Should a woman with breast cancer, or an increased risk of breast or ovary cancer, or who is BrCa mutation positive have her uterus removed with prophylactic oophorectomy?

Risk for uterine cancers: Age and overweight are the most common risk factors for uterine cancer. Women with breast cancer, ovary cancer, colon cancer, and women who are BrCa positive **all have an increased risk of uterine carcinoma and poorer survival.** Women who are BrCa positive should consider having their uterus removed with prophylactic oophorectomy.[1-4]

Here are the research facts:

- Women with a body mass index over 25 have a 4-12x risk over and above the usual 4% lifetime risk of uterine cancer. These women should not take the hormone progesterone to prevent hyperplasia or cancer because progesterone's cause a 26% increase in breast cancer, and increase heart disease, stroke, and blood clots (WHI).

- Women with a history of breast cancer often need to take Tamoxifen, which causes uterine lining bleeding and abnormalities in some 38% of them and cancer in about 8%. Women with breast cancer who develop uterine cancer have more aggressive uterine cancers and poorer survival. (Chan et al Gyn Oncol, 2006)

- Women with BrCa positivity have been shown to develop the types of uterine cancer that microscopically resemble the Fallopian Tube cancers and Ovarian cancers that have been more frequently seen in +BrCa women. This cancer is not the usual highly curable endometrial cancer, but a more aggressive type, that spreads like ovarian and tubal cancer.(Lavie et al, gyn Oncol, 2005)

- Hysterectomy does not cause any increase in incontinence (WHI), prolapse (WHI), or sexual dysfunction (see hysterectomy data in other handouts). Hysterectomy adds little morbidity to needed oophorectomy, and prevents risk of needing another surgery in the future.

- Women having their uterus removed can take estrogen alone, which is associated with a 33% decrease in breast cancer risk, no increase in heart disease, stroke or blood clots in women ages 50-59(WHI)(Rebbeck, JCO, 2005). They will not need annual pap smears, and have zero risk of cervical and uterine cancer.

BIBLIOGRAPHY

Read the bibliography for these statements, with highlights in the published research abstracts that follow:

Axelrod, J. H., R. Fruchter, et al. (1984). "**Multiple primaries among gynecologic malignancies**." Gynecol Oncol **18**(3): 359-72.

Seventy-eight synchronous or metachronous tumors among 2362 patients followed by the Downstate Gynecologic Tumor Registry are reviewed. Significant synchronous tumor pairs include cervix (invasive and in situ)-ovary, cervix (in situ)-uterus, cervix (in situ)-kidney, **endometrium-ovary**, **endometrium-rectosigmoid, and ovary-breast**. Significant metachronous pairs include cervix (invasive and in situ combined)-lung, **cervix (invasive and in situ combined)-upper alimentary tract**, and **cervix (invasive)-rectosigmoid**. In the case of in situ and invasive cervical cancer-lower genital tract, significance was determined for both synchronous and metachronous pairs. Long survival is an important factor in the appearance of a second tumor as demonstrated in patients with cervical carcinoma. Synchronous data prove to be valuable in assessing in risk of second primaries in patients surviving for short periods. The roles of cigarette smoking, hormones, immunosuppression, radiotherapy, and screening are discussed.

Goshen, R., W. Chu, et al. (2000). "**Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome?**" Gynecol Oncol **79**(3): 477-81.

BACKGROUND: Uterine papillary serous carcinoma (UPSC) shares common pathologic, genetic, and clinical features with other serous cancers of mullerian origin. The most common histologic type of ovarian tumor associated with BRCA mutations is papillary serous. Because of these histologic similarities, we postulated that, in some cases, UPSC may be a manifestation of a field defect in BRCA1 carriers, which also includes ovarian carcinoma, fallopian tube carcinoma, and primary peritoneal carcinoma. METHODS: Fifty-six living patients with UPSC were contacted through their treating physicians and agreed to a family history interview and to provide a blood specimen for BRCA testing. The protein truncation test was used to detect mutations in exons 10 and 11 of BRCA1 and in exon 11 of BRCA2. The presence of four common mutations was assessed by PCR-based specific assays. RESULTS: **A high proportion of patients had a past history of breast cancer (11%) or a first-degree relative with breast cancer (29%). Four patients were from families with site-specific hereditary breast cancer.** However, there was no clear example of the hereditary breast-ovarian cancer syndrome, and none of the 56 patients was found to carry a BRCA1 or BRCA2 mutation. CONCLUSIONS: BRCA mutations do not appear to predispose to UPSC and this type of cancer does not appear to be a manifestation of the classical hereditary breast-ovarian cancer syndrome. **The observed association between UPSC and breast cancer may be due to the presence of mutations in other cancer predisposing genes.**

Hemminki, K. and C. Granstrom (2004). "**Familial clustering of ovarian and endometrial cancers.**" Eur J Cancer **40**(1): 90-5.

Data on the association of ovarian cancer with other cancers in families are limited, and no data are available on the involvement of specific morphological types.

The nationwide Swedish Family-Cancer Database on 10.2 million individuals and 19175 invasive ovarian cancers was used to calculate standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) for familial ovarian cancer in 0-66-year-old daughters when mothers or sisters were affected. The SIR for concordant ovarian cancers was increased. When the mother or sister had breast cancer, the SIRs were 1.21 and 1.48, respectively; when they had endometrial cancer, the SIRs were 1.45 and 2.53. Multiple myeloma in the mother was associated with a risk of ovarian cancer in the daughter. The risk of endometrioid ovarian cancer was 3.40 in the daughter when the mother presented with endometrial cancer. **Our data show a strong familial coupling of ovarian and endometrial cancers, which appears to be specific to the endometrioid morphology.**

Hornreich, G., U. Beller, et al. (1999). "**Is uterine serous papillary carcinoma a BRCA1-related disease? Case report and review of the literature**." Gynecol Oncol **75**(2): 300-4.

OBJECTIVES: Type II endometrial carcinomas are estrogen-independent and have adverse histologic features and a substantially poorer prognosis. No risk factors have been identified. Interestingly, there is a striking clinical and histopathological similarity between serous papillary carcinomas of the ovary (OSPC), endometrium, and peritoneal cavity, suggesting a common oncogenic mechanism. Several common molecular alterations were found using molecular comparative analysis of OSPC and uterine serous papillary carcinoma (USPC). Germline mutations in the BRCA1 tumor suppressor gene predispose to breast and ovarian cancer but no association with sporadic endometrial cancer has been found. A family of Ashkenazi Jewish origin, in which one sister was first diagnosed with USPC and the second diagnosed with OSPC, led to the hypothesis that a BRCA mutation may contribute to USPC. METHODS: Genomic DNA from both patients as well as two unaffected siblings was analyzed for the three mutations common in Ashkenazi Jews. Loss of heterozygosity (LOH) analysis was performed on DNA extracted from USPC tumor tissue. RESULTS: Both affected sisters tested positive for BRCA1 5382insC germline mutation. LOH analysis confirmed the results. CONCLUSIONS: **We present a breast-ovarian cancer family including two sisters with advanced serous papillary carcinomas of endometrial and ovarian origins, carrying the same BRCA1 mutation** (5382insC). LOH analysis on USPC tumor DNA showed loss of the wild-type allele, **suggesting a causal relationship between the germline BRCA1 mutation and USPC**. We believe a study examining BRCA1 mutations in a large cohort of women with this high-risk endometrial carcinoma is warranted. A positive finding may have implications for surveillance and prophylactic surgery in carriers of BRCA1 mutations.

Lavie, O., G. Hornreich, et al. (2004). "**BRCA germline mutations in Jewish women with uterine serous papillary carcinoma.**" Gynecol Oncol **92**(2): 521-4.

OBJECTIVE: Our recent study determined the possible effects and incidence of BRCA1 and BRCA2 germline mutations in uterine serous papillary carcinoma (USPC). The purpose of this study was to determine the incidence of these mutations in an enlarged series of USPC. METHODS: We screened DNA from 27 women with USPC for BRCA1 and BRCA2 germline mutations common in the Jewish population (BRCA1-

185delAG and 5382 insC,BRCA2-6174delT). In women with germline mutations, tumor DNA was screened for loss of heterozygosity (LOH) at the appropriate loci. RESULTS: Women (20) were of Jewish Ashkenazi origin and seven were non-Ashkenazi. Four of 20 (20%) Ashkenazi women were carriers of germline mutations: three 185delAG mutation and one 5382insC mutation. All carriers had strong family histories of breast-ovarian carcinoma. Seven out of 20 (35%) women had been diagnosed for breast carcinoma before diagnosis of USPC. Family histories of 12 women (60%) showed at least one first-degree relative with breast, ovarian, or colon carcinoma. Loss of heterozygosity analysis found a loss of the wild-type BRCA1 allele in three of the four primary uterine tumors that were examined. CONCLUSIONS: **Our findings further support our previous published data suggesting a high incidence of BRCA carriers among USPC Ashkenazi Jewish patients**. The loss of heterozygosity in the tumor tissue of carriers coupled with the high frequency of patient and family history of breast and ovarian malignancies suggest that **USPC might be part of the manifestation of familial breast-ovarian cancer in Ashkenazi Jewish patients**.

Paley, P. J., E. M. Swisher, et al. (2001). "**Occult cancer of the fallopian tube in BRCA-1 germline mutation carriers at prophylactic oophorectomy: a case for recommending hysterectomy at surgical prophylaxis.**" Gynecol Oncol **80**(2): 176-80.

OBJECTIVE: BRCA-1 and BRCA-2 germline mutations increase the risk of ovarian and breast cancer. Primary cancer of the fallopian tube is rare; however, recent evidence suggests that patients harboring a germline mutation conferring an increased risk of ovarian cancer may be at risk for fallopian tube cancer as well. We discuss the finding of occult fallopian tube cancer diagnosed at surgical prophylaxis in women harboring BRCA-1 mutations. METHODS/RESULTS: Two patients undergoing surgical prophylaxis to address an increase in ovarian cancer risk were discovered to harbor occult primary fallopian tube carcinoma on final pathology review. Mutational analysis confirmed the presence of a deleterious mutation in BRCA-1 in both patients. CONCLUSION: Currently, consensus opinions regarding ovarian cancer surgical prophylaxis in gene mutation carriers do not include hysterectomy as part of the preventative procedure. **This report as well as a growing number of cases of fallopian tube cancer reported in known BRCA-1 and BRCA-2 mutation carriers has important implications for recommendations regarding surgical prophylaxis in these women.**

Pere, H., J. Tapper, et al. (1998). "**Genomic alterations in fallopian tube carcinoma: comparison to serous uterine and ovarian carcinomas reveals similarity suggesting likeness in molecular pathogenesis.**" Cancer Res **58**(19): 4274-6.

Serous carcinomas of the fallopian tube, uterus, and ovary resemble each other both histologically and in clinical behavior. Comparative genomic hybridization was performed on 20 primary fallopian tube carcinoma specimens to find regions of the genome involved in tubal carcinogenesis and to compare the genomic alterations with those previously detected in serous ovarian and uterine carcinomas. The most frequent changes detected in fallopian tube carcinoma were gains at 3q (70%) and 8q (75%), with high-level amplifications in several cases. Other common gains occurred at 1q, 5p, 7q,

12p, and 20q. The most frequent losses were found at 18q, 8p, 4q, and 5q. **The frequency and the pattern of chromosomal changes detected in tubal carcinoma were strikingly similar to those observed in serous ovarian and uterine carcinomas, suggesting common molecular pathogenesis**.

Thompson, D. and D. F. Easton (2002). "**Cancer Incidence in BRCA1 mutation carriers.**" J Natl Cancer Inst **94**(18): 1358-65.

BACKGROUND: Germline BRCA1 mutations confer a substantial lifetime risk of breast and ovarian cancer, but whether cancer at other sites is increased is less clear. To evaluate the risks of other cancers in BRCA1 mutation carriers, we conducted a cohort study of 11 847 individuals from 699 families segregating a BRCA1 mutation that were ascertained in 30 centers across Europe and North America. METHODS: The observed cancer incidence was compared with the expected cancer incidence based on population cancer rates. Relative risks (RRs) of each cancer type in BRCA1 carriers relative to risks for the general population were estimated by weighting individuals according to their estimated probability of being a mutation carrier. All statistical tests were two-sided. RESULTS: **BRCA1 mutation carriers were at a statistically significantly increased risk for several cancers, including pancreatic cancer (RR = 2.26, 95% confidence interval [CI] = 1.26 to 4.06, P =.004) and cancer of the uterine body and cervix (uterine body RR = 2.65, 95% CI = 1.69 to 4.16, P<.001; cervix RR = 3.72, 95% CI = 2.26 to 6.10, P<.001).** There was some evidence of an elevated risk of prostate cancer in mutation carriers younger than 65 years old (RR = 1.82, 95% CI = 1.01 to 3.29, P =.05) but not in those 65 years old or older (RR = 0.84, 95% CI = 0.53 to 1.33, P =.45). Overall, increases in the risk for cancer at sites other than the breast or ovary were small and evident in women (RR = 2.30, 95% CI = 1.93 to 2.75, P =.001) but not in men (RR = 0.95, 95% CI = 0.81 to 1.12, P =.58). CONCLUSIONS: In carriers of BRCA1 mutations, the overall increased risk of cancer at sites other than breast and ovary is small and is observed in women but generally not in men. BRCA1 mutations may confer increased risks of other abdominal cancers in women and increased risks of pancreatic cancer in men and women.

Rebbeck, T. R., T. Friebel, et al. (2005). "Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group." J Clin Oncol **23**(31): 7804-10.

PURPOSE: Bilateral prophylactic oophorectomy (BPO) is widely used for cancer risk reduction in women with BRCA1/2 mutations. Many premenopausal women choose to take hormone replacement therapy (HRT) after undergoing BPO to abrogate immediate symptoms of surgically-induced menopause. Thus, we evaluated whether the breast cancer risk reduction conferred by BPO in BRCA1/2 mutation carriers is altered by use of post-BPO HRT. METHODS: We identified a prospective cohort of 462 women with disease-associated germline BRCA1/2 mutations at 13 medical centers to evaluate breast cancer risk after BPO with and without HRT. We determined the incidence of breast cancer in 155 women who had undergone BPO and in 307 women who had not undergone BPO on whom we had complete information on HRT use. Postoperative follow-up was 3.6 years. RESULTS: Consistent with previous reports, BPO was significantly associated with breast cancer risk reduction overall (hazard ratio [HR] =

0.40; 95%CI, 0.18 to 0.92). Using mutation carriers without BPO or HRT as the referent group, HRT of any type after BPO did not significantly alter the reduction in breast cancer risk associated with BPO (HR = 0.37; 95% CI, 0.14 to 0.96). CONCLUSION: Short-term HRT use does not negate the protective effect of BPO on subsequent breast cancer risk in BRCA1/2 mutation carriers.

1. Goshen R, Chu W, Elit L, et al. Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome? *Gynecologic oncology*. Dec 2000;79(3):477-481.

BACKGROUND: Uterine papillary serous carcinoma (UPSC) shares common pathologic, genetic, and clinical features with other serous cancers of mullerian origin. The most common histologic type of ovarian tumor associated with BRCA mutations is papillary serous. Because of these histologic similarities, we postulated that, in some cases, UPSC may be a manifestation of a field defect in BRCA1 carriers, which also includes ovarian carcinoma, fallopian tube carcinoma, and primary peritoneal carcinoma. METHODS: Fifty-six living patients with UPSC were contacted through their treating physicians and agreed to a family history interview and to provide a blood specimen for BRCA testing. The protein truncation test was used to detect mutations in exons 10 and 11 of BRCA1 and in exon 11 of BRCA2. The presence of four common mutations was assessed by PCR-based specific assays. RESULTS: **A high proportion of patients had a past history of breast cancer (11%) or a first-degree relative with breast cancer (29%).** Four patients were from families with site-specific hereditary breast cancer. However, there was no clear example of the hereditary breast-ovarian cancer syndrome, and **none of the 56 patients was found to carry a BRCA1 or BRCA2 mutation**. CONCLUSIONS: BRCA mutations do not appear to predispose to UPSC and this type of cancer does not appear to be a manifestation of the classical hereditary breast-ovarian cancer syndrome. **The observed association between UPSC and breast cancer may be due to the presence of mutations in other cancer predisposing genes.**

2. Geisler JP, Sorosky JI, Duong HL, et al. Papillary serous carcinoma of the uterus: increased risk of subsequent or concurrent development of breast carcinoma. *Gynecologic oncology*. Dec 2001;83(3):501-503.

OBJECTIVE: Some women with endometrial cancer may be at increased risk for developing breast cancer. The histologic type of endometrial cancer associated with synchronous or subsequent breast cancer has not been clearly established. Our purpose was to determine if a certain histologic type of endometrial cancer was associated with an increased risk of synchronous or subsequent breast cancer. METHODS: The University of Iowa Hospitals and Clinics tumor registry was queried to ascertain all patients with the diagnosis of uterine cancer from January 1, 1983, to December 31, 1994. Statistics were performed utilizing SPSS for Windows version 9.0 (SPSS Inc., Chicago, IL), including Student's t tests and chi(2) tests. RESULTS: Five hundred ninety-two patients had endometrial adenocarcinoma during the study period. Five hundred thirty-six women had endometrioid adenocarcinoma, 23 women had papillary serous carcinoma (UPSC), 21 women had adenosquamous carcinoma, 10 women had clear-cell carcinoma, and 1

woman each had mucinous or squamous carcinoma. Twelve patients had previously been diagnosed with breast carcinomas. **Twenty-five patients were diagnosed with breast cancer either concurrently or subsequent to their diagnosis of endometrial cancer. Synchronous or subsequent breast cancers developed in 3.2% of patients with endometrioid carcinoma and in 25% of patients with UPSC (P < 0.001).** CONCLUSION: Patients with UPSC have an increased risk of development of breast cancer as compared to patients with endometrioid adenocarcinoma of the uterus.

3. Chan JK, Manuel MR, Cheung MK, et al. Breast cancer followed by corpus cancer: is there a higher risk for aggressive histologic subtypes? *Gynecologic oncology*. Sep 2006;102(3):508-512.

OBJECTIVE: To analyze corpus cancer patients with a breast cancer history for risk of developing aggressive uterine histologic types. METHODS: Corpus cancer patients with a history of breast cancer were identified from the Surveillance Epidemiology and End Results database from 1988 to 2001. Demographics, clinico-pathologic, and survival data were analyzed using Kaplan-Meier and logistic regression analyses. RESULTS: Of 52,109 women diagnosed with corpus cancer, 1922 had a history of breast cancer. **Women with a history of breast cancer had a significantly higher proportion of uterine papillary serous carcinomas (UPSC) and sarcomas compared to those without a breast cancer history (9.4% vs. 6.3% for UPSC and 10.3% vs. 8.4% for sarcoma; P < 0.001).** Patients with endometrioid or sarcoma of the uterus after breast cancer had significantly worse 5-year survivals than patients without a breast cancer history (84.4% vs. 90.5%; P < 0.001 and 49.0% vs. 63.6%, P < 0.001, respectively). Older age, advanced stage, lack of surgery and radiation treatment, poor histologic types, and **history of breast cancer were independent prognostic factors for poorer survival**. CONCLUSION: **In this study, the proportional incidence of UPSC and sarcoma was significantly higher in women with a breast cancer history. These findings highlight the association of breast cancer and high-risk corpus cancer subtypes.**

4. Slomovitz BM, Burke TW, Eifel PJ, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. *Gynecologic oncology*. Dec 2003;91(3):463-469.

OBJECTIVE: The aim of this study was to identify clinical and pathologic characteristics of patients with uterine papillary serous carcinoma (UPSC) who were all surgically managed at a single institution. The identified characteristics were then correlated with overall survival (OS). METHODS: One hundred twenty-nine patients with FIGO stage I-IV UPSC who were surgically staged at the University of Texas M. D. Anderson Cancer Center between 1989 and 2002 were identified. For each patient, medical records and pathology reports were reviewed. The Kaplan-Meier method was used to generate OS data. Factors predictive of outcome were compared using the log-rank test and Cox regression analysis. RESULTS: There were 52 patients with stage I disease, 5 with stage II, 41 with stage III, and 31 with stage IV. The median age at the time of diagnosis was 68 years (range, 44-93 years). A personal history of breast cancer was reported by 12.4% of the patients, and a family history of breast cancer was reported by 16%. The 5-year OS

among all patients was 45.9%. Among the stage I patients (IA, n = 19; IB, n = 26; and IC, n = 7), the 5-year OS was 62.9% (IA, 81.5%; IB, 58.6%; and IC, 34.3%). The 5-year OS for patients with stage III and IV disease was 37.3 and 19.9%, respectively. Pathologic features predictive of OS included lymph node status (P </= 0.01), lymph vascular invasion (P </= 0.05), and depth of uterine invasion (P </= 0.05). Among patients with no uterine invasion (n = 32), surgical staging revealed that 37% had stage III or IV disease. Among stage III patients, those who received chemotherapy had a longer OS than those who did not receive chemotherapy (P = 0.03). CONCLUSION: **In this population of nonselected patients with UPSC, approximately 20% had a personal or family history of breast cancer.** Stage, lymph node status, lymph vascular invasion, and depth of myometrial invasion were all risk factors for a worse prognosis. Traditional risk factors, however, did not predict the presence or the absence of metastasis. Among patients with noninvasive uterine disease, there was a high proportion with abdominal metastasis. Therefore, complete surgical staging of these patients is vital in determining their prognosis.