Endometrium and Cancer Literature

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death.Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researched on the cancer and the endometrium.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Alcazar, J. L. and R. Galvan (2009). "Three-dimensional power Doppler ultrasound scanning for the prediction of endometrial cancer in women with postmenopausal bleeding and thickened endometrium." Am J Obstet Gynecol **200**(1): 44 e1-6.

OBJECTIVE: The purpose of this study was to evaluate the role of 3-dimensional power Doppler angiography (3D-PDA) to discriminate between benign and malignant endometrial disease in women with postmenopausal bleeding and thickened endometrium. STUDY DESIGN: Ninety-nine postmenopausal women (median age, 63.1 years; range, 48-84 years) with uterine bleeding and a thickened endometrium (>or= 5 mm) at baseline transvaginal sonography were assessed by 3D-PDA before endometrial biopsy. Endometrial volume, vascularity index (VI), flow index, and vascularity-flow index were calculated with the virtual organ computer-aided analysis method. RESULTS: Histologic diagnoses were endometrial cancer (44 cases), hyperplasia (13 cases), polyp (23 cases), cystic atrophy (14 cases), and submucous myoma (5 cases). Endometrial volume, VI, and vascularity-flow index were significantly higher in malignant vs benign conditions. Receiver operating characteristic analysis revealed that VI was the best parameter for the prediction of endometrial cancer. CONCLUSION: The findings show that 3D-PDA may be useful for the prediction of endometrial cancer in women with postmenopausal bleeding and thickened endometrium at baseline sonography.

Ascher, S. M. and C. Reinhold (2002). "Imaging of cancer of the endometrium." Radiol Clin North Am **40**(3): 563-76.

Transvaginal US is often the initial imaging examination for women with dysfunctional (postmenopausal or intermenstrual) uterine bleeding. However, once the diagnosis of endometrial cancer has been made, contrast-enhanced MRI should be performed in patients who require multifactorial assessment (eg, depth of myometrial invasion, cervical involvement, lymph node metastasis). The results of contrast-enhanced MRI help distinguish patients who need more aggressive therapy and referral to a gynecologic oncologist from those who will do well treated by a community gynecologist.

Ayhan, A., H. Yarali, et al. (1989). "Lymph node metastasis in early endometrium cancer." Aust N Z J Obstet Gynaecol **29**(3 Pt 2): 332-5.

The incidences of pelvic and paraaortic lymph node metastases in 106 patients with clinical Stage 1 endometrium cancer are presented. All patients were primarily surgically staged and treatment consisted of peritoneal cytology assessment, type II radical hysterectomy, bilateral salpingooophorectomy, pelvic and paraaortic total lymphadenectomy. Pelvic lymph node metastases were present in 15.1% and paraaortic lymph node metastases in 8.5% of the patients. Multiple prognostic factors were evaluated in respect to nodal status. This study adds credence to primary surgical staging with total pelvic and paraaortic lymphadenectomy regardless of presence or absence of the various risk factors.

Baanders-van Halewyn, E. A., M. A. Blankenstein, et al. (1996). "A comparative study of risk factors for hyperplasia and cancer of the endometrium." Eur J Cancer Prev **5**(2): 105-12.

A cohort study has been carried out to investigate risk factors for cancer as well as hyperplasia of the endometrium. Over the 13 years for which we followed 25,000 women aged 40-65 (who took part in a population-based screening programme for breast cancer), 111 cases of endometrial cancer and 109 cases of endometrial hyperplasia were diagnosed. A comparison of the outcome between the two disease entities revealed that large body weight among postmenopausal women and the use of oestrogenic drugs at all ages were risk factors for both cancer and hyperplasia of the endometrium. However, reproductive histories and premenopausal steroid profiles differed. Steroid excretion determinations in urine samples collected years before diagnosis provided further evidence in favour of the hypothesis of unopposed action of oestrogens in the aetiology of endometrial cancer. In women who were to develop endometrial hyperplasia or cancer the obesity-oestrogen relationship was stronger than in those who remained free of endometrial disease during the period of follow-up. The possible significance of differences in aromatase activity among the obese is considered.

Barakat, R. R., T. A. Gilewski, et al. (2000). "Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy." J Clin Oncol **18**(20): 3459-63.

PURPOSE: To determine the frequency of developing abnormal pathologic changes in the endometria of tamoxifen-treated women. To characterize the type of pathologic changes involved. PATIENTS AND METHODS: Between October 1991 and September 1998, 159 patients initiating tamoxifen therapy for breast cancer confined to the breast and axillary lymph nodes were entered in a prospective study. In this study, office endometrial biopsies (EMBs) were obtained during the initiation of tamoxifen and at 6-month intervals for a 2-year period. Three subsequent annual EMBs were recorded for each patient, amounting to a 5-year surveillance. RESULTS: One hundred fifty-nine patients with a median age of 50 years were entered onto study. Patients were assessable if EMBs were performed at least 1 year after the initiation of tamoxifen treatment. Nine patients (5. 7%) were considered protocol violations. The remaining 111 assessable patients underwent a total of 635 EMBs (mean, 5.8 EMBs), with a median surveillance time of 36 months. Eighty-two (12.9%) of the 635 biopsies revealed tissue insufficient for diagnosis. Fourteen patients (12.6%) underwent dilation and curettage (D&C) for an abnormal EMB, persistent bleeding, or for evaluation of adnexal masses at the time of laparoscopy. Findings at D&C included complex hyperplasia (n = 1), abnormal histiocytes (n = 1), simple hyperplasia (n = 2), polyps (n = 4), endocervical polyp (n = 1), and decidualization (n = 2). Three D&Cs were negative. Three patients have undergone hysterectomy. CONCLUSION: EMB was used to monitor the endometrium in the majority (95%) of breast cancer patients on tamoxifen in this trial, but the utility of routine EMB for screening in tamoxifen-treated women seems limited.

Bertelli, G., M. Venturini, et al. (1998). "Tamoxifen and the endometrium: findings of pelvic ultrasound examination and endometrial biopsy in asymptomatic breast cancer patients." Breast Cancer Res Treat **47**(1): 41-6.

The need for endometrial surveillance in breast cancer patients undergoing adjuvant treatment with tamoxifen is still controversial. In this study, 164 asymptomatic breast cancer patients (110 on treatment with tamoxifen, 20 mg/day, and 54 controls) were examined with pelvic ultrasound and endometrial biopsy. No differences in ultrasound and biopsy findings were observed in the pre- and perimenopausal group between patients treated with tamoxifen and controls. Postmenopausal patients on tamoxifen had a significantly thicker endometrium (mean+/-SD, 7.2+/-8.5 vs. 1.5+/-4.3 mm, p=0.00002) and significantly larger uterine volume (mean+/-SD, 63.2+/-39.9 vs. 43.7+/-38.8 cm3, p=0.0001) than controls. Fifty-four percent of patients on tamoxifen had an endometrial thickness > or = 5 mm, often with multiple irregular sonolucencies suggesting the presence of cysts. Ultrasound findings, however, did not correlate with the presence of endometrial abnormalities on biopsy, and no endometrial cancer or atypical hyperplasia were found. This lack of correlation makes questionable the use of routine sonography in asymptomatic breast cancer patients on tamoxifen. Obtaining routine endometrial samples, on the other hand, may be difficult in some patients because of cervical stenosis or refusal. Until the benefits of endometrial surveillance will be proved, asymptomatic patients should not be submitted routinely to ultrasound examination or biopsy, but encouraged to report promptly any abnormal vaginal bleeding.

Bese, T., D. Kosebay, et al. (1996). "Ultrasonographic appearance of endometrium in postmenopausal breast cancer patients receiving tamoxifen." Eur J Obstet Gynecol Reprod Biol **67**(2): 157-62.

OBJECTIVES: To assess the ultrasonographic appearance and associated pathological changes of the endometrium in postmenopausal breast cancer patients with tamoxifen therapy. STUDY DESIGN: Forty-eight postmenopausal breast cancer patients receiving 20 mg/day tamoxifen for 6-84 months (mean 29) and 38 control breast cancer patients without any hormonal treatment were examined by transvaginal ultrasonography and endometrial biopsy. Any thickening of the endometrium with cystic formations or homogeneous endometrial thickening > 10 mm detected by ultrasonography was defined as abnormal endometrial appearance. Homogeneous endometrial thickening < 10 mm without cystic formations was accepted as normal. Statistical analysis was performed using the Student's t-test and Mann-Whitney U test. RESULTS: The two groups were similar in age and menopausal period. The patients on tamoxifen therapy had a thicker endometrium (8.6 +/- 6.6 mm) than the non-treated women (4.8 +/- 3.1 mm), which was found to be a statistically significant difference ($P < 0.01$). The sonographic evaluations showed abnormal endometrial appearance in 8 cases of tamoxifen treated women while the others revealed homogeneous thickness < 10 mm without cystic formations or a thin linear echo with or without fluid in the endometrial cavity. All 8 patients with cystic appearance had endometrial thickness > 10 mm. Only 1 patient had endometrial cancer on biopsy and no pathology was observed in the remaining 7 patients. In the control group, only 1 patient had abnormal ultrasonographic finding who had insufficient endometrial tissue on biopsy. CONCLUSIONS: Tamoxifen can produce a sonographic image of the endometrium that resembles endometrial neoplasia. It is suggested that the discrepancy between the sonographic findings and histology may be the result of the stromal edema of the endometrium from tamoxifen treatment. Until more data are gathered, all postmenopausal breast cancer patients who are being treated with tamoxifen should have a periodic ultrasonographic examination and those presenting with a sonogram suggestive of endometrial pathology should undergo biopsy.

Buijs, C., P. H. Willemse, et al. (2009). "Effect of tamoxifen on the endometrium and the menstrual cycle of premenopausal breast cancer patients." Int J Gynecol Cancer **19**(4): 677-81.

OBJECTIVE: Tamoxifen, a nonsteroidal antiestrogen, is the agent of choice in the treatment of premenopausal receptor-positive breast cancer. This study aimed to investigate the influence of tamoxifen on the menstrual cycle and serum hormone levels and the subsequent endometrial response in premenopausal breast cancer patients. METHODS: In tamoxifen-using breast cancer patients aged 55 years or younger, the last menstrual period was registered, serum hormone levels measured, and the endometrial response visualized by transvaginal ultrasonography every 6 months. Premenopausal status was defined as serum levels of estradiol (E2) 0.10 nmol/L or more and follicle-stimulating hormone 30 IU/L or less. Premenopausal patients with an endometrial response of greater than 12 mm were offered a hysteroscopy and curettage. RESULTS: In 121 patients, a total of 241 measurements were performed. Amenorrhea predicted menopausal status incorrectly in 85 (35%) of the 241 measurements in 47 patients. In 8 of 47 endocrinologic premenopausal patients, transvaginal ultrasonography showed an endometrial response of greater than 12 mm (range,15-29 mm). Histopathology in women with an endometrial thickness of greater than 12 mm showed no malignancy. No relation between E2 levels and endometrial thickness was found. CONCLUSIONS: Tamoxifen leads to a disconnection between clinical and endocrinologic menopause in breast cancer patients aged 55 years or less. In premenopausal patients, tamoxifen has a predominantly antiestrogenic effect on the endometrium without a correlation between E2 levels and endometrial response.

Ceci, O., S. Bettocchi, et al. (2000). "Sonographic, hysteroscopic, and histologic evaluation of the endometrium in postmenopausal women with breast cancer receiving tamoxifen." J Am Assoc Gynecol Laparosc **7**(1): 77-81.

STUDY OBJECTIVE: To evaluate the estrogenic effects of tamoxifen on the endometrium in postmenopausal women with breast cancer. DESIGN: Consecutive study (Canadian Task Force classification II-2). SETTING: University-affiliated hospital. PATIENTS: Thirty-three women. Interventions. All patients underwent transvaginal sonography (TVS) and color flow Doppler of endometrial vessels, hysteroscopy, and, if necessary, endometrial biopsy or other operative hysteroscopic procedures. MEASUREMENTS AND MAIN RESULTS: In four women the endometrium was thin on TVS and atrophic at hysteroscopic assessment. In 29 women with thick endometrium on TVS, hysteroscopy and endometrial biopsy showed atrophy (11 patients), hyperplasia (5), polyps (11), and well-differentiated adenocarcinoma (2). The two endometrial cancers were present in women with uterine bleeding. In women with positive histologic findings, the endometrium was significantly thicker ($p = 0.04$) and duration of tamoxifen therapy longer than in those with negative findings, although this was not statistically significant ($p = 0.067$). CONCLUSION:

We believe regular assessment of the endometrium by TVS should be performed in postmenopausal patients at the start of the tamoxifen therapy, and hysteroscopy in women with a thick endometrium or postmenopausal bleeding. We believe that patients with thin endometrium on TVS at the beginning of tamoxifen therapy, who have no abnormal uterine bleeding should be screened with these examinations for 2 years.

Cherubini, A., G. L. Taddei, et al. (2000). "HERG potassium channels are more frequently expressed in human endometrial cancer as compared to non-cancerous endometrium." Br J Cancer **83**(12): 1722-9.

HERG K(+)channels, besides contributing to regulate cardiac and neuronal excitability, are preferentially expressed in tumour cell lines of different histogenesis, where their role in the development and maintenance of the neoplastic phenotype is under study. We show here that both herg gene and HERG protein are expressed with high frequency in primary human endometrial cancers, as compared to normal and hyperplastic endometrium. RT-PCR and immunohistochemistry, using specific anti-HERG antibodies developed in our laboratory, were applied to tissue specimens obtained from 18 endometrial cancers and 11 non-cancerous endometrial tissues. herg RNA and HERG protein are expressed in 67% and 82%, respectively, of cancerous, while in only 18% of non-cancerous tissues. In particular, no expression was found in endometrial hyperplasia. Moreover, electrophysiological experiments confirmed the presence of functioning HERG channels on the plasma membrane of tumour cells. On the whole, these data are the first demonstration of the presence of HERG channels in primary human neoplasias, and could candidate HERG as a potential tool capable of marking cancerous versus hyperplastic endometrial growth.

Cohen, I., M. M. Altaras, et al. (1997). "Estrogen and progesterone receptors in the endometrium of postmenopausal breast cancer patients treated with tamoxifen and progestogens." Gynecol Oncol **65**(1): 83-8.

Postmenopausal breast cancer patients who were treated with tamoxifen and progestogens showed a uniform decidual reaction of the endometrium. It is well established that progestogens antagonize the estrogen effect on the endometrium by reducing its receptors in the endometrium. To assess in vivo such a possible effect of progestogens on endometrium primarily exposed to tamoxifen, we analyzed estrogen and progesterone receptors (ER, PR) on endometrial specimens showing decidualization from nine postmenopausal breast cancer patients on tamoxifen and progestogen treatment and on endometrial polyps with areas of decidualization from two other similar patients. ER was weakly detected in the endometrial glands of four (36.4%) patients and in the endometrial stroma of one (9.1%) patient. PR was detected in the endometrial gland of only one (9.1%) patient. No PR was detected in the endometrial stroma. There was no correlation between the length of tamoxifen treatment, the tamoxifen dosage, or the length of progestogen treatment and the ER or PR content, although progestogens were administered for more than 3 consecutive months in all patients. This relatively very low ER and PR content may be attributed to the antagonistic effect of progestogens on the "priming" estrogen-like effect of tamoxifen on the endometrium.

Dallenbach-Hellweg, G., D. Schmidt, et al. (2000). "The endometrium in breast cancer patients on tamoxifen." Arch Gynecol Obstet **263**(4): 170-7.

We restudied histologically and immunohistochemically 17 endometrial carcinomas, 2 malignant mixed tumors and 180 endometria with benign changes during or after tamoxifen therapy. The carcinomas were subtyped according to the 1994 WHO-classification. Endometrial biopsies were taken only if the endometrial thickness was > 8 mm sonographically, when a polyp was seen, or for postmenopausal bleeding. About half of the endometrial specimens showed simple or cystic atrophy, 55-76% had cystic-atrophic polyps or regressive hyperplasia. Depending upon the dose of tamoxifen, 7-19% (30 mg) to 27-36% (20 mg) showed moderate glandular proliferation. 20-33% had foci of mucinous, clear cell or serous-papillary metaplasia. 68-70% revealed diffuse extensive fibrosis of the endometrial stroma. None of 11 patients biopsied before starting tamoxifen therapy had advanced endometrial glandular proliferation in the second endometrial biopsy after tamoxifen treatment. None of the 19 endometrial neoplasms after tamoxifen therapy was of the endometrioid type: 11 were mucinous adenocarcinomas, 4 clear cell carcinomas, 2 serous-papillary carcinomas, one carcinosarcoma and one malignant Mullerian mixed tumor. The reasons for discrepancies between suspicious sonograms and endometrial atrophy are discussed.

De Goeij, A. F., H. M. Scheres, et al. (1988). "Progesterone receptor quantification with radiolabeled promegestone (R 5020) in frozen sections of endometrium and breast cancer tissue." J Steroid Biochem **29**(5): 465-74.

A technique for the determination of the progesterone receptor content at sections was developed. Series of coverglass-mounted unfixed

frozen sections were incubated with [3H]R5020 only, to determine total binding, or with excess unlabeled R5020, to determine non-specific binding. Ligand binding in the tissue sections was measured by liquid scintillation counting after repeated washing of the coverslips. Elution of ligand binding proteins into the incubation buffer was quantitated with the dextran-coated charcoal method. Specific ligand binding was related to the total tissue protein content which was determined on parallel, unmounted sections. Scatchard analysis showed specific saturable and high affinity (Kd = 0.01-2 nM) section-bound and soluble binding sites in cryostat sections of calf uterus, human endometrium and breast cancer samples. Ligand specificity was studied by competition of [3H]R5020 with a 100-fold excess of various steroid receptor ligands. The competition was excellent for R5020 and progesterone, negligible for estrogens and slight for androgens and corticosteroids. These binding characteristics provide evidence that with this assay progesterone receptors are determined. Exchange experiments showed that with this method total, free as well as occupied, progesterone receptors can be measured. A highly significant linear correlation, and agreement in PR status classification between assay on cytosol and sections was obtained for a series of 21 breast cancer samples. Finally, progesterone receptor analysis using cryostat sections results in the recovery of 2-3 times more PR from the same amount of tissue as compared to the use of cytosol. These results indicate that progesterone receptors can be reliably assayed with Scatchard analysis using cryostat sections, which requires less tissue than the cytosol assay. This method, which is simple and easy to perform could be of practical importance, particularly when only small tissue samples (which also have to be analyzed morphologically or histochemically) are available and when quantitative radiochemical progesterone receptor data are required for direct comparison with (immuno-) histochemical information.

DeCruze, B. and D. Guthrie (1999). "Radiotherapy in poor risk patients with stage I cancer of the endometrium: results of not giving external beam radiotherapy." Clin Oncol (R Coll Radiol) **11**(4): 252-4.

Poor prognosis (poorly differentiated and/or deep myometrial invasion) Stage I endometrial cancer can have a relapse rate as high as 50%. Traditionally, most clinical oncologists treat these patients with external beam radiotherapy after surgery but there is no evidence to show that this improves survival. The retrospective study looks at the results of not giving external beam radiotherapy in 25 consecutive patients and compares the results with a group of 13 consecutive patients who did have such treatment. The two groups were comparable with regard to age, degree of differentiation and degree of invasion. Survival was comparable in the two groups. There is no evidence of any obvious decrease in survival from withholding external beam radiotherapy, but this was not a prospective randomized controlled trial. This study illustrates that it is essential that the Medical Research Council ASTEC trial should be supported because this will determine the true place of external beam radiotherapy in such patients.

Develioglu, O. H., M. Omak, et al. (2004). "The endometrium in asymptomatic breast cancer patients on tamoxifen: value of transvaginal ultrasonography with saline infusion and Doppler flow." Gynecol Oncol **93**(2): 328-35.

OBJECTIVE: To define by transvaginal ultrasonography an optimal cutoff for endometrial thickness measurements to be used in screening for endometrial pathologies in asymptomatic breast cancer patients on tamoxifen, and to evaluate the incorporation of saline infusion sonohysterography and Doppler studies into the diagnostic scheme. METHODS: Sixty tamoxifen-treated women examined by transvaginal ultrasonography with saline infusion were included in this retrospective study. Variables of interest were endometrial thickness and texture, and the presence of intracavitary fluid at ultrasonography, total endometrial thickness, defined as the sum of the two endometrial layers and the presence of polypoid masses at sonohysterography, and uterine artery flow indices at Doppler ultrasonography. The dilatation and curettage performed after the sonographic scan detected pathological endometrial changes in nine cases, including six endometrial polyps, two endometrial hyperplasias, and one endometrial cancer. All parameters evaluated were compared between patients with benign and pathological endometria. Continuous variables that differed significantly between the groups were investigated further by receiver operating characteristics curve analyses and the diagnostic value of combinations of various parameters by binary logistic regression. RESULTS: The endometrial thickness in patients with proven endometrial pathologies was significantly greater compared with women with benign endometria, both by transvaginal ultrasonography (12.7 +/- 5.5 vs. 7.0 +/- 4.5 mm; P = 0.003) and by sonohysterography (6.3 +/- 2.8 vs. 4.1 +/- 1.7 mm; P = 0.036). While saline infusion sonohysterography also revealed a significantly higher frequency of polypoid masses in the former group (67% vs. 2%; P < 0.001), no other significant differences were defined between the groups in regard to any other sonographic or Doppler parameter

evaluated. For the diagnosis of any endometrial pathology, the optimal cutoffs of endometrial thickness at ultrasonography and total endometrial thickness at sonohysterography were 9.5 and 5.5 mm, with sensitivities of 89% and 78% and specificities of 78% and 84%, respectively. A logistic regression model including polypoid lesions (B = -4.935; P < 0.001) and total endometrial thickness at sonohysterography (B = 0.432; P = 0.027) as the only two independent variables had a sensitivity of 100% and specificity of 84%. CONCLUSION: Saline infusion sonohysterography does, yet Doppler ultrasonography does not, add to the value of endometrial thickness measurements by transvaginal ultrasonography in the screen for endometrial pathologies in asymptomatic breast cancer patients on tamoxifen.

Duffy, S. R. and L. Taylor (2004). "Molecular markers in the endometrium at baseline of postmenopausal patients with early breast cancer in the ATAC (Arimidex, tamoxifen, alone, or in combination) trial." Am J Obstet Gynecol **191**(6): 1921-7.

OBJECTIVE: This study was undertaken to assess baseline endometrial molecular events in the ATAC (Arimidex, tamoxifen, alone, or in combination) trial of breast cancer adjuvant therapy. STUDY DESIGN: Estrogen receptor (ER) and progesterone receptor (PR) levels and markers of cell proliferation (Ki67) and apoptosis (Bcl -2) were assessed in 93 patients at baseline. RESULTS: An inactive/atrophic endometrium was found in 63 patients, 5 had a proliferative endometrium, and 12 had a secretory endometrium. Thirteen endometrial polyps were analyzed. Inactive endometrium showed high levels of ER in the glandular epithelium, whereas in more than 50% of samples, PR expression was negative or low (+) in the glandular epithelium, and stroma. Ki67 expression was low in both the glandular epithelium and the stroma of the inactive endometrium, whereas Bcl -2 expression was mostly high or very high (+++/++++) in the glandular epithelium. Bcl -2 was strongly expressed (+++/++++) in the glandular epithelium of polyps. CONCLUSION: Although all patients were asymptomatic, some had endometrial pathology.

Dumitru, D. M., M. Onofriescu, et al. (2009). "The endovaginal ultrasound finding of a thin and regular endometrium is uncommon in endometrial cancer." Rev Med Chir Soc Med Nat Iasi **113**(1): 132-5.

AIM: To present the clinical and ultrasound features in patients with endometrial cancer in whom the endometrial thickness was less that 5 mm. METHOD: Retrospective study on 263 patients with endometrial carcinoma in whom the ultrasound evaluation of the endometrium was performed. The features noticed in the patients with endometrial thickness below 5 mm are presented. RESULTS: In 249 (94.68%) of our patients with endometrial carcinoma the mean endometrial thickness was 15 mm. In 14 patients (5.32%), in whom biopsy was performed prior to ultrasound examination, endometrial thickness was less than 5 mm. CONCLUSIONS: A thin and regular endometrium (below 5 mm) rules out an endometrial carcinoma provided that no biopsy has been performed within 3 months before ultrasound examination.

Fons, G., S. M. Hasibuan, et al. (2007). "Validation of tissue microarray technology in endometrioid cancer of the endometrium." J Clin Pathol **60**(5): 500-3.

AIM: To validate tissue microarray (TMA) for endometrial cancer by comparing immunohistochemical staining results of triplicate core biopsies on TMA with the results of full-section analysis. METHODS: The study material consisted of slides and selected tissue blocks of 41 patients with endometrioid cancer of the endometrium. A TMA was constructed. Both the TMA and the slides were stained with the same antibodies against progesterone receptor (PR), oestrogen receptor, p53 and epithelial membrane antigen (EMA). Concordance between results was expressed as the kappa statistic. RESULTS: Concordance between the staining results of TMA and whole slides was good for PR (kappa = 0.69), oestrogen receptor (kappa = 0.78), p53 (kappa = 0.81) and EMA (kappa = 0.72). Concordance between the results on TMA and slides depends on the number of assessable cores per tumour. Three assessable cores per case result in outcomes that are at least 94% similar to those achieved using conventional tissue sections with a two-class scoring system. This is independent of focal or diffuse staining patterns. CONCLUSION: TMA is a useful tool for further analysis of the molecular pathways in endometrial cancer. The effect of selection has to be taken into account when the prognostic value of protein expression on TMA is determined.

Fujimoto, J., M. Hori, et al. (1996). "Estrogen induces expression of c-fos and c-jun via activation of protein kinase C in an endometrial cancer cell line and fibroblasts derived from human uterine endometrium." Gynecol Endocrinol **10**(2): 109-18.

Endometrial fibroblasts derived from uterine endometrium as controls and endometrial cancer cell lines (Ishikawa and HHUA cells) were analyzed for the induction manner of c-fos and c-jun transcripts in endometrial cancers, some of which are estrogen-dependent in growth. Estrogen increased c-fos

expression and protein kinase C (PKC) activity in fibroblasts and Ishikawa cells, but not in HHUA cells. Progesterone diminished c-fos and c-jun expression and PKC activity induced by estradiol in the fibroblasts, but not in Ishikawa cells, which persistently overexpressed c-fos and c-jun. In these cells, 12-0-tetra-decanoylphorbol-13-acetate (TPA) increased c-fos and c-jun expression as did estradiol. Pretreatment with 1-(5-isoquinolinesulfonyl)-2-methylpiperazine dihydrochloride (H-7) abolished estrogen-inducible over-expression of c-fos and c-jun. The combination of both estradiol and TPA at maximum effective concentration exerted no additive and synergistic effect on induction of c-fos and c-jun expression. In conclusion, persistent activation of PKC might lead to overexpression of c-fos and c-jun in some endometrial cancers with an estrogen predominant milieu, which might be, at least in part, associated with the transformation or growth potential.

Garuti, G., F. Grossi, et al. (2007). "Pretreatment and prospective assessment of endometrium in menopausal women taking tamoxifen for breast cancer." Eur J Obstet Gynecol Reprod Biol **132**(1): 101-6.

OBJECTIVES: To estimate the pretreatment incidence of endometrial pathology and to prospectively assess the endometrial morbidity emerging during tamoxifen intake for breast cancer. STUDY DESIGN: One-hundred and forty-six menopausal breast cancer patients, candidate to receive tamoxifen underwent endometrial assessment by Transvaginal Ultrasonography (TU) before the start of therapy. A double-layered endometrial stripe measuring more than 4mm indicated hysteroscopy and endometrial biopsy. Endometrial abnormalities detected before the start of tamoxifen were treated by operative hysteroscopy or by hysterectomy; no therapy and yearly hysteroscopic follow-up was scheduled for patients showing non-atypical hyperplasias. All women were asked to undergo TU on a yearly basis; during the follow-up period, indication for hysteroscopy and endometrial biopsy were the following: (i) an endometrial lining measured above 4mm at the first time, (ii) at least a 50% increase of endometrial thickness since the last finding in patients previously assessed by hysteroscopy, (iii) a recorded vaginal bleeding, and (iv) previous findings of endometrial hyperplasia. Histopathologic result from biopsy or hysterectomy was the reference test to establish the baseline prevalence of endometrial pathology and the emerging prevalences of morbidity after 12, 24, 36, 48 and 60 months of tamoxifen therapy. RESULTS: One-hundred and five patients were followed for 60 months, whereas 113, 126, 137 and 141 patients were evaluated up to 48, 36, 24 and 12 months, respectively. In 44 out of 146 patients, pretreatment TU showed an endometrium thicker than 4mm and in 31 (21.2%) of these patients abnormalities consisting of 16 endometrial polyps, seven polyps harboring simple hyperplasia, four simple hyperplasias, three atypical hyperplasias and one adenocarcinoma were found. During tamoxifen intake benign endometrial abnormalities were detected in 36 out of 114 assessable patients showing normal endometrium before the start of tamoxifen therapy (31.5%) and in seven out of 27 patients with baseline endometrial abnormalities (25.9%). Overall, an endometrial pathology emerged in 30.4% of patients during tamoxifen administration and in no patients we found an atypical lesion. CONCLUSIONS: In menopausal breast cancer patients the incidence of endometrial abnormalities before the start of tamoxifen therapy is high and includes 2.7% of atypical pathology. After the diagnosis and treatment of baseline atypical lesions were accomplished, no atypical endometrial lesion emerged after the start of tamoxifen administration. Based on these findings, we believe that pretreatment assessment of endometrium is recommended in all menopausal women candidate to receive tamoxifen therapy.

Gerber, B., A. Krause, et al. (2000). "Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound." J Clin Oncol **18**(20): 3464-70.

PURPOSE: To study the value of transvaginal ultrasound (TVS) in endometrial screening of postmenopausal breast cancer patients treated with tamoxifen. PATIENTS AND METHODS: In 247 tamoxifen-treated (20 to 30 mg/d for >/= 2 years) women and 98 controls, the endometrium was prospectively followed-up by means of TVS every 6 months for up to 5 years. Patients with homogeneous endometrium of more than 10-mm thickness were then scanned repeatedly every 3 months. RESULTS: The mean endometrial thickness was 3.5 +/- 1.1 mm before treatment and increased to a maximum of 9. 2 +/- 5.1 mm after 3 years of tamoxifen application (P: <.0001), which was significantly (P: <.0001) thicker compared with controls. Fifty-two asymptomatic patients with thickened or morphologically suspect endometrium underwent hysteroscopy and dilatation and curettage (D&C), resulting in four uterine perforations. Histopathologically, atrophy was found in 38 patients (73.1%), polyps in nine, hyperplasia in four, and endometrial cancer in one case. In 20 screened patients who reported vaginal bleeding, five atrophies (25%), five polyps, four hyperplasias, and two endometrial cancers were found. Before hysteroscopy

and D&C were performed, 36 (69.2%) of 52 asymptomatic and four (20%) of 20 symptomatic patients were scanned by repeated TVS over 2 to 30 months. Invasive diagnostic procedures were significantly (P: <.05) more frequent in younger and obese patients. In the controls, one asymptomatic polyp and one symptomatic hyperplasia were found. CONCLUSION: In tamoxifen-treated patients, TVS offered a high false-positive rate, even with a cutoff value of 10 mm for endometrial thickness and repeated TVS scans. Increased iatrogenic morbidity and only one asymptomatic endometrial carcinoma do not warrant endometrial screening by TVS in tamoxifen-treated patients.

Gielen, S. C., L. C. Kuhne, et al. (2005). "Tamoxifen treatment for breast cancer enforces a distinct gene-expression profile on the human endometrium: an exploratory study." Endocr Relat Cancer **12**(4): 1037-49.

Tamoxifen treatment for breast cancer increases proliferation of the endometrium, resulting in an enhanced prevalence of endometrial pathologies, including endometrial cancer. An exploratory study was performed to begin to understand the molecular mechanism of tamoxifen action in the endometrium. Gene-expression profiles were generated of endometrial samples of tamoxifen users and compared with matched controls. The pathological classification of samples from both groups included atrophic/inactive endometrium and endometrial polyps. Unsupervised clustering revealed that samples of tamoxifen users were, irrespective of pathological classification, fairly similar and consequently form a subgroup distinct from the matched controls. Using SAM analysis (a statistical method to select genes differentially expressed between groups), 256 differentially expressed genes were selected between the tamoxifen and control groups. Upon comparing these genes with oestrogen-regulated genes, identified under similar circumstances, 95% of the differentially expressed genes turned out to be tamoxifen-specific. Finally, construction of a gene-expression network of the differentially expressed genes revealed that 69 genes centred around five well-known genes: TP53, RELA, MYC, epidermal growth factor receptor and beta-catenin. This could indicate that these well-known genes, and the pathways in which they function, are important for tamoxifen-controlled proliferation of the endometrium.

Goncalves, M. A., W. J. Goncalves, et al. (1999). "Hysteroscopic evaluation of the endometrium of post-menopausal patients with breast cancer before and after tamoxifen use." Int J Gynaecol Obstet **66**(3): 273-9.

OBJECTIVE: To evaluate by hysteroscopy and histopathology the influence of tamoxifen in the endometrium of post-menopausal women with previous breast cancer. METHOD: Out of 46 patients studied, 20 of them had been using tamoxifen for an average length of 12 months, and are still being followed-up. Hysteroscopy with endometrial biopsy was performed before and after the use of the drug. RESULTS: The prevalence of endometrial activity before and after this hormoniotherapy was the same, i.e. 10.0%, showing a non-significant variation. CONCLUSION: The hormoniotherapy with tamoxifen has not increased the endometrial proliferactive activity of postmenopausal patients with breast cancer. The most common hysteroscopical finding was numerous vesicles disseminated throughout the uterine cavity probably due to atrophy of the endometrium.

Gull, B., B. Karlsson, et al. (2003). "Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer." Am J Obstet Gynecol **188**(2): 401-8.

OBJECTIVE: The purpose of this study was to evaluate postmenopausal bleeding and transvaginal sonographic measurement of endometrial thickness as predictors of endometrial cancer and atypical hyperplasia in women whose cases were followed for > or =10 years after referral for postmenopausal bleeding. STUDY DESIGN: Women (n = 394) who had postmenopausal bleeding from November 1987 to October 1990 underwent transvaginal sonographic measurement of endometrial thickness and curettage. It was possible to assess the medical records (regarding recurrence of a postmenopausal bleeding, development of endometrial cancer, and death) in 339 of the 394 women (86%) > or =10 years after referral for postmenopausal bleeding. RESULTS: Thirty-nine of the 339 women (11.5%) had endometrial cancer, and 5 women (1.5%) had atypical hyperplasia. The relative risk of endometrial cancer in women who were referred for postmenopausal bleeding was 63.9 (95% CI, 46.0-88.8); the corresponding relative risk for endometrial cancer and atypical hyperplasia together was 72.1 (95% CI, 52.8-98.5) compared with women of the same age from the general population of the same region of Sweden. No woman with an endometrial thickness of < or =4 mm was diagnosed as having endometrial cancer. The relative risk of the development of endometrial cancer in women with an endometrial thickness of >4 mm was 44.5 (95% CI, 6.5-320.1) compared with women with an endometrial thickness of < or =4 mm. The reliability of endometrial thickness (cutoff value, < or =4 mm) as a

diagnostic test for endometrial cancer was assessed: Sensitivity, 100%; specificity, 60%; positive predictive value, 25%; and negative predictive value, 100%. The incidence of endometrial cancer or atypical hyperplasia in women with an intact uterus whose cases had been followed for > or =10 years was 5.8% (15/257 women) compared with 22.7% (15/66 women) in women who had < or =1 episode of recurrent bleeding. No endometrial cancer was diagnosed in women with a recurrent postmenopausal bleeding who had an endometrial thickness of < or =4 mm at the initial scan. CONCLUSION: Postmenopausal bleeding incurs a 64-fold increase risk for endometrial cancer. There was no increased risk of endometrial cancer or atypia in women who did not have recurrent bleeding, whereas women with recurrent bleeding were a high-risk group. No endometrial cancer was missed when endometrial thickness measurement (cutoff value, < or =4 mm) was used, even if the women were followed up for < or =10 years. We conclude that transvaginal sonographic scanning is an excellent tool for the determination of whether further investigation with curettage or some form of endometrial biopsy is necessary

Hachisuga, T., H. Tsujioka, et al. (2005). "K-ras mutation in the endometrium of tamoxifen-treated breast cancer patients, with a comparison of tamoxifen and toremifene." Br J Cancer **92**(6): 1098-103.

The putative presence of a mutation in codon 12 of the K-ras gene was investigated in the endometrium of tamoxifen (TAM) and toremifene (TOR)-treated breast cancer patients. DNA was extracted from fresh cytologic samples of the endometrium in 86 TAM and 21 TOR-treated breast cancer patients. Mutations were detected by enriched PCR and an enzyme-linked mini-sequence assay (ELMA). K-ras mutation was found in 35 TAM-treated endometrial samples, and in only one TOR-treated endometrium (P<0.003). In 24 premenopausal patients, K-ras mutation was found in seven (43.8%) of 16 patients with less than 47 months of TAM treatment, while none was found in eight patients with more than 48 months of TAM treatment (P<0.03). In 62 postmenopausal-amenorrheic patients, K-ras mutation was found in three (15.8%) of 19 patients with less than 23 months of TAM treatment, while it was found in 16 (61.5%) of 26 patients with 24-47 months of TAM treatment and nine (52.9%) of 17 patients with more than 48 months of TAM treatment (P=0.002). The presence of K-ras mutation is significantly influenced by the duration of TAM treatment and menstrual status of the patients. TOR may have a lower potential genotoxicity than TAM.

Hasengaowa, J. Kodama, et al. (2006). "Heparanase expression in both normal endometrium and endometrial cancer." Int J Gynecol Cancer **16**(3): 1401-6.

The aim of this study was to investigate the relationship between heparanase expression and prognostic factors in endometrial cancer, as well as the relationship between heparanase expression during phases of the normal endometrial cycle. Immunohistochemical analysis of 166 endometrial cancers and 34 normal endometria in various phases of growth was performed. The heparanase expression in the late-proliferative phase of normal endometria was found to be significantly higher than in either the early-proliferative or the secretory phases (P= .012 and P= .044, respectively). Heparanase expression was also significantly higher in endometrial cancer patients with tumors of an advanced FIGO stage (P= .0003) and high FIGO grade (P= .004) and with cancers showing either deep myometrial invasion (P= .023), lymph node metastasis (P= .006), lymphvascular space involvement (P= .048), or positive peritoneal cytology (P= .010). The disease-free and overall survival rates of patients with intense heparanase expression were significantly lower than those of patients with absent or moderate heparanase expression (P= .004 and P= .002, respectively). Heparanase may participate in normal endometrial remodeling and can serve as an indicator of the aggressive potential and poor prognosis of endometrial cancers.

Hayata, T. (1991). "Ultrastructural study of glandular epithelium in adenomyosis in comparison with those of proliferative endometrium and well-differentiated endometrial cancer." Am J Obstet Gynecol **165**(1): 225-8.

Adenomyotic glandular tissue from five patients underwent electron microscopic investigation to observe its ultrastructural characteristics. The adenomyotic epithelium was compared with that of proliferative normal epithelium (two patients) and well-differentiated endometrial adenocarcinoma (two patients). The results revealed that morphologically the adenomyotic glandular epithelium is somewhat less differentiated than proliferative endometrium and that its cytoplasmic organelles have some similarities with those of endometrial cancer. Whether these similarities predispose the adenomyotic glandular tissue to malignant degeneration remains to be elucidated.

Hearns-Stokes, R., C. Mayers, et al. (2006). "Expression of the proto-oncoprotein breast cancer nuclear receptor auxiliary factor (Brx) is altered in

eutopic endometrium of women with endometriosis." Fertil Steril **85**(1): 63-70.

OBJECTIVE: To evaluate the expression of estrogen receptor alpha (ERalpha), estrogen receptor beta (ERbeta), and breast cancer nuclear receptor auxiliary factor (Brx) in eutopic endometrium of normal women and women with endometriosis. DESIGN: Prospective observational study. SETTING: Tertiary care and research center. PATIENT(S): Twenty-nine women with endometriosis and 35 healthy ovulatory volunteers of similar ages. INTERVENTION(S): Endometrial biopsy. MAIN OUTCOME MEASURE(S): Expression of immunohistochemical staining intensity and localization of ERalpha, ERbeta, and Brx proteins in eutopic endometrium during the menstrual cycle. RESULT(S): Expression of ERalpha and ERbeta was highest in the proliferative phase and was similar in both groups. Brx expression differed between healthy volunteers and those with endometriosis. During the proliferative phase, immunostaining intensity of Brx was greater in both the glandular and the stromal compartments of biopsies from patients with endometriosis compared to healthy volunteers; nuclear stromal Brx staining was more common in patients with endometriosis. CONCLUSION(S): The spatiotemporal expression of Brx was altered in eutopic endometrium of women with endometriosis. These findings suggest a fundamental alteration in the endometrium of women who have endometriosis. The role of Brx in ectopic implantation of endometrium deserves further study.

Hirata, S., N. Yamada-Mouri, et al. (1995). "Presence of alternatively spliced-estrogen receptor mRNA variants in normal human uterine endometrium and endometrial cancer." Endocr J **42**(2): 289-93.

Presence of alternatively spliced-estrogen receptor (ER) mRNA variants has been revealed in the breast cancer tissues. The ER variants transcribed from these mRNA variants were supposed to cause changes in the estrogen responsiveness of breast cancer. Although uterine endometrial cancer also has an estrogen-dependent profile, these ER mRNA variants have not yet been reported in the tumor. In the present study, we attempted to detect the exon 7 deletion- (del.7-) and exon 5 deletion (del.5) ER mRNA variants in normal human uterine endometrium (hEM) and uterine endometrial cancer tissue (hEC) by the use of reverse transcription-polymerase chain reaction-Southern blotting (RT-PCR-SB) with the PCR primers: hE4 (forward), hE6 (reverse), and hE8 (reverse), which were located in exons 4, 6, and 8, respectively. Two major products were generated from RNAs of both hEM and hEC with primers hE4 and hE8. The nucleotide sequence of the longer product was identical to exon 4-8 of human ER cDNA, whereas that of the shorter one completely deleted exon 7. Moreover, when the RT-PCR was done with the primers hE4 and hE6, the shorter product lacking exon 5 was detected with the longer one having the same sequence as exon 4-6 of human ER cDNA. Since the RT-PCR-SB with primers hE4 and hE8 produced a very low or undetectable level of the signals corresponding to del.5 ER mRNA variant, the level of del.7 ER mRNA variant seemed to be higher than that of del.5 ER mRNA variant.(ABSTRACT TRUNCATED AT 250 WORDS)

Hirose, K., K. Tajima, et al. (1996). "Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer." Jpn J Cancer Res **87**(9): 1001-9.

In Japan the incidence of cervical cancer has been high, but has recently been decreasing gradually, while the incidence of endometrial cancer is running at lower levels but is gradually increasing. To clarify the common and/or specific risk and/or protective factors of cervical cancer(CC) in contrast with endometrial cancer (EC), a comparative case-control study was conducted at the Aichi Cancer Center Hospital, Japan. In total, 556 CC cases and 145 EC cases were included and 26,751 women, confirmed as free of cancer, were chosen as the common control group. Odds ratio and its 95% confidence interval (95%CI) for each exposure variable were estimated by using an unconditional logistic regression model adjusted for age and first-visit year. Habitual smoking and experience of pregnancy increased the risk of CC, while decreasing the risk of EC. Greater body mass index (>20), daily intake of fruit and more frequent intake of boiled or broiled fish (>1-2 times/week) decreased the risk of CC, whereas they increased the risk of EC. Daily intake of milk decreased the risk of CC. The results obtained from this study suggest that several EC-increasing risk factors are in fact CC-decreasing determinants. The observed risk reduction in both CC and EC by physical exercise and dietary control for health is noteworthy from the public health standpoint and warrants further investigation.

Huang, K. T., C. A. Chen, et al. (1996). "Sonographic characteristics of adenofibroma of the endometrium following tamoxifen therapy for breast cancer: two case reports." Ultrasound Obstet Gynecol **7**(5): 363-6.

Adenofibroma of the endometrium is thought to be a rare benign variant of the mixed mesodermal tumor, and its preoperative diagnosis is difficult. We describe the sonographic characteristics of two cases of adenofibroma of the endometrium. In both cases the patient was receiving prolonged tamoxifen therapy

following surgery for breast cancer. Sonographically, this rare disease is observed as an intracavitary mass containing multiple small cysts with low-resistance intratumor blood flow. The unique sonographic findings make the preoperative diagnosis possible.

Hubbard, J. L. and J. K. Holcombe (1990). "Cancer of the endometrium." Semin Oncol Nurs **6**(3): 206-13.

Cancer of the endometrium is the most common and curable gynecologic malignancy. It has a most easily recognizable symptom in its usual presentation as postmenopausal bleeding. Treatment may vary considerably based on prognostic factors and may include surgery, radiotherapy, hormonal manipulation, or cytotoxic chemotherapy. Rehabilitation is the focus of nursing intervention and is initiated at the time of the cancer diagnosis. The continued effort by investigators to define intermediate and high-risk populations and, thus, appropriate adjuvant treatment will continue to reduce mortality from endometrial carcinoma.

Ichikawa, Y., H. Tsunoda, et al. (2002). "Microsatellite instability and immunohistochemical analysis of MLH1 and MSH2 in normal endometrium, endometrial hyperplasia and endometrial cancer from a hereditary nonpolyposis colorectal cancer patient." Jpn J Clin Oncol **32**(3): 110-2.

Hereditary nonpolyposis colorectal cancer (HNPCC)-related endometrial cancer is associated with mutations in DNA mismatch repair genes. However, chronological changes of these genes in the endometrium have not been studied in women from HNPCC families. Tissue samples of normal endometrium, endometrial hyperplasia without atypia and endometrial cancer were collected at different times from a 41-year-old Japanese woman with a family history of HNPCC. Combined microsatellite instability (MSI) and immunohistochemical analysis of MLH1 and MSH2 predicted the presence of a mutation in MSH2 when she had endometrial hyperplasia without atypia 7 months before the diagnosis of endometrial cancer. Endometrial hyperplasia without atypia may indicate an early development of endometrial cancer in women from HNPCC families.

Kavak, Z. N., S. Binoz, et al. (2000). "The effect of tamoxifen on the endometrium, serum lipids and hypothalamus pituitary axis in the postmenopausal breast cancer patients." Acta Obstet Gynecol Scand **79**(7): 604-7.

BACKGROUND: There is still no cost-effective endometrial screening method for asymptomatic postmenopausal breast cancer patients using tamoxifen. We investigated the effectivity of transvaginal ultrasonography and endometrial sampling as a screening method for asymptomatic patients. Additionally the effect of tamoxifen on hypothalamus-pituitary axis and serum lipid profiles were investigated. METHODS: Sixty-seven gynecologically asymptomatic postmenopausal breast cancer patients were enrolled in this randomized crossover study. Endometrial thickness was determined by transvaginal ultrasonography, endometrial biopsy was obtained by Pipelle or fractional curettage, hormone and lipid profiles were compared in the two groups which consisted of forty-seven tamoxifen user (cases) and twenty nonuser (controls) patients. RESULTS: The mean endometrial thickness measured by transvaginal sonography was 7.8 mm (3-20 mm) versus 3.7 mm respectively. The difference was significant in tamoxifen users. The most common histopathologic finding was endometrial polyp, detected in five patients. In the control group there was no endometrial polyp. The positive histopathologic findings were present in twenty-two patients in the case group but there were only two patients with positive histopathologic findings in the control group. Ultrasound findings did not correlate with the presence of endometrial abnormalities on biopsy and no endometrial cancer or hyperplasia were detected. In tamoxifen users serum FSH and LH levels were significantly lower than in nonusers. Serum HDL levels were significantly higher in the case group. CONCLUSION: Ultrasonographic imaging of the endometrium in asymptomatic postmenopausal breast cancer patients using tamoxifen should be interpreted with caution. Other imaging techniques should be used for more specific information about the endometrium.

Kelloff, G. J., C. W. Boone, et al. (1995). "Strategies for phase II cancer chemoprevention trials: cervix, endometrium, and ovary." J Cell Biochem Suppl **23**: 1-9.

Well-designed and conducted Phase II clinical trials are very important to cancer chemoprevention drug development. Three critical aspects govern the design and conduct of these trials--well-characterized agents, suitable cohorts, and reliable biomarkers for measuring efficacy that can serve as surrogate endpoints for cancer incidence. Requirements for the agent are experimental or epidemiological data showing chemopreventive efficacy, safety on chronic administration, and a mechanistic rationale for the chemopreventive activity observed. Agents that meet these criteria for chemoprevention of cervical cancer include antiproliferative drugs (e.g., 2-difluoromethylornithine), retinoids, folic acid, antioxidant vitamins and other agents that prevent

cellular oxidative damage. Because of the significant cervical cancer risk associated with human papilloma virus (HPV) infection, agents that interfere with the activity of HPV products may also prove to be effective chemopreventives. In endometrium, unopposed estrogen exposure has been associated with cancer incidence. Thus, pure antiestrogens and progestins may be chemopreventive in this tissue. Ovarian cancer risk is correlated to ovulation frequency; therefore, oral contraceptives are potentially chemopreventive in the ovary. Recent clinical observations also suggest that retinoids, particularly all-trans-N-4-hydroxyphenylretinamide, may be chemopreventive in this tissue. The cohort should be suitable for measuring the chemopreventive activity of the agent and the intermediate biomarkers chosen. In the cervix, patients with cervical intraepithelial neoplasia (CIN) and in endometrium, patients with atypical hyperplasia, fit these criteria. Defining a cohort for a Phase II trial in the ovary is more difficult. This tissue is less accessible for biopsy; consequently, the presence of precancerous lesions is more difficult to confirm. The criteria for biomarkers are that they fit expected biological mechanisms (i.e., differential expression in normal and high-risk tissue, on or closely linked to the causal pathway for the cancer, modulated by chemopreventive agents, and short latency compared with cancer), may be assayed reliably and quantitatively, measured easily, and correlate to decrease cancer incidence. They must occur in sufficient incidence to allow their biological and statistical evaluation relevant to cancer. Since carcinogenesis is a multipath process, single biomarkers are difficult to validate as surrogate endpoints, perhaps appearing on only one or a few of the many possible causal pathways. Panels of biomarkers, particularly those representing the range of carcinogenesis pathways, may prove more useful as surrogate endpoints. It is important to avoid solely on biomarkers that do not describe cancer but represent isolated events that may or may not be on the causal pathway or otherwise associated with carcinogenesis. These include markers of normal cellular processes that may be increased or expressed during carcinogenesis. Chemoprevention trials should be designed to evaluate fully the two or three biomarkers that appear to be the best models of the cancer. Additional biomarkers should be considered only if they can be analyzed efficiently and the sample size allows more important biomarkers to be evaluated completely. Two types of biomarkers that stand out regarding their high correlation to cancer and their ability to be quantified are measures of intraepithelial neoplasia and indicators of cellular proliferation. Measurements made by computer-assisted image analysis that are potentially useful as surrogate endpoint biomarkers include nuclear polymorphism comprising nuclear size, shape (roundness), and texture (DNA distribution patterns); nucleolar size and number of nucleoli/nuclei; DNA ploidy, and proliferation biomarkers such as S-phase fraction and PCNA...

Kesim, M. D., Y. Aydin, et al. (2008). "Long-term effects of the levonorgestrel-releasing intrauterine system on serum lipids and the endometrium in breast cancer patients taking tamoxifen." Climacteric **11**(3): 252-7.

OBJECTIVE: To investigate the long-term effects of a levonorgestrel-releasing intrauterine system on the endometrium and lipid profile of breast cancer patients taking tamoxifen. STUDY DESIGN: A total of 142 postmenopausal women taking tamoxifen were included in the study. A levonorgestrel-releasing intrauterine system was fitted to 70 women in the study group; a further 72 women acted as the control group. All women were followed for 36 months. Serum lipids were measured at the beginning and at the end of 36 months. Endometrial biopsies were obtained by hysteroscopy at the beginning and at the end of the 36th month in both groups. RESULTS: After 36 months, there were minor changes in serum lipids, fewer endometrial polyps and no endometrial hyperplasia in the study group compared to the control group. CONCLUSION: The levonorgestrel-releasing intrauterine system does not affect serum lipid levels significantly and may prevent the increased risk of endometrial polyps and hyperplasia associated with the use of tamoxifen in women with breast cancer. This may reduce the need for investigation of side-effects in women taking tamoxifen and also reduce patient discomfort while improving treatment adherence.

Kim, H. S., Y. T. Jeon, et al. (2008). "The effect of adjuvant hormonal therapy on the endometrium and ovary of breast cancer patients." J Gynecol Oncol **19**(4): 256-60.

OBJECTIVE: To investigate the effect of adjuvant hormonal therapy on the endometrium and ovary of breast cancer patients. METHODS: A retrospective review was performed on the 207 patients who had taken tamoxifen or anastrozole, as adjuvant hormonal therapy after breast cancer surgery between January 2003 and December 2006. Gynecologic surveillance constituted of ultrasonographic exam of the endometrial thickness and ovarian cyst formation. The patients were classified into three groups and analyzed; premenopausal/postmenopausal women receiving tamoxifen and women receiving anastrozole. RESULTS: Mean duration of follow up was 20.6+/-

6.6 months. There was no difference of mean endometrial thickness before hormonal therapy among the three groups (p=0.327). In women receiving tamoxifen, the endometrium was continuously thickened in proportion to the duration of the therapy irrespective of menopausal status while it remained unchanged in women receiving anastrozole (p<0.05). Endometrial biopsies were performed in 28 patients receiving tamoxifen. The most common histologic finding was proliferative endometrium in premenopausal women (7/21) and atrophic endometrium in postmenopausal women (6/7). There was no case of endometrial cancer in both groups. Ovarian cyst was found in 32 women and the most were developed in premenopausal women receiving tamoxifen (30/32). All of them showed benign nature on transvaginal ultrasonographic findings. CONCLUSION: Women undergoing adjuvant hormonal therapy after breast cancer surgery exhibited changes in the endometrium and ovary. However most changes were not a serious problem in this study and frequent gynecologic surveillance in these patients needs further investigation.

Koumantaki, Y., A. Tzonou, et al. (1989). "A case-control study of cancer of endometrium in Athens." Int J Cancer **43**(5): 795-9.

Eighty-three women with invasive adenocarcinoma of the endometrium and 164 control women hospitalized for various orthopedic conditions were interviewed regarding demographic, reproductive, socio-economic and biomedical characteristics, including their use of tobacco, drugs and exogenous estrogens. The data were analyzed by modelling rate ratio (r) through multiple logistic regression. The main results were as follows: women with invasive adenocarcinoma of the endometrium had earlier menarche (r = 0.82 for every additional year; one-tailed p approx. 0.04), later menopause (r = 1.50 for a 5-year difference; one-tailed p approx. 0.004), and fewer live-born children (r = 0.86 for every additional child; one-tailed p approx. 0.08); they were also taller (r = 1.33 for a 5-cm difference; one-tailed p approx 0.03), whereas weight, adjusted for height, was not a statistically significant risk indicator (one-tailed p approx. 0.38). Regular use of combination oral contraceptives was associated with a reduced risk of endometrial cancer (r = 0.56), whereas intake of menopausal estrogens for more than 6 months was associated with an increased risk (r = 2.04); however, because of the low frequency of use of exogenous estrogen preparations in Greece, neither of these 2 results was statistically significant. Tobacco smoking was associated with a significantly reduced risk of endometrial cancer; smoking 15-20 cigarettes per day for 20 years was associated with a rate ratio of 0.49 (one-tailed p approx. 0.03). The protective effect of tobacco smoking was evident only among post-menopausal women. These results indicate that the risk profile of endometrial cancer is similar in high-risk and low-risk countries, and underline the importance of unopposed estrogenic stimulation in the pathogenesis of this cancer.

Laatikainen, T. J., E. I. Tomas, et al. (1995). "The expression of insulin-like growth factor and its binding protein mRNA in the endometrium of postmenopausal patients with breast cancer receiving tamoxifen." Cancer **76**(8): 1406-10.

BACKGROUND: Insulin-like growth factor I (IGF-I) is known to mediate estrogen effect in the uterus, whereas IGF binding proteins (IGFBPs) modulate the biologic effects of IGF-I. Tamoxifen may act via the IGF-IGFBP system in the postmenopausal endometrium. METHODS: Endometrial samples were collected from 16 postmenopausal women with breast cancer of whom 9 received tamoxifen and the remaining 7 received no hormonal treatment. The expression of messenger RNA for IGF-I, IGF-II, and the IGFBPs 1-6 was studied using dot blot and Northern blot techniques. RESULTS: Expression of mRNA for IGF-I, IGFBP-2, -3, -4, and -6 was present in endometrial specimens. The expression of IGF-I mRNA was similar in the tamoxifen-treated and control patients, whereas mRNA expression for IGF-II was not detected. The expression of IGFBP-2 and -4 mRNA predominated in the endometrium of patients who received tamoxifen. CONCLUSIONS: These findings demonstrate that the IGF-IGFBP system is present in the postmenopausal endometrium and may be modulated by tamoxifen.

Lacey, J. V., Jr., L. A. Brinton, et al. (2000). "Tubal sterilization and risk of cancer of the endometrium." Gynecol Oncol **79**(3): 482-4.

OBJECTIVE: Surgical sterilization is a common method of contraception among U.S. women. Most surgical sterilizations are tubal ligations, but few studies have investigated their potential impact on endometrial cancer risk. METHODS: A case-control study included 405 women diagnosed with endometrial cancer at 5 U.S. medical centers between 1987 and 1990 and 297 age-, race-, and location-matched controls who were identified by random-digit-dialing. Questionnaires ascertained information on tubal sterilization, and logistic regression models generated odds ratios (ORs) to estimate relative risk. RESULTS: The OR and 95% confidence interval for tubal sterilization, which was reported by 47 cases and 40 controls, was 0.9 (0.6-1.4) before adjustment and 1. 4 (0.8-2.4) after adjustment

for age, parity, and oral contraceptive use. Age at surgery, years since surgery, or calendar years of surgery were not associated with endometrial cancer, and associations did not vary according to parity or stage of disease at diagnosis. CONCLUSIONS: Tubal sterilization is not substantially associated with endometrial cancer.

Lien, H. H., V. Blomlie, et al. (1991). "Cancer of the endometrium: value of MR imaging in determining depth of invasion into the myometrium." AJR Am J Roentgenol **157**(6): 1221-3.

The depth of invasion into the myometrium correlates with the frequency of lymph node metastases in patients with cancer of the endometrium. A distinction between superficial invasion (less than 50% of the thickness of the myometrium) and deep invasion (greater than 50%) is particularly important. The ability to distinguish between these two groups on MR was studied in 33 patients with endometrial cancer who had primary hysterectomy. The overall accuracy of MR in showing deep invasion was 82%, with a sensitivity of 91% and a specificity of 64%. The main limitation of MR was four false-positive results with regard to deep invasion. In all of these, the erroneous diagnosis was found at histologic examination to be due to a large polypoid tumor that distended the uterus so that a thin rim of myometrium was stretched over it rather than being deeply infiltrated by it. Our experience shows that MR can be used to distinguish between superficial and deep invasion of the myometrium. However, degree of invasiveness may be overestimated in exophytic polypoid tumors with significant intraluminal extension.

Lindahl, B., E. Andolf, et al. (2008). "Adjuvant tamoxifen in breast cancer patients affects the endometrium by time, an effect remaining years after end of treatment and results in an increased frequency of endometrial carcinoma." Anticancer Res **28**(2B): 1259-62.

Tamoxifen is the most used adjuvant drug in breast cancer treatment. Its main action is as an anti-oestrogen, but in the endometrium of some patients it acts as an oestrogen. Some investigators have even reported an increased risk of developing endometrial carcinoma. The question of how to follow-up these patients and how to identify patients at risk of developing endometrial premalignant changes was investigated by the noninvasive ultrasound method. The follow-up of 292 patients from before the start of adjuvant treatment with tamoxifen and 94 without tamoxifen treatment was conducted at regular intervals. The changes in endometrial thickness as measured by ultrasound and histopathological changes are reported. A thicker endometrium was found in patients with receptor positive breast cancer even before the treatment with tamoxifen started. Cumulative increasing thickness was found during treatment and this thicker endometrium remained until almost 3 years after the end of treatment. If the endometrium was <3 mm after 3 months of treatment the probability that it would be thin after 5 years was high. An increased risk of developing endometrial carcinoma was found, however due to this regular follow-up the cancer was identified at an early stage.

Lumbiganon, P. (1994). "Depot-medroxyprogesterone acetate (DMPA) and cancer of the endometrium and ovary." Contraception **49**(3): 203-9.

This review addresses possible associations between depot-medroxy-progesterone acetate (DMPA) and endometrial and epithelial ovarian cancers. Two unexpected endometrial carcinomas were observed at autopsy of rhesus monkeys treated for 10 years with 50 times the human doses of DMPA. A record linkage in the USA did not suggest any association between DMPA and endometrial cancer. A multicentre case-control study in Thailand showed a strong protective effect of DMPA for endometrial cancer. Studies from the USA, Mexico and Thailand did not observe any association between use of DMPA and epithelial ovarian cancer. The available information, therefore, indicates that use of DMPA protects against endometrial cancer and is not associated with epithelial ovarian cancer.

Markovitch, O., R. Tepper, et al. (2009). "Long-term "protective" effect of aromatase inhibitors on the endometrium of postmenopausal breast cancer patients." Breast Cancer Res Treat **113**(2): 321-6.

BACKGROUND: Decrement of endometrial thickness was recorded following short-term aromatase inhibitor treatment in breast cancer patients previously treated with tamoxifen. It is necessary to verify if long-term aromatase inhibitor treatment can maintain this phenomenon. METHODS: Prospective long-term comparison of the last ultrasonographic endometrial thickness measurement taken before discontinuation of long-term tamoxifen treatment in 64 postmenopausal breast cancer patients, with further repeated measurements, performed following administration of aromatase inhibitors. RESULTS: There was a significant decrement of endometrial thickness, following 36.5 +/- 15.7 months of tamoxifen treatment, from a mean value of 8.7 +/- 5.2 mm, measured at the last ultrasonographic measurement performed before discontinuation of tamoxifen treatment, down to a mean value of 6.2 +/- 4.6 mm, measured following 5.3 +/- 4.8 months of aromatase inhibitor therapy ($P < 0.001$). Further

ultrasonographic studies revealed the same significant trend. In the first ultrasonographic study performed during aromatase inhibitor treatment, five (7.8%) patients demonstrated a significant increase of endometrial thickness. Hysteroscopy revealed a benign endometrial polyp in three patients and atrophic endometrium in the other 2. In 35 patients (54.7%), endometrial thickness was reduced following the administration of aromatase inhibitors and in 24 patients (37.5%) there was no change in endometrial thickness. With longer duration of aromatase inhibitor therapy, more patients showed decrement of endometrial thickness. CONCLUSIONS: Reversal of endometrial thickening induced by long-term tamoxifen treatment in postmenopausal breast cancer patients is maintained throughout long-term aromatase inhibitor treatment.

Marquez, R. T., K. A. Baggerly, et al. (2005). "Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon." Clin Cancer Res **11**(17): 6116-26.

PURPOSE: Epithelial ovarian cancers are thought to arise from flattened epithelial cells that cover the ovarian surface or that line inclusion cysts. During malignant transformation, different histotypes arise that resemble epithelial cells from normal fallopian tube, endometrium, and intestine. This study compares gene expression in serous, endometrioid, clear cell, and mucinous ovarian cancers with that in the normal tissues that they resemble. EXPERIMENTAL DESIGN: Expression of 63,000 probe sets was measured in 50 ovarian cancers, in 5 pools of normal ovarian epithelial brushings, and in mucosal scrapings from 4 normal fallopian tube, 5 endometrium, and 4 colon specimens. Using rank-sum analysis, genes whose expressions best differentiated the ovarian cancer histotypes and normal ovarian epithelium were used to determine whether a correlation based on gene expression existed between ovarian cancer histotypes and the normal tissues they resemble. RESULTS: When compared with normal ovarian epithelial brushings, alterations in serous tumors correlated with those in normal fallopian tube ($P = 0.0042$) but not in other normal tissues. Similarly, mucinous cancers correlated with those in normal colonic mucosa ($P = 0.0003$), and both endometrioid and clear cell histotypes correlated with changes in normal endometrium ($P = 0.0172$ and 0.0002, respectively). Mucinous cancers displayed the greatest number of alterations in gene expression when compared with normal ovarian epithelial cells. CONCLUSION: Studies at a molecular level show distinct expression profiles of different histologies of ovarian cancer and support the long-held belief that histotypes of ovarian cancers come to resemble normal fallopian tube, endometrial, and colonic epithelium. Several potential molecular markers for mucinous ovarian cancers have been identified.

Morales, L., P. Neven, et al. (2009). "Prospective assessment of the endometrium in postmenopausal breast cancer patients treated with fulvestrant." Breast Cancer Res Treat **117**(1): 77-81.

This prospective study assessed the endometrial effects of fulvestrant, a pure estrogen-receptor antagonist, in postmenopausal women with breast cancer. This single-center study enrolled postmenopausal patients who had an intact uterus at baseline with progressive metastatic breast cancer on tamoxifen followed by an oral aromatase inhibitor (AI). Fulvestrant (250 mg) was administered every 28 +/- 3 days via IM injection. Transvaginal ultrasonography (TVUS) was performed at baseline and after 3 months of therapy. Primary and secondary endpoints were changes from baseline in double endometrial thickness (DET) and uterine volume (UV), respectively. No interventions were performed on any asymptomatic uterine abnormalities that were detected at baseline. In total, 32 women were enrolled. Five patients had no repeat TVUS because of early progression before 3 months, leaving 27 evaluable patients for final analysis. After 3 months therapy, mean DET had significantly decreased by 23.08% ($P = 0.010$). Mean UV also decreased by 10.88%, although this change was not significant ($P = 0.119$). After 3 months of therapy, none reported vaginal bleeding, there were no changes noted in most of the uterine pathologies present at baseline and no new uterine abnormalities were detected. We observed that 3 months of fulvestrant treatment resulted in a significant decrease in endometrial growth and a non-significant decrease in UV in postmenopausal women with metastatic breast cancer previously exposed to tamoxifen and AIs. Furthermore, no new uterine pathologies were detected, indicating that fulvestrant behaves as a pure antiestrogen at the uterine level.

Moss, E. L., A. Stevens, et al. (2003). "Toxicity, recurrence and survival after adjuvant radiotherapy treatment for FIGO stage I cancer of the endometrium." Clin Oncol (R Coll Radiol) **15**(5): 250-4.

We conducted a retrospective observational study to determine the rate of toxicity, pattern of tumour recurrence and survival associated with radiotherapy treatment for FIGO stage I cancer of the endometrium. All patients had undergone definitive surgery and had been referred to the oncology department of the University Hospital Birmingham, U.K. Two hundred and forty-five women were

included in the study; 228 patients were treated with radiotherapy; 160 had external beam radiation alone; 32 had vaginal vault brachytherapy alone; 36 patients had both modalities; and 17 patients were not given radiotherapy. There were nine cases of Grade 3 and 4 radiation reactions, of which four were acute, four were late and one was acute and late toxicity. The severity of both acute and late radiation effects was significantly associated with the delivery of vault brachytherapy (external beam radiotherapy alone compared with brachytherapy alone (1/158 vs 3/32; P = 0.02). Thirty-four patients were diagnosed with tumour recurrence (11 distant, 14 local, 4 patients had both distant and local disease and 5 patients had recurrence diagnosed at the time of death). Patients who received no radiotherapy were at greater risk of local pelvic tumour recurrence (P < 0.0001; hazard ratio [HR] 9.6, 95% confidence interval (CI) 3.5-26.3). Vaginal vault brachytherapy had no discernible effect on the pattern of tumour recurrence. Forty-six patients died during the follow-up period, 28 of these were attributable to carcinoma of the endometrium. There was no difference in survival between the four treatment groups (P = 0.68). The overall 5-year survival rate in our study group was 89.6% (85.4-93.8%). In a proportional hazards model, tumour grade (HR 2.0 per level [1.25, 3.17]; P = 0.004]) and age (HR 1.74 per 10 years [1.12, 2.69]; P = 0.01) were the only factors found to have an independent influence on survival. This study suggests that, although pelvic radiation may not alter overall survival, it does reduce the risk of local disease recurrence. In this study population, vaginal vault brachytherapy using a vaginal stock/dobbie showed no additional benefits compared with external beam radiotherapy; it was, however, associated with a higher rate of both acute and late radiation effects.

Mourits, M. J., A. G. Van der Zee, et al. (1999). "Discrepancy between ultrasonography and hysteroscopy and histology of endometrium in postmenopausal breast cancer patients using tamoxifen." Gynecol Oncol **73**(1): 21-6.

BACKGROUND: The increased risk of endometrial carcinoma following the use of tamoxifen has stimulated studies on endometrial diagnostic screening methods. In tamoxifen users the endometrial thickening observed with transvaginal ultrasonography (TVU) frequently cannot be confirmed by hysteroscopy or histology. OBJECTIVE: The aim was to investigate the relationship between TVU and hysteroscopic and histologic endometrial findings in postmenopausal patients using tamoxifen. METHODS: Fifty-three asymptomatic postmenopausal tamoxifen-using breast cancer patients underwent a gynecological examination combined with TVU. Patients with an endometrial thickness of >5 mm were offered hysteroscopy and endometrial biopsy. FINDINGS: Thirty-one patients (58%) had an endometrial thickness of >5 mm with enhanced, inhomogeneous echogenicity. Hysteroscopy was performed in 22 patients and 3 underwent hysterectomy. Seven of 22 patients had endometrial polyps, histologically characterized by cystically dilated glands lined with atrophic epithelium and periglandular stromal condensation. Histology of the three hysterectomy specimens showed a similar picture of atrophic luminal epithelium, covering dilated glands lined with atrophic epithelium and surrounded by dense stroma, which resembled the histology of the endometrial polyps. In all three specimens the histologically measured endometrial thickness corresponded with that on TVU. INTERPRETATION: Tamoxifen can induce specific endometrial changes consisting of cystically dilated glands with periglandular stromal condensation while the overlying epithelium remains atrophic. The changes occur either in the endometrium itself or as a protrusion of the endometrium, i.e., as endometrial polyps. These findings explain the discrepancy between ultrasound, hysteroscopy, and histology. Due to the high number of false-positive findings, TVU is not an effective screening instrument in these patients.

Moutsatsou, P., E. Kassi, et al. (1998). "Detection of oestrogen receptor variants in endometrium, myometrium, leiomyoma and peripheral blood mononuclear cells: comparison to variants present in breast cancer." J Cancer Res Clin Oncol **124**(9): 478-84.

Oestradiol has mitogenic and regulatory effects on various organs and cells, mediated mainly by its nuclear receptor (ER). The presence of aberrant ER forms in Oestrogen-dependent tumours has been discussed in correlation with tumour progression. ER variants, generated by alternative splicing, have been detected in human breast cancer, but also in normal mammary glands, therefore their role in tumorigenesis has been questioned. We have investigated, by the use of the reverse transcription polymerase chain reaction amplification technique, the possible existence of ER variants in other normal oestrogen target organs and cells, such as uterus (myometrium and endometrium), in peripheral blood mononuclear cells and in a benign uterus tumour (leiomyoma). We have detected variant ER in these samples and have compared the variant profile to that observed in breast cancer. All tissues and cells studied expressed both wild-type ER and variant species. Variant forms encompassed ER with deletions of exons 2, 5 and 7. Variants with exon 5 deleted were detected only in peripheral blood

mononuclear cells and in breast cancer. Variants with exons 2 and 7 deleted were present in all specimens tested. These results corroborate previous findings that the presence of ER variants is not a characteristic of breast cancer. The physiological significance and possible clinical relevance of the variant ER forms remain to be elucidated.

Munstedt, K., P. Grant, et al. (2004). "Cancer of the endometrium: current aspects of diagnostics and treatment." World J Surg Oncol **2**: 24.

BACKGROUND: Endometrial cancer represents a tumor entity with a great variation in its incidence throughout the world (range 1 to 25). This suggests enormous possibilities of cancer prevention due to the fact that the incidence is very much endocrine-related, chiefly with obesity, and thus most frequent in the developed world. As far as treatment is concerned, it is generally accepted that surgery represents the first choice of treatment. However, several recommendations seem reasonable especially with lymphadenectomy, even though they are not based on evidence. All high-risk cases are generally recommended for radiotherapy. METHODS: A literature search of the Medline was carried out for all articles on endometrial carcinoma related to diagnosis and treatment. The articles were systematically reviewed and were categorized into incidence, etiology, precancerosis, early diagnosis, classification, staging, prevention, and treatment. The article is organized into several similar subheadings. CONCLUSIONS: In spite of the overall good prognosis during the early stages of the disease, the survival is poor in advanced stages or recurrences. Diagnostic measures are very well able to detect asymptomatic recurrences. These only seem justified if patients' chances are likely to improve, otherwise such measures increases costs as well as decrease the patients' quality of life. To date neither current nor improved concepts of endocrine treatment or chemotherapy have been able to substantially increase patients' chances of survival. Therefore, newer concepts into the use of antibodies e.g. trastuzumab in HER2-overexpressing tumors and the newer endocrine compounds will need to be investigated. Furthermore, it would seem highly desirable if future studies were to identify valid criteria for an individualized management, thereby maximizing the benefits and minimizing the risks.

Nasu, K., K. Kai, et al. (2001). "Expression of cathepsin L in normal endometrium and endometrial cancer." Eur J Obstet Gynecol Reprod Biol **99**(1): 102-5.

OBJECTIVE: To evaluate the expression of cathepsin L in normal endometrium and endometrial adenocarcinoma. STUDY DESIGN: Tissue from eight cases of G1 and eight of G2 endometrioid adenocarcinoma, and 15 normal endometrial specimens were examined by immunohistochemistry. RESULTS: In the normal endometrium, cathepsin L was expressed in a few cell layers of the apical part of the glandular epithelium throughout the menstrual cycle. In the carcinomas, there was an inverse correlation between the grade of tumor and the cathepsin L expression. CONCLUSION: Cathepsin L expression may cease during endometrial carcinogenesis and its expression may be less important in tumor progression than it is in tumors of other tissues.

Noh, S. K., J. Y. Yoon, et al. (2008). "A case report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium." J Gynecol Oncol **19**(4): 265-9.

Multiple primary cancer is defined as the multiple occurrence of malignant neoplasms in the same individual. Due to the development of new diagnostic techniques and the rise in long-term survival of cancer, reports of multiple primary cancers have gradually increased. Herein, we describe the case of a 68-year-old female patient with quadruple primary cancer of the breast, rectum, ovary, and endometrium. For its great rarity, we report this case with a review of the literature.

Nowak-Markwitz, E., A. Jankowska, et al. (2004). "Human chorionic gonadotropin-beta in endometrium cancer tissue." Eur J Gynaecol Oncol **25**(3): 351-4.

PURPOSE: Determination of the correlation between expression of human chorionic gonadotropin mRNA and serum free hCGb immunoreactivity in endometrial cancer tissue. METHODS: The study included 56 patients with endometrial carcinoma Stages IB-III. The expression of mRNA hCGbeta was determined by the RT PCR method in 18 cases of cancerous and precancerous tissues. The serum-free hCGbeta immunoreactivity was analyzed by sequential immunometric assay in all patients. RESULTS: In 15 study specimens of endometrial carcinoma tissue mRNA of hCGbeta was detected. Also in endometrial atypical hyperplasia, expression of hCGbeta was found. Noncancerous tissue demonstrated lack of the hCGbeta transcript. The serum immunoreactivity in the endometrial cancer group was detectable in 86% of cases. There were no significant differences between FIGO stages and grading. CONCLUSION: The results of the present study confirmed the presence of active genes of hCGbeta in endometrial cancer tissue, even in precancerous changes. The serum immunoreactivity of free hCGbeta is a less common feature and is not

linked with tumor stage or grade in endometrial cancer patients.

Ohno, Y., H. Fujibayashi, et al. (1990). "Medroxyprogesterone acetate binding sites in human endometrium and endometrial cancer." Gynecol Obstet Invest **29**(3): 227-31.

Medroxyprogesterone acetate (MPA) binding sites in both human normal endometrium and endometrial carcinoma were identified and characterized by sucrose gradient centrifugation. These binding components were divided into two classes by saturation analysis, one with high affinity and low capacity and the other with low affinity and high capacity. The concentrations of low-affinity binding sites for MPA in endometrial carcinoma were higher than those in normal endometrium (p less than 0.01). By sucrose gradient centrifugation, 4S and 8S components were observed in both high- and low-affinity binding sites of normal endometrium. These components were moved to 4S by the addition of salt. However, in endometrial carcinoma, low-affinity binding sites were displayed at about 4S under either low- or high-salt conditions. High-affinity binding sites in endometrial carcinoma had the same sedimentation patterns as in normal endometrium. An obvious difference between normal endometrium and endometrial cancer was observed in low-affinity binding sites. Our results on the binding sites for MPA suggest that low-affinity binding sites may be related to the response of endometrial cancer to high-dose MPA treatment.

Ohwada, M., M. Suzuki, et al. (1996). "Glutathione peroxidase activity in endometrium: effects of sex hormones and cancer." Gynecol Oncol **60**(2): 277-82.

The aim of this study was to determine whether glutathione peroxidase (GSH-Px) activity in endometrial tissue is regulated by sex hormones and to compare the GSH-Px activity of normal and cancerous endometrium. The localization of GSH-Px in human normal endometrium and endometrial cancer was determined immunohistochemically. GSH-Px activity was assayed in endometrial tissue obtained from women with endometrial cancer and age-matched controls, as well as in rat uterine tissue. GSH-Px immunoreactivity was localized in the glandular epithelium of normal human endometrium and reached a maximum in the late proliferative and early secretory phases of the menstrual cycle. In spayed rats, uterine GSH-Px activity was significantly increased by exogenous estrogen ($P < 0.01$) and significantly reduced by exogenous progesterone ($P < 0.01$). GSH-Px activity in endometrial cancer tissue was significantly higher ($P < 0.01$) than that in endometrial tissue from age-matched healthy controls. Among endometrial cancer tissues, a significant increase in GSH-Px activity was associated with well-differentiated rather than moderately or poorly differentiated adenocarcinoma ($P < 0.01$), with slight rather than marked myometrial invasion ($P < 0.01$), and with the presence of concurrent endometrial hyperplasia ($P < 0.01$). These results show that endometrial GSH-Px activity is regulated by sex hormones, being stimulated by estrogen and suppressed by progesterone, and that the level of GSH-Px activity in endometrial cancer tissue may be a significant prognostic factor.

Orejuela, F. J., L. M. Ramondetta, et al. (2005). "Estrogen and progesterone receptors and cyclooxygenase-2 expression in endometrial cancer, endometrial hyperplasia, and normal endometrium." Gynecol Oncol **97**(2): 483-8.

OBJECTIVES: To determine whether cyclooxygenase-2 (COX-2) expression is seen in endometrial cancer, endometrial hyperplasia, and normal endometria and whether it correlates with expression of estrogen and progesterone receptors. METHODS: The study was a retrospective, IRB-approved analysis of biopsy samples from 14 patients with endometrial adenocarcinoma, 19 with endometrial hyperplasias, and 10 with normal endometrium. Excluded were samples from women with a history of pelvic radiation, NSAID use, or treatment with hormones during previous year. Immunohistochemical analyses were performed on formalin-fixed, paraffin-embedded tissues. Expression of COX-2, estrogen and progesterone receptors were scored according to the proportion of positive-staining cells: 1(+), <10%; 2(+), 10-50%; and 3(+), >50%. A score > or =2(+) was considered positive. Fisher's exact test and analysis of variance were used to compare proportions and continuous variables, respectively. RESULTS: Overexpression of COX-2 was seen in 4 (29%) of the endometrial cancers, 6 (32%) of the endometrial hyperplasia, and 4 (20%) of the normal endometria. These differences were not statistically significant ($P = 0.90$). No COX-2 expression was found in stromal tissue. Of 14 endometrial cancers, 7 (50%) expressed any COX-2, with 4 (29%) having an expression score of > or =2(+). Of 19 endometrial hyperplasias, 11 (58%) expressed any COX-2; with 6 (32%) having a score of > or =2(+). All 10 normal endometria showed only 1(+) expression. No significant differences were detected in COX-2 expression by grade or stage of cancer. Although 100% and 95% of both hyperplasia and normal endometrium samples expressed in estrogen and progesterone receptors, respectively, only 71% and 79% of endometrial cancers expressed estrogen and progesterone receptors ($P = 0.01$). A

nonparametric trend was performed to detect a relationship, between COX-2 and estrogen receptor or progesterone receptor expression; no significant trend was found. CONCLUSIONS: In this study, the immunohistochemical analysis showed a trend toward increased COX-2 expression in endometrial cancer and hyperplasia compared to normal endometria. A larger sample size is needed to confirm these results. The increased COX-2 expression in hyperplasia may signify an early step in carcinogenesis. These findings may represent an important treatment opportunity for synergism in the hormonal therapy of endometrial cancer.

Ortac, F., M. Bahceci, et al. (1991). "Myometrial invasion of endometrium cancer assessed by transrectal ultrasonography." Gynecol Obstet Invest **32**(2): 115-7.

Transrectal ultrasonographic examinations before surgery were performed on 27 patients with stage I endometrial cancer to assess myometrial invasion. The findings were compared with the histopathologic data obtained by surgery. Sensitivity and specificity of transrectal ultrasonography in myometrial invasion of endometrium cancer were 82.6 and 100%, respectively. Therefore, transrectal ultrasonography may be a useful diagnostic tool to determine the myometrial invasion, which is the most important prognostic factor in endometrial cancer.

Oshima, H., H. Miyagawa, et al. (2002). "Adenofibroma of the endometrium after tamoxifen therapy for breast cancer: MR findings." Abdom Imaging **27**(5): 592-4.

We report a case of adenofibroma of the endometrium in a 69-year-old woman. This patient was receiving tamoxifen therapy after surgery for breast cancer. Magnetic resonance imaging showed an intracavitary mass containing multiple cystic components. We suggest adenofibroma as a possible diagnosis in cases of uterine masses with multiple cystic components and no clinical evidence of malignancy.

Osler, M. (1987). "Obesity and cancer. A review of epidemiological studies on the relationship of obesity to cancer of the colon, rectum, prostate, breast, ovaries, and endometrium." Dan Med Bull **34**(5): 267-74.

Cancer of the colon, rectum, prostate, breast, ovaries and endometrium may be associated with obesity. The present paper reviews both prospective and retrospective studies of the potential associations between obesity and these cancers. This research is especially difficult because of the complex interrelations between weight and diet, physical activity, cigarette smoking, and other conditions. Epidemiological studies of body weight are subject not only to biases of sampling, selection, and confounding but also to marked difficulties in definition and measurement. Bearing in mind the methodological shortcomings, there is a distinct and reproducible association between obesity and cancer of the endometrium and postmenopausal breast cancer. The studies of cancer of the colon, rectum, prostate, and ovaries are too inconclusive to elucidate whether obesity implies an increased risk. It is recommended that future studies in this field include a standardised assessment of the distribution of fat tissue, the onset and duration of the condition, and the associated confounding factors. It is concluded that obesity, especially in females, should be avoided as a part of the general cancer preventive effort.

Papageorgiou, I., P. K. Nicholls, et al. (2009). "Expression of nodal signalling components in cycling human endometrium and in endometrial cancer." Reprod Biol Endocrinol **7**: 122.

BACKGROUND: The human endometrium is unique in its capacity to remodel constantly throughout adult reproductive life. Although the processes of tissue damage and breakdown in the endometrium have been well studied, little is known of how endometrial regeneration is achieved after menstruation. Nodal, a member of the transforming growth factor-beta superfamily, regulates the processes of pattern formation and differentiation that occur during early embryo development. METHODS: In this study, the expression of Nodal, Cripto (co-receptor) and Lefty A (antagonist) was examined by RT-PCR and immunohistochemistry across the menstrual cycle and in endometrial carcinomas. RESULTS: Nodal and Cripto were found to be expressed at high levels in both stromal and epithelial cells during the proliferative phase of the menstrual cycle. Although immunoreactivity for both proteins in surface and glandular epithelium was maintained at relatively steady-state levels across the cycle, their expression was significantly decreased within the stromal compartment by the mid-secretory phase. Lefty expression, as has previously been reported, was primarily restricted to glandular epithelium and surrounding stroma during the late secretory and menstrual phases. In line with recent studies that have shown that Nodal pathway activity is upregulated in many human cancers, we found that Nodal and Cripto immunoreactivity increased dramatically in the transition from histologic Grade 1 to histologic Grades 2 and 3 endometrial carcinomas. Strikingly, Lefty expression was low or absent in all cancer tissues. CONCLUSION: The expression of Nodal in normal and malignant endometrial cells that lack Lefty

strongly supports an important role for this embryonic morphogen in the tissue remodelling events that occur across the menstrual cycle and in tumourogenesis.

Park, D. W., D. S. Choi, et al. (2003). "A well-defined in vitro three-dimensional culture of human endometrium and its applicability to endometrial cancer invasion." Cancer Lett **195**(2): 185-92.

A three-dimensional (3-D) endometrium culture was established, in which human endometrial stromal cells embedded in a mixture of collagen I, a major component of extracellular matrix, and matrigel, a basement membrane material, supports the epithelial cells seeded on top of the collagen/matrigel matrix. The biological growth and differentiation of the epithelial cells were studied microscopically and immunohistochemically. Transmission electron microscopy showed a polarized columnar epithelium in monolayer with basally positioned nuclei. Scanning electron microscopy revealed a confluent epithelium with an abundance of microvilli and cilia as well as pinopodes on the apical surface. An immunohistochemical staining showed that integrin alpha1, alpha4, and beta3 were co-localized with cytokeratin, confirming the epithelial origin of the cells. In contrast, immunoreactivity against cyclooxygenase-1 or -2 was positive in both epithelial and stromal cells. When epithelial cells were replaced by KLE cells, an endometrial cancer cell of epithelial origin, invasion of KLE cells into the stromal fraction was observed. The invasion was closely correlated to expression of matrix metalloproteinases and their tissue inhibitors of metalloproteinases in a manner consistent with paracrine fashion. The present 3-D culture imitates the normal endometrium physiologically as well as morphologically, thus provides an excellent in vitro tissue suitable for reproducing in vivo physiological processes, including endometrial cancer invasion.

Paszkowska, A., M. Cybulski, et al. (2000). "Total sialic acid content in endometrial cancer tissue in relation to normal and hyperplastic human endometrium." Cancer Detect Prev **24**(5): 459-63.

The aim of this study was to measure the total sialic acid (TSA) content in endometrial cancer tissue and to assess its relationship to clinicopathologic features of the malignancy. Tissue TSA content was measured in 42 women with endometrial cancer, 14 women with endometrial hyperplasia, and 45 women with normal endometrium in the proliferative phase (n = 16) and secretory phase (n = 29) of the menstrual cycle using the Warren procedure. The mean TSA content in endometrial cancer (2.16 micromol/gm) was significantly higher in comparison to normal endometrium in both proliferative (1.23 micromol/gm) and secretory (1.51 micromol/gm) phases. TSA content in the hyperplastic endometrium (1.56 micromol/gm) was higher as compared to the normal endometrium, but the differences were not statistically significant. An increased TSA content in the neoplastic endometrium in relation to the normal endometrium supports the view that the development of endometrial cancer is associated with the increasing content of sialic acid in the tumor tissue.

Potish, R. A. (1987). "Radiation therapy of periaortic node metastases in cancer of the uterine cervix and endometrium." Radiology **165**(2): 567-70.

Thirty-eight women with surgically confirmed periaortic lymph node metastases from cervical or endometrial carcinoma received radiation therapy. The 5-year observed actuarial survival and relapse-free rates were 42% and 41%, respectively. Concomitant peritoneal metastases conferred a bleak prognosis. There were no differences in survival as a function of site of origin, histologic characteristics, or bulk of periaortic metastases. Earlier stage disease tended to have a higher probability of cure. Morbidity was acceptable. The results confirmed the importance of radiation therapy in the management of lymph node metastases in uterine cancer.

Potish, R. A. (1989). "Abdominal radiotherapy for cancer of the uterine cervix and endometrium." Int J Radiat Oncol Biol Phys **16**(6): 1453-8.

From 1973 through 1985, 49 women received postoperative open-field whole abdominal radiotherapy as primary management for peritoneal metastases from uterine cancer. The 5-year relapse-free rate was 63% in women with endometrial carcinoma, and two prognostic subsets were identified. Five-year relapse-free rates fell from 77% in women with spread to the adnexa or peritoneal fluid to 36% in women with macroscopic spread of cancer beyond the adnexa. Any peritoneal spread of cervical carcinoma yielded a 3-year relapse-free rate of 31%. Although abdominal spread of cervical cancer was associated with other poor prognostic factors, peritoneal metastases frequently occurred in otherwise early endometrial cancer. Four percent of patients developed small bowel obstruction requiring surgical intervention. The utility and limitations of whole abdominal radiation are discussed.

Re, A., T. H. Taylor, et al. (1997). "Risk for breast and colorectal cancers subsequent to cancer of the endometrium in a population-based case series." Gynecol Oncol **66**(2): 255-7.

The purpose of this study was to estimate the relative risk of breast and colorectal cancers in women

who were previously diagnosed with endometrial cancer. This study was conducted using a population-based cohort of 2347 women diagnosed with invasive cancer of the endometrium between January 1, 1984, and December 31, 1995 in Orange County, California. Only women with a diagnosis of invasive endometrial cancer at age 80 years old or below were included in the analysis (N = 2170). In this same cohort, metachronous and synchronous breast and colorectal cancers were ascertained and the risk of developing one or the other type of neoplasm was compared to the expected number of cases derived from cancer incidence in California by age, 1988-1992. We found a statistically increased risk of breast cancer as a second primary, while the observed incidence in colorectal risk did not reach statistical significance. The association between endometrial cancer and breast and possibly colorectal cancer indicates the importance of common etiologies for these cancers.

Rutanen, E. M., T. Nyman, et al. (1994). "Suppressed expression of insulin-like growth factor binding protein-1 mRNA in the endometrium: a molecular mechanism associating endometrial cancer with its risk factors." Int J Cancer **59**(3): 307-12.

The insulin-like growth factor (IGF) system is thought to function as a mediator of steroid hormone actions in the endometrium. IGFs (IGF-I and IGF-II) are also potent mitogens in endometrial cancer. The biological actions of IGFs are modulated by specific binding proteins (IGFBP)--6 cloned and sequenced so far--which may either inhibit or enhance the effects of IGF at the cellular level. In the endometrium, IGFBP-1 gene expression is stimulated by progesterone and inhibited by insulin, while IGFBP-1 inhibits the mitogenic action of IGF-I. In this study, we used a quantitative reverse transcriptase polymerase chain reaction (RT-PCR) to investigate IGFBP-1, IGFBP-2, IGFBP-4, IGFBP-5 and IGFBP-6 gene expression in endometrial cancer tissues. Endometrial cancer tissue samples were collected from 20 women (aged 54-79 yrs) with stage I to II well-differentiated endometrial adenocarcinoma. Samples of normal endometrium (n = 14) obtained from women undergoing tubal ligation in various phases of the menstrual cycle, and normal early-pregnancy endometrium (decidua) were studied for comparison. In endometrial cancer tissues, the IGFBP-1 mRNA was undetectable or minimally expressed when studied by RT-PCR. The mean (+ SD) levels of IGFBP-2 and IGFBP-4 and IGFBP-5 mRNAs in endometrial cancer tissues did not differ from those in normal endometrium, in which no cyclic variation was observed, suggesting that the genes encoding IGFBP-2, IGFBP-4 and IGFBP-5 are not hormonally regulated in the endometrium. The IGFBP-6 mRNA expression showed a significant cyclic variation in normal endometrium, with low levels in late-proliferative and early- to mid-secretory phases and high expression in late-secretory and early-proliferative phases. In endometrial cancer tissues, the mean IGFBP-6 mRNA level was similar to that in cycling endometrium during the peri-ovulatory period. In summary, a continuous stimulation of the endometrial epithelial cells by IGFs with suppressed IGFBP-1 expression may lead to an imbalance in the IGF system of the endometrium and trigger an uncontrolled cell proliferation, ultimately resulting in malignant transformation.

Saito, T., A. Schneider, et al. (1997). "Proliferation-associated regulation of telomerase activity in human endometrium and its potential implication in early cancer diagnosis." Biochem Biophys Res Commun **231**(3): 610-4.

Telomerase activity was detected in normal endometrium in association with proliferation and regulated during the menstrual cycle in a hormone-dependent manner. The activity was maximal at the late-proliferative phase to mid-secreting phase, and was absent or extremely low at early-proliferative phase and late-secreting phase. Activity was also detected in all endometrial simple hyperplasias tested (16 of 16) and in most cancers (28 of 30), but none was detected in endometrium of either pregnant or postmenopausal women in the absence of hyperplasia. Our data provide evidence that the telomerase activity in postmenopausal endometrium reflects a hyperproliferative condition. Therefore, we conclude that telomerase can provide a novel marker for early endometrial cancer diagnosis. Hormone-dependent regulation of telomerase suggests the possibility of therapeutic and preventive strategies for endometrial cancers through the management of ovarian steroid hormones or other agents that regulate telomerase activity.

Sato, S., G. Matsunaga, et al. (1998). "Mass screening for cancer of the endometrium in Miyagi Prefecture, Japan." Acta Cytol **42**(2): 295-8.

OBJECTIVE: To survey the results of mass screening for cancer of the endometrium performed over a six-year period in Miyagi Prefecture, Japan. STUDY DESIGN: Materials were cytodiagnostic samples of the endometrium examined by the Miyagi Cancer Society. The samples were classified into two groups: The mass screening group, from whom samples were collected according to the Health and Medical Service Law for the Aged, and the outpatient group, consisting of samples from other patients. The rates of subjects judged to require close examination and the detection rate of cancer of the endometrium in

the two groups were compared. RESULTS: In the mass screening group, the rate of subjects judged to require close examination and the detection rate of cancer of the endometrium were 2.3% and 0.11%, respectively, while they were 5.9% and 0.39%, respectively, in the outpatient group; the differences between the two groups were significant. CONCLUSION: To improve the detection rate in mass screening for endometrial cancer according to the Health and Medical Service Law for the Aged, it is necessary to establish a new criterion for selecting subjects.

Signorile, P. G., F. Baldi, et al. (2009). "Ectopic endometrium in human foetuses is a common event and sustains the theory of mullerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer." J Exp Clin Cancer Res **28**: 49.

BACKGROUND: Endometriosis is a gynecological disease defined by the histological presence of endometrial glands and stroma outside the uterine cavity. Women with endometriosis have an increased risk of different types of malignancies, especially ovarian cancer and non-Hodgkin's lymphoma. Though there are several theories, researchers remain unsure as to the definitive cause of endometriosis. Our objective was to test the validity of the theory of mullerianosis for endometriosis, that is the misplacing of primitive endometrial tissue along the migratory pathway of foetal organogenesis METHODS: We have collected at autopsy 36 human female foetuses at different gestational age. We have performed a morphological and immunohistochemical study (expression of oestrogen receptor and CA125) on the pelvic organs of the 36 foetuses included en-block and totally analyzed. RESULTS: In 4 out of 36 foetuses we found presence of misplaced endometrium in five different ectopic sites: in the recto-vaginal septum, in the proximity of the Douglas pouch, in the mesenchimal tissue close to the posterior wall of the uterus, in the rectal tube at the level of muscularis propria, and in the wall of the uterus. All these sites are common location of endometriosis in women. CONCLUSION: We propose that a cause of endometriosis is the dislocation of primitive endometrial tissue outside the uterine cavity during organogenesis.

Siufi, A. A., G. D. S. I. D. Cotrim, et al. (2003). "Effects of tamoxifen therapy on the expression of p27 protein in the endometrium of women with primary breast cancer." Int J Oncol **23**(6): 1545-51.

The cyclin-dependent kinase inhibitor, p27, has been shown to mediate cell growth arrest thereby significantly reducing the percentage of proliferating cells. It seems that p27 expression is essential for the control of normal endometrial proliferation, and reduced or absent p27 expression may be an important step in endometrial carcinogenesis. Our aim was to demonstrate the effects of tamoxifen therapy on the expression of p27 protein in the endometrium of postmenopausal breast cancer patients. Fifty-three pre- and post-tamoxifen treatment endometrium samples were examined immunohistochemically using p27 antibody. Tamoxifen therapy (20 mg/day) for 60 days increased the expression of p27 protein in the endometrium of postmenopausal breast cancer patients. We conclude that tamoxifen therapy does not seem to be directly involved in the carcinogenesis of endometrial carcinoma since the expression of p27 is not decreased.

Song, J. Y., J. W. Kim, et al. (2008). "BAG-1 expression in normal endometrium, endometrial hyperplasia and endometrial cancer." Acta Obstet Gynecol Scand **87**(8): 862-7.

BACKGROUND: BAG-1 (Bcl-2-associated athanogene 1) is a BCL-2 binding anti-apoptotic protein that may play a role in carcinogenesis. The purpose of this study is to compare the expression rate of BAG-1 in normal endometrium, endometrial hyperplasia and endometrial cancer, and further to determine a correlation between BAG-1 expression and clinicopathological parameters, and overall survival. METHODS: Tissue samples from 43 patients who were diagnosed with endometrial cancer, tissue samples from 20 patients with endometrial hyperplasia and tissue samples from 20 normal patients were included in the study. Immunohistochemical analyses were performed using a polyclonal anti-BAG-1 antibody from paraffin-embedded blocks. RESULTS: Cytoplasmic BAG-1 expression of the normal endometrium, endometrial hyperplasia and endometrial cancer samples was 4/20 (20%), 3/20 (15%) and 27/43 (62%), respectively. Nuclear BAG-1 expression was 17/20 (85%), 12/20 (60%) and 16/43 (37%), respectively. Cytoplasmic BAG-1 expression correlated with cancer grade (p=0.02). The mean survival of patients with positive/negative cytoplasmic BAG-1 expression and nuclear BAG-1 expression was 49.4/45.4 and 54.0/41.1 months, respectively, but there was no statistical difference for survival (log-rank p=0.31, p=0.55). CONCLUSION: Cytoplasmic BAG-1 is more frequently expressed in endometrial cancer tissues than in normal and endometrial hyperplasia tissues (p=0.0007), and its expression correlates with cancer grade. Nuclear BAG-1 is more frequently expressed in the normal endometrium and hyperplasia tissues than in endometrial cancer tissues (p=0.002). Neither cytoplasmic nor nuclear BAG-1 expression is associated with survival.

Srinivasan, R., E. Benton, et al. (1999). "Expression of the c-erbB-3/HER-3 and c-erbB-4/HER-4 growth factor receptors and their ligands, neuregulin-1 alpha, neuregulin-1 beta, and betacellulin, in normal endometrium and endometrial cancer." Clin Cancer Res **5**(10): 2877-83.

The objective of this study was to determine the immunohistochemical expression of the c-erbB-3 and c-erbB-4 growth factor receptors and their principal ligands, the neuregulins and betacellulin, in normal endometrium and determine whether there was evidence of under- or overexpression in endometrial adenocarcinoma. There was variable expression of the growth factor receptors and the ligands in the two principal phases of the menstrual cycle as well as in endometrial adenocarcinoma. In normal endometrium, the c-erbB-3 receptor was weakly expressed in both phases. The c-erbB-4 receptor and all of the ligands examined, neuregulin alpha, neuregulin beta, and betacellulin, were expressed at significantly higher levels in the secretory as compared with the proliferative phase of the menstrual cycle, suggesting a role for these proteins in endometrial maturation. In endometrial adenocarcinoma, overexpression of c-erbB-3, c-erbB-4, and betacellulin with underexpression of neuregulin a as compared with normal controls was observed. Neuregulin beta expression was not found to be significantly different in the two groups. These results suggest that signaling through the c-erbB-3 and c-erbB-4 receptors and the ligands neuregulin alpha, neuregulin beta, and betacellulin are important in endometrial carcinogenesis.

Tang, X., Y. Muramatsu, et al. (1993). "Endometrium-myometrium ratio: a newly proposed diagnostic parameter on magnetic resonance imaging assessment of myometrial invasion by endometrial cancer." Jpn J Clin Oncol **23**(5): 278-83.

In order to improve the accuracy of magnetic resonance (MR) imaging assessment of myometrial invasion by endometrial cancer, the usefulness of a new diagnostic parameter, the endometrium-myometrium (EM) ratio has been evaluated. EM ratio is the proportion of the widest length of endometrium to the length of myometrium measured at the same line, this being vertical to the parallel of the long axis of the uterine body in the sagittal plane of the MR images. Myometrial invasion was defined as a value of the EM ratio > 1, and the tumor was limited to the endometrium for values < 1. In 25 consecutive patients, both the EM ratio-based assessment and the well-established junctional zone-based assessment with T2-weighted MR imaging and enhanced MR imaging with gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) were compared with the results from pathological examinations of postoperative specimens. In identifying myometrial invasion by endometrial cancer, the sensitivity of the EM ratio-based assessment was better than that of the junctional zone-based assessment. The overall sensitivity of the former was 96% in both the T2-weighted and enhanced MR imaging with Gd-DTPA, whereas that of the latter was 84% in the T2-weighted MR imaging and 72% ($P < 0.05$) in the enhanced MR imaging. The use of the EM ratio with MR imaging improves the ability to assess myometrial invasion by endometrial cancer.

Tunuguntla, R., D. Ripley, et al. (2003). "Expression of matrix metalloproteinase-26 and tissue inhibitors of metalloproteinases TIMP-3 and -4 in benign endometrium and endometrial cancer." Gynecol Oncol **89**(3): 453-9.

OBJECTIVE: Matrix metalloproteinases (MMPs) and their physiological inhibitors, the tissue inhibitors of MMPs (TIMPs), play a key role in tumor cell invasion, angiogenesis, and growth. The aim of this study was to determine the expression and cellular distribution of MMP-26, TIMP-3, and TIMP-4 in endometrial cancers and benign endometrium throughout the menstrual cycle and the correlation with tumor histological subtype, stage, and grade. METHODS: Immunohistochemical analysis using polyclonal antibodies generated against pro- and active MMP-26, and mono- and polyclonal antibodies specific to TIMP-3 and TIMP-4, respectively, was performed. RESULTS: MMP-26, TIMP-3, and TIMP-4 are expressed in endometrial carcinomas ($N = 86$) and benign endometrium ($N = 50$) from various stages of the menstrual cycle. Semi-quantitative analysis of staining intensity indicated that endometrial carcinomas expressed more MMP-26, TIMP-3, and TIMP-4 compared to benign endometrium from the postmenopausal period, but not from the secretory phase of the menstrual cycle. The highest staining intensity was associated with endometrial epithelial cells, followed by vascular endothelial cells, myometrial smooth muscle cells, and endometrial stromal cells. Increased staining intensity of MMP-26 and TIMP-3 correlated with grade III tumors and MMP-26 and TIMP-4 with the depth of myometrial invasion in tumors histologically characterized as endometrioid adenocarcinoma, clear-cell, and papillary serous carcinoma staged/graded based on FIGO criteria. CONCLUSION: MMP-26 and TIMP-4 are expressed in endometrium and endometrial carcinoma and their elevated expression and correlation with myometrial invasion suggests that MMP-26 and TIMP-4 may play a key role in endometrial tumor progression.

Vaeth, J. M., J. Fontanesi, et al. (1988). "External radiation therapy of stage I cancer of the endometrium: a need for reappraisal of this adjunctive modality." Int J Radiat Oncol Biol Phys **15**(6): 1291-7.

One hundred and eighty-five patients with Stage I cancer of the endometrium were irradiated preoperatively. All were irradiated to the whole pelvis by external beam only using supermegavoltage apparati. The total mid-pelvis dose ranged from 4500 cGy/5 weeks to 5500 cGy/6 1/2 weeks. Surgery followed usually in 6 weeks. Complications were minimal. Disease-free survival at Stage IA was 92.4% 5-year, 87.7% 10-year; Stage IB was 83.5% 5-year, 74.6% 10-year. Prognosis was related to stage, grade, depth of myometrial penetration, the presence of "residual" tumor at hysterectomy. External beam preoperative irradiation is recommended for all Stage I patients; Stage IB with higher grade pathology should have intracavitary irradiation supplemental to the external irradiation.

Wang, Y., P. Hanifi-Moghaddam, et al. (2009). "Progesterone inhibition of Wnt/beta-catenin signaling in normal endometrium and endometrial cancer." Clin Cancer Res **15**(18): 5784-93.

PURPOSE: Wnt signaling regulates the fine balance between stemness and differentiation. Here, the role of Wnt signaling to maintain the balance between estrogen-induced proliferation and progesterone-induced differentiation during the menstrual cycle, as well as during the induction of hyperplasia and carcinogenesis of the endometrium, was investigated. EXPERIMENTAL DESIGN: Endometrial gene expression profiles from estradiol (E(2)) and E(2) + medroxyprogesterone acetate-treated postmenopausal patients were combined with profiles obtained during the menstrual cycle (PubMed; GEO DataSets). Ishikawa cells were transfected with progesterone receptors and Wnt inhibitors dickkopf homologue 1 (DKK1) and forkhead box O1 (FOXO1), measuring Wnt activation. Expression of DKK1 and FOXO1 was inhibited by use of sequence-specific short hairpins. Furthermore, patient samples (hormone-treated endometria, hyperplasia, and endometrial cancer) were stained for Wnt activation using nuclear beta-catenin and CD44. RESULTS: In vivo, targets and components of the Wnt signaling pathway (among them DKK1 and FOXO1) are regulated by E(2) and progesterone. In Wnt-activated Ishikawa cells, progesterone inhibits Wnt signaling by induction of DKK1 and FOXO1. Furthermore, using siRNA-mediated knockdown of both DKK1 and FOXO1, progesterone inhibition of Wnt signaling was partly circumvented. Subsequently, immunohistochemical analysis of the Wnt target gene CD44 showed that progesterone acted as an inhibitor of Wnt signaling in hyperplasia and in well-differentiated endometrial cancer. CONCLUSION: Progesterone induction of DKK1 and FOXO1 results in inhibition of Wnt signaling in the human endometrium. This Wnt inhibitory effect of progesterone is likely to play a rate-limiting role in the maintenance of endometrial homeostasis and, on its loss, in tumor onset and progression toward malignancy.

Widschwendter, M., S. Apostolidou, et al. (2009). "HOXA methylation in normal endometrium from premenopausal women is associated with the presence of ovarian cancer: a proof of principle study." Int J Cancer **125**(9): 2214-8.

DNA methylation of polycomb group target (PCGT) genes is an early step in carcinogenesis and could potentially be assayed to determine cancer risk prediction. To assess whether methylation changes in PCGT genes in normal tissue is able to predict the presence of cancer, we studied HOXA gene methylation in normal endometrium from premenopausal ovarian cancer patients and age-matched healthy controls without ovarian cancer. DNA methylation of HOXA9 and HOXA11 genes in normal endometrium was associated with ovarian cancer in an initial test set and this was subsequently confirmed in independent validation sample sets. The overall risk of ovarian cancer was increased 12.3-fold by high HOXA9 methylation for all stages, and 14.8-fold for early stage ovarian cancers, independent of age, phase of the menstrual cycle and histology of the cancer. The results of this proof of principle study demonstrate the potential to detect ovarian cancer via analysis of normal endometrial cells and provide insight into the possible contribution of this novel approach in ovarian cancer risk prediction and prevention.

Yamada, S. D. and K. F. McGonigle (1998). "Cancer of the endometrium and corpus uteri." Curr Opin Obstet Gynecol **10**(1): 57-60.

Uterine cancer is often diagnosed at an early stage and is therefore considered one of the most curable gynecologic malignancies. Despite this, a substantial number of women who present at more advanced stage or with unfavorable histologies suffer significant morbidity and death from this disease. Research continues along several fronts in an attempt to improve the prognosis for this group of women. Basic scientific research has continued to evaluate mechanisms of carcinogenesis in the hope that better targets for treatment and prevention of disease will be found. Epidemiologic studies have attempted to

further define risk factors as well as elucidate risk in those patients receiving combination estrogen and progestin hormone replacement therapy. Clinical studies have further defined prognostic factors, and examined new surgical staging techniques and the need for adjuvant therapy after primary surgery. However, treatment options for advanced and recurrent disease remain limited.

Yamamoto, T., J. Kitawaki, et al. (1993). "Estrogen productivity of endometrium and endometrial cancer tissue; influence of aromatase on proliferation of endometrial cancer cells." J Steroid Biochem Mol Biol **44**(4-6): 463-8.

Aromatase, estrone (E1) sulfatase and E1 sulfotransferase activities were examined in endometrium and endometrial cancer tissue preparations. Aromatase and E1 sulfatase activities in endometrial cancer tissues were found to be significantly higher than in normal endometrial tissues. However, E1 sulfotransferase activity did not differ between benign and malignant tissue. We also examined the effect of testosterone (T) on aromatase activity and tritiated thymidine uptake (DNA synthesis) in various cultured cervical or corpus endometrial cancer cell lines (OMC-4, HHUA, Ishikawa, HEC-59). The results demonstrated that only the HEC-59 cell line had high aromatase activity and increased its DNA synthesis in response to T. This increase of DNA synthesis by T was not suppressed by simultaneous addition of cyproterone acetate, but was by tamoxifen. These data suggest that in situ estrogen production in endometrial cancer tissue is biologically important and that aromatase in cancer cells may contribute partially to cell proliferation if androgen substrate is provided.

Yedema, K. A., P. Kenemans, et al. (1991). "Carcinoma-associated mucin serum markers CA M26 and CA M29: efficacy in detecting and monitoring patients with cancer of the breast, colon, ovary, endometrium and cervix." Int J Cancer **47**(2): 170-9.

Two recently developed monoclonal antibody (MAb)-based anti-mucin assays, CA M26 and CA M29, were studied in 250 cancer patients and compared to 3 well-established marker tests, viz., CA 125, CA 15.3 and SCC, in order to assess their clinical usefulness as serum tumor markers. Pre-treatment sera were obtained from patients with predominantly low-stage epithelial malignancies comprising 200 adenocarcinomas (of the ovary, endometrium, breast and large intestine) and 50 squamous-cell carcinomas (of the uterine cervix). Pretreatment sera of 50 patients with benign ovarian tumors were included to evaluate levels in benign disease, CA M26 and CA M29 cut-off levels were established in 89 healthy controls. In patients with adenocarcinomas, overall positivity for CA M29 was 24%, ranging from 10% in breast cancer to 60% in ovarian cancer. Overall positivity was highest for CA 125 (30%) and lowest for CA M26 (18%) with CA M29 (24%) being similar to CA 15.3 (25%). In adenocarcinomas the combined CA M26-CA M29 assays equalled results obtained with the CA 125-CA 15.3 combination (33% vs. 36%). Elevation of 2 or more markers was highly indicative of advanced disease (p less than 0.025). A majority of positive patients showed either CA M26 or CA M29 elevations, indicating that both antibodies detect distinct epitopes. After adjustment for tumor site and stage, the profile of CA M26 as a single marker differed significantly from the profiles of CA 125 and of CA M29. CA M26 was frequently (32%) elevated in patients with squamous-cell carcinoma of the cervix and CA M26 levels were often independently elevated. CA M26 seems to be valuable as an additional marker in breast cancer and perhaps as a new marker in cervical cancer. CA M29 may be useful in ovarian cancer in addition to CA 125.

Zhou, X. H., X. D. Teng, et al. (2008). "Expression of receptor-binding cancer antigen expressed on SiSo cells and estrogen receptor subtypes in the normal, hyperplastic, and carcinomatous endometrium." Int J Gynecol Cancer **18**(1): 152-8.

The objectives were to study the expression of receptor-binding cancer antigen expressed on SiSo cells (RCAS1) and estrogen receptor (ER) subtypes in the normal, hyperplastic, and carcinomatous endometrium and to explore their possible role in carcinogenesis and progression of endometrial carcinoma. Immunohistochemistry and semiquantitative reverse transcriptase-polymerase chain reaction (RT-PCR) were applied to detect protein and messenger RNA expression of RCAS1, ER-alpha, and ER-beta in normal, hyperplastic, and carcinomatous endometrium. Western blotting was also used to detect the RCAS1 protein expression. Immunohistochemistry showed that the high expressions of RCAS1 protein were 0% (0/20), 9.1% (2/22), 40% (8/20), and 68.0% (34/50) in normal, simple, and complex hyperplasia, atypical hyperplasia, and endometrial carcinoma, respectively. There was a significant difference between each group ($P < 0.05$). The high-level expression of RCAS1 was detected more frequently in endometrial cancer with deep myometrial invasion, vascular invasion, and positive ER-alpha ($P < 0.05$). Two staining patterns of RCAS1 were observed. All normal, simple, and complex hyperplastic endometrium showed P pattern, while all malignant endometrium were of the D pattern. In atypical endometrium, 25% (5/20) cases showed D pattern. The Western blotting and RT-PCR results

correlated with the immunohistochemistry results. The expression and distribution of RCAS1 may be involved in the malignant transformation of endometrium, and RCAS1 coexpression with ER-alpha may be associated with development and metastasis of endometrial carcinoma.

References

1. Alcazar, J. L. and R. Galvan (2009). "Three-dimensional power Doppler ultrasound scanning for the prediction of endometrial cancer in women with postmenopausal bleeding and thickened endometrium." Am J Obstet Gynecol **200**(1): 44 e1-6.
2. Ascher, S. M. and C. Reinhold (2002). "Imaging of cancer of the endometrium." Radiol Clin North Am **40**(3): 563-76.
3. Ayhan, A., H. Yarali, et al. (1989). "Lymph node metastasis in early endometrium cancer." Aust N Z J Obstet Gynaecol **29**(3 Pt 2): 332-5.
4. Baanders-van Halewyn, E. A., M. A. Blankenstein, et al. (1996). "A comparative study of risk factors for hyperplasia and cancer of the endometrium." Eur J Cancer Prev **5**(2): 105-12.
5. Barakat, R. R., T. A. Gilewski, et al. (2000). "Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy." J Clin Oncol **18**(20): 3459-63.
6. Bertelli, G., M. Venturini, et al. (1998). "Tamoxifen and the endometrium: findings of pelvic ultrasound examination and endometrial biopsy in asymptomatic breast cancer patients." Breast Cancer Res Treat **47**(1): 41-6.
7. Bese, T., D. Kosebay, et al. (1996). "Ultrasonographic appearance of endometrium in postmenopausal breast cancer patients receiving tamoxifen." Eur J Obstet Gynecol Reprod Biol **67**(2): 157-62.
8. Buijs, C., P. H. Willemse, et al. (2009). "Effect of tamoxifen on the endometrium and the menstrual cycle of premenopausal breast cancer patients." Int J Gynecol Cancer **19**(4): 677-81.
9. Ceci, O., S. Bettocchi, et al. (2000). "Sonographic, hysteroscopic, and histologic evaluation of the endometrium in postmenopausal women with breast cancer receiving tamoxifen." J Am Assoc Gynecol Laparosc **7**(1): 77-81.
10. Cherubini, A., G. L. Taddei, et al. (2000). "HERG potassium channels are more frequently expressed in human endometrial cancer as compared to non-cancerous endometrium." Br J Cancer **83**(12): 1722-9.
11. Cohen, I., M. M. Altaras, et al. (1997). "Estrogen and progesterone receptors in the endometrium of postmenopausal breast cancer patients treated with tamoxifen and progestogens." Gynecol Oncol **65**(1): 83-8.
12. Dallenbach-Hellweg, G., D. Schmidt, et al. (2000). "The endometrium in breast cancer patients on tamoxifen." Arch Gynecol Obstet **263**(4): 170-7.
13. De Goeij, A. F., H. M. Scheres, et al. (1988). "Progesterone receptor quantification with radiolabeled promegestone (R 5020) in frozen sections of endometrium and breast cancer tissue." J Steroid Biochem **29**(5): 465-74.
14. DeCruze, B. and D. Guthrie (1999). "Radiotherapy in poor risk patients with stage I cancer of the endometrium: results of not giving external beam radiotherapy." Clin Oncol (R Coll Radiol) **11**(4): 252-4.
15. Develioglu, O. H., M. Omak, et al. (2004). "The endometrium in asymptomatic breast cancer patients on tamoxifen: value of transvaginal ultrasonography with saline infusion and Doppler flow." Gynecol Oncol **93**(2): 328-35.
16. Duffy, S. R. and L. Taylor (2004). "Molecular markers in the endometrium at baseline of postmenopausal patients with early breast cancer in the ATAC (Arimidex, tamoxifen, alone, or in combination) trial." Am J Obstet Gynecol **191**(6): 1921-7.
17. Dumitru, D. M., M. Onofriescu, et al. (2009). "The endovaginal ultrasound finding of a thin and regular endometrium is uncommon in endometrial cancer." Rev Med Chir Soc Med Nat Iasi **113**(1): 132-5.
18. Fons, G., S. M. Hasibuan, et al. (2007). "Validation of tissue microarray technology in endometrioid cancer of the endometrium." J Clin Pathol **60**(5): 500-3.
19. Fujimoto, J., M. Hori, et al. (1996). "Estrogen induces expression of c-fos and c-jun via activation of protein kinase C in an endometrial cancer cell line and fibroblasts derived from human uterine endometrium." Gynecol Endocrinol **10**(2): 109-18.
20. Garuti, G., F. Grossi, et al. (2007). "Pretreatment and prospective assessment of endometrium in menopausal women taking tamoxifen for breast cancer." Eur J Obstet Gynecol Reprod Biol **132**(1): 101-6.
21. Gerber, B., A. Krause, et al. (2000). "Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound." J Clin Oncol **18**(20): 3464-70.
22. Gielen, S. C., L. C. Kuhne, et al. (2005). "Tamoxifen treatment for breast cancer enforces a distinct gene-expression profile on the human endometrium: an exploratory study." Endocr Relat Cancer **12**(4): 1037-49.
23. Goncalves, M. A., W. J. Goncalves, et al. (1999). "Hysteroscopic evaluation of the endometrium of post-menopausal patients with breast cancer before and after tamoxifen use." Int J Gynaecol Obstet **66**(3): 273-9.
24. Gull, B., B. Karlsson, et al. (2003). "Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer." Am J Obstet Gynecol **188**(2): 401-8.
25. Hachisuga, T., H. Tsujioka, et al. (2005). "K-ras mutation in the endometrium of tamoxifen-treated breast cancer patients, with a comparison of tamoxifen and toremifene." Br J Cancer **92**(6): 1098-103.
26. Hasengaowa, J. Kodama, et al. (2006). "Heparanase expression in both normal endometrium and endometrial cancer." Int J Gynecol Cancer **16**(3): 1401-6.

27. Hayata, T. (1991). "Ultrastructural study of glandular epithelium in adenomyosis in comparison with those of proliferative endometrium and well-differentiated endometrial cancer." Am J Obstet Gynecol **165**(1): 225-8.
28. Hearns-Stokes, R., C. Mayers, et al. (2006). "Expression of the proto-oncoprotein breast cancer nuclear receptor auxiliary factor (Brx) is altered in eutopic endometrium of women with endometriosis." Fertil Steril **85**(1): 63-70.
29. Hirata, S., N. Yamada-Mouri, et al. (1995). "Presence of alternatively spliced-estrogen receptor mRNA variants in normal human uterine endometrium and endometrial cancer." Endocr J **42**(2): 289-93.
30. Hirose, K., K. Tajima, et al. (1996). "Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer." Jpn J Cancer Res **87**(9): 1001-9.
31. Huang, K. T., C. A. Chen, et al. (1996). "Sonographic characteristics of adenofibroma of the endometrium following tamoxifen therapy for breast cancer: two case reports." Ultrasound Obstet Gynecol **7**(5): 363-6.
32. Hubbard, J. L. and J. K. Holcombe (1990). "Cancer of the endometrium." Semin Oncol Nurs **6**(3): 206-13.
33. Ichikawa, Y., H. Tsunoda, et al. (2002). "Microsatellite instability and immunohistochemical analysis of MLH1 and MSH2 in normal endometrium, endometrial hyperplasia and endometrial cancer from a hereditary nonpolyposis colorectal cancer patient." Jpn J Clin Oncol **32**(3): 110-2.
34. Kavak, Z. N., S. Binoz, et al. (2000). "The effect of tamoxifen on the endometrium, serum lipids and hypothalamus pituitary axis in the postmenopausal breast cancer patients." Acta Obstet Gynecol Scand **79**(7): 604-7.
35. Kelloff, G. J., C. W. Boone, et al. (1995). "Strategies for phase II cancer chemoprevention trials: cervix, endometrium, and ovary." J Cell Biochem Suppl **23**: 1-9.
36. Kesim, M. D., Y. Aydin, et al. (2008). "Long-term effects of the levonorgestrel-releasing intrauterine system on serum lipids and the endometrium in breast cancer patients taking tamoxifen." Climacteric **11**(3): 252-7.
37. Kim, H. S., Y. T. Jeon, et al. (2008). "The effect of adjuvant hormonal therapy on the endometrium and ovary of breast cancer patients." J Gynecol Oncol **19**(4): 256-60.
38. Koumantaki, Y., A. Tzonou, et al. (1989). "A case-control study of cancer of endometrium in Athens." Int J Cancer **43**(5): 795-9.
39. Laatikainen, T. J., E. I. Tomas, et al. (1995). "The expression of insulin-like growth factor and its binding protein mRNA in the endometrium of postmenopausal patients with breast cancer receiving tamoxifen." Cancer **76**(8): 1406-10.
40. Lacey, J. V., Jr., L. A. Brinton, et al. (2000). "Tubal sterilization and risk of cancer of the endometrium." Gynecol Oncol **79**(3): 482-4.
41. Lien, H. H., V. Blomlie, et al. (1991). "Cancer of the endometrium: value of MR imaging in determining depth of invasion into the myometrium." AJR Am J Roentgenol **157**(6): 1221-3.
42. Lindahl, B., E. Andolf, et al. (2008). "Adjuvant tamoxifen in breast cancer patients affects the endometrium by time, an effect remaining years after end of treatment and results in an increased frequency of endometrial carcinoma." Anticancer Res **28**(2B): 1259-62.
43. Lumbiganon, P. (1994). "Depot-medroxyprogesterone acetate (DMPA) and cancer of the endometrium and ovary." Contraception **49**(3): 203-9.
44. Markovitch, O., R. Tepper, et al. (2009). "Long-term "protective" effect of aromatase inhibitors on the endometrium of postmenopausal breast cancer patients." Breast Cancer Res Treat **113**(2): 321-6.
45. Marquez, R. T., K. A. Baggerly, et al. (2005). "Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon." Clin Cancer Res **11**(17): 6116-26.
46. Morales, L., P. Neven, et al. (2009). "Prospective assessment of the endometrium in postmenopausal breast cancer patients treated with fulvestrant." Breast Cancer Res Treat **117**(1): 77-81.
47. Moss, E. L., A. Stevens, et al. (2003). "Toxicity, recurrence and survival after adjuvant radiotherapy treatment for FIGO stage I cancer of the endometrium." Clin Oncol (R Coll Radiol) **15**(5): 250-4.
48. Mourits, M. J., A. G. Van der Zee, et al. (1999). "Discrepancy between ultrasonography and hysteroscopy and histology of endometrium in postmenopausal breast cancer patients using tamoxifen." Gynecol Oncol **73**(1): 21-6.
49. Moutsatsou, P., E. Kassi, et al. (1998). "Detection of oestrogen receptor variants in endometrium, myometrium, leiomyoma and peripheral blood mononuclear cells: comparison to variants present in breast cancer." J Cancer Res Clin Oncol **124**(9): 478-84.
50. Munstedt, K., P. Grant, et al. (2004). "Cancer of the endometrium: current aspects of diagnostics and treatment." World J Surg Oncol **2**: 24.
51. Nasu, K., K. Kai, et al. (2001). "Expression of cathepsin L in normal endometrium and endometrial cancer." Eur J Obstet Gynecol Reprod Biol **99**(1): 102-5.
52. Noh, S. K., J. Y. Yoon, et al. (2008). "A case report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium." J Gynecol Oncol **19**(4): 265-9.
53. Nowak-Markwitz, E., A. Jankowska, et al. (2004). "Human chorionic gonadotropin-beta in endometrium cancer tissue." Eur J Gynaecol Oncol **25**(3): 351-4.
54. Ohno, Y., H. Fujibayashi, et al. (1990). "Medroxyprogesterone acetate binding sites in human endometrium and endometrial cancer." Gynecol Obstet Invest **29**(3): 227-31.
55. Ohwada, M., M. Suzuki, et al. (1996). "Glutathione peroxidase activity in endometrium: effects of sex hormones and cancer." Gynecol Oncol **60**(2): 277-82.

56. Orejuela, F. J., L. M. Ramondetta, et al. (2005). "Estrogen and progesterone receptors and cyclooxygenase-2 expression in endometrial cancer, endometrial hyperplasia, and normal endometrium." Gynecol Oncol **97**(2): 483-8.
57. Ortac, F., M. Bahceci, et al. (1991). "Myometrial invasion of endometrium cancer assessed by transrectal ultrasonography." Gynecol Obstet Invest **32**(2): 115-7.
58. Oshima, H., H. Miyagawa, et al. (2002). "Adenofibroma of the endometrium after tamoxifen therapy for breast cancer: MR findings." Abdom Imaging **27**(5): 592-4.
59. Osler, M. (1987). "Obesity and cancer. A review of epidemiological studies on the relationship of obesity to cancer of the colon, rectum, prostate, breast, ovaries, and endometrium." Dan Med Bull **34**(5): 267-74.
60. Papageorgiou, I., P. K. Nicholls, et al. (2009). "Expression of nodal signalling components in cycling human endometrium and in endometrial cancer." Reprod Biol Endocrinol **7**: 122.
61. Park, D. W., D. S. Choi, et al. (2003). "A well-defined in vitro three-dimensional culture of human endometrium and its applicability to endometrial cancer invasion." Cancer Lett **195**(2): 185-92.
62. Paszkowska, A., M. Cybulski, et al. (2000). "Total sialic acid content in endometrial cancer tissue in relation to normal and hyperplastic human endometrium." Cancer Detect Prev **24**(5): 459-63.
63. Potish, R. A. (1987). "Radiation therapy of periaortic node metastases in cancer of the uterine cervix and endometrium." Radiology **165**(2): 567-70.
64. Potish, R. A. (1989). "Abdominal radiotherapy for cancer of the uterine cervix and endometrium." Int J Radiat Oncol Biol Phys **16**(6): 1453-8.
65. Re, A., T. H. Taylor, et al. (1997). "Risk for breast and colorectal cancers subsequent to cancer of the endometrium in a population-based case series." Gynecol Oncol **66**(2): 255-7.
66. Rutanen, E. M., T. Nyman, et al. (1994). "Suppressed expression of insulin-like growth factor binding protein-1 mRNA in the endometrium: a molecular mechanism associating endometrial cancer with its risk factors." Int J Cancer **59**(3): 307-12.
67. Saito, T., A. Schneider, et al. (1997). "Proliferation-associated regulation of telomerase activity in human endometrium and its potential implication in early cancer diagnosis." Biochem Biophys Res Commun **231**(3): 610-4.
68. Sato, S., G. Matsunaga, et al. (1998). "Mass screening for cancer of the endometrium in Miyagi Prefecture, Japan." Acta Cytol **42**(2): 295-8.
69. Signorile, P. G., F. Baldi, et al. (2009). "Ectopic endometrium in human foetuses is a common event and sustains the theory of mullerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer." J Exp Clin Cancer Res **28**: 49.
70. Siufi, A. A., G. D. S. I. D. Cotrim, et al. (2003). "Effects of tamoxifen therapy on the expression of p27 protein in the endometrium of women with primary breast cancer." Int J Oncol **23**(6): 1545-51.
71. Song, J. Y., J. W. Kim, et al. (2008). "BAG-1 expression in normal endometrium, endometrial hyperplasia and endometrial cancer." Acta Obstet Gynecol Scand **87**(8): 862-7.
72. Srinivasan, R., E. Benton, et al. (1999). "Expression of the c-erbB-3/HER-3 and c-erbB-4/HER-4 growth factor receptors and their ligands, neuregulin-1 alpha, neuregulin-1 beta, and betacellulin, in normal endometrium and endometrial cancer." Clin Cancer Res **5**(10): 2877-83.
73. Tang, X., Y. Muramatsu, et al. (1993). "Endometrium-myometrium ratio: a newly proposed diagnostic parameter on magnetic resonance imaging assessment of myometrial invasion by endometrial cancer." Jpn J Clin Oncol **23**(5): 278-83.
74. Vaeth, J. M., J. Fontanesi, et al. (1988). "External radiation therapy of stage I cancer of the endometrium: a need for reappraisal of this adjunctive modality." Int J Radiat Oncol Biol Phys **15**(6): 1291-7.
75. Wang, Y., P. Hanifi-Moghaddam, et al. (2009). "Progesterone inhibition of Wnt/beta-catenin signaling in normal endometrium and endometrial cancer." Clin Cancer Res **15**(18): 5784-93.
76. Widschwendter, M., S. Apostolidou, et al. (2009). "HOXA methylation in normal endometrium from premenopausal women is associated with the presence of ovarian cancer: a proof of principle study." Int J Cancer **125**(9): 2214-8.
77. Yamada, S. D. and K. F. McGonigle (1998). "Cancer of the endometrium and corpus uteri." Curr Opin Obstet Gynecol **10**(1): 57-60.
78. Yamamoto, T., J. Kitawaki, et al. (1993). "Estrogen productivity of endometrium and endometrial cancer tissue; influence of aromatase on proliferation of endometrial cancer cells." J Steroid Biochem Mol Biol **44**(4-6): 463-8.
79. Yedema, K. A., P. Kenemans, et al. (1991). "Carcinoma-associated mucin serum markers CA M26 and CA M29: efficacy in detecting and monitoring patients with cancer of the breast, colon, ovary, endometrium and cervix." Int J Cancer **47**(2): 170-9.
80. Zhou, X. H., X. D. Teng, et al. (2008). "Expression of receptor-binding cancer antigen expressed on SiSo cells and estrogen receptor subtypes in the normal, hyperplastic, and carcinomatous endometrium." Int J Gynecol Cancer **18**(1): 152-8.
81. PubMed (2011). http://www.ncbi.nlm.nih.gov/pubmed.
82. Cancer. Wikipedia. (2011) http://en.wikipedia.org/wiki/Cancer.

2/2/2012