The effects of regular exercise and yoga on health-related quality of life among ovarian cancer survivors

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Objective: Exercise has long been known to have a positive effect on health-related quality of life (HRQOL) in patients with cancer and there is currently a growing interest in understanding if yoga can enhance HRQOL. Several studies have shown that biweekly yoga practice can significantly reduce anxiety and fatigue in breast cancer patients while enhancing physical functioning. Our study sought to evaluate the effects of participating in regular exercise and/or yoga on HRQOL after diagnosis among 219 ovarian cancer survivors.

Methods: HRQOL was assessed using the SF-36, which is a well-validated tool for measuring mental and physical well-being. Women were categorized into three groups based on their self-reported participation in regular exercise and/or yoga: no exercise or yoga (n = 93, 42.5%), regular exercise only (n = 98, 44.7%), and both regular exercise and yoga (n = 28, 12.8%). Using the non-exercisers as the reference group, multivariate logistic regression was used to assess the association between each exercise category on the eight SF-36 scales (physical functioning, limitations associated with physical health, limitations associated with emotional problems, vitality, emotional well-being, social functioning, pain, and general health), adjusting for factors that are known to be associated with HRQOL (i.e.: stage at diagnosis, years since diagnosis, age, and education).

Results: When comparing across the three categories of exercise (i.e.: no exercise as the reference vs. regular exercise only vs. both regular exercise and yoga), women who reported participating in both regular exercise and yoga tended to have higher scores than women who reported only participating in regular exercise on measures of physical functioning (β = 19.32, p < 0.001; β = 10.8, p < 0.001, respectively). They also reported fewer limitations associated with physical health (β = 28.4, p = 0.003; β = 12.61, p = 0.05, respectively), fewer limitations associated with emotional health (β = 21.4, p = 0.006; β = 14.2, p = 0.006, respectively), and less pain (β = 12.1, p = 0.02; β = 8.9, p = 0.008, respectively). The two exercise groups had similar scores for vitality (β = 11.8, p = 0.02; β = 11.5, p = 0.001; respectively) and social functioning (β = 11.0, p = 0.02; β = 12.2, p = 0.001, respectively).

Conclusion: Our results highlight the utility of exercise as a potential predictor of HRQOL in ovarian cancer survivors and suggest that adding yoga to an exercise program has a positive effect on quality of life beyond what can be obtained from regular exercise alone.


Enhancing anti-angiogenic therapy by blocking focal adhesion kinase

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Objective: Focal adhesion kinase (FAK) represents a central point of convergence for many signaling pathways implicated in cancer progression and metastasis. Pazopanib is a pan-VEGFR and PDGFR inhibitor. In the present study, we examined whether pazopanib treatment would result in greater anti-tumor activity in combination with the novel FAK-inhibitor, GSK2256098.

Methods: The in vitro effects of GSK2256098 on invasion and migration were examined using the HeyA8 and SKOV3-IP1 human ovarian cancer cell lines. In vivo effects of pazopanib with and without GSK2256098 were then assessed using an orthotopic mouse model of human ovarian cancer.

Results: GSK2256098 resulted in reduced levels of FAK phosphorylation at Y397 (pFAKY397) at 1 μM concentration in SKOV3-IP1 cells. GSK2256098 resulted in reduced invasion (p < 0.001) and decreased migration (p < 0.001) in SKOV3-IP1 cells. Dose-finding studies performed in vivo demonstrated that a 75 mg/kg dose resulted in a significant reduction in pFAKY397. Monotherapy with GSK2256098 resulted in a 58% decrease in mean tumor weight compared to control (p = 0.038). The combination of GSK2256098 with pazopanib resulted in a 71% decrease in mean tumor weight compared to pazopanib monotherapy (p = 0.04).

Conclusion: In summary, FAK inhibition results in substantial anti-angiogenic and anti-tumor effects in combination with pazopanib and represents a viable strategy for further development.


Depth of myometrial invasion to predict lymph node metastases in women with endometrial cancer

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Objective: Endometrial adenocarcinoma affects approximately 43,000 women annually in the United States. Hysterectomy and surgical staging have superior cure rates compared to high-dose progestin therapy and radiation. Analysis of retroperitoneal lymph nodes for the presence of metastatic tumor remains controversial as to whether it should be included in the surgical management of all women with endometrial cancer. Some advocate lymph node assessment in all cases, some in only selected high-risk patients, and some advocate node sampling only when there is deep myometrial invasion at the time of hysterectomy. The objective of this study was to determine the accuracy of the surgeon to assess the depth of myometrial invasion as a predictor of lymphatic metastases.

Methods: From 1993 to December 31, 2010, 2200 women have undergone hysterectomy for endometrial cancer at one of three tertiary medical centers and eight community hospitals within our geographic and study area. Of these, 353 had their surgery performed by one of three gynecologic oncologists who analyzed the hyster-
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Objective: Glucose-regulated protein (GRP) 78, a critical component of the unfolded protein response (UPR), is activated in conditions of endoplasmic reticulum (ER) stress, such as obesity. Evolving evidence also highlights the importance of ER stress in cancer progression. Given the association of endometrial carcinoma with obesity, we hypothesize that higher levels of GRP78 in visceral adipocytes in patients with endometrial carcinoma are associated with increased risk of recurrence.

Methods: A retrospective cohort study was conducted among endometrial cancer patients using paraffin-embedded specimens of endometrial tumor, normal endometrium (as a paired control), and visceral adipose tissue (e.g., omental- or peri-nodal adipocytes) for each patient from 1999 to 2010. Semi-quantitative GRP78 expression in all samples was determined by immunohistochemical analysis of the distribution of expression as a percentage as well as intensity of staining. Correlations with clinico-pathological information and clinical outcomes were analyzed by uni- and multivariate analyses.

Results: Among the 266 patients in the study, the median age was 53 years old (range 24–80), and the median presenting body mass index was 34.6 kg/m² (range 15.6–74.1). Endometrioid histology was seen in 83.1% of patients, and 60.9% had FIGO Stage I disease. GRP78 expression was evaluated in 244 primary endometrial tumors, 129 normal endometrium samples, and 198 visceral adipose tissues. GRP78 overexpression was seen in 66.0% and 86.8% of endometrial tumors and normal endometrium, respectively. When comparing GRP78 expression in the primary tumor paired with a section of normal endometrium in the same patient, the majority of tumor-normal endometrium pairs (68.1%) showed the same degree of GRP78 expression, while 24.1% of paired samples showed decreased expression in the tumor compared to the normal endometrium, and 7.8% of paired samples showed increased expression in the tumor compared to the normal endometrium. Increased tumoral GRP78 expression relative to the paired normal endometrium was associated with decreased progression-free survival (PFS) when compared to cases with the same or decreased expression (log-rank, \( p = 0.02 \)). GRP78 expression in visceral adipocytes was detected in 28.6% (range, 0–92.6%) of adipocytes. The percentage of visceral adipocyte GRP78 expression was positively correlated to the intensity of visceral adipocyte GRP78 expression (Spearman’s \( r = 0.37, p < 0.001 \)), FIGO stage (\( r = 0.19, p = 0.006 \)), and tumor grade (\( r = 0.21, p = 0.003 \)). The percent expression of GRP78 in visceral adipocytes was significantly associated with PFS and overall survival (OS) in multivariate analyses after adjusting for FIGO stage and grade (both, \( p < 0.001 \)). An optimal cut-off value for the extent of GRP78 expression in visceral adipocytes was determined to be 60.4%. Therefore, high adipocyte GRP78 expression (\( \geq 60.4\% \)) was associated with decreased PFS compared to low expression (<60.4%), hazard ratio 5.49, 95%CI 2.38–12.6, adjusted \( p \)-value = 0.008.

Conclusion: GRP78 expression in visceral adipocytes is associated with other indicators of poor prognosis in endometrial cancer patients including tumor grade, tumor stage, time to recurrence, and early death. The results suggest a novel link between obesity and endometrial cancer via ER stress and the UPR.


Visceral adipocyte glucose-regulated protein (GRP) 78 is an independent risk factor for endometrial cancer survival

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Objective: Glucose-regulated protein (GRP) 78, a critical component of the unfolded protein response (UPR), is activated in conditions of endoplasmic reticulum (ER) stress, such as obesity. Evolving evidence also highlights the importance of ER stress in cancer progression. Given the association of endometrial carcinoma with obesity, we hypothesize that higher levels of GRP78 in visceral adipocytes in patients with endometrial carcinoma are associated with increased risk of recurrence.

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Conclusion: GRP78 expression in visceral adipocytes is associated with other indicators of poor prognosis in endometrial cancer patients including tumor grade, tumor stage, time to recurrence, and early death. The results suggest a novel link between obesity and endometrial cancer via ER stress and the UPR.


Novel expression profile of the Wnt inhibitor Secreted Frizzled-Related Protein 1 (SFRP1) in endometrial carcinoma—A potential role as marker of progression

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Objective: To determine differential expression patterns and the functional significance of Wnt inhibitors in endometrial cancer, in an effort to identify potential biomarkers and therapeutic targets.

Methods: Wnt-pathway-specific cDNA expression profiling was used to compare normal endometrial tissue to a matched endometrial cancer tissue. Real-time RT-PCR confirmed differential gene expression of SFRP1 in six matched normal–endometrial cancer tissue pairs. Additionally, eleven Stage I tissues and seven Stage III/IV tissues (all endometrioid) were compared, as were six Type II endometrial cancer tissues. The endometrial cancer cell line ECC1 and the normal endometrial cell line HESC were similarly compared via real-time RT-PCR. A dual-luciferase assay using the β-catenin-responsive luciferase vector Super8XTOPFlash, measured the induction of canonical Wnt signaling in ECC-1 cells treated with exogenous SFRP1.

Results: In Wnt-pathway specific cDNA profiling, the Wnt inhibitor SFRP1 was significantly downregulated in our endometrial cancer sample as compared to its matched normal sample. SFRP1 expression was also decreased in five of six endometrial cancer-matched normal tissue pairs (\( p = 0.0007 \)). Additionally, SFRP1 expression was reduced in late stage disease compared to early stage (\( p = 0.01 \)). Comparison of 18 Type I and six Type II EC tissues, with six normal endometrial tissues, showed significantly reduced SFRP1 mRNA expression in EC tissues (\( p < 0.0001 \)). In vitro, SFRP1 gene expression was decreased in ECC-1 cells when compared to HESC (\( p < 0.0001 \)). In dual-luciferase assays, exogenous SFRP1 inhibited the β-catenin/TCF signaling path-