullness. She had an ovarian benign simple cyst but it appears to have solid component and her CA125 is 213 one year later. She was referred to a gynecologic oncologist.

Screening for ovarian cancer does not work

JAMA, 305:2295, 2011 (June 8)

- 78,216 women undergo annual screening with TVU and CA-125 testing
- Screening did not result in fewer deaths from the disease
- False-positive results (5%) often led to unnecessary surgeries and other serious complications
- Many of the positive screening results from TVU and CA-125 turned out not to be cancer
- Only 1.6 out of every 100 women who test positive actually have cancer

High-grade ovarian serous carcinoma is difficult for early detection (Type II tumors)
Hypothesis

Tubal intraepithelial carcinoma (TIC)

Why from fallopian tube?

Ovarian cancer is a heterogeneous group of diseases… with different clinicopathological and molecular features…

Ovarian carcinoma is theoretically an imported disease… Ovary itself is innocent to develop carcinoma. Type I tumors: ancestor is endometriosis then CA develops Type II tumors: ancestor is TIC…widespread disease

Potential paradigm shift in managing ovarian cancer patients prophylaxis- salpingectomy instead of salpingectomy+oophorectomy detection- detection of low-volume Dx rather then serum markers therapy- targeted therapy for Type I Dx

Tubal origin of ovarian high-grade serous carcinoma

• “Ovarian” serous carcinoma originates from fallopian tube epithelium
• “Ovarian” cancer progresses from STIC then spreads from the tube to ovary, pelvis, abdomen/pelvic soft tissues and distant sites
• Ovary is only secondly involved
**Integrated genomic analyses of ovarian carcinoma**

The Cancer Genome Atlas Research Network.*

An analysis of molecular alterations that cause ovarian cancer is critical for developing and deploying therapies that will improve patient's lives. The Cancer Genome Atlas (TCGA) project has analyzed messenger RNA expression, recurrent mutations, and copy number in 477 high-grade serous ovarian adenocarcinoma and the DNA sequences of 51 normal ovaries and 661 samples of three tumors. Here we report that high-grade serous ovarian carcinoma is characterized by a spectrum of genetic alterations involving DNA damage and repair pathways. Although there are familial ovarian cancer syndromes associated with mutations in the mismatch repair genes, BRCA1 and BRCA2, most cases arise through somatic mutational events in the tumor genome. Other genes, including TP53, PTEN, RB1, KEAP1, and LKB1, harbor germline alterations that contribute to cancer risk. A small number of tumors have mutations in genes involved in epigenetic regulation. In parallel, analysis of microRNAs suggests a role for microRNA-21 and other microRNAs in cancer progression. The biological impact of these findings is being further studied, and they provide opportunities for the development of targeted therapies for ovarian cancer.
**Nanopore sequencing** - Towards the 15-minute genome

Genetics: Pulling strands of DNA through nanopores could dramatically speed up the sequencing of human genomes.