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Objective
To assess the association between polycystic ovary syndrome (PCOS) and cancer, especially of the endometrium, breast and ovary.

Methods
The Danish National Patient Register was used to identify 12,070 in- and outpatients in whom PCOS was diagnosed when they were aged 9–49 years during 1977–2012. Using the Danish Cancer Registry, we followed the cohort through 2012 and compared the women's cancer incidence with that of the general Danish female population by means of standardized incidence ratios (SIRs).

Results
Cancer was diagnosed in 279 women with PCOS (SIR = 1.19; 95% CI = 1.06–1.34). We found an almost fourfold increased risk for endometrial cancer (numbers observed (N) = 16, SIR = 3.9; 95% CI = 2.2–6.3), the large majority of cases being type 1 (N = 14, SIR = 4.7; 95% CI = 2.6–7.9). We found no association between PCOS and breast (N = 59, SIR = 1.1; 95% CI = 0.8–1.4) or ovarian cancer (N = 10, SIR = 1.8; 95% CI = 0.8–3.2); however, significantly increased risks were found for kidney, colon and brain cancers.
Conclusion

The results of this large cohort study support those of case–control studies showing that women with PCOS are at increased risk for endometrial cancer, whereas their risks for breast and ovarian cancer are similar to those of women in the general population. Our finding that women with PCOS also are at increased risk for cancers of the kidney, colon and brain requires further study.

2. Proteomic biomarkers for ovarian cancer risk in women with polycystic ovary syndrome: a systematic review and biomarker database integration

Objective

To review and identify possible biomarkers for ovarian cancer (OC) in women with polycystic ovary syndrome (PCOS).

Design

Systematic literature searches of MEDLINE, EMBASE, and Cochrane using the search terms “proteomics,” proteomic,” and “ovarian cancer” or “ovarian carcinoma.” Proteomic biomarkers for OC were then integrated with an updated previously published database of all proteomic biomarkers identified to date in patients with PCOS.

Setting

Academic department of obstetrics and gynecology in the United Kingdom.

Patient(s)

A total of 180 women identified in the six studies.

Intervention(s)
Tissue samples from women with OC vs. tissue samples from women without OC.

Main Outcome Measure(s)
Proteomic biomarkers, proteomic technique used, and methodologic quality score.

Result(s)
A panel of six biomarkers was overexpressed both in women with OC and in women with PCOS. These biomarkers include calreticulin, fibrinogen-γ, superoxide dismutase, vimentin, malate dehydrogenase, and lamin B2.

Conclusion(s)
These biomarkers could help improve our understanding of the links between PCOS and OC and could potentially be used to identify subgroups of women with PCOS at increased risk of OC. More studies are required to further evaluate the role these biomarkers play in women with PCOS and OC.

3. Evaluation of the Pro-inflammatory Cytokine Tumor Necrosis Factor-alpha in Adolescents with Polycystic Ovary Syndrome

Background
Patients with polycystic ovary syndrome (PCOS) often suffer from comorbidities associated with chronic inflammation characterized by elevations in pro-inflammatory cytokines. There is limited data on markers of chronic inflammation, in particular Tumor Necrosis Factor-alpha (TNF-α), in adolescents with PCOS.
Objectives
To compare serum levels of TNF-α in overweight or obese adolescents with PCOS and obese controls. In the PCOS group, to correlate serum TNF-α levels with body mass index (BMI) z-score, severity of hyperandrogenism, degree of insulin resistance, and ovarian ultrasonographic characteristics.

Methods
We performed a cross-sectional retrospective analysis of clinical and biochemical findings in 23 overweight or obese adolescent females with PCOS (mean BMI z-score 2, mean age 15.2 yrs) and 12 obese age- and sex-matched controls (mean BMI z-score 2, mean age 14.1 y). All subjects were post-menarchal. Serum TNF-α levels were compared between groups. In the PCOS group, cytokine levels were correlated with BMI z-score, androgen levels, fasting insulin and glucose levels as well as ovarian ultrasonographic features.

Results
Both groups were comparable in age, BMI z-score, fasting glucose, and fasting insulin. Mean free testosterone was 9.76 ± 5.13 pg/mL in the PCOS group versus 5 ± 2.02 pg/mL in the control group (P = .0092). Serum TNF-α was 7.4 ± 4 pg/mL in the PCOS group versus 4.8 ± 3.16 pg/mL in the control group (P = .0468). There was no significant correlation between serum TNF-α and BMI z-score, free testosterone, fasting insulin, or fasting glucose. No correlation existed between serum TNF-α and ovarian follicle number, distribution, or volume.

Conclusions
Serum TNF-α is elevated in overweight/obese adolescents with PCOS. Chronic inflammation in adolescents with PCOS render them at a potential increased risk for the development of atherosclerosis, type 2 diabetes, cancer, infertility, and other comorbidities. Every effort should be made to identify adolescents with PCOS early and initiate aggressive therapy to prevent future complications.
Objective

To determine the safety and efficacy of the novel combination of docetaxel, oxaliplatin, and bevacizumab as first-line treatment of advanced cancer of the ovary, peritoneum or fallopian tube after initial debulking surgery.

Methods

Eligible patients (stage IB-IV) were treated with 6 cycles of oxaliplatin (85 mg/m2), docetaxel (75 mg/m2), and bevacizumab (15 mg/kg) every 3 weeks, followed by single-agent bevacizumab 15 mg/kg every 3 weeks to complete one year of therapy. The primary endpoint was 12-month progression-free survival (PFS).

Results

A total of 132 patients (80 with measurable disease at baseline; 52 with non-measurable, evaluable disease at baseline) enrolled and received study treatment. At diagnosis, 76.5% of patients had stage III disease and 20% had stage IV. 62.9% were optimally cytoreduced. The most common grade 3/4 adverse events were neutropenia (42.4%), leukopenia (13.6%), hypertension (8.3%), fatigue (6.1%), and nausea (6.1%). One patient (0.8%) had a fatal gastrointestinal perforation.
The best overall confirmed response rate (complete response + partial response [measurable disease subgroup]) was 58.6% (95% CI 49%, 67%). CA-125 response rates for the measurable and non-measurable disease subgroups were 83.0% and 81.5%, respectively. The 12-month PFS rate for the measurable disease subgroup was 65.7% (95% CI 53.4%, 76.7%); median PFS was 16.3 (95% CI 12.6, 19.6) months. Median overall survival was 47.3 (95% CI 34.1, upper limit not applicable) months.

Conclusions

This novel treatment regimen may provide a promising therapeutic approach for women with ovarian, primary peritoneal, or fallopian tube carcinoma. No unanticipated safety concerns were identified.

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5. Development of disulfiram-loaded vaginal rings for the localized treatment of cervical cancer

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Cervical cancer is the third most prevalent cancer in women and disproportionately affects those in low resource settings due to limited programs for screening and prevention. In the developed world treatment for the disease in the non-metastasised state usually takes the form of surgical intervention and/or radiotherapy. In the developing world such techniques are less widely available. This paper describes the development of an intravaginal ring for the localised...
delivery of a chemotherapeutic drug to the cervix that has the potential to reduce the need for surgical intervention and will also provide a novel anti-cancer therapy for women in low resource settings. Disulfiram has demonstrated antineoplastic action against prostate, breast and lung cancer. Both PEVA and silicone elastomer were investigated for suitability as materials in the manufacture of DSF eluting intravaginal rings. DSF inhibited the curing process of the silicone elastomer, therefore PEVA was chosen as the material to manufacture the DSF-loaded vaginal rings. The vaginal rings had an excellent content uniformity while the DSF remained stable throughout the manufacturing process. Furthermore, the rings provided diffusion controlled release of DSF at levels well in excess of the IC50 value for the HeLa cervical cancer cell line.
Objective

28 women under 35 years with early-stage cervical cancer and strong desire for fertility preservation that do not fulfil standard criteria for fertility-sparing surgery (tumour larger than 2 cm or with deep of infiltration more than half of stroma) were included in prospective study.

Methods

Dose-dense neoadjuvant chemotherapy (NAC) was performed on all 28 patients in 10-day intervals: cisplatin plus ifosfamide in squamous cell cancer (15 women—53.6%) or cisplatin plus doxorubicin in adenocarcinoma (13 women—46.3%). Patients underwent laparoscopic lymphadenectomy and vaginal simple trachelectomy after NAC. Patients with positive lymph nodes or inadequate free surgical margins underwent radical hysterectomy.

Results

No residual disease was found in 6 women (21.4%), microscopic disease was observed in 11 women (39.3%) and macroscopic tumour in was observed in 11 women (39.3%). Ten women (35.7%) lost fertility. Four women (20%) after fertility-sparing surgery recurred, two died of the disease (10%). Fertility was spared in 20 (71.4%) women and 10 of them became pregnant (50%). Eight women delivered ten babies (6 term and four preterm deliveries). There were two miscarriages in second trimester (in one woman) and one in first trimester. One woman underwent four unsuccessful cycles of IVF, one failed to become pregnant and one recurred too early. Two women underwent chemoradiotherapy for recurrence and lost chance for pregnancy.

Conclusions
Downstaging by NAC in IB1 and IB2 cervical cancer before fertility-sparing surgery is still an experimental procedure, but shows some promise. Long-term results in relation to oncological outcome for this concept are still needed.

7. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy

Objective

Since the Group Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC–ESTRO) published recommendations for 3D MRI-based image-guided adaptive brachytherapy (IGBT) in the treatment of cervical cancer, many institutions have implemented this technique and favourable results were documented. We investigated if introduction of IGBT in our centre indeed improved treatment outcomes and reduced toxicity compared to conventional brachytherapy (CBT).

Methods

A retrospective analysis was done of outcomes of patients with stage IB-IVA cervical cancer treated with primary radiation therapy with curative intent between 2000 and 2012. Outcome measures were overall and disease-free survival, pelvic control, distant metastasis and treatment related adverse events (AE).

Results
126 patients were analysed; 43 had been treated with CBT between 2000–2007, and 83 with IGBT between 2007–2012. External beam radiation (mean; 46.6 Gy) was combined with concurrent weekly cisplatin (51.6%), or hyperthermia (24.6%); radiation alone was used in 23.8%. Median follow-up was 121.8 months for CBT patients, vs. 42.3 months for IGBT. Complete remission was achieved in 83.7% of patients in the CBT group and in 98.8% of IGBT patients (p < 0.01). Overall survival at 3 years was 51% and 86%, respectively (p = 0.001). Pelvic recurrence was found in 32% vs. 7% (p < 0.001). Most patients had low grade adverse events. High grade (3–4) AE occurred in 15.4% vs. 8.4% at 3 years (p = 0.06).

Conclusion
Introduction of IGBT for cervical cancer has led to significantly increased 3-year locoregional control and survival rates, whilst reducing late morbidity.

8. Synergistic effect of photodynamic therapy and cisplatin: A novel approach for cervical cancer

Cervical cancer is a neoplasia primarily caused by Human papillomavirus (HPV) infection. Current treatment modalities involve cisplatin, a potent chemotherapeutic agent with severe adverse effects. Photodynamic therapy (PDT) is a promising modality for the treatment of cancer and infections, which has been associated with innovative therapeutic approaches, especially for the...
treatment of neoplasias. This study aimed to investigate the anticancer potential of PDT mediated by methylene blue (MB) or Photogem (PG) individually and combined with cisplatin in vitro. SiHa, C-33 A and HaCaT cells were incubated with MB, PG and/or cisplatin and received no further treatment or were irradiated with a 630 or a 660 nm LED light source at energy densities varying according to the photosensitizer (PS). The MTT assay was employed to assess cell viability. Both PS were effective in reducing cell viability with the cytotoxicity being dependent on the light dose. When compared to PDT groups, cisplatin was less effective. The cell viability of the combined therapy groups was significantly lower compared to monotherapies. The sequence of treatments (PDT + cisplatin/cisplatin + PDT) was important and had different results when varying the PS, but combination therapy resulted in an enhanced anticancer effect regardless of treatment protocol.
Background
The relationship between reproductive breast risk factors and breast cancer survival in patients with different breast cancer subtypes is not well known.

Methods
We examined a large-sized, retrospective study of 23,882 subjects from the Korean Breast Cancer Registry. The breast cancer subtype was determined by immunohistochemical staining for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). Information regarding reproductive factors, including breastfeeding, age at first birth (AFB), and parity, was gathered. Multivariate Cox regression analysis was used to estimate the association among breast cancer subtypes, such as luminal A, luminal B, Her-2/neu overexpressing, and triple negative breast cancer (TNBC), and breast cancer survival as dependent variables and adjusting for age and stage.

Results
High parity (≥ 5) increased the recurrence risk of luminal A and B breast cancer (hazard ratio [HR], 1.95; 95% confidence interval [CI], 0.96-3.97; P = .0055 and HR, 1.12; 95% CI, 0.42-3.02, respectively; P = .0073) in breast cancer–specific survival (BCSS), but 1 to 3 child births decreased the recurrence risk of luminal A breast
cancer (HR, 0.56; 95% CI, 0.34-0.91; P = .0055) and luminal B breast cancer (HR, 0.32; 95% CI, 0.17-0.61; P = .0073) in BCSS. Early AFB (< 20 years) increased the recurrence risk of luminal A breast cancers (HR, 1.61; 95% CI, 0.62-4.26; P = .039) in BCSS and of TNBC (HR, 1.31; 95% CI, 0.78-2.21; P = .0006) in overall survival. Her-2/neu overexpressing breast cancer had no correlation with parity and AFB in breast cancer survival.

Conclusions
High parity (≥ 5) and early AFB (< 20 years) were correlated with worse clinical outcomes in patients with luminal breast cancer, but not with other subtyped breast cancers.
There is ample evidence that the Mediterranean diet reduces breast cancer risk, despite the fact that findings across studies and populations have not been consistent. The protective effect of the Mediterranean diet is in line with the fact that some of its key components, such as fruit, vegetables, folate, and olive oil, have also been shown to have beneficial effects with regards to breast carcinogenesis.

The mechanisms through which these components are hypothesized to exert their protective effects include epigenetics and more specifically DNA methylation, antioxidant functions, biological response modification, antiestrogenic, antiproliferative, and antiangiogenic activities.

Further research to investigate the effects of intensity and timing of exposure and to elucidate the mechanistic pathways involved in the relationship is essential. The answers to these questions will provide biomarkers for prevention and early detection as well as targets for therapy, establishing the causality of the association and supporting adherence to the Mediterranean diet as a prevention strategy for breast cancer.
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