Ovary Cancer

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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 researches on the ovary cancer.
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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., M. J. Galan, et al. (2003). "Transvaginal gray scale and color Doppler sonography in primary ovarian cancer and metastatic tumors to the ovary." J Ultrasound Med **22**(3): 243-7.

OBJECTIVE: To compare gray scale and color Doppler features of primary and metastatic ovarian carcinomas. METHODS: Clinical, sonographic (gray scale and color Doppler), and histopathologic data of 143 patients with primary (n = 127 adnexal masses) and metastatic (n = 34 adnexal masses) ovarian cancer were reviewed. Morphologic gray scale parameters assessed were bilaterality, tumor volume, echogenicity, and presence of septa, papillary projections, or solid areas. Color Doppler parameters were presence of blood flow, tumor blood flow location (central versus peripheral), subjective impression of blood flow amount (scanty, moderate, or abundant), lowest resistive index, lowest pulsatility index, and maximal peak systolic velocity (centimeters per second). RESULTS: No statistical differences were found in bilaterality, tumor volume, presence of septa, papillary projections or solid areas, presence of blood flow, tumor blood flow location, subjective impression of blood flow amount, lowest resistive index, lowest pulsatility index, and maximal peak systolic velocity. Metastatic carcinomas were more frequently purely solid tumors (47% versus 26%; P = .001; likelihood ratio, 2.4; 95% confidence interval, 1.2-4.7). CONCLUSIONS: The presence of a purely solid tumor indicates a higher probability of metastatic carcinoma than primary ovarian cancer. However, with the use of gray scale and color Doppler sonography, it is difficult to differentiate primary ovarian carcinomas from metastatic tumors to the ovary.

Altaras, M. M., G. L. Goldberg, et al. (1986). "The value of cancer antigen-125 as a tumor marker in malignant germ cell tumors of the ovary." Gynecol Oncol **25**(2): 150-9.

The value of cancer antigen-125 (CA-125) as a tumor marker for malignant germ cell tumors (MGCT) of the ovary was investigated and compared with the other recognized tumor markers (human chorionic gonadotrophin (hCG), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) isoenzymes. In the 10 months following June 1984, 4 new cases with MGCT and 1 patient with active disease on treatment were evaluated. In all cases prior to planned surgery the levels of CA-125 were significantly elevated. The serum values ranged from 154 to 617 U/ml (normal less than 20 U/ml). In 1 case (pure dysgerminoma) CA-125 was the only tumor marker. In 3 patients (2 mixed germ cell tumors and 1 immature teratoma) serum LDH (LD 1, 2, and 3) was elevated, and AFP was elevated in 1 of these. In the fifth case (mixed germ cell tumor), on treatment, serum AFP was used to monitor the disease. Four patients underwent cytoreductive surgery followed by combination chemotherapy. The changes in the serum levels of CA-125 paralleled those of the other tumor markers while on therapy. In our experience CA-125 is an invaluable indicator of the clinical status of the patient and could be a new tumor marker in patients with MGCT.

Anthony, H. M. (1976). "Age-specific incidence of cancer of the endometrium, ovary and breast in the United Kingdom and the United States." Int J Epidemiol **5**(3): 231-6.

The published data for overall cancer incidence for the registries of Birmingham (UK) and Connecticut (US) show remarkable similarity for men but diverge for women. The incidence of cancer of the endometrium, ovary and breast in Connecticut is higher than in Birmingham, and in each case the menopausal dislocation in the age-specific incidence plot of the Birmingham data is obscured in that for Connecticut. For endometrial cancer, the difference correlates with differences in the two countries in the use of oestrogen replacement therapy, recently implicated in the aetiology of endometrial cancer. The similarity in the pattern for ovarian and breast cancer, and the changing pattern of breast cancer incidence in Birmingham suggest a similar aetiological effect.

Atiomo, W., A. Read, et al. (2009). "Local recruitment experience in a study comparing the effectiveness of a low glycaemic index diet with a low calorie healthy eating approach at achieving weight loss and reducing the risk of endometrial cancer in women with polycystic ovary syndrome (PCOS)." Contemp Clin Trials **30**(5): 451-6.

OBJECTIVE: Feasibility of a clinical-trial comparing a low-glycaemic diet with a low-calorie healthy eating approach at achieving weight loss and reducing the risk of endometrial cancer in women with PCOS. DESIGN: A pilot Randomised-Controlled-Trial using different recruitment strategies. SETTING: A University Hospital in the United Kingdom. PATIENTS: Women seen at specialist gynaecology clinics over a 12 month period in one University Hospital, and women self identified through a website and posters. INTERVENTIONS: Potential recruits were assessed for eligibility, gave informed consent, randomised, treated and assessed as in the definitive trial. MAIN OUTCOME MEASURES: Eligibility and recruitment rates, compliance with the allocated diet for 6 months and with clinical assessments, blood tests, pelvic ultrasound scans and endometrial biopsies. RESULTS: 1433 new and 2598 follow up patients were seen in 153 gynaecology clinics for over 12 months. 441 (11%) potentially eligible women were identified, 19 (0.4%) of whom met the trial entry criteria. Eleven consented to take part, of which 8 (73%) completed the study. CONCLUSIONS: Planned future trials on over-weight women with PCOS should be multicentre and should incorporate primary care. This data will help other researchers plan and calculate the sample size and potential recruitment rates in future clinical trials in PCOS. The results will also be useful for inclusion in future meta-analyses.

Backstrom, M., T. Link, et al. (2003). "Recombinant MUC1 mucin with a breast cancer-like O-glycosylation produced in large amounts in Chinese-hamster ovary cells." Biochem J **376**(Pt 3): 677-86.

We have developed an expression system for the production of large quantities of recombinant MUC1 mucin in CHO-K1 (Chinese-hamster ovary K1) cells. The extracellular part of human MUC1, including 16 MUC1 tandem repeats, was produced as a fusion protein with murine IgG Fc, with an intervening enterokinase cleavage site for the removal of the Fc tail. Stable MUC1-IgG-producing CHO-K1 clones were generated and were found to secrete MUC1-IgG into the culture medium. After adaptation to suspension culture in protein-free medium in a bioreactor, the fusion protein was secreted in large quantities (100 mg/l per day) into the culture supernatant. From there, MUC1 could be purified to homogeneity using a two-step procedure including enterokinase cleavage and ion-exchange chromatography. Capillary liquid chromatography MS of released oligosaccharides from CHO-K1-produced MUC1 identified the main O-glycans as Galbeta1-3GalNAc (core 1) and mono- and di-sialylated core 1. The glycans occupied on average 4.3 of the five potential O-glycosylation sites in the tandem repeats, as determined by nano-liquid chromatography MS of partially deglycosylated Clostripain-digested protein. A very similar O-glycan profile and site occupancy was found in MUC1-IgG produced in the breast carcinoma cell line T47D, which has O-glycosylation typical for breast cancer. In contrast, MUC1-IgG produced in another breast cancer cell line, MCF-7, showed a more complex pattern with both core 1- and core 2-based O-glycans. This is the first reported production of large quantities of recombinant MUC1 with a breast cancer-like O-glycosylation that could be used for the immunotherapy of breast cancer.

Badiglian Filho, L., C. T. Oshima, et al. (2009). "Canonical and noncanonical Wnt pathway: a comparison among normal ovary, benign ovarian tumor and ovarian cancer." Oncol Rep **21**(2): 313-20.

The Wnt family is involved in tumorigenesis of several tissues. In ovarian cancer, the role played by Wnts and its pathways is not clearly defined. In order to analyze the canonical and noncanonical Wnt pathway in normal ovary, benign ovarian tumor and ovarian cancer, we evaluated the immunohistochemical expression of Wnt1, Frizzled-1 (FZD1), Wnt5a, Frizzled-5 (FZD5) and beta-catenin. Ovarian specimens were obtained from surgeries performed between 1993 and 2004. The patients were

divided in three groups: group A, epithelial ovarian cancer (n=38); group B, benign epithelial neoplasia (n=28); and group C, normal ovaries (n=26). Immunoreactivity for Wnt1, FZD1, Wnt5a, FZD5 and beta-catenin was scored for each group. The proportion of Wnt1 positive women in group A (29.4%) was significantly higher than in group B (4.3%) and C (9.1%) (p=0.020). The proportion of FZD1 positive patients in group C (54.5%) was significantly lower than in group A (97.1%) and B (90.0%) (p<0.001). The proportion of Wnt5a positive women was significantly higher for group A (80.0%) compared to group B (25.0%) and C (27.3%) (p<0.001). The proportion of beta-catenin positive patients in group C (95.8%) was significantly higher than group B (52.4%) (p=0.004). Comparison of the survival curves in group A according to Wnt5a expression showed a significant difference between positive and negative patients, whereas the Wnt5a positive women showed worse results (p=0.050). Our findings suggest that the pathways related to Wnt5a have an important role in ovarian malignant neoplasia. Furthermore, Wnt5a was found to be a predictor of poor prognosis for ovarian cancer.

Balen, A. (2001). "Polycystic ovary syndrome and cancer." Hum Reprod Update **7**(6): 522-5.

The polycystic ovary syndrome (PCOS) is the most common endocrine disturbance affecting women, but disagreements in diagnostic criteria make it difficult to compare epidemiological studies on long-term health risks such as cancer. The association between PCOS and endometrial adenocarcinoma has been reported for many years. Although the degree of risk has not been clearly defined, it is generally accepted that for women with PCOS who experience symptoms of amenorrhoea or oligomenorrhoea, the induction of artificial withdrawal bleeds to prevent endometrial hyperplasia is prudent management. Studies examining the relationship between PCOS and breast carcinoma have not always identified a significantly increased risk, although one recent study examined the standardized mortality rate (SMR) calculated for patients with PCOS compared with the normal population and found that the SMR for all neoplasms was 0.91 (95% CI 0.60-1.32) and for breast cancer 1.48 (95% CI 0.79-2.54). Few studies have addressed the possibility of an association between polycystic ovaries and ovarian cancer, and the results are conflicting and generally reassuring.

Barber, H. R. and T. H. Kwon (1976). "Current status of the treatment of gynecologic cancer by site: ovary." Cancer **38**(1 SUPPL): 610-9.

Cancer of the ovary is the leading cause of death from gynecologic cancer. The constant challenge presented by ovarian cancer is that about 11,000 women die from ovarian cancer each year and the results in 1974 are no better than have been achieved in the previous two decades. Standard practice of treatment for truly invasive common epithelial ovarian cancer includes total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, and post-surgical insertion of tubes and administration of P32 (if the disease is of limited extent). Although it is occasionally necessary to resect isolated segments of bowel, exenterative or ultraradical surgery in the management of ovarian cancer is not usually chosen because of the natural history of the disease. However, aggressive surgery is indicated not so much because it is curative, but because it potentiates other forms of treatment. All stages I through IV are treated surgically, to remove as much tumor as possible without running a risk of a gastrointestinal or genitourinary fistula. Radiation therapy has been utilized in addition to the surgical therapy in stage IV to control supraclavicular and/or inguinal node involvement. Single agent alkylating chemotherapy is chosen for the treatment of common epithelial ovarian cancers. Combination chemotherapy does not produce better results at this time, except in the treatment of embryonal tumors. The treatment of the common epithelial tumors by stage is outlined. The treatment of germ cell tumors, gonadal stromal tumors, ovarian tumors in childhood, ovarian tumors in pregnancy, as well as tumors not specific for the ovary, will also be discussed.

Battaglia, F., F. Plotti, et al. (2006). "Successful pregnancy after conservative surgery for stage IC ovarian cancer with serous borderline tumor on controlateral ovary: a case report." Gynecol Oncol **100**(3): 612-4.

BACKGROUND: In invasive ovarian cancer, fertility saving surgery is confined to early-stage and low-grade disease, and only few study reported sparing fertility up to FIGO stage IC ovarian cancer. CASE: We present a rare case of a 30-year-old woman affected by IC ovarian cancer with borderline tumor on controlateral ovary who underwent "conservative" debulking surgery followed by adjuvant chemotherapy. A spontaneous planned pregnancy occurred 5 years postsurgery. At 60-month follow-up, patients have no evidence of disease. CONCLUSIONS: Nowadays, preservation of ovarian function in women with tumors in early stage should be evaluated for conservative surgery. It is important to emphasize that patients selected for conservative surgery should have complete surgical staging. Careful follow-up is mandatory to ensure safety of this procedure.

Bedaiwy, M. A. and T. Falcone (2004). "Ovarian tissue banking for cancer patients: reduction of post-transplantation ischaemic injury: intact ovary freezing and transplantation." Hum Reprod **19**(6): 1242-4.

Despite reasonable achievements in different animal species, the debate about many technical aspects of ovarian tissue banking is continuing. Human ovarian tissue banks are increasingly established around the world without a clear plan about how to make the best use of such tissue. One of the important challenges facing this growing technology is to determine the ideal method for the use of this cryopreserved ovarian tissue. It is not uncommon in medicine to introduce a technology without a clear understanding of the consequences. If it is decided that ovarian tissue is to be autotransplanted, what is the most suitable place? Which technique should be implemented? As a part of the ongoing debate on ovarian tissue banking in cancer patients, this paper supports the notion that cryopreservation of an intact ovary with its vascular pedicle may be a viable alternative to the currently available techniques. Research in the development of technology to cryopreserve whole organs as well surgical techniques for the auto-transplantation of an ovary with its vascular pedicle should be encouraged.

Bera, T. K., D. B. Zimonjic, et al. (2002). "POTE, a highly homologous gene family located on numerous chromosomes and expressed in prostate, ovary, testis, placenta, and prostate cancer." Proc Natl Acad Sci U S A **99**(26): 16975-80.

We have identified a gene located on chromosomes 21 that is expressed in normal and neoplastic prostate, and in normal testis, ovary, and placenta. We name this gene POTE (expressed in prostate, ovary, testis, and placenta). The POTE gene has 11 exons and 10 introns and spans approximately equal 32 kb of chromosome 21q11.2 region. The 1.83-kb mRNA of POTE encodes a protein of 66 kDa. Ten paralogs of the gene have been found dispersed among eight different chromosomes (2, 8, 13, 14, 15, 18, 21, and 22) with preservation of ORFs and splice junctions. The synonymous:nonsynonymous ratio indicates that the genes were duplicated rather recently but are diverging at a rate faster than the average for other paralogous genes. In prostate and in testis, at least five different paralogs are expressed. In situ hybridization shows that POTE is expressed in basal and terminal cells of normal prostate epithelium. It is also expressed in some prostate cancers and in the LnCAP prostate cancer cell line. The POTE protein contains seven ankyrin repeats between amino acids 140 and 380. Expression of POTE in prostate cancer and its undetectable expression in normal essential tissues make POTE a candidate for the immunotherapy of prostate cancer. The existence of a large number of closely related but rapidly diverging members, their location on multiple chromosomes and their limited expression pattern suggest an important role for the POTE gene family in reproductive processes.

Bidzinski, M., B. Lemieszczuk, et al. (1993). "Evaluation of the hormonal function and features of the ultrasound picture of transposed ovary in cervical cancer patients after surgery and pelvic irradiation." Eur J Gynaecol Oncol **14 Suppl**: 77-80.

Conventional surgical methods for treatment of invasive cervical cancer inevitably lead to castration. In young women premature cessation of ovarian function may lead to serious short term and long term complications. The preservation of ovarian function if possible is crucial to improving quality of life. 48 patients with Ia and Ib carcinoma of the cervix entered this study. All patients were treated by Wertheim's radical hysterectomy with ovarian transposition. Some of them had adjuvant radiotherapy. It appears that radical surgery even with postoperative brachytherapy has not had adverse effect on ovarian function. It has been found that depletion of ovarian function might be expected in patients treated by external beam irradiation if the distance between the upper margin of the inlet field and the transposed ovary was less than 3 cm. In 91% cases, in USG examinations distinct reduction of transposed ovary echostructure were found.

Brandenberger, A. W., M. K. Tee, et al. (1998). "Estrogen receptor alpha (ER-alpha) and beta (ER-beta) mRNAs in normal ovary, ovarian serous cystadenocarcinoma and ovarian cancer cell lines: down-regulation of ER-beta in neoplastic tissues." J Clin Endocrinol Metab **83**(3): 1025-8.

The prognosis in ovarian carcinoma, the most lethal of the gynecologic neoplasms, is poor and has changed little in the last three decades. Only a small number respond to antiestrogen therapy, although the classic estrogen receptor, ER-alpha, has been identified in ovarian surface epithelium, from which approximately 90% of ovarian cancers originate. We have previously shown that ER-beta mRNA is most abundant in human fetal ovaries, suggesting that it might play an important role in ovarian development. Therefore, we investigated the mRNA levels of both ERs in normal ovaries, ovarian serous cystadenocarcinomas, granulosa cells from patients undergoing in vitro fertilization (IVF), the ovarian surface epithelium cell line IOSE-Van, and the ovarian cancer cell lines SKOV3, HEY and OCC1. Northern blots of normal and neoplastic ovaries were hybridized with an ER-beta riboprobe that spans the

A/B domain. We detected two major hybridizing bands at approximately 8 and 10 kb. An RNase protection assay using the same probe revealed a single band of the expected size. Hybridizing the same blot with an ER-alpha riboprobe showed a strong hybridizing band at approximately 6.5 kb. In ovarian cancer samples, ER-beta mRNA level was decreased when compared to normal ovaries. Using 25 cycles of RT-PCR followed by Southern blotting, we found equal amounts of ER-alpha and -beta mRNAs in normal ovaries in all age groups from 33 to 75 years; however, in ovarian cancer tissue, the level of ER-alpha mRNA was similar or slightly higher, comparable to 10(3) to 10(4) copies of plasmid DNA, but ER-beta mRNA levels were markedly decreased. Granulosa cells from IVF patients expressed high levels of ER-beta mRNA. The OSE cell line expressed a low level of ER-alpha, detectable after 40 cycles of RT-PCR and no ER-beta mRNA. SKOV3 showed a low level of ER-alpha and -beta mRNAs, whereas OCC1 showed a low level of ER-beta and a relatively high level of ER-alpha. HEY did not contain detectable amounts of either ER after 40 cycles of RT-PCR. We found no evidence of differential splicing or major deletions in almost the entire coding region of ER-beta in either normal ovaries or tumor samples.

Burns, B. A., J. P. Geisler, et al. (2003). "Malignant mixed mullerian tumor of the ovary and bilateral breast cancer: an argument for BRCA3, or a coincidental cluster of unconnected cancers?" Gynecol Oncol **91**(2): 426-8.

OBJECTIVES: Malignant mixed mullerian tumors (MMMTs) of the ovary are a rare, aggressive subtype of ovarian cancer without a clear relationship to familial breast-ovarian cancer syndromes. CASE: We present the case of a woman with bilateral breast cancers who subsequently developed a stage IIIc MMMT of the ovary. The patient had a first-degree female relative with breast and ovarian cancer (not MMMT), as well as second- and third-degree female relatives each with bilateral breast cancers. BRCA1 and BRCA2 sequencing of germline DNA revealed no evidence of a heritable mutation. CONCLUSIONS: Ovarian MMMTs may be a hallmark of breast/ovarian cancer secondary to genetic risk independent of classic BRCA1/2 pathways.

Carrera, M. P., M. J. Ramirez-Exposito, et al. (2005). "Pyrrolidon carboxypeptidase activities in the hypothalamus-pituitary-thyroid and hypothalamus-pituitary-ovary axes of rats with mammary gland cancer induced by N-methyl nitrosourea." Horm Metab Res **37**(2): 74-8.

Pyrrolidon carboxypeptidase is an omega-peptidase that hydrolyses N-terminal pyroglutamyl residues from biologically active peptides such as gonadotropin-releasing and thyrotrophin-releasing hormones. We previously described a decrease in both rat and human pyrrolidon carboxypeptidase activity with breast cancer, suggesting that gonadotropin-releasing hormone may be an important local intracrine, autocrine and/or paracrine hormonal factor in the pathogenesis of breast cancer while playing a role in the tumoral process. However, the other susceptible substrate of pyrrolidon carboxypeptidase, thyrotrophin-releasing hormone, may also be modified with breast cancer, supporting an association between breast cancer and thyroid disorders. The present work analyses soluble and membrane-bound pyrrolidon carboxypeptidase activities in the hypothalamus-pituitary-thyroid and hypothalamus-pituitary-ovary axes in N-methyl nitrosourea-induced breast cancer in rats. Our aim was to determine the possible relationship between gonadotropin-releasing hormone and thyrotrophin-releasing hormone regulation through pyrrolidon carboxypeptidase activity. We propose that pyrrolidon carboxypeptidase activity dysregulation at various local and systemic levels may participate in the initiation, promotion and progression of breast cancer induced in rat by N-methyl nitrosourea through the increase in gonadotropin-releasing hormone. Since pyrrolidon carboxypeptidase activity also acts on thyrotrophin-releasing hormone, the dysregulation of this enzyme's activity could indirectly affect hypothalamus-pituitary-thyroid axis function, and thus potentially represent a link between the diseases of thyroid and breast cancer.

Cauchi, M. N., S. H. Koh, et al. (1981). "Oncofoetal antigens in cancer of the cervix and ovary." Br J Cancer **44**(3): 403-9.

The incidence of oncofoetal antigens has been reported to be increased in patients with gynaecological cancers. In this study the incidence of CEA, AFP, and hCG (beta subunit) were studied in patients with adenocarcinoma of the ovary, adenocarcinoma of the cervix, and squamous-cell carcinoma of the cervix. Using a low cut-off point (CEA 2.5 microgram/l, AFP 5 microgram/l, and hCG 3 i.u./l) there is an unacceptably high proportion of control patients having one or more positive tests (42-54%) compared to cancer-bearing patients (67%). The specificity of the tests can be increased to over 95% by increasing the cut-off point to CEA 10 microgram/l, AFP 10 microgram/l, and hCG 10 i.u./l). Although this reduces the sensitivity considerably, the incidence of false positives in the control population is reduced to nil in non-cancer patients and to 2% in cancer patients tested when free of tumour, compared to 17% of patients with cancer of the ovary, 33% with adenocarcinoma of the cervix, and 6% with

squamous-cell carcinoma of the cervix. Patients with adenocarcinoma of the cervix were clearly distinguishable from those with squamous-cell carcinoma of the cervix by these tests. There was also a significant correlation between AFP and hCG levels in adenocarcinoma of the cervix (r = 0.53, P less than 0.05).

Chittenden, B. G., G. Fullerton, et al. (2009). "Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review." Reprod Biomed Online **19**(3): 398-405.

The objective of this study was to perform a systematic review of the literature to determine whether there is an association between polycystic ovary syndrome (PCOS) and gynaecological malignancy. Medline and Embase databases (1968-2008) were searched to identify publications on the association between PCOS and gynaecological cancers including breast cancer. Studies were selected that examined the association between PCOS and all types of gynaecological malignancies. A total of 19 studies exploring the association between PCOS and breast, endometrial and ovarian cancer were identified. Of these, only eight could be included after review. The data showed variability in the definition of PCOS. A meta-analysis of the data suggests that women with PCOS are more likely to develop cancer of the endometrium (OR 2.70, 95% CI 1.00-7.29) and ovarian cancer (OR 2.52, 95% CI 1.08-5.89) but not breast cancer (OR 0.88, 95% CI 0.44-1.77). Women with PCOS appear to be three times more likely to develop endometrial cancer but are not at increased risk of breast cancer. There is insufficient evidence to implicate PCOS in the development of vaginal, vulval, cervical or ovarian cancers. The paucity of studies investigating the association between PCOS and gynaecological cancers is likely to affect the reliability of the conclusions.

Costello, M., B. Shrestha, et al. (2007). "Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome." Cochrane Database Syst Rev(1): CD005552.

BACKGROUND: Insulin-sensitizing drugs (ISDs) have recently been advocated as possibly a safer and more effective long-term treatment than the oral contraceptive pill (OCP) in women with polycystic ovary syndrome (PCOS). It is important to directly compare the efficacy and safety of ISDs versus OCPs in the long-term treatment of women with PCOS. OBJECTIVES: To assess the effectiveness and safety of ISDs versus the OCP (alone or in combination) in improving clinical, hormonal, and metabolic features of PCOS. SEARCH STRATEGY: We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (September 2005), Cochrane Central Register of Controlled Trials (CENTRAL (Ovid), third quarter 2005), MEDLINE (1966 to September 2005), CINAHL (1982 to September 2005), and EMBASE (1988 to September 2005). References of the identified articles were handsearched, and pharmaceutical companies and experts in the field were also contacted for additional relevant studies. SELECTION CRITERIA: Randomised controlled trials which compared ISDs versus the OCP (alone or in combination). DATA COLLECTION AND ANALYSIS: Performed independently by two review authors. MAIN RESULTS: Six trials were included for analysis, four of which compared metformin versus OCP (104 participants) and two of which compared OCP combined with metformin versus OCP alone (70 participants). Limited data demonstrated no evidence of difference in effect between metformin and the OCP on hirsutism and acne. There was either insufficient or no data on the relative efficacy of metformin or the OCP (alone or in combination) for preventing the development of diabetes, cardiovascular disease, or endometrial cancer. Metformin was less effective than the OCP in improving menstrual pattern (Peto odds ratio (OR) 0.08, 95% CI 0.01 to 0.45). Metformin resulted in a higher incidence of gastrointestinal (Peto OR 7.75, 95% CI 1.32 to 45.71), and a lower incidence of non-gastrointestinal (Peto OR 0.11, 95% CI 0.03 to 0.39), severe adverse effects requiring stopping of medication. Metformin was less effective in reducing serum androgen levels (total testosterone: weighted mean difference (WMD) 0.54, 95% CI 0.22 to 0.86; free androgen index: WMD 3.69, 95% CI 2.56 to 4.83). Metformin was more effective than the OCP in reducing fasting insulin (WMD -3.46, 95% CI -5.39 to -1.52) and not increasing triglyceride (WMD -0.48, 95% -0.86 to -0.09) levels, but there was insufficient evidence regarding comparative effects on reducing fasting glucose or cholesterol levels. AUTHORS' CONCLUSIONS: Up to 12-months treatment with the OCP is associated with an improvement in menstrual pattern and serum androgen levels compared with metformin; but metformin treatment results in a reduction in fasting insulin and lower triglyceride levels than with the OCP. Side-effect profiles differ between the two drugs. There is either extremely limited or no data on important clinical outcomes such as the development of diabetes, cardiovascular disease, or endometrial cancer. There are no data comparing ISDs other than metformin (that is rosiglitazone, pioglitazone, and D-chiro-inositol) versus OCPs (alone or in combination).

Czeczuga-Semeniuk, E., T. Bielawski, et al. (2009). "Vitamin A family compounds, estradiol, and docetaxel in proliferation, apoptosis and immunocytochemical profile of human ovary endometrioid cancer cell line CRL-11731." Folia Histochem Cytobiol **47**(5): S127-35.

Endometrioid carcinoma represents approximately 10% of cases of the malignant ovarian epithelial tumors. According to literature, the vitamin A (carotenoids and retinoids) plays an essential role in cell proliferation, differentiation and apoptosis in both normal and neoplastic ovarian tissues. Apart from that, the retinoids alter a cytotoxic effect of chemiotherapeutics, i.e. docetaxel, on ovarian cancer cell lines. Retinoids act on cancer cells throughout different mechanism than taxanes, so they may be the potential candidates for the new treatment strategies of ovarian cancer. The aim of the study was to determine the effects of vitamin A family compounds (retinol, beta-carotene, lycopene, all-trans -, 9-cis - and 13-cis retinoic acid) on the growth and proliferation of CRL-11731 endometrioid ovary cancer cell line and on docetaxel and estradiol activity in this culture. The assay was based on [3H] thymidine incorporation and the proliferative activity of PCNA- and Ki 67-positive cells. The apoptotic index and expression of the Bcl-2 and p53 antigens in CRL-11731 cells were also studied. Among vitamin A family compounds retinol and carotenoids, but not retinoids, inhibited the growth of cancer cells in dose dependent manner. Only the concentration of 100 muM of docetaxel inhibited incorporation [3H] thymidine into CRL-11731 cancer cells. Retinol (33.4%+/-8.5), carotenoids (beta-carotene 20 muM 4.7%+/-2.9, 50 muM 2.2%+/-0.9; lycopene 10 muM 7.6%+/-0.8, 20 muM 5.2%+/-2.5, 50 muM 2.9%+/-1.2), and 13-cis retinoic acid (19.7%+/-2.2) combined with docetaxel (100 muM) significantly decreased the percentage of proliferating cells ($p<0.0001$). The antiproliferative action of lycopene alone and in combination with docetaxel was also confirmed in immunohistochemical examination (decreased the percentage of PCNA and Ki67 positive cells). Also retinol (10 muM) and lycopene (20 and 50 muM) combined with estradiol (0.01 muM) statistically decreased the percentage of proliferating cells compared to the control ($p<0.0001$) and estradiol ($p<0.01$, $p<0.0001$) group (63.5%+/-14.8, 61.0%+/-20.6, 15.0%+/-5.5 respectively). In our experiments, the compounds tested induced an apoptotic effect. Docetaxel and estradiol increased the percentage of apoptotic cells (71% apoptotic cells after administration of 10 muM all-trans retinoic acid combined with 0.01 muM estradiol, $p<0.0001$). beta-carotene, lycopene and all-trans retinoic acid alone and in combination with docetaxel were found to influence the expression of bcl-2 and p53 antigen in the cells examined. The results of our study justified an important role of vitamin A in the pathophysiology of the ovarian endometrioid cancer.

de Koning, H. J., A. Auvinen, et al. (2002). "Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial." Int J Cancer **97**(2): 237-44.

Two large-scale randomized screening trials, the Prostate, Lung, Colorectal and Ovary (PLCO) cancer trial in the USA and the European Randomized Screening for Prostate Cancer (ERSPC) trial in Europe are currently under way, aimed at assessing whether screening reduces prostate cancer mortality. Up to the end of 1998, 102,691 men have been randomized to the intervention arm and 115,322 to the control arm (which represents 83% of the target sample size) from 7 European countries and 10 screening centers in the USA. The principal screening method at all centers is determination of serum prostate-specific antigen (PSA). The PLCO trial and some European centers use also digital rectal examination (DRE) as an ancillary screening test. In the core age group (55-69 years), 3,362 of 32,486 men screened (10%) had a serum PSA concentration of 4 ng/ml or greater, which is 1 cut-off for biopsy (performed in 84%). An additional 6% was referred for further assessment based on other criteria, with much less efficiency. Differences in PSA by country are largely attributable to the age structure of the study population. The mean age-specific PSA levels are lower in the PLCO trial (1.64 ng/ml [in the age group 55-59 years], 1.80 [60-64 years] and 2.18 [65-69 years) than in the ERSPC trial (1.28-1.71 [55-59], 1.75-2.87 [60-64] and 2.48-3.06 [65-69 years]). Detection rates at the first screen in the ERSPC trial range from 11 to 42/1,000 men screened and reflect underlying differences in incidence rates and screening procedures. In centers with consent to randomization design, adherence in the screening arm is 91%, but less than half of the men in the target population are enrolled in the trial. In population-based centers in which men were randomized prior to consent, all eligible subjects are enrolled, but only about two-thirds of the men in the intervention arm undergo screening. Considerable progress has been made in both trials. Enrollment will be completed in 2001. A substantial number of early prostate cancers have been detected. The differences between countries seem to reflect both underlying prostate cancer incidence and screening policy. The trials have the power to show definitive results in 2005-2008.

Dennefors, B. L., F. Knutson, et al. (1985). "Ovarian steroid production in a woman with polycystic ovary syndrome associated with endometrial cancer." Acta Obstet Gynecol Scand **64**(5): 387-92.

A young woman with typical polycystic ovary syndrome (PCO) underwent laparotomy for moderately differentiated endometrial cancer. Specimens from the hyperplastic thecal and stromal tissue of the ovaries were incubated for 2 hours in the presence or absence of hCG, 100 IU/ml. Following incubation the tissue content of cyclic AMP and the amounts of progesterone (P), androstenedione (A), testosterone (T) and estradiol-17 beta (E2) in the incubation medium were analysed. For comparison, thecal cells from normal ovaries of regularly menstruating women were incubated under identical conditions. In vivo, the PCO ovaries secreted several-fold greater amounts of T than normal ovaries. In vitro, the thecal cells were much more active, steroidogenically, than the stromal cells of the PCO ovary. Furthermore, the hyperplastic thecal cells of the PCO ovary produced several-fold greater amounts of androgens, and appeared more sensitive to stimulation with hCG, as compared with thecal cells from normal ovaries. The results indicate that in women with PCO associated with endometrial cancer the hyperplastic thecal cells are a significant site of abnormal androgen production and abnormal sensitivity to gonadotropin.

Di Re, F., R. Fontanelli, et al. (1989). "Pelvic and para-aortic lymphadenectomy in cancer of the ovary." Baillieres Clin Obstet Gynaecol **3**(1): 131-42.

The role of the lymphadenectomy in ovarian carcinoma is widely discussed. The natural history of disease, its tendency to spread to peritoneal cavity and the lack of any reported series of careful node dissections undertaken during surgical exploration has made it difficult to establish the real significance of nodal metastatization and the optimal therapeutic approach for patients with positive nodes. At the Istituto Nazionale Tumori, Milan, 341 patients with ovarian carcinoma have been subjected to lymph node dissection. In 253 cases in which lymphadenectomy has been carried out during first surgery, the lymphonodal diffusion has been evaluated by stage, grading and histology. The incidence of lymphonodal metastases increased with the diffusion of the primitive tumour and this is particularly evident for the serous adenocarcinoma. From our data (as shown in our series of 173 cases Stage III with peritoneal and retroperitoneal diffusion) the lymphonodal involvement has to be considered as a negative prognostic factor, influencing survival in a statistically significant way. In the 88 patients subjected to radical lymphadenectomy during second-look surgery, after chemotherapy, a smaller percentage of positive nodes was observed as compared to untreated cases but, on the other hand, we documented a portion of positive nodes not sterilized by sistemic therapy. All this data confirm the necessity to perform radical lymphadenectomy not only as a staging procedure (because of low sensitivity of lymphangiography) but also as a therapeutic one for some patients.

Durocher, F., P. Tonin, et al. (1996). "Mutation analysis of the BRCA1 gene in 23 families with cases of cancer of the breast, ovary, and multiple other sites." J Med Genet **33**(10): 814-9.

Germline mutations in the BRCA1 tumour suppressor gene on chromosome 17q21 are responsible for approximately half of the cases of hereditary breast cancer, including the majority of familial breast/ovarian cancers. To increase our knowledge of the spectrum of BRCA1 mutations, we have extended our analysis to include patients with varied family histories of cancer of the breast, ovary, and at multiple other sites. We have analysed 23 unrelated familial cases using direct sequencing or a combination of dideoxy fingerprinting and sequencing procedures. Twenty one of these families contained three or more cases of breast or ovarian cancer and two families had one case of breast cancer diagnosed before the age of 40 and one case of ovarian cancer. The common frameshift mutation 5382insC was detected in two patients, and the 185delAG mutation was found in a family of Ashkenazi Jewish descent. The novel frameshift mutation 3450del4 (CAAG) was detected in a patient who developed breast cancer at the age of 28 and ovarian cancer at the age of 34. Three other women in this family were diagnosed with breast cancer at the ages of 26, 29, and 40. The novel framshift mutation 2953del3+C was found in a French Canadian woman who had developed two primary cancers of the breast at the age of 37 and 38 and renal cancer at the age of 38.

Fine, B. A., R. Yazigi, et al. (1991). "Prognosis of ovarian cancer developing in the residual ovary." Gynecol Oncol **43**(2): 164-6.

Elective oophorectomy at the time of hysterectomy for benign disease in women during their fifth decade is an important issue for both gynecologist and patient. It has been suggested that cancer developing in the residual ovary has a worse prognosis than the national average (L. McGowan, Obstet. Gynecol. 69, 386, 1987). In an effort to corroborate such finding, 36 women with epithelial ovarian cancer developing in the residual ovary after prior hysterectomy were compared to a group of 121 patients with epithelial ovarian cancer and no previous surgery. Analysis was made of age, stage at diagnosis, feasibility of cytoreductive surgery, and survival in

both groups. Only age distribution was found to be significantly different between the two groups of patients (P less than 0.001). Neither FIGO staging or quality of cytoreductive surgery showed a statistically significant difference between both groups. At 3 years, 41% of the subjects with cancer in the residual ovary were alive, compared to 42% in the group without previous hysterectomy. The corresponding figures for 5-year survival are 34 and 27%, respectively (P = 0.939). On the basis of our findings we conclude that the overall prognosis for patients with ovarian cancer developing in the residual ovary does not appear to be any worse than that reported for ovarian cancer in general.

Fiorentini, G., M. Filippeschi, et al. (2009). "Advanced cancer of the ovary: intraperitoneal chemotherapy as a new therapeutical option." In Vivo **23**(2): 317-21.

Intraperitoneal (IP) chemotherapy has been used in patients presenting different stages of ovarian cancer. We performed a critical review of the available literature on IP as first-line treatment in advanced ovarian cancer to consider if this new option should be incorporated into the commonly applied guidelines for treatment of ovarian cancer. We concluded that without further data, it would not be ethically correct to administer chemotherapy intraperitoneally. Outside of planned clinical trials, patients should not be exposed to this treatment modality and its associated toxicity. The present international guidelines are still valid and recommended chemotherapy in advanced ovarian cancer remains treatment with paclitaxel and carboplatin. Further studies on this topic are, however, warranted.

Frei, K. A., H. M. Bonel, et al. (2002). "Primary breast lymphoma, contralateral breast cancer, and bilateral Brenner tumors of the ovary." Obstet Gynecol **100**(5 Pt 2): 1079-82.

BACKGROUND: Primary lymphoma of the breast is an unusual clinical entity. Its presence with invasive breast cancer and bilateral Brenner tumors of the ovary is very rare. CASE: We report a 62-year-old woman referred for further evaluation of a palpable mass in her breast. She was diagnosed and treated for simultaneous primary lymphoma of the right breast, contralateral invasive ductal carcinoma, and bilateral Brenner tumors of the ovary. One year after treatment, she is free of recurrence or progression. CONCLUSION: Compared with breast carcinoma, primary breast lymphoma is a rare disease but should be considered in the differential diagnosis of breast masses. The presence of both breast malignancies presents a challenge in treatment decisions.

Gendron, L., P. Fradette, et al. (2001). "The importance of rock crab (Cancer irroratus) for growth, condition and ovary development of adult American lobster (Homarus americanus)." J Exp Mar Bio Ecol **262**(2): 221-241.

The rock crab (Cancer irroratus) fishery is a growing industry in eastern Canada. Considering that American lobster (Homarus americanus) is highly dependent on the rock crab as a food source, questions have arisen as to the impacts such a fishery would have. This study examines how different rations of rock crab can affect somatic growth, condition and ovary development of mature lobster, following molt. We tested the effect of four diets containing various amounts of rock crab, blue mussel and green sea urchin. The four diets were: a reference diet where 80% of the energy was provided by rock crab (T), a diet with half the crab content of the reference diet but containing as much protein (isoproteinic) as the reference diet (E1), a diet without crab but isoproteinic with the reference diet (E2), and a diet without crab but with as much energy (isocaloric) as the reference diet (E3). In general, lobsters fed a diet without rock crab showed lower glycogen and lipid content and higher water content in the digestive gland. Growth of chela muscles was lower, although diet did not have any effect on protein concentration. Ovary development was stunted in females. Differences were mostly striking in diet E3, which contained less proteins than the reference diet. Results obtained from diet E2 were also significantly different from the reference diet and not from E3, suggesting that mussel and urchin, even if given in a greater amount, are not equivalent to crab and cannot fully compensate the absence of this essential component of the lobster's diet. The importance of rock crab for lobster may be due to its high protein content and presence of particular amino acids. Our results strongly suggest that the development and management of a rock crab fishery should be cautious and governed by a multi-species approach.

Gerber, B., M. Dieterich, et al. (2008). "Controversies in preservation of ovary function and fertility in patients with breast cancer." Breast Cancer Res Treat **108**(1): 1-7.

Improved treatment of breast cancer in premenopausal patients increased survival rates, but the therapy may influence fertility and ovarian function. Currently there is a big public and individual interest of breast cancer affected women in preservation of ovarian function and fertility. Chemotherapy induced amenorrhea (CIA) has many objective (osteoporosis, cardiovascular, urogenital atrophy, cognitive etc.) and subjective (hot flushes,

sleep disturbances, change of mood etc.) consequences. In patients with breast cancer who wish to avoid a CIA and to preserve their fertility ovarian protection by GnRH agonists, cryopreservation of operative sampled ovarian tissue or obtained fertilized or non-fertilized eggs after stimulation and puncture or embryos after in vitro fertilization are technically possible. However there are no evidence-based recommendations for preservation of fertility or ovarian function in breast cancer patients. Except the cryopreservation of embryos all other procedures are experimental. It is also undefined who is going to carry the costs. Moreover, there are recent data that the reappearance of ovarian hormones may stimulate occult tumor cells in hormone sensitive breast cancer. Therefore it seems necessary to inform breast cancer patients about the possible negative effects of preservation of ovarian function.

Gharoro, E. P. and O. Eirewele (2006). "Cancer of the ovary at the University of Benin Teaching Hospital: a 10-year review, 1992-2001." Afr J Med Med Sci **35**(2): 143-7.

Forty-nine patients managed for primary ovarian cancer between January 1992 and December 2001 were analyzed, to appraise the incidence, clinical presentation and management. Data of relevance to the socio- demographic profile, clinical presentation, histopathological types, treatment modality and outcome of management were extracted from patients' case notes. A total of 412 patients with gynaecological malignancies, including 49 (11.9%) ovarian cancer were admitted in the gynaecological wards in the study period. The peak age of incidence was between 51- 60. mean 58 years. Social classes I and II were in the majority, 21.7% and 32.6% respectively. Late presentation, with stage III (76.2% of the patients) is the modal stage at presentation. The majority (73.8%) of the tumours were of epithelial origin. Gastrointestinal symptoms (86.9%) were the most common clinical features at presentation. The majority of patients (91.3%) had surgery (cytoreductive) as first line treatment, while 36/42 patients had adjuvant chemotherapy. Intraoperative haemorrhage (11.9%) was the most common complication. 2.4% of the patients died intraoperatively Primary ovarian carcinomas in Benin are predominantly epithelial in origin. It is the second most frequent gynaecological malignancy. Patients present late. mortality is high and unsatisfactory despite multimodal therapy. Public enlightenment to increase awareness and introduction of screening program for early detection is advocated.

Hales, D. B., Y. Zhuge, et al. (2008). "Cyclooxygenases expression and distribution in the normal ovary and their role in ovarian cancer in the domestic hen (Gallus domesticus)." Endocrine **33**(3): 235-44.

Cyclooxygenase (COX) (PTGS) is the rate-limiting enzyme in the biosynthesis of prostaglandins. Two COX isoforms have been identified, COX-1 and COX-2, which show distinct cell-specific expression and regulation. Ovarian cancer is the most lethal gynecological malignancy and the disease is poorly understood due to the lack of suitable animal models. The laying hen spontaneously develops epithelial ovarian cancer with few or no symptoms until the cancer has progresses to a late stage, similar to the human disease. The purpose of this study was to examine the relative expression and distribution of COX-1 and COX-2 in the ovaries of normal hens and in hens with ovarian cancer. The results demonstrate that COX-1 was localized to the granulosa cell layer and cortical interstitium, ovarian surface epithelium (OSE) and postovulatory follicle (POF) of the normal ovary. In ovarian cancer, COX-1 mRNA was significantly increased and COX-1 protein was broadly distributed throughout the tumor stroma. COX-2 protein was localized to the granulosa cell layer in the follicle and the ovarian stroma. COX-2 mRNA expression did not change as a function of age or in ovarian cancer. There was significantly higher expression of COX-1 mRNA in the first POF (POF-1) compared to POF-2 and POF-3. COX-2 mRNA expression was not significantly different among POFs. There was no difference in COX-1 or COX-2 mRNA in the OSE isolated from individual follicles in the follicular hierarchy. The results confirm previous findings of the high expression of COX-1 in ovarian tumors further supporting the laying hen as a model for ovarian cancer, and demonstrate for the first time the high expression of COX-1 in POF-1 which is the source of prostaglandins needed for oviposition.

Hata, K., R. Fujiwaki, et al. (2000). "Expression of TP and TIE2 genes in normal ovary with corpus luteum and in ovarian cancer: correlation with ultrasound-derived peak systolic velocity." Mol Hum Reprod **6**(4): 319-23.

Transvaginal colour and pulsed Doppler ultrasonography analyses of blood flow velocity have indicated that intra-tumoral peak systolic velocity (PSV) is a good indicator of ovarian malignancy. Therefore, we examined whether there was an association between the expression of angiogenic genes, e.g. thymidine phosphorylase (TP) and TIE2 and the PSV of blood flow in normal and cancerous ovaries. Initially, 40 patients were examined by transvaginal ultrasonography and 23 ovaries were surgically removed; 14 were normal with corpora lutea (CL) and nine showed ovarian cancer. The ovarian tissue was dissected according to areas of high

blood velocity and gene expression was examined using the reverse transcriptase-polymerase chain reaction (RT-PCR). No significant differences were found between PSV in the normal ovary with CL and ovarian cancer (P = 0.95). TP gene expression was significantly higher in ovarian cancer than in normal ovary with CL (P = 0.02), while TIE2 gene expression was not significantly different (P = 0.186). There was a significant correlation between TIE2 gene expression and PSV in the normal ovary with CL (r = 0.633, P = 0.015), while TP expression was significantly correlated with the PSV in ovarian cancer (r = 0.757, P = 0.018). These results indicate that there is a biological difference between physiological and pathological angiogenesis, TIE2 having a physiological role and TP being involved in pathological angiogenesis.

Hata, K., J. Udagawa, et al. (2002). "Expression of angiopoietin-1, angiopoietin-2, and Tie2 genes in normal ovary with corpus luteum and in ovarian cancer." Oncology **62**(4): 340-8.

OBJECTIVE: The recent discovery of angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2) has provided novel and important insights into the molecular mechanisms of blood vessel formation. Ang1 and Ang2 bind with similar affinity to the endothelial cell tyrosine kinase receptor Tie2. Our purpose was to assess the potential role of the Ang/Tie2 system in physiological and pathological angiogenesis in the ovary. METHODS: Ang1, Ang2, and Tie2 gene expression in 14 normal ovaries with corpus luteum (CL) and in 19 cases of ovarian cancer were analyzed by polymerase chain reaction of RNA after reverse transcription. The level of each gene expression was presented by the relative yield of each gene to the beta(2)-microglobulin gene, respectively. Furthermore, cellular distribution of Ang1 and Ang2 mRNA was examined by in situ hybridization, and localization of Tie2 was studied by immunochemistry. RESULTS: The Ang1, Ang2, and Tie2 gene expression in normal ovary with CL ranged from 0.18 to 1.06 (median 0.54), 0.31-2.64 (median 1.01), and 0.10-0.47 (median 0.20), respectively. The expression of these same genes in ovarian cancer ranged from 0.06 to 0.75 (median 0.14), 0.69-1.59 (median 1.12), and 0.04-0.35 (median 0.15), respectively. Ang1 gene expression in normal ovary with CL was significantly higher than that in ovarian cancer (p = 0.0004). The gene expression levels of Ang2 and Tie2 were statistically the same in both groups. There was a significant correlation between Ang1 gene expression and Tie2 gene expression in normal ovary with CL (r = 0.619, p = 0.018). No such significant correlation was found in ovarian cancer. Moreover, Ang2 gene expression showed no significant correlation with the Tie2 gene expression either in normal ovary with CL or in ovarian cancer. Transcripts for Ang1 were observed in CL cells and endothelial cells around CL, and in tumor cells and endothelial cells at the periphery of tumor invasion. Ang2 transcripts were expressed in the same patterns. Tie2 expression was positive primarily in the endothelial cells around CL and in those at the periphery of tumor invasion. CONCLUSION: Our results indicate that there is a difference in the Ang/Tie2 gene expression between physiological and pathological angiogenesis in the ovary. This finding may aid in the development of new therapeutic interventions for ovarian cancer.

Hepp, R., M. R. Baeza, et al. (2002). "Adjuvant whole abdominal radiotherapy in epithelial cancer of the ovary." Int J Radiat Oncol Biol Phys **53**(2): 360-5.

PURPOSE: To reexamine the use of adjuvant radiotherapy in optimally debulked patients. METHODS AND MATERIALS: Between January 1985 and April 1998, 60 patients were treated with adjuvant whole abdominal radiotherapy (A-WART). The stage distribution was Stage IC in 17 patients, Stage II in 9, and Stage III in 34. The grade distribution was Grade 1 in 9 patients, Grade 2 in 27, and Grade 3 in 24; thus, 60% of the patients had Stage III disease and 40% had Grade 3 tumors. After surgery, no residuum was left in 42 (70%), <or=2 cm in 13 (22%), and >2 cm in 5 (8%) of 60 patients. Of the 60 patients, 19 also received platinum-based chemotherapy; in 12 of the 19, the chemotherapy was before A-WART. Thirty-seven of the patients had undergone previous abdominal procedures and a second-look operation was performed in 25% of them. A-WART consisted of 22 Gy in 22 fractions, at 5 fractions weekly in 90% of the patients. The remaining 10% received 25 Gy in 25 fractions within 5 weeks. The A-WART was delivered using a 4-MV linear accelerator. After abdominal irradiation, a boost to the pelvis was given to reach 45 Gy at 1.8 cGy/fraction, using a 4-15-MV linear accelerator. RESULTS: Treatment was delivered in a median of 50 days (range 48-70). In 12 (20%) of the 60 patients, a transient treatment interruption occurred because of acute toxicity, mainly vomiting and diarrhea. The overall survival rate was 55% at 5 years (median follow-up 96.5 months). Patients with low-histologic grade tumors (Grade 1-2) had a better 5-year survival rate (66%) than those with Grade 3 tumors (35%; p <0.03). A tendency for better survival was found for those with Stage I-II than for those with Stage III (69% vs. 43%). Nonetheless, this difference did not reach statistical significance (p = 0.17). For patients receiving chemotherapy, the 5-year survival rate was 51%, not statistically different from the 58% 5-year survival rate observed among those patients without

adjuvant chemotherapy (p = 0.9). The abdominal control rate was 83%. Thirty-five percent of the patients sustained acute Grade 2-3 complications. Late complications were observed in 6 of 60 patients, 4 had Grade 3 (7%) and 2 had Grade 4 (3%). Two patients died of intestinal occlusion, both had undergone previous abdominal procedures and in 1, no tumor was found in the abdomen at the postmortem examination. CONCLUSION: A-WART achieves a quite favorable 5-year survival rate with a low complication rate in properly selected patients. A-WART should be included in the elective postoperative treatment of ovarian cancer patients who are at risk of abdominal failure, and this should be explored in a randomized trial.

Hermsen, B. B., P. J. van Diest, et al. (2006). "Low prevalence of (pre) malignant lesions in the breast and high prevalence in the ovary and Fallopian tube in women at hereditary high risk of breast and ovarian cancer." Int J Cancer **119**(6): 1412-8.

To analyse the prevalence of (pre) malignant lesions occurring in breast and adnexal tissue at prophylactic surgery in women at hereditary high risk of breast and/or ovarian cancers. Tissue was obtained from 85 women who underwent prophylactic bilateral salpingo-oophorectomy (pBSO) and from 59 women who underwent prophylactic mastectomy (pM). Control tissue samples were obtained from women undergoing breast reduction surgery (N = 99) or adnexal surgery for benign reasons (N = 72). In women with a BRCA1/2 mutation, the prevalence of a (pre) malignant adnexal lesion was 50% (95% CI 26-74) if older than 40 years and 14% (95% CI 0-58) if younger. The prevalences of (pre) malignant breast lesions in women older than 40 years, with and without a BRCA1/2 mutation, were 0% (95% CI 0-16) and 47% (95% CI 21-73), respectively. No association was found between (pre) malignant lesions in breast and adnexal tissue occurring in 28 women who underwent surgery on both organs (R = 0.155, p = 0.432), but the prevalence of lesions was significantly higher in adnexal tissue than in the breast (p = 0.023). Compared to controls, women at hereditary high risk had a higher chance of (pre) malignant lesions in the breast and an even higher chance of such lesions in the adnexal tissue. There was no indication for concomitant presence of such lesions in both organs at the time of prophylactic surgery. The high frequency of (pre) malignant lesions in the adnexal tissue stresses further the importance of pBSO from the age of 40 onwards in women at hereditary high risk.

Husain, A., X. J. Yan, et al. (1997). "UCN-01 in ovary cancer cells: effective as a single agent and in combination with cis-diamminedichloroplatinum(II)independent of p53 status." Clin Cancer Res **3**(11): 2089-97.

Our goal was to determine the cytotoxicity of 7-OH-hydroxystaurosporine (UCN-01) as a single agent and in combination with cis-diamminedichloroplatinum(II) (CDDP) in a panel of ovarian carcinoma cells. We sought to examine the role of p53 gene function and alterations in cell cycle progression or other mechanisms of action of UCN-01 including perturbation of the apoptosis pathway mediated by NF-kappaB and Bcl-2/Bax. Cytotoxicity was determined from dose-response curves established by the Alamar blue vital dye indicator assay. Restoration of wild-type p53 in a p53 null cell line, SKOV 3, was achieved by transfection of a p53 expression vector. Cell cycle distribution was measured by fluorescence-activated cell sorting analysis of ethidium bromide-stained nuclei. Apoptosis was measured by quantitative fluorescence microscopy. NF-kappaB DNA binding activity was measured by electrophoretic mobility shift assay. Bcl-2 and Bax levels were determined by Western immunoblotting. UCN-01 was effective as a cytotoxic agent alone and in combination with CDDP in all cell lines studied, regardless of p53 status. The degree of sensitization to CDDP conferred by UCN-01, however, was found to correlate with p53 gene status. p53 wild-type cells seem to be more sensitive to the cytotoxic effects of the combination of UCN-01 + CDDP than the p53 mutant cells. This was confirmed in cells in which p53 wild-type function was restored by transfection of p53 cDNA, but these cells are also significantly more sensitive to CDDP alone. The effects of UCN-01 on cell cycle progression also appear to be p53 dependent but may not be the primary mechanism of action. The rate of apoptosis is increased 4-fold in UCN-01 + CDDP-treated cells compared to either agent alone. UCN-01 does not effect NF-kappaB DNA binding activity or Bcl-2 and Bax levels. UCN-01 enhances CDDP cytotoxicity and apoptosis in ovary cancer cells. This occurs regardless of p53 status, but wild-type p53 seems to increase the degree of sensitization.

Isola, J., O. P. Kallioniemi, et al. (1990). "Steroid receptors and Ki-67 reactivity in ovarian cancer and in normal ovary: correlation with DNA flow cytometry, biochemical receptor assay, and patient survival." J Pathol **162**(4): 295-301.

Steroid hormone receptors and reactivity for Ki-67 proliferation antigen were studied immunohistochemically in non-neoplastic post-menopausal human ovary and in 29 ovarian cancers. In the normal ovary, oestrogen (OR) and progesterone receptors (PR) were found in the surface epithelium and PR also in the ovarian stroma. Of the ovarian

carcinomas 38 per cent (11/29) contained OR and 69 per cent (20/29) PR. Oestrogen receptor expression was confined to malignant cells, whereas PR was present occasionally also in the tumour stroma. In most cases, ORs and PRs were found only in a small population of cancer cells. The growth fractions assessed by the percentage of Ki-67-positive cells ranged from 1 to 59 per cent (mean 19.7 per cent) with a significant correlation (r = 0.74, P less than 0.0001) to S-phase values (mean 12.9 per cent, range 1.2-25.9 per cent) determined by DNA flow cytometry. High Ki-67 (greater than or equal to 15 per cent) and S-phase levels (greater than or equal to 7.5 per cent) correlated with advanced disease stage and patient survival but not with OR or PR status, suggesting that hormone-receptor pathways and proliferative activity are not related in ovarian cancer. Positive OR status, however, identified patients with a better prognosis (P = 0.02), suggesting a correlation with tumour differentiation. The independent prognostic value of oestrogen receptor status and Ki-67 remains to be determined, but the prognostic impact of Ki-67 was comparable to that of S-phase values.

Izembart, M., J. Chavaudra, et al. (1992). "Retrospective evaluation of the dose received by the ovary after radioactive iodine therapy for thyroid cancer." Eur J Nucl Med **19**(4): 243-7.

In an earlier study, we evaluated the frequency of clinical manifestations of ovarian insufficiency after radioiodine therapy for thyroid cancer. We were thus led to consider the dose received by the ovary (DRO) during these treatments. In the literature, this dose is expressed as a function of the activity administered. However, in our study, the disorders were not correlated with the activity administered. Faced with this discrepancy, we have attempted to establish a dosimetric model using the parameters available for each patient. The results obtained show that besides the activity administered, which plays a role, morphological and kinetic factors specific to each individual have an importance that cannot be ignored when addressing this problem.

Jan, C. R., C. An-Jen, et al. (2003). "The anti-breast cancer drug tamoxifen alters Ca2+ movement in Chinese hamster ovary (CHO-K1) cells." Arch Toxicol **77**(3): 160-6.

The anti-breast cancer drug tamoxifen has recently been shown to cause an increase in intracellular free-Ca(2+) concentrations ([Ca(2+)](i)) in renal tubular cells, breast cells and bladder cells. Because tamoxifen is known to alter ovary function in human patients and in rats, the present study was aimed at exploring whether tamoxifen could alter Ca(2+) movement in Chinese hamster ovary (CHO-K1) cells. Cytosolic free-Ca(2+) levels in populations of cells have been explored by using fura-2 as a fluorescent Ca(2+) indicator. Tamoxifen at concentrations above 1 micro M increased [Ca(2+)](i) in a concentration-dependent manner with an EC(50) value of 8 micro M. The Ca(2+) signal was reduced by removing extracellular Ca(2+), but was not affected by nifedipine, verapamil, diltiazem or ICI 182,780 (an estrogen receptor antagonist). Pretreatment with 1 micro M thapsigargin (an endoplasmic reticulum Ca(2+) pump inhibitor) to deplete the endoplasmic reticulum Ca(2+) abolished 10 micro M tamoxifen-induced Ca(2+) release. Neither inhibition of phospholipase C with 2 micro M U73122 nor depletion of ryanodine-sensitive Ca(2+) stores with 50 micro M ryanodine affected tamoxifen-induced Ca(2+) release. Cell proliferation assays using ELISA revealed that overnight incubation with 5-10 micro M tamoxifen inhibited cell proliferation by 20%, and 20 micro M tamoxifen killed all cells. Together, the results suggest that, in CHO-K1 cells, tamoxifen induced a [Ca(2+)](i) increase by causing store-Ca(2+) release from the endoplasmic reticulum in an phospholipase C-independent manner, and by inducing Ca(2+) influx. The action of tamoxifen appears to be dissociated from estrogen receptor activation. Longer incubation with tamoxifen (>5 micro M) was cytotoxic.

Jones, A. P., R. Haynes, et al. (2008). "Travel time to hospital and treatment for breast, colon, rectum, lung, ovary and prostate cancer." Eur J Cancer **44**(7): 992-9.

The aim was to examine the effect of geographical access to treatment services on cancer treatment patterns. Records for patients in northern England with breast, colon, rectal, lung, ovary and prostate tumours were augmented with estimates of travel time to the nearest hospital providing surgery, chemotherapy or radiotherapy. Using logistic regression to adjust for age, sex, tumour stage, selected tumour pathology characteristics and deprivation of place of residence, the likelihood of receiving radiotherapy was reduced for all sites studied with increasing travel time to the nearest radiotherapy hospital. Lung cancer patients living further from a thoracic surgery hospital were less likely to receive surgery, and both lung cancer and rectal cancer patients were less likely to receive chemotherapy if they lived distant from these services. Services provided in only a few specialised centres, involving longer than average patient journeys, all showed an inverse association between travel time and treatment take-up.

Jongen, V. H., A. V. Sluijmer, et al. (2002). "The postmenopausal ovary as an androgen-producing

gland; hypothesis on the etiology of endometrial cancer." Maturitas **43**(2): 77-85.

Postmenopausal estrogens originate from the peripheral conversion of androgens, which are produced by the adrenal glands and the ovaries. Estrogens are considered to contribute to the neoplastic development of endometrium. Hyperplasia of ovarian stroma is associated with an increased androgen production by the ovaries and with the development of endometrial pathology. We hypothesize that, in cases of endometrial pathology, an increased production of aromatizable androgens by postmenopausal ovaries will lead to elevated prehormone availability for estrogen formation in utero. Following the conversion of ovarian androgens, a reaction catalyzed by the cytochrome p450 aromatase, estrogens may function as a local mitogenic factor eventually leading to the development of endometrial cancer. We consider the local availability of androgens and the local activity of aromatase relevant for this process. If this hypothesis proves to be right it may give rise to the introduction of aromatase inhibitors in treatment strategies of hormone dependent endometrial malignancies.

Kamo, K. and T. Sobue (2004). "Cancer statistics digest. Mortality trend of prostate, breast, uterus, ovary, bladder and "kidney and other urinary tract" cancer in Japan by birth cohort." Jpn J Clin Oncol **34**(9): 561-3.

Kang, S. K., K. C. Choi, et al. (2003). "Potential role of gonadotrophin-releasing hormone (GnRH)-I and GnRH-II in the ovary and ovarian cancer." Endocr Relat Cancer **10**(2): 169-77.

Gonadotrophin-releasing hormone (GnRH) functions as a key neuroendocrine regulator of the hypothalamic-pituitary-gonadal axis. In addition to the hypothalamus and pituitary gland, GnRH and its receptor have been detected in other reproductive tissues including the gonads, placenta and tumours arising from these tissues. Recently, a second form of GnRH (GnRH-II) and type II GnRH receptor have been found in normal ovarian surface epithelium and neoplastic counterparts. The two types of GnRH may play an important role as an autocrine/paracrine regulator of reproductive functions and ovarian tumour growth. In this review, the distribution and potential roles of GnRH-I/-II and their GnRH receptors in the ovarian cells and ovarian cancer will be discussed.

Kaplan, E. (1977). "Cancer of the ovary." S Afr Med J **52**(28): 1123-8.

One hundred and forty-two cases of ovarian cancer seen at the Johannesburg General Hospital are reviewed. The poor prognosis associated with this disease is directly related to the fact that at the time of presentation the cancer had spread beyond the confines of the ovary. Results of therapy are poor, with no major impact recorded on survival rates for many years. Therapeutic possibilities are reviewed. When the disease is in stage I and the tumour is completely removed by surgery, the use of postoperative chemotherapy is suggested as a possible means of preventing recurrence or to destroy unrecognized areas of microscopical spread.

Karaferic, A., D. Jovanovic, et al. (2009). "Expression of HER2/neu, estrogen and progesterone receptors, CA 125 and CA19-9 on cancer cell membrane in patients with serous and mucinous carcinoma of the ovary." J Buon **14**(4): 635-9.

PURPOSE: To examine the expression of the membrane markers of estrogen (ER) and progesterone receptors (PR), CA-125, CA 19-9 and HER2/neu in ovarian cancer tissues. METHODS: Fifty-four samples of ovarian cancer tissues originating from 55 patients were examined by immunohistochemistry. Forty-three had serous papillary ovarian cancer, 9 of which were grade I, 12 grade II and 2 grade III. Twelve patients had a classic mucinous ovarian cancer, 5 of which were grade I, 4 grade II and 0 grade III. RESULTS: Out of 43 patients with serous ovarian cancer, 7 expressed both steroid receptors, 22 had only one (10 ER and 12 PR), while 14 were negative. Only 2/12 patients with classic mucinous ovarian cancer expressed of both receptors. CA-125 was expressed in 37/43 patients with serous ovarian cancer and in 4/12 patients with classic mucinous ovarian cancer. CA 19-9 was expressed in 3/43 patients with serous ovarian cancer, and coexpressed with CA-125 in 2/3 patients. In patients with classic mucinous ovarian cancer, 4/12 had expression of CA 19-9 without coexpression with CA-125. HER2/neu positivity (3+) was proven in only one case with classic mucinous ovarian cancer, and any other expression (1+) in 7 additional patients (1 mucinous and 6 serous ovarian cancers). CONCLUSION: Positive HER2/neu expression in the cells of ovarian cancer is very rare and HER2/neu overexpression is even rarer. Expression of ER and PR does not depend on tumor grade and/or at least not in grade I and II. Positive CA 19-9 expression may be present not only in cases of classic mucinous ovarian cancer but also in typical serous ovarian cancer. However, in the classic mucinous ovarian cancer, CA-125 may be expressed, though in relatively low percentage.

Kawano, K., K. Ushijima, et al. (2007). "Peptide YY producing strumal carcinoid of the ovary as the cause

of severe constipation with contralateral epithelial ovarian cancer." J Obstet Gynaecol Res **33**(3): 392-6.

Primary ovarian carcinoid tumors are rare. It has been reported that constipation was a presenting symptom in some patients with ovarian carcinoid. A case of strumal carcinoid of the ovary with contralateral clear cell adenocarcinoma of the ovary discovered with a complaint of constipation is described. Constipation was dramatically improved by resectioning the tumor. The tumor cells were positive for peptide YY (PYY) in the carcinoid component, but not in any other components. The present case could provide evidence of the correlation between constipation and PYY that has been reported elsewhere. Interestingly, the constipation caused by PYY also helped in discovering epithelial ovarian cancer.

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...

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.

Kuipers, T. (1976). "Report on treatment of cancer of the ovary." Br J Radiol **49**(582): 526-32.

A malignant ovarian tumour has been diagnosed in 373 patients referred to the R.R.T.I. from January 1966 to Jun 1972. Serious ovarian carcinoma was the commonest type and occurred in 254 patients. The results in these patients are studied in detail after staging according to F.I.G.O. recommendations. Following surgery and postoperative radiotherapy, chemotherapy was started immediately in all patients with progressive disease and after randomization also in 50 per cent of the others. The three-year survival rate in Stage II patients tended to be more favourable following irridation ofthe pelvis and lumboaortic nodes (55 per cent) than following radiotherapy restricted to the pelvic area (40 per cent). The dose should be 5-6 krad. The five-year survival was 68 per cent for Stage I, 26 per cent for Stage II and nearly zero for Stages III and IV, as well as for patients referred for treatment of a recurrence. In spite of whole-abdomen irradiation 50 per cent of the patients in the latter three groups were deceased within eight months; therefore chemotherapy should be preferred. The main problem in ovarian cancer is late diagnosis. Evaluation of results is difficult because numerous variable factors concerning pathology and treatment make it necessary to sub-divide the patients into groups too small for statistically reliable conclusions. Each treatment factor should be studied by a group of hospitals.

Lambert, H. E., G. J. Rustin, et al. (1993). "A randomized trial comparing single-agent carboplatin with carboplatin followed by radiotherapy for advanced ovarian cancer: a North Thames Ovary Group study." J Clin Oncol **11**(3): 440-8.

PURPOSE: To determine in a randomized trial of advanced ovarian carcinoma whether consolidation therapy with whole-abdominal radiotherapy (RT) after chemotherapy improves survival and disease-free survival compared with the continued chemotherapy. PATIENTS AND METHODS: Two hundred fifty-four patients with advanced epithelial ovarian cancer (stages IIB to IV) were entered onto a study of five monthly courses of 400 mg/m2 of carboplatin. One hundred seventeen patients with residual disease of 2 cm or less at second-look laparotomy or laparoscopy were then randomized to receive consolidation therapy, either five further courses of carboplatin at the same dosage or whole-abdominal RT (24 Gy). There was no control arm. RESULTS: Chemotherapy was well tolerated and was usually administered on an outpatient basis. Myelosuppression that was sufficient to delay chemotherapy occurred in only 3% of 1,418 courses analyzed. The main toxicity of carboplatin was nausea and vomiting, but this was easier to control than that with cisplatin. Although RT was well tolerated in the majority of the 58 patients, one patient who had been found to have multiple adhesions at second-look surgery developed fecal fistulae post-RT that resulted in the patient's death from peritonitis. Median survival for the whole group from date of surgery was 25 months. No statistical difference was found in either survival or disease-free survival between those patients who received consolidation chemotherapy and those who were treated with abdominal RT. Prognostic factors used to assess survival were stage, histology, amount of residual disease after primary surgery, and presence of tumor at second-look surgery. CONCLUSION: There seems to be no significant advantage for consolidation whole-abdominal RT compared with the continuation of the same chemotherapy in the management of advanced epithelial carcinoma of the ovary, even when no macroscopic residual disease is apparent at second-look surgery.

Leiser, A. L., D. S. Chi, et al. (2007). "Carcinosarcoma of the ovary treated with platinum

and taxane: the memorial Sloan-Kettering Cancer Center experience." Gynecol Oncol **105**(3): 657-61.

INTRODUCTION: Due to the rarity of ovarian carcinosarcomas, the optimal chemotherapeutic regimen to treat this aggressive disease is yet to be determined. The purpose of this study was to determine the response rate, recurrence-free survival, and overall survival of patients with ovarian carcinosarcoma who were treated with the combination of platinum and a taxane as first-line chemotherapy. METHODS: We identified all patients with ovarian carcinosarcoma who received a combination of platinum and taxane either after initial tumor resection or as neoadjuvant therapy. Data extracted from the medical records included residual tumor after surgery, number, type and dose of chemotherapy cycles, tumor response, and survival outcome. RESULTS: Between 1991 and 2005, 30 patients were identified for analysis. Twenty-four patients had stage III disease, 5 had stage IV disease, and 1 had stage II disease. All patients underwent surgical resection and 17 (57%) were cytoreduced to less than 1 cm. Twenty-eight patients received chemotherapy after surgery, and 2 patients received chemotherapy before surgery. Twenty-four patients (80%) received carboplatin and paclitaxel, 3 (10%) received carboplatin and docetaxel, and 3 (10%) received cisplatin and paclitaxel. Twelve (40%) had a complete response, 7 (23%) a partial response, 2 (7%) stable disease, and 9 (30%) progression of disease. The median time to progression for responders was 12 months. With a median follow-up of 23 months, the median overall survival was 43 months for survivors. The 3- and 5-year survival rates were 53% and 30%, respectively. CONCLUSION: The combination of platinum and a taxane is a viable first-line treatment option for patients with ovarian carcinosarcoma.

Lemaire, R., S. A. Menguellet, et al. (2007). "Specific MALDI imaging and profiling for biomarker hunting and validation: fragment of the 11S proteasome activator complex, Reg alpha fragment, is a new potential ovary cancer biomarker." J Proteome Res **6**(11): 4127-34.

MALDI imaging mass spectrometry represents a new analytical tool to directly provide the spatial distribution and relative abundance of proteins in tissue. Twenty-five ovary carcinomas (stages III and IV) and 23 benign ovaries were directly analyzed using MALDI-TOF MS. The biomarker with the major prevalence (80%) has been fully identified using MALDI MS and nanoESI MS and MS/MS after separation by RP-HPLC and trypsin enzymatic digestion. This marker with an m/z of 9744 corresponds to 84 amino acid residues from the 11S proteasome activator complex, named PA28 or Reg-alpha. Validation of this marker has been performed using MALDI imaging, classical immunocytochemistry with an antibody raised against the C-terminal part of the protein, specific MALDI imaging, and Western blot analysis. The validation, using immunocytochemistry, confirmed the epithelial localization of this fragment with nucleus localization in benign epithelial cells and a cytoplasmic localization in carcinoma cells. This indicates that this antibody could be used to discriminate the borderline tumor cases. At this point, a multicentric study needs to be conducted in order to clearly establish the potential of this biomarker. Taken together these studies reflect that direct tissue analysis and specific MALDI imaging strategies facilitate biomarker hunting and validation which can be named pathological proteomics.

Lv, W., X. Sheng, et al. (2008). "Jaceosidin induces apoptosis in human ovary cancer cells through mitochondrial pathway." J Biomed Biotechnol **2008**: 394802.

We examined the antiproliferation effect of Jaceosidin (4', 5, 7-trihydroxy-3', 6-dimethoxyflavone) isolated from the herb of Artemisia vestita Wall on several human cancer cell lines. Jaceosidin significantly reduced the proliferation of CAOV-3, SKOV-3, HeLa, and PC3 cells in a concentration-dependent manner. A time-dependent inhibition was also observed in CAOV-3 cells by Jaceosidin. By flow cytometric analysis, we found that Jaceosidin treatment resulted in an increased apoptosis in CAOV-3 cells. The cells treated with Jaceosidin exhibited a decreased mitochondrial membrane potential. Jaceosidin also increased the level of cleaved caspase-9 and induced the cleavage of caspase-3 and poly (ADP-ribose) polymerase (PARP), while caspase-3 inhibitor Z-DEVD-FMK significantly reversed the proapoptotic effect of Jaceosidin in CAOV-3 cells. Moreover, Jaceosidin elevated the level of cytochrome c in cytosol. These findings suggest that the anticancer effect of Jaceosidin may be contributed by an induction of apoptosis involving cytochrome c release from mitochondria to cytosol.

McCormick, C. C., R. L. Giuntoli, 2nd, et al. (2007). "The role of cytoreductive surgery for colon cancer metastatic to the ovary." Gynecol Oncol **105**(3): 791-5.

OBJECTIVE: We sought to further elucidate the survival impact of cytoreductive surgery among patients with colon cancer metastatic to the ovary. METHODS: All women diagnosed with primary colon cancer metastatic to the ovary at a single institution from 1980 to 2005 were retrospectively identified. Survival analyses and comparisons were

performed using Kaplan-Meier plots and the log rank test. RESULTS: A total of 39 patients with 40 cases of colon cancer metastatic to the ovary were identified. Patients with metastatic disease confined to the ovaries (n=11) had a median overall survival (OS) time of 61 months (range 15-120) compared to 17 months (range 0.5-73) for those with more extensive metastases (n=24) (p=0.0428). Patients undergoing optimal cytoreduction (residual < or =1 cm) had a median progression-free survival (PFS) of 11 months (range 0.5-120, n=26) compared to 2.5 months (range 0.5-12, n=9) for those receiving suboptimal cytoreduction (p=0.0001). Optimal cytoreduction was also associated with a significantly longer median OS (35 months, range 0.5-120) compared to suboptimal cytoreduction (median OS=7 months, range=0.5-17) (p<0.0001). The peri-operative mortality rate was 5%. Significant morbidity occurred in 10% of the cases. All major complications occurred in women with diffuse disease who underwent extensive cytoreductive surgery. CONCLUSIONS: The observation that optimal cytoreduction was associated with prolonged PFS and OS in both patients with localized ovarian and widespread metastases of colon cancer suggests a role for surgical management of metastatic colon cancer in women.

Miller, A. B., J. B. Madalinska, et al. (2001). "Health-related quality of life and cost-effectiveness studies in the European randomised study of screening for prostate cancer and the US Prostate, Lung, Colon and Ovary trial." Eur J Cancer **37**(17): 2154-60.

Decisions on policies for screening for prostate cancer require that information upon health-related quality of life (HRQL) and cost-effectiveness (CE) be available, as the lead time for some of the cases detected by screening will be very long and detriments in quality of life could have a major impact on the subjects remaining life-span. A framework within which both HRQL and cost-effectiveness of prostate cancer screening can be assessed is presented. Studies of both are ongoing in the European Randomised Study of screening for prostate cancer and the US Prostate, Lung, Colon and Ovary trial. Preliminary information confirms that it is important to study screened subjects and controls, and not to assume that inferences derived from study of prostate cancer outside screening trials can be extrapolated to the trials. However, it will require prolonged study to enable the overall effects on quality of life, and on cost-effectiveness to be determined. Such studies are ongoing for the two trials.

Miller, B. E., B. Pittman, et al. (1997). "Colon cancer with metastasis to the ovary at time of initial diagnosis." Gynecol Oncol **66**(3): 368-71.

Colon cancer with a synchronous ovarian metastasis is occasionally diagnosed at the time of laparotomy for a pelvic mass. The purpose of this retrospective study is to evaluate the clinical presentation as well as the impact of the type of metastatic spread and surgical intervention on overall survival. We reviewed charts of 23 patients treated between 1980 and 1995. Pain was the initial symptom in 14 patients (61%), with only four patients (17%) complaining of rectal bleeding, but with five patients (22%) complaining of uterine bleeding. At the time of laparotomy, the ovarian capsule was intact in 12 patients. Metastatic disease to the peritoneum was seen in seven patients and to the liver in six patients. On pathological evaluation, the median ovarian tumor size was 10 cm, significantly larger than the median colon tumor size of 4.5 cm. Surgical treatment consisted of colon resection in all but one patient, bilateral or unilateral salpingo-oophorectomy in 22 patients, and hysterectomy in nine patients. Only one patient survived 5 years. Sixteen patients died of colon cancer. The median survival time was 17.8 months, ranging from 1 to 86 months. Tumor size was of no prognostic importance. Median survival time of patients with peritoneal disease (10.8 months) was significantly shorter compared to patients without peritoneal disease (25.2 months). In the presence of liver metastasis, the median survival time was, likewise, significantly reduced from 20.1 months to 8.1 months. In conclusion, macroscopic metastatic disease to the ovary is a poor prognostic factor in colon cancer. In selected patients who can be rendered disease-free by surgery, prolonged survival is possible and an aggressive approach is recommended. Survival of patients with peritoneal disease or liver metastasis is short and a mainly palliative approach is recommended.

Nakanishi, T., T. Okamoto, et al. (1995). "A novel human monoclonal antibody against cervical cancer: its immunoreactivity with normal tube and ovary and with ovarian tumor tissue." Arch Gynecol Obstet **256**(4): 177-84.

1-1-2D, a novel human monoclonal antibody (MAb) raised against cervical cancer, was examined for its immunohistochemical reactivity with ovarian cancer. Six of 10 ovarian cancer cell lines showed positive staining, while 3 of 5 cervical cancer cell lines were positive. Among tumor tissues, 15 of 18 (83%) ovarian serous cystadenocarcinomas and 10 of 12 (83%) ovarian clear cell adenocarcinomas were positive. We also performed immunohistochemical staining of the same cancer specimens with OC 125 and compared their reactivity. The frequency of positivity was similar, but the reactivity of the two MAbs was different. 1-1-2D stained the apical surface

of the glandular epithelial cells and secretory products of the gland. On the other hand, OC 125 stained the cytoplasm as well as the plasma membrane of the glandular epithelial cells. These results suggest that 1-1-2D MAb recognizes a different antigen from that recognized by OC 125.

Nandakumar, A., N. Anantha, et al. (1995). "A case-control investigation on cancer of the ovary in Bangalore, India." Int J Cancer **63**(3): 361-5.

Cancer of the ovary is the sixth leading cancer among females in Bangalore, and is a leading site of cancer in other population-based cancer registries in India. A case-control investigation was conducted utilizing the data from the population-based cancer registry in Bangalore. In addition to the core patient information, certain other details pertaining to consumption of tobacco, reproductive and obstetric factors and those related to the practice of family planning, including the method adopted, were available with the registry, for the period 1982-1985. Identical information was also available for patients residing in the registry area who did not have cancer. Ninety-seven cases of ovarian cancer in ever-married women were age-matched with 194 controls from the same area who showed no evidence of cancer. The risk of ovarian cancer was not influenced by tobacco habits, alcohol consumption, diet or the various reproductive factors. However, tubectomy as a method of family planning appeared to reduce the risk of development of ovarian cancer. This reduction in risk was not influenced by parity or age of the woman at the time of birth of the first child.

Navaratnarajah, R., O. C. Pillay, et al. (2008). "Polycystic ovary syndrome and endometrial cancer." Semin Reprod Med **26**(1): 62-71.

An association between polycystic ovary syndrome (PCOS) and endometrial carcinoma was first suggested in 1949. Since then, several studies have been published that appear to support this association, and it is common practice among gynecologists and physicians to prescribe hormonal treatment to reduce this perceived risk, although there is no consensus as to the subgroup of PCOS in whom this is required. The mechanism(s) underlying any association are also unclear, but it is again widely assumed that chronic anovulation, which results in continuous estrogen stimulation of the endometrium unopposed by progesterone, is a major factor. However, obesity, hyperinsulinemia, and hyperandrogenism, which are also features of PCOS, are risk factors for endometrial carcinoma, but it does not necessarily follow that the incidence or mortality from endometrial cancer is increased in women with the syndrome. Potential strategies to prevent endometrial cancer in PCOS women are discussed.

Nelson, P. T., P. J. Zhang, et al. (2007). "Cancer/testis (CT) antigens are expressed in fetal ovary." Cancer Immun **7**: 1.

Cancer/testis (CT) antigens are named after their expression pattern as they are typically present in various types of tumors and in the germ cells of normal adult testis. Adult ovarian tissue is usually reported to be CT antigen negative. Based on the differences in female versus male gonadal development, the ovarian counterpart of the most predominant CT antigen positive testicular germ cells are not prevalent in the adult ovary. Hence, we analyzed the protein expression of several CT antigens in fetal ovary by immunohistochemistry with various monoclonal antibodies (mAbs) previously generated by our group. The mAbs used were: MA454 (MAGE-A1), M3H67 (MAGE-A3), 57B (MAGE-A4), CT7-33 (CT7/MAGE-C1), and ES121 (NY-ESO-1). All mAbs showed some immunopositivity in fetal ovarian germ cells. The most intense staining was seen with mAbs M3H67, 57B, and CT7-33 during weeks 16-23 of gestation. The most prevalent cells stained were oogonia, with only focal staining of oocytes of the primordial follicle. We conclude that CT antigens are regularly expressed in fetal ovarian germ cells and might play an important role in male and female germ cell biology.

Neville, A. J., K. W. Gilchrist, et al. (1984). "The chemotherapy of granulosa cell tumors of the ovary: experience of the Wisconsin Clinical Cancer Center." Med Pediatr Oncol **12**(6): 397-400.

We reviewed the clinical records of 32 patients with granulosa cell tumor of the ovary treated at the Wisconsin Clinical Cancer Center (WCCC) between 1970 and 1982. Eleven of these patients were treated with one or more chemotherapeutic regimens, yielding a total of 22 treatment trials. Objective response was observed in 7 of 17 evaluable treatment trials (41%). The response to chemotherapy could not be assessed in five treatment trials due to the concomitant administration of radiotherapy. We conclude that granulosa cell tumor of the ovary is responsive to chemotherapy. However, the optimal chemotherapeutic regimen for this rare neoplasm remains to be established on the basis of prospective clinical trials.

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.

Obel, E. B. (1976). "A comparative study of patients with cancer of the ovary, who have survived more or less than 10 years." Acta Obstet Gynecol Scand **55**(5): 429-39.

With the purpose of elucidating the characteristics in patients with cancer of the ovary who have survived 10 years compared with patients who have not survived 10 years, 161 patients with epithelial cancer and 15 patients with granulosa cell tumor who have survived 10 years, group A, have been compared with 157 patients with epithelial cancer and 14 patients with granulosa cell tumor, who have not survived 10 years, group B. The study showed that among epithelial tumors the stage of tumor and the histological picture in the form of "low potential malignance" or adenocarcinoma was of decisive importance for 10 years survival. No correlation between information such as age, marital status, profession, duration of symptoms, and the nature of symptoms and 10 years survival could be found in patients with tumor in stages I and II. Neither could the gynaecological examination, the nature of the surgical treatment nor radiation therapy be correlated with 10 years survival in stages I and II. 32 of the 152 patients with epithelial cancer in stages I and II, who have survived 10 years, have either died from their ovarian disease or have later on developed cancer localized to cervix ro corpus uteri. The author points out the risk of not removing both ovaries as well as the uterus and recommends that such patients are followed for many years after the treatment. In 29 patients with granulosa cell tumor neither the medical history, the stage of the tumor nor the treatment could be correlated with 10 years survival.

Ovesen, L., J. Hannibal, et al. (1993). "The interrelationship of weight loss, dietary intake, and quality of life in ambulatory patients with cancer of the lung, breast, and ovary." Nutr Cancer **19**(2): 159-67.

One hundred four consecutive patients with newly diagnosed small cell lung cancer, metastatic breast cancer, and ovarian cancer in good physical functional condition (performance rating 0-1 on Eastern Cooperative Oncology Group scale) were divided into a weight-losing group (> or = 5% unintentional weight loss within 3 mo; n = 48) and a weight-stable group (n = 56). Dietary intakes in relation to fat-free mass were not different in the two groups. According to the Quality of Life index and the General Health Questionnaire, weight-losing patients had significantly lower quality of life than weight-stable patients. In patients with weight loss, daily intakes of energy and protein correlated significantly with scores on the General Health Questionnaire. This study has shown that many ambulatory cancer patients do not eat enough to maintain weight and that even a moderate weight loss is associated with psychological distress and lower quality of life.

Ovesen, L., J. Hannibal, et al. (1991). "Food intake, eating-related complaints, and smell and taste sensations in patients with cancer of the lung, ovary and breast undergoing chemotherapy." Clin Nutr **10**(6): 336-41.

Nutritional status and energy and protein intake were studied in 52 patients with cancer of the breast, ovary or lung before, after 1, and after 3 cycles of aggressive chemotherapy. Pre-treatment intakes were somewhat lower than recommended and did not change after 3 cycles of chemotherapy, neither did nutritional status. Many patients had eating-related complaints, but these complaints did not increase significantly with chemotherapeutic treatment. In 31 patients electrical taste detection thresholds and chemical smell detection thresholds were measured before and after 3 cycles of chemotherapy. Changes in thresholds had no relation to changes in energy and protein intake. Perceived taste and smell changes were not reflected in chemosensory threshold values.

Pai, S. A., S. B. Desai, et al. (1998). "Uteruslike masses of the ovary associated with breast cancer and raised serum CA 125." Am J Surg Pathol **22**(3): 333-7.

We describe three cases of a uteruslike mass of the ovary, a condition in which the ovary is replaced by a mass that grossly and microscopically resembles the uterus. The patients were 38, 43, and 39 years of age, and only the first was nulliparous. Two of them also had breast carcinomas. Two patients also had elevated CA 125 levels that gave rise to a clinical suspicion of ovarian malignancy. There were no anatomic abnormalities in any of the patients. The presence of residual ovarian stroma in two of the patients (both of whom had breast cancer) suggests that metaplasia rather than a congenital anomaly is the cause. Elevated CA 125 levels are consistent with the endomyometriosis nature of the lesion.

Pather, S. and M. A. Quinn (2005). "Clear-cell cancer of the ovary-is it chemosensitive?" Int J Gynecol Cancer **15**(3): 432-7.

The records of all patients with clear-cell ovarian cancer (CCC) who underwent complete surgical staging and chemotherapy between 1984 and 2001 were reviewed and 39 patients identified as suitable for study. The mean patient age was 56 years, and the stage distribution was as follows: stage I, 53%; stage II, 13%; stage III, 32%; and stage IV, 2%. One in three patients with stage I disease developed recurrent disease despite adjuvant chemotherapy. Seventy percent of tumors demonstrated a response to combination carboplatin and paclitaxel. Tumors which had either a partial response or failed to respond to first-line chemotherapy demonstrated no response to second-line nonplatinum chemotherapy. Endometriosis was identified in 31% of tumors, and 18% of patients developed deep venous thrombosis (DVT); however, neither endometriosis nor DVT was associated with a poorer outcome. CCC has a high recurrence rate in early-stage disease despite adjuvant treatment with cytotoxic chemotherapy. Advanced disease does respond to carboplatin and paclitaxel, which should be the chemotherapeutic regimen of choice. New second-line agents are urgently required.

Pecorelli, S., H. C. Wagenaar, et al. (1999). "Cisplatin (P), vinblastine (V) and bleomycin (B) combination chemotherapy in recurrent or advanced granulosa(-theca) cell tumours of the ovary. An EORTC Gynaecological Cancer Cooperative Group study." Eur J Cancer **35**(9): 1331-7.

The aim of this study was to investigate the clinical activity and toxicity of a modified PVB regimen (cisplatin, vinblastine and bleomycin) in patients with advanced or recurrent, pure granulosa cell tumours (GCTs) or mixed granulosa-theca cell tumours (GTCTs). The PVB regimen consisted of cisplatin (P) 20 mg/m2 intravenous (i.v.) days 1-5, vinblastine (V) 0.15 mg/kg i.v. days 1-2 and bleomycin (B) 30 mg i.v. on day 2, and 15 mg on day 15, for 28 days. 38 eligible patients were entered in this trial. Prior to PVB all patients underwent surgery and 13 received postoperative radio- or other prior chemotherapy. The median number of PVB cycles was 4 in both groups. In the group of 25 patients who had received prior surgery only, 7 and 6 patients had complete and partial responses, respectively (response rate: 52%, 95% confidence limits: 31.3-72.2%). At a median follow-up of 39 months, 6 patients were alive with no evidence of disease, 6 were alive with disease, 12 died due to malignant disease and 1 died due to intercurrent disease. The median time to progression was 13.9 months. The median survival was 25.4 months. 3-year survival was 49% (95% confidence limits: 29-69%). In the group of 13 patients who had previously received postoperative radio- or chemotherapy, 5 complete and 5 partial responses were observed on PVB (response rate: 77%, 95% confidence limit: 46.2-95.0%). At a median follow-up of 50 months, 6 patients were still alive, only 1 without evidence of disease, 6 died due to malignant disease and 1 died due to intercurrent disease. The median time to progression was 19.3 months. The median duration of survival was 41.1 months. Accompanying toxicity was distributed in a similar pattern for both groups. Severe toxicity was mainly documented as haematological toxicity, nausea/vomiting and alopecia. Furthermore cisplatin-related peripheral neurotoxicity and mild/moderate signs of bleomycin-related pulmonary toxicity were observed. The present data confirm the therapeutic activity of the PVB regimen in advanced/recurrent GCTs. The response rate was moderately high compared with previous studies, with a median duration of response of 20 months for both groups.

Pereyra Pacheco, B., J. M. Mendez Ribas, et al. (2001). "Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report." Gynecol Oncol **81**(3): 391-7.

OBJECTIVE: Recent success in polychemotherapy (PCT) in adolescent female cancer patients has become a source of concern for specialists who also strive to preserve fertility. We studied whether gonadotropin-releasing hormone (GnRH) analogs could prevent the early onset of ovarian insufficiency postchemotherapy and protect fertility. METHODS: The patients were divided into three groups: Control group 1 (Group A), premenarchal patients aged 3 to 7.5 years (n = 5), were not given GnRH analogs administered prior to PCT. Postmenarchal patients (Group B), aged 14.7 to 20 years (n = 12) with normal menstrual rhythm and ovulatory cycles, received treatment with GnRH analogs prior to PCT. Control group 2 (Group C), postmenarchal patients aged 15.9 to 20 years (n = 4), received PCT but no GnRH analog protection. All groups received the PCT regimens CAVPE, CVPP, ABVD, TAMO, ARA-C, and MTT. In group B, leuprolide acetate inhibition was obtained with a depot injection administered each month before and during treatment with PCT. To accelerate the timing of ovarian regression, a subcutaneous injection (0.2 mg) was administered simultaneously. RESULTS: In Group A, patients had spontaneous menarche between the ages of 12 and 17.9 years, followed by normal menstruation and ovulatory cycles. Three patients became pregnant. After GnRH analog withdrawal, Group B patients continued with normal ovulatory

cycles. Two patients became pregnant. Group C patients presented hypergonadotrophic hypoestrogenic amenorrhea. CONCLUSION: GnRH analog treatment before and during PCT enhances ovarian function and preserves adolescent fertility. The results must be confirmed in a larger study.

Ramirez, P. T., K. M. Schmeler, et al. (2008). "Efficacy of letrozole in the treatment of recurrent platinum- and taxane-resistant high-grade cancer of the ovary or peritoneum." Gynecol Oncol **110**(1): 56-9.

OBJECTIVE: To evaluate the efficacy and safety of letrozole in patients with recurrent platinum- and taxane-resistant estrogen receptor-positive (ER+) high-grade cancer of the ovary or peritoneum. METHODS: A single-institution, phase II study was performed in women with recurrent ER+ epithelial carcinoma of the ovary or peritoneum. All patients had measurable disease. Letrozole was administered at a dose of 2.5 mg orally once daily until disease progression or toxicity occurred. RESULTS: Thirty-three patients were enrolled. The median age was 63 years (range, 38 to 83 years). Twenty-three patients (74%) had received three or more prior chemotherapy regimens. The 31 patients evaluable for response received a total of 81 cycles (4 weeks/cycle) of therapy (range, 1 to 14 cycles/patient). The median treatment duration was 8 weeks (range, 4 to 52 weeks). None of the patients had a complete response (CR), 1 (3%) had a partial response (PR), and 7 (23%) had stable disease (SD). The median duration of clinical benefit (SD and PR) was 9 weeks (range, 7 to 46 weeks). The median follow-up for all patients was 25 weeks. All patients were evaluable for toxicity. The most common adverse effects were fatigue (36%) and diaphoresis (21%). No grade 3 or 4 toxicities were reported, and no patients discontinued treatment owing to adverse effects. Eighteen patients (58%) went on to receive additional therapy with other agents. CONCLUSION: In patients with ER-positive, platinum- and taxane-resistant high-grade ovarian and primary peritoneal cancer treated with letrozole, 26% derived a clinical benefit (SD and PR).

Rose, D. P., A. P. Boyar, et al. (1986). "International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption." Cancer **58**(11): 2363-71.

The 1978-1979 mortality rates for cancers of the breast, prostate, ovary, and colon in 26 to 30 countries were related to the average 1979-1981 food availability data published by the United Nations. The previously described relationship between breast cancer mortality rates and animal fat consumption continues to be evident, and applies also to the other three tumor types. The correlation with breast cancer was particularly strong in postmenopausal women. Since 1964, particularly notable increases in both breast cancer mortality rate and dietary fat intake have occurred in those countries with a relatively low breast cancer risk. The international comparisons support evidence from animal experiments that diets in which olive oil is a major source of fat are associated with reduced breast cancer risk. The excess in mortality rates for breast and ovarian cancer in Israel relative to the national animal fat consumption may be due to the mixed ethnic origin of the Israeli population. Positive correlations between foods and cancer mortality rates were particularly strong in the case of meats and milk for breast cancer, milk for prostate and ovarian cancer, and meats for colon cancer. All four tumor types showed a negative correlation with cereal intake, which was particularly strong in the case of prostate and ovarian cancer. Although, in general, there was a good positive correlation between prostate and breast cancer mortality rates and between prostate cancer and animal fat, discrepancies in national ranking indicate the operation of other etiologic factors that modify risk. The observed positive correlations between the four cancer mortality rates and caloric intake from animal sources, but negative correlations for vegetable-derived calories, suggest that, of the two, animal fat and not energy is the major dietary influence on cancer risk.

Ruppert, C., S. Ehrenforth, et al. (1997). "Protease levels in breast, ovary, and other gynecological tumor tissues: prognostic importance in breast cancer." Cancer Detect Prev **21**(5): 452-9.

Proteolytic destruction of basement membrane and tumor surrounding is a prerequisite of invasion and metastasis. In 587 frozen samples of malignant and nonmalignant tissue of breast, uterus, vulva, and ovary, levels of urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1) were examined with enzyme-linked immunosorbent assay (ELISA) and cathepsin D (cath D) with radioimmunoassay. UPA, PAI-1 and cath D were raised in malignant tissue with significantly higher levels in breast cancer (uPA, PAI-1) and ovarian cancer (cath D). TPA levels were lower in malignant tissue. In 393 primary breast cancer samples, uPA, PAI-1, and cath D were not related to other prognostic factors, whereas tPA levels were significantly raised in prognostic more favorable carcinomas. Over a follow-up period up to 46 months (median 30 months) the log-rank test showed in the whole group of breast cancer patients a significantly higher rate of relapse ($p < 0.05$) and death ($p < 0.001$) with tPA levels < 2.5 ng/mg. PAI-1 levels > 3 ng/mg were associated with

shorter overall ($p < 0.02$; $p = 0.01$), disease-free ($p < 0.008$; $p < 0.01$), and metastasis-free ($p < 0.04$; $p = 0.005$) survival in all patients and in the node-negative subgroup, respectively. Higher uPA and cath D levels were not associated with rate of relapse or death over this follow-up period. The prognostic value of tumor-associated proteases could be of interest also in ovarian and cervical cancer.

Schildkraut, J. M., P. J. Schwingl, et al. (1996). "Epithelial ovarian cancer risk among women with polycystic ovary syndrome." Obstet Gynecol **88**(4 Pt 1): 554-9.

OBJECTIVE: To investigate the relationship between polycystic ovary syndrome (PCOS) and ovarian cancer, and to present three hypotheses regarding hormonal factors and the risk of ovarian cancer in women. METHODS: Data were analyzed from a population-based, case-control study, the Cancer and Steroid Hormone Study, to test the hypotheses. Four hundred seventy-six subjects with histologically confirmed epithelial ovarian cancer were identified from eight tumor registries of the Surveillance Epidemiology and End Results program. The study included 4081 controls ascertained via random-digit telephone dialing. All subjects and controls were aged 20-54 years. RESULTS: Seven subjects with ovarian cancer and 24 controls reported that they had been diagnosed with PCOS before the study period. Ovarian cancer risk was found to increase 2.5-fold (95% confidence interval [CI] 1.1-5.9) among women with PCOS. This association is found to be stronger among women who never used oral contraceptives (odds ratio [OR] 10.5, 95% CI 2.5-44.2) and women who were in the first quartile of body mass index (13.3-18.5 kg/m2) at age 18 (OR 15.6, 95% CI 3.4-71.0). CONCLUSION: The data suggest that the hormonal status of women with PCOS featuring abnormal patterns of gonadotropic secretion (enhanced levels of LH) in lean women may be a mitigating factor for the observed association between PCOS and ovarian cancer. We hope that our preliminary data stimulate further investigation of the testable hypotheses.

Shi, J., X. Chang, et al. (2007). "Expression of an ovarian cancer anti-idiotype antibody (6B11VLVHCH3) in Chinese hamster ovary (CHO) cells with improved immunoactivity and stability over proteins expressed in prokaryotic cells." Hybridoma (Larchmt) **26**(5): 289-95.

The 6B11VLVHCH3 is an anti-idiotype antibody to ovarian cancer. It can mimic the ovarian cancer-associated antigen OC166-9. We have previously expressed it in Escherichia coli. We now express the 6B11VLVHCH3 in a Chinese hamster ovary (CHO) cell system. The 6B11VLVHhCH3 sequence was amplified from the prokaryotic vector and cloned into the eukaryotic expression vector pSecTag2. The construct was transfected into CHO cells. Then the transfected monoclonal CHO cells were sequentially adapted to growth in serum-free medium. Functional differences between the antibody produced in E. coli or CHO cells were assessed. The antibody produced by CHO cells was able to both mimic ovarian cancer antigen and retain FC region functionality. Importantly, the antigen mimicry activity of 6B11VLVHhCH3 produced by CHO cells is approximately 20 times higher than antibody expressed by E. coli. This method of expression provides a safer and higher quality antibody for clinical drug development.

Smith, D. B., G. J. Rustin, et al. (1991). "A phase II study of ondansetron as antiemetic prophylaxis in patients receiving carboplatin for advanced ovarian cancer. The North Thames Ovary Group." Ann Oncol **2**(8): 607-8.

Thirty four patients who were receiving carboplatin 400 mg/m2 for advanced epithelial ovarian cancer were treated with ondansetron antiemetic prophylaxis. Ondansetron was given as 4 mg oral +4 mg iv 30 minutes prior to carboplatin followed by 8 mg oral tds for 5 days. Of the evaluable patients complete or major control of emesis on day one was achieved in 94% of previously untreated patients and 81% of patients refractory to conventional antiemetic therapy. For the 5 day period as a whole 88% of untreated patients and 69% of those with refractory emesis reported complete or major control of nausea and vomiting. Fifteen patients noted no side effects with mild headache (30%) and constipation (21%) the most frequent problems in the remainder. Ondansetron is effective antiemetic prophylaxis for carboplatin chemotherapy and should allow the majority of these patients to be managed on an out-patient basis.

Smith, J. P., F. N. Rutledge, et al. (1975). "Postoperative treatment of early cancer of the ovary: a random trial between postoperative irradiation and chemotherapy." Natl Cancer Inst Monogr **42**: 149-53.

One hundred and forty-nine patients with early cancer of the ovary who were suitable for postoperative radiotherapy were treated in a random study in which the efficacy of whole abdominal irradiation with additional irradiation to the pelvis was compared to that of chemotherapy with melphalan. The number of patients without evidence of disease at 2 years indicates that both treatments give similar results. However, the survivals among patients with stage I ovarian cancer showed an improvement for

women treated with irradiation, survivals among patients with stage II ovarian cancer showed only a minor difference between women treated with irradiation and those treated with chemotherapy, and survivals among patients with stage III ovarian cancer improved for women treated with chemotherapy. The complications resulting from both treatments differed greatly. Melphalan was well tolerated; it caused serious bone marrow depression in only one patient. The blood counts of all patients after completing their prescribed chemotherapy promptly returned to normal levels. Seven patients treated with irradiation developed small bowel injury requiring surgery. Six of these patients, however, were treated with irradiation to the pelvis followed by strip irradiation to the entire abdomen. Since this treatment plan probably gives excessive doses of irradiation to the pelvis, it has been discontinued.

Sonnendecker, E. W. (1988). "Cancer of the ovary. The Johannesburg Hospital experience." S Afr Med J **73**(12): 713-5.

Experience with 100 patients with epithelial ovarian cancer, who underwent primary definitive surgery at Johannesburg Hospital between 1 January 1979 and 31 July 1987, is presented and the absolute 4-year survival figures are compared with those from 1977. For patients with advanced disease (stages III and IV) the 4-year survival rate has improved from 4.4% to 42% (P = 0.001). Reasons for this substantial progress are outlined. Fifty per cent of the patients had nonspecific gastro-intestinal symptoms at the time of diagnosis and 20% had previously undergone hysterectomy. A case is made for prophylactic oophorectomy at the time of hysterectomy.

Spencer, J. A., K. Anderson, et al. (2006). "Image guided biopsy in the management of cancer of the ovary." Cancer Imaging **6**: 144-7.

When used in the context of multidisciplinary team discussion, image guided biopsy using ultrasound (US) or computed tomography (CT) guidance is of value in planning management of women with suspected ovarian cancer and peritoneal carcinomatosis (PC) of uncertain aetiology. It is essential in women believed to have ovarian cancer but with poor performance status or with advanced disease believed beyond the scope of primary cytoreductive surgery for whom staging surgical pathology will not be obtained. It provides a site-specific primary tumour diagnosis in 93% of cases and it should replace diagnostic laparoscopy or laparotomy for this purpose. It allows provision of primary (neoadjuvant) chemotherapy based on a firm histological diagnosis. It is mandatory in women with a history of cancer whose metastases may mimic ovarian cancer (e.g. breast, GI tract, melanoma). More women with prior breast cancer who re-present with peritoneal cancer will have a new gynaecological primary than recurrence of their original primary tumour; the two options require radically different therapies. Finally it is a valuable problem solving tool in situations of diagnostic uncertainty, e.g. unusual imaging patterns of disease such as PC with bilateral solid ovarian masses or non-enlarged ovaries and with an unusual tumour marker profiles suggesting primary tumours outwith the ovary. The technique is simple, safe and effective and can be combined with palliative drainage of ascites at the same procedure.

Spinelli, J. J., R. P. Gallagher, et al. (1984). "Multiple myeloma, leukemia, and cancer of the ovary in cosmetologists and hairdressers." Am J Ind Med **6**(2): 97-102.

In order to evaluate occupational mortality, age standardized proportional mortality ratios (PMR) were calculated for 160 female cosmetologists and hairdressers and 1,001 male barbers and hairdressers utilizing cause of death and occupation statements from British Columbia death registrations collected from 1950 to 1978. Female cosmetologists had elevated risks of death from multiple myeloma (PMR = 619, p = .03) and ovarian cancer (PMR = 204, p = .09). Male barbers and hairdressers had no corresponding elevated risk of myeloma but had a significantly high risk of death from leukemia (PMR = 188, p = .05). Further detailed studies of these occupations would be worthwhile to confirm and extend these findings.

Spirtos, N. M., G. M. Gross, et al. (1995). "Cytoreductive surgery in advanced epithelial cancer of the ovary: the impact of aortic and pelvic lymphadenectomy." Gynecol Oncol **56**(3): 345-52.

Beginning in July 1988, a planned program was undertaken to assess the role of aortic and pelvic lymphadenectomy in patients with advanced epithelial cancer of the ovary (Stages IIIa-IVa) undergoing cytoreductive surgery. Our intent was to perform a complete aortic and pelvic lymphadenectomy in all patients in whom we could surgically remove all intra- or retroperitoneal disease measuring 1 cm or greater. Accordingly, 56/77 patients (73%) underwent complete aortic and pelvic lymphadenectomy. The remaining 21/77 patients (27%) did not, either because the lymphadenectomy would not have impacted on the patient's cytoreductive status or because intraoperative conditions precluded it. Positive lymph nodes were found in 36/56 patients (64%). Of these, 23/36 (64%) were macroscopically positive, and if left in situ would have affected the patient's cytoreductive status. Thirteen of 36 (36%) were positive microscopically.

Reassessment laparotomy was performed in 44/56 (79%) of the patients having had a lymphadenectomy and is correlated to disease status. Median follow-up is 30 months (range 2-64 months). Survival analysis reveals: 10/20 patients (50%) with negative lymph nodes; 6/13 patients (46%) with microscopically positive lymph nodes; 10/23 patients (43%) with macroscopically positive, but surgically removed lymph nodes; and only 2/21 patients (10%) with residual disease measuring at least 1 cm in diameter are alive without evidence of disease. These preliminary findings suggest that the removal of macroscopically negative lymph nodes offers little benefit to the patient with advanced epithelial cancer and minimal residual (less than 1 cm) disease. However, the concept of cytoreductive surgery, whether it be intra- or retroperitoneal, appears to be validated by the fact that the patients undergoing removal of macroscopically positive lymph nodes have approximately the same chance of survival as those with microscopically positive and/or negative lymph nodes.

Staquet, M., B. W. Brown, Jr., et al. (1987). "Validation of the clinical predictive values of the in vitro phase II clonogenic assay in cancer of the breast and ovary." Am J Clin Oncol **10**(6): 485-90.

The in vitro evaluation of new antineoplastic agents has been advocated as a method of selecting drugs for Phase I-II trials in patients. This paper is an attempt to validate, in an unbiased manner, the so-called in vitro Phase II clonogenic assay with regard to its predictive power in the clinic. Breast and ovarian cancer were chosen because of the relatively large number of drugs clinically evaluated for these diseases; 298 patients were studied. For metastatic breast cancer 12 drugs, six clinically active and six inactive, were tested. It was found that in patients without prior chemotherapy, there is an association between results in vitro and in vivo. In metastatic ovarian cancer, 11 drugs, four of which are known to be clinically inactive, were studied. The same positive association was seen for patients without prior chemotherapy. The implications of these findings are discussed.

Sundfeldt, K., Y. Piontkewitz, et al. (1997). "E-cadherin expression in human epithelial ovarian cancer and normal ovary." Int J Cancer **74**(3): 275-80.

The ovarian surface epithelium (OSE) is the origin of the majority of human ovarian cancers. These adenocarcinomas are characterized by initial local growth followed by spreading into the peritoneal cavity at later stages of tumor progression. The cell-adhesion molecule E-cadherin (E-cad) plays an important role in maintaining tissue integrity. Disappearance or impaired function of E-cad have often been associated with tumor formation and invasion in vivo and in vitro. The cell-specific expression of E-cad was investigated in normal human ovaries (n = 12), in benign (n = 5) and borderline (n = 4) ovarian epithelial tumors and in adenocarcinomas of different stages and histological grades (n = 18), by immunohistochemistry and immunoblotting. An ovarian cancer cell line (NIH-OVCAR3) was used as a reference. The epithelial origin of the cells was confirmed with cytokeratin (AE1/AE3) staining. In normal ovaries, the expression of E-cad was limited to inclusion cysts or deep clefts lined with OSE, whereas no staining of the OSE could be demonstrated at the surface of the ovary. In contrast, benign and borderline tumors uniformly expressed E-cad. This was observed in malignant tumors of all stages despite their degree of differentiation. E-cad was also present in metastasis from such tumors. The cell-specific expression of E-cad in inclusion cysts of normal ovaries and in epithelial layers of borderline tumors indicates a role for E-cad in the early events of the progression to a malignant phenotype. E-cad was not downregulated in later stages of ovarian cancer progression.

Swenerton, K. D. and J. L. Pater (1992). "Carboplatin in the treatment of carcinoma of the ovary: the National Cancer Institute of Canada experience. Ovarian Cancer Subcommittee." Semin Oncol **19**(1 Suppl 2): 114-9.

The National Cancer Institute of Canada Clinical Trials Group has used carboplatin in two studies in women with ovarian carcinoma. In a phase II study, carboplatin produced a clinical response rate of 28% among patients with tumor persistence or recurrence following one prior cisplatin-containing regimen. Carboplatin was most efficacious in those with smaller tumors, in those who had the best responses to prior cisplatin therapy, and in those with longer intervals between the primary cisplatin treatment and the secondary carboplatin course. In this setting, a starting dose of 320 mg/m2 is suggested. A phase III randomized trial of first-line therapy compared the efficacy of cyclophosphamide/cisplatin with cyclophosphamide/carboplatin. Four hundred eighteen eligible patients were enrolled. The regimens demonstrated comparable efficacy; however, the carboplatin-based regimen was more easily administered and caused less symptomatic toxicity. The long-term results in this population with macroscopic residual disease remain disappointing.

Szaniawska, B., K. Gawrychowski, et al. (1998). "The effect of protein kinase C inhibitors on invasion of human ovary cancer cells." Neoplasma **45**(1): 7-11.

In the present work we tested whether invasiveness of ovarian carcinoma cells could be considered as protein kinase C (PKC) dependent process. The migration and invasion studies were performed in Transwell chambers. Staurosporine, sphingosine and tamoxifen were used as PKC inhibitors. Also the effect of prolonged treatment with TPA was the subject of observation. The obtained results indicated that invasion understood as three step process (attachment, migration and matrix degradation) was affected by PKC inhibitors. The detailed studies, however, showed that attachment and matrix degradation ability of ovarian cancer cells was not changed by PKC inhibitors as opposed to migration which was, at least partly, regulated by protein kinase C.

Tang, H., M. A. Davis, et al. (1994). "Influence of cell cycle phase on radiation-induced cytotoxicity and DNA damage in human colon cancer (HT29) and Chinese hamster ovary cells." Radiat Res **138**(1 Suppl): S109-12.

We have previously shown that fluorodeoxyuridine (FdUrd) radiosensitizes HT29 human colon carcinoma cells. Since treatment with FdUrd arrests cells at the G1/S-phase interface, a condition associated with increased radiation sensitivity in some cells, it seemed possible that redistribution of cells in the phases of the cell cycle might account for FdUrd-mediated radiosensitization. To begin to test this, HT29 cells were separated by centrifugal elutriation according to cell cycle phase and assessed for radiosensitivity, using a clonogenic assay, and radiation-induced DNA damage, using pulsed-field gel electrophoresis. We found that all of the elutriated fractions (which contained cells enriched in G1, G1/early S, mid to late S or G2/M phase) had the same radiation sensitivity and expressed a similar extent of radiation-induced DNA damage. To determine if the techniques used in this study could detect differences between the radiation sensitivity of cells in different phases of the cell cycle, analogous experiments were carried out using Chinese hamster ovary (CHO) cells. In contrast with the results of experiments with HT29 cells, but in agreement with previous studies, CHO cells separated under the same conditions as were used for HT29 cells showed a marked dependence on cell age of both clonogenic survival and radiation-induced DNA damage. Thus, within the limitations of the purity of separation obtained using elutriation, the radiation sensitivity of HT29 cells does not vary substantially as a function of cell cycle phase. Therefore, it seems unlikely that cell cycle redistribution alone explains the radiation sensitivity produced by exposure to FdUrd.

Tilly, J. L. and R. N. Kolesnick (2002). "Sphingolipids, apoptosis, cancer treatments and the ovary: investigating a crime against female fertility." Biochim Biophys Acta **1585**(2-3): 135-8.

Premature ovarian failure and infertility are well-known side-effects observed in young girls and reproductive-age women treated for cancer. Although the need for tumor eradication in these patients is clear, the long-term consequences of chemotherapy and radiation on non-target tissues, such as the ovaries where large numbers of germ cells (oocytes) are also killed off, are substantial. Unfortunately, the mechanism mediating the undesirable toxicity of cancer therapies in the female gonads has only recently been explored. Nevertheless, some important insights into the role of ceramide and sphingosine-1-phosphate (S1P) as a mediator and suppressor, respectively, of cancer therapy-induced oocyte apoptosis have emerged over the past few years. Such findings are exciting in that a better understanding of the crime--how radiation and chemotherapy kill off this irreplaceable population of innocent cells in the ovaries--may finally allow for the development of novel lipid-based strategies to combat infertility and premature menopause in female cancer patients.

Tornos, C., R. Soslow, et al. (2005). "Expression of WT1, CA 125, and GCDFP-15 as useful markers in the differential diagnosis of primary ovarian carcinomas versus metastatic breast cancer to the ovary." Am J Surg Pathol **29**(11): 1482-9.

Metastatic breast carcinoma to the ovary is sometimes difficult to differentiate from primary ovarian carcinoma. This problem is often encountered in breast carcinoma patients who develop adnexal masses. ER and PR can be positive in a high percentage of breast and ovarian carcinomas, and therefore cannot be used in the differential diagnosis of these entities. WT1 and CA125 have been identified as possible markers for ovarian cancer. However, no studies have been done that specifically compare the immunophenotype of breast carcinoma metastatic to ovary with that of primary ovarian cancer. Thirty-nine cases of metastatic breast carcinoma to the ovary, 36 primary breast carcinomas, and 42 primary ovarian carcinomas were examined immunohistochemically for the expression of WT1, CA125, carcinoembryonic antigen, MUC2, MUC1, and GCDFP. The percentage of cells stained and the intensity of staining were recorded. Thirty-two ovarian carcinomas (76%) were positive for WT1, including 31 of 33 (94%) serous carcinomas. Most of them had strong and diffuse staining. None of the breast cancers either primary or metastatic to the ovary expressed WT1. Thirty-eight (90%) ovarian carcinomas were positive for CA125, most of them

with strong and diffuse staining. Most breast carcinomas were negative for CA125, with only 6 (16%) of the primary ones and 5 (12%) of the metastatic showing weak and focal positivity. All ovarian carcinomas were negative for GCDFP. Five primary breast cancers (14%) and 17 (43%) metastatic to the ovary were positive for GCDFP. Nine (21%) ovarian carcinomas, 8 (22%) primary breast carcinomas, and 13 (33%) metastatic to the ovary were positive for carcinoembryonic antigen. Almost all tumors examined were positive for MUC1 (100% ovarian carcinomas, 100% primary breast carcinomas, and 95% metastatic breast carcinomas to ovary). MUC2 was positive in 10 (24%) ovarian carcinomas, 3 (8%) primary breast cancers, and 12 (30%) metastases to the ovary. The presence of immunoreactivity for WT1 and CA125 in a carcinoma involving ovary strongly favors a primary lesion. Most ovarian carcinomas are positive for both markers, whereas the majority of metastatic breast carcinomas to the ovary are negative. GCDFP can be complementary in this differential diagnosis.

Tresserra, F., P. J. Grases, et al. (1998). "Histological features of the contralateral ovary in patients with unilateral ovarian cancer: a case control study." Gynecol Oncol **71**(3): 437-41.

OBJECTIVE: Most of the surface epithelial-stromal tumors of the ovary are thought to arise from epithelial inclusion cysts, thus these cysts, and the original surface epithelium, are precursor lesions of ovarian carcinoma. MATERIAL AND METHODS: The histological features in contralateral ovary from 20 patients with unilateral ovarian carcinoma were compared with 20 ovaries of patients without ovarian pathology and with 12 normal ovaries of women with contralateral benign ovarian pathology. RESULTS: Cortical invaginations were more frequent and numerous in ovaries of patients with contralateral ovarian carcinoma. The presence of cortical invaginations and epithelial inclusion cysts showed correlation in patients with cancer and in those without ovarian pathology, but there were no differences in the number of inclusion cysts when the three groups were compared. Mild cytological atypia was detected more frequently in the surface epithelium of contralateral ovaries of patients with ovarian carcinoma. Ovarian size, cortical thickness, stromal hyperplasia, psammoma bodies, and surface papillae did not show differences when comparing patients with cancer and control groups. CONCLUSION: Cortical invaginations, a previous step in the formation of epithelial inclusion cysts, can also play an important role in the genesis of ovarian carcinoma.

van Asperen, C. J., R. M. Brohet, et al. (2005). "Cancer risks in BRCA2 families: estimates for sites other than breast and ovary." J Med Genet **42**(9): 711-9.

BACKGROUND: In BRCA2 mutation carriers, increased risks have been reported for several cancer sites besides breast and ovary. As most of the families included in earlier reports were selected on the basis of multiple breast/ovarian cancer cases, it is possible that risk estimates may differ in mutation carriers with a less striking family history. METHODS: In the Netherlands, 139 BRCA2 families with 66 different pathogenic mutations were included in a nationwide study. To avoid testing bias, we chose not to estimate risk in typed carriers, but rather in male and female family members with a 50% prior probability of being a carrier (n = 1811). The relative risk (RR) for each cancer site with the exception of breast and ovarian cancer was determined by comparing observed numbers with those expected, based on Dutch cancer incidence rates. RESULTS: We observed an excess risk for four cancer sites: pancreas (RR 5.9; 95% confidence interval (CI) 3.2 to 10.0), prostate (2.5; 1.6 to 3.8), bone (14.4; 2.9 to 42.1) and pharynx (7.3; 2.0 to 18.6). A small increase was observed for cancer of the digestive tract (1.5; 1.1 to 1.9). Histological verification was available for 46% of the tumours. Nearly all increased risks reached statistical significance for men only. Cancer risks tended to be higher for people before the age of 65 years. Moreover, families with mutations outside the previously defined ovarian cancer cluster region tended to have a higher cancer risk. CONCLUSIONS: We found that BRCA2 carriers are at increased risk for cancers of the prostate and pancreas, and possibly bone and pharynx. Larger databases with extended follow up are needed to provide insight into mutation specific risks of selected carriers in BRCA2 families.

van den Brule, F., S. Califice, et al. (2003). "Galectin-1 accumulation in the ovary carcinoma peritumoral stroma is induced by ovary carcinoma cells and affects both cancer cell proliferation and adhesion to laminin-1 and fibronectin." Lab Invest **83**(3): 377-86.

Galectin-1 (gal-1) is a 14-kDa laminin-binding galectin involved in several biologic events including regulation of cancer cell proliferation and adhesion to the matrix. In this study, we examined gal-1 expression in 30 human epithelial ovary carcinoma samples by Western and Northern blotting and by immunohistochemistry. Gal-1 mRNA levels were increased in more than 95% of the examined ovary carcinoma samples, compared with a wedge resection of a normal ovary. Immunohistochemical analysis of the samples demonstrated gal-1 expression in cancer epithelial cells from 17 of 30 samples, with a

cytoplasmic pattern. Gal-1 immunostaining was significantly increased in the stroma associated with carcinoma cells compared with the normal, noninvaded stroma (p = 0.003). This pattern of expression was confirmed by examination of 12 other frozen epithelial ovary carcinomas, using in situ hybridization. Immunohistochemical staining of the specimens demonstrated colocalization of gal-1, laminin-1, and fibronectin. In vitro experiments were conducted to elucidate the potential biologic role of gal-1 in ovarian cancer progression. Gal-1 protein expression and release was detected in AZ364, SK-OV-3, and AZ224, but not in OVCAR-3, AZ419, and AZ382, human ovary carcinoma cell lines. Incubation of 84BR fibroblasts with conditioned media harvested from the ovary carcinoma cell lines induced an increased expression of gal-1 in the cultured fibroblasts in all cases except AZ419 and SK-OV-3. High concentrations of gal-1 (100 micro g/ml) induced significantly decreased cell proliferation in all cell lines, as defined by bromodeoxyuridine incorporation. Additionally, recombinant gal-1 induced a dose-dependent increase in in vitro adhesion of AZ224, SK-OV-3, and AZ382 cells to laminin-1; adhesion to fibronectin was increased by gal-1 in OVCAR-3, AZ224, and SK-OV-3. No effect was observed in the other cases. Our data contribute to define a role for gal-1 during the interactions between human ovary carcinoma cells and host fibroblasts.

Vranes, H. S., P. Klaric, et al. (2007). "Antropologic factors in prediction of ovary cancer." Coll Antropol **31**(2): 541-4.

The aim of the study was to determine a combination of anthropometric variables that would enable better differentiation between benign and malignant ovarian masses. Prospective study has been performed in a two year period in which 208 women with ovarian lesions were analyzed and correlated with histopathologic surgical findings. We examined the relation between self-reported anthropometric and other variables (height, weight, body mass index--BMI, parity, marital status, education, age, rural versus urban residence, menopausal status) and incidence of ovarian cancer. Age, parity, marital status and menopausal status individually showed statistical significance.

Waltz, P. and G. Chodick (2008). "Assessment of ecological regression in the study of colon, breast, ovary, non-Hodgkin's lymphoma, or prostate cancer and residential UV." Eur J Cancer Prev **17**(3): 279-86.

Recent ecological studies have suggested a possible association between exposure to ultraviolet-B (UVB) radiation and reduction in the risk of various cancers; however, ecological studies are known to be subject to bias. The objective of this study was to demonstrate difficulties with the ecological approach. We conducted a multicountry ecological study using cancer incidence rates, residential UV levels, dietary intake, and different sociodemographic variables for 38 locations spanning 33 countries worldwide. The effect of residential UV exposure on cancer incidence was assessed using multiple linear regression models. The results of our multivariate analyses show no indication of an inverse association between residential UV levels and the risk of colon, non-Hodgkin's lymphoma (NHL), ovarian, prostate, or breast cancer in women. For colon cancer and NHL, a significant positive association was calculated. The rates of melanoma, which were used to examine the methods of this study, showed a strong and significant (P<0.01) association with solar radiation. Our results provide no evidence to support previous ecological results that UV exposure may reduce the risk of NHL, colon, breast, ovary, or prostate cancer. The study demonstrates the high sensitivity of ecological studies to adjustments for various confounders, and casts doubts on results of ecological analyses in this field.

Wiltshaw, E., S. Subramarian, et al. (1979). "Cancer of the ovary: a summary of experience with cis-dichlorodiammineplatinum(II) at the Royal Marsden Hospital." Cancer Treat Rep **63**(9-10): 1545-8.

A review of the use of cis-dichlorodiammineplatinum(II) (cis-platinum) as a single agent in 82 patients with advanced ovarian carcinoma, previously treated with chemotherapy, shows that response rates of 33% and 52% are achieved with doses of 30 and 100 mg/m2 respectively. In 58 previously untreated patients a combination of chlorambucil and cis-platinum (regimen B) was compared in a randomized study with a combination of chlorambucil, cis-platinum, and Adriamycin (regimen C). Complete responses were seen in 32% and 41% of the patients respectively. Remissions were most prolonged in patients with complete regressions, the median being greater than 15 months for both regimens. Because of the good regressions, second-look operations have been possible in 12 patients for the purpose of confirming regression and performing radical surgical removal. In six of these patients, all specimens failed to show evidence of residual carcinoma. The major toxic effects of cis-platinum in our hands are neurologic effects and anemia; both have been reversible after cessation of treatment.

Yamada, T., N. Iwao, et al. (2003). "A case of malignant lymphoma of the ovary manifesting like an advanced ovarian cancer." Gynecol Oncol **90**(1): 215-9.

BACKGROUND: In recent years, true primary ovarian lymphoma has been considered to carry a favorable prognosis, although most studies of supposedly primary ovarian lymphoma have reported a poor outcome. CASE: A 47-year-old woman presented with signs and symptoms suggestive of an advanced ovarian cancer. Ultrasonography and magnetic resonance imaging revealed bilateral abdominal tumors, each measuring 10 cm in diameter, thickened omentum, and a large amount of ascitic fluid, but no enlarged lymph nodes. The diagnosis of malignant lymphoma was established from the biopsy specimen after exploratory laparotomy. Six years following chemotherapy, the patient is alive and disease free without additional surgery. CONCLUSION: The prognosis of ovarian lymphoma was evaluated according to clinical stage, modality of onset, histologic type, and phenotype. It remains controversial whether this case can be considered truly primary ovarian lymphoma and not merely a localized initial manifestation of a generalized disease. But if this case of advanced ovarian lymphoma were not primary, it could still be managed successfully with chemotherapy appropriate for the specific histology.

Yasumizu, T. and J. Kato (1995). "Clinical trial of daily low-dose oral etoposide for patients with residual or recurrent cancer of the ovary or uterus." J Obstet Gynaecol (Tokyo 1995) **21**(6): 569-76.

OBJECTIVE: To determine the efficacy of long-term therapy of oral etoposide in patients with residual or recurrent gynecological malignancies. METHODS: Twenty-five Japanese patients with resistant or recurrent carcinoma of the uterus or ovary were treated with oral etoposide at a dose of 25 mg/day/body for 21 consecutive days, and cycles were repeated every 4 weeks. The residual or recurrent lesion could be objectively evaluated in all patients by measuring it directly. RESULTS: The response rate after 6 cycles of therapy was 40% for the group of all patients, and 42.8%, 28.6% and 50% for those with ovarian carcinoma, cervical carcinoma, and endometrial carcinoma, respectively. Side effects of etoposide treatment included gastrointestinal discomfort in 14 patients and leukopenia of grade 3 or higher in 2 patients. However, these side effects were mild, and all patients could continue treatment. CONCLUSION: These findings indicate that long-term, low-dose oral etoposide was effective for and well-tolerated by patients with refractory or recurrent carcinoma of the ovary or uterus.

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.

Yeole, B. B. (2008). "Trends in cancer incidence in female breast, cervix uteri, corpus uteri, and ovary in India." Asian Pac J Cancer Prev **9**(1): 119-22.

Trends in breast, cervix uteri, corpus uteri and ovarian cancers in six population based cancer registries (Mumbai, Bangalore, Chennai, Delhi, Bhopal, and Barshi) were evaluated over a period of the last two decades. For studying trends we used a model that fits this data is the logarithm of Y=ABx which represents a Linear Regression model. This approach showed a decreasing trend for cancer of the cervix and increasing trends for cancers of breast, ovary and corpus uteri throughout the entire period of observation in most of the registries. The four cancers, breast, cervix, corpus uteri and ovary, constitute more than 50% of total cancers in women. As all these cancers are increasing, to understand their etiology in

depth, analytic epidemiology studies should be planned in a near future on a priority basis.

Yoshida, H., W. Cheng, et al. (2004). "Lessons from border cell migration in the Drosophila ovary: A role for myosin VI in dissemination of human ovarian cancer." Proc Natl Acad Sci U S A **101**(21): 8144-9.

Dissemination of ovarian cancer is a major clinical challenge and is poorly understood at the molecular level due to a lack of suitable experimental models. During normal development of the Drosophila ovary, a dynamic process called border cell migration occurs that resembles the migratory behavior of human ovarian cancer cells. In this study, we found that myosin VI, a motor protein that regulates border cell migration, is abundantly expressed in high-grade ovarian carcinomas but not in normal ovary and ovarian cancers that behave indolently. Inhibiting myosin VI expression in high-grade ovarian carcinoma cells impeded cell spreading and migration in vitro. Optical imaging and histopathologic studies revealed that inhibiting myosin VI expression reduces tumor dissemination in nude mice. Therefore, using genetic analysis of border cell migration in Drosophila is a powerful approach to identify novel molecules that promote ovarian cancer dissemination and represent potential therapeutic targets.

Yoshida, H., J. Liu, et al. (2005). "Steroid receptor coactivator-3, a homolog of Taiman that controls cell migration in the Drosophila ovary, regulates migration of human ovarian cancer cells." Mol Cell Endocrinol **245**(1-2): 77-85.

Border cell migration is a process that occurs during Drosophila ovarian development in which cells derived from a simple epithelium migrate and invade neighboring tissue. This process resembles the behavior of cancerous cells that derive from the simple epithelium of the human ovary. One important regulator of border cell migration is Taiman, a homolog of steroid receptor coactivator-3 (SRC-3). Because increasing evidence indicates that similarities exist between the molecular control of migration of border cells and of cancer cells, we investigated whether SRC-3 controls ovarian cancer cell migration. Little or no SRC-3 expression was detected in normal ovarian surface epithelium, ovarian cysts and borderline ovarian tumors that lack stromal invasion. In contrast, SRC-3 was abundantly expressed in high-grade ovarian carcinomas. Inhibiting SRC-3 expression in ovarian cancer cells markedly reduced cell spreading and migration, and altered intracellular localization of focal adhesion kinase. This inhibitory effect on cell migration was independent of the estrogen receptor (ER) status of the cells. These studies reveal a novel role for SRC-3 in ovarian cancer progression by promoting cell migration, independently of its role in estrogen receptor signaling.

Zanghi, J. A., T. P. Mendoza, et al. (1998). "Ammonia inhibits neural cell adhesion molecule polysialylation in Chinese hamster ovary and small cell lung cancer cells." J Cell Physiol **177**(2): 248-63.

Ammonia is a major concern in biotechnology because it often limits recombinant protein production by animal cells. Conditions, such as ammonia accumulation, in large-scale production systems can parallel those that develop within fast-growing solid tumors such as small cell lung cancer (SCLC). Ammonia's specific inhibition of the sialylation of secreted glycoproteins is well documented, but it is not known how ammonia affects membrane-bound proteins, nor what role it may have on important glycosylation determinants in cancer. We therefore examined the effects of NH4Cl on polysialic acid (PolySia) in the neural cell adhesion molecule (NCAM). By using flow cytometry combined with two NCAM antibodies, one specific for the peptide backbone and another that recognizes PolySia chains, we show that ammonia causes rapid, dose-dependent, and reversible inhibition of NCAM polysialylation in Chinese hamster ovary (CHO) and SCLC NCI-N417 cells. The decrease in PolySia was accompanied by a small increase in NCAM, suggesting that the changes were specific to the oligosaccharide. Inhibition by ammonia was greater for CHO cells, with PolySia cell surface content decreasing to 10% of control after a 4-day culture with 10 mM NH4Cl, while N417 cell PolySia was reduced by only 35%. Ammonia caused a 60% decrease in the CHO cell yield from glucose, while N417 cells were barely affected, suggesting that increased resistance to ammonia by N41 7 cells is a global rather than glycosylation-specific phenomenon. The data presented show that the tumor microenvironment may be an important factor in the regulation of PolySia expression.

Zehetleitner, G., I. Thiel, et al. (2002). "Long-term disease-free survival after breast cancer metastatic to the ovary." Int J Gynecol Cancer **12**(3): 317-8.

The prognosis of patients with breast cancer symptomatically metastatic to the ovary is almost uniformly poor. In this case report, we present a 33-year-old para-4 with a symptomatic metastasis to the ovary. Previously, a modified radical mastectomy with adjuvant radiotherapy had been performed for invasive ductal carcinoma of the left breast. Laparotomy showed a 13-cm tumor of the left ovary; frozen section histology showed malignancy

consistent with the previous breast cancer. The patient received adjuvant combination chemotherapy. About 5 years later, a carcinoma of the right breast was treated with conservative surgery and adjuvant radiation and chemotherapy. After a further 4 years, a recurrence at the left chest wall was treated with radiation. At the last follow-up, more than 13 years after the first breast cancer and 12 years after the ovarian metastasis, the patient was alive and well without evidence of disease. Bilateral oophorectomy is a therapeutic option in premenopausal patients with localized or advanced breast cancer. Our patient experienced long-term disease-free survival following an isolated metastasis to one ovary. This represents the first report of long-term survival of such a patient in the literature.

Zheng, L., Q. Tong, et al. (2004). "Growth-inhibitory effects of curcumin on ovary cancer cells and its mechanisms." J Huazhong Univ Sci Technolog Med Sci **24**(1): 55-8.

To study the growth-inhibitory effects of curcumin on human ovary cancer A2780 cells in vitro and its molecular mechanisms, the growth inhibition rates of A2780 cancer cells, after being treated with 10 micromol/L-50 micromol/L curcumin for 6-24 h, were examined by MTT method. The morphological changes of cancer cells were observed under inversion microscopy. Cellular apoptotic rates were determined by using TUNEL. The protein expression levels of bcl-2, p53 and MDM2 in cancer cells were examined by SP immunohistochemistry. After being treated by various concentrations of curcumin, the growth of cancer cells was inhibited significantly. Some cancer cells presented characteristic morphological changes of apoptosis. The rates of apoptosis were 6.41%-28.48% ($P<0.01$). The expression of bcl-2 and p53 was decreased, which depended on the action time ($P<0.01$). There were no obvious changes in MDM2 expression. It was concluded that curcumin could significantly inhibit the growth of ovary cancer cells. The induction of apoptosis by down-regulating the expression of bcl-2 and p53 was probably one of its molecular mechanisms.

Zheng, W., X. O. Shu, et al. (1993). "Occupational physical activity and the incidence of cancer of the breast, corpus uteri, and ovary in Shanghai." Cancer **71**(11): 3620-4.

BACKGROUND: A sedentary life style has been consistently associated with an increased risk of colon cancer, but the evidence for its association with breast and other gynecologic cancers is limited. METHODS: Occupational information for 3783 incident patients with cancer (breast, 2736; corpus uteri, 452; and ovary, 595) whose disease was diagnosed during the period 1980-1984 was compared with 1982 census data on employment in Shanghai urban areas. The standardized incidence ratios (SIR) of these cancers were estimated for each occupational group classified by job titles and physical activity levels. RESULTS: A significantly increased incidence of breast cancer was found among professionals (SIR = 158), government officials (SIR = 131), and clerical workers (SIR = 143); the incidence was reduced among service workers (SIR = 87) and craftsmen (SIR = 91). Occupational physical activity, as measured by sitting time and energy expenditure, was inversely related to breast cancer incidence, with SIR of 127-131 for inactive jobs (sedentary or low-energy expenditure) and 79-93 for active jobs (long periods of standing or high energy expenditure). Similar associations, although to a lesser extent, were also seen for cancer of the corpus uteri and ovary. CONCLUSIONS: Women with low physical activity occupations had an increased incidence of cancer of the breast, corpus uteri, and ovary; the incidence was reduced among women with high-activity jobs. These findings were consistent with observations from earlier studies and provided further evidence that physical activity may lower the risk of these female hormone-dependent cancers.

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