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INTERNATIONAL GYNECOLOGIC CANCER SOCIETY

IN THE KNOW

Gyn Onc Literature of Significance

Prepared by Ed Pavlik, PhD

Ed's List June 2020

In the Know (Ed's List) is prepared by Edward Pavlik, PhD, Professor and Director of Ovarian Screening Research Program, University of Kentucky on a monthly basis. Ed's lists provide a compilation of abstracts related to the field of gynecologic oncology from multiple scholarly journals.

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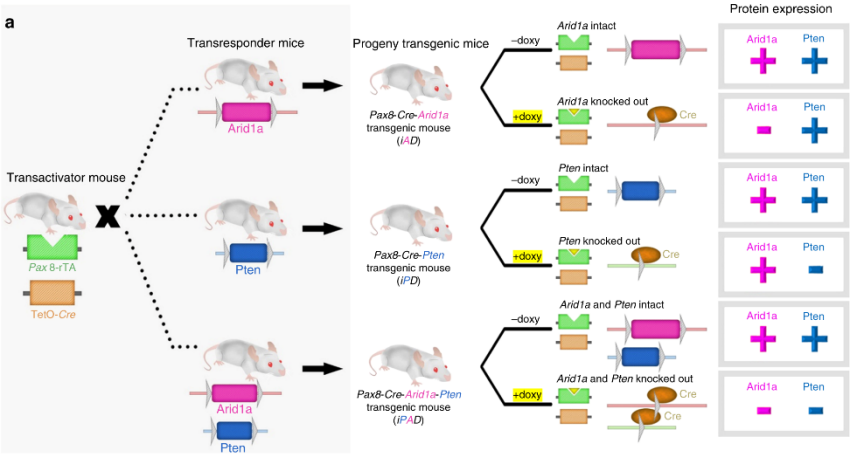
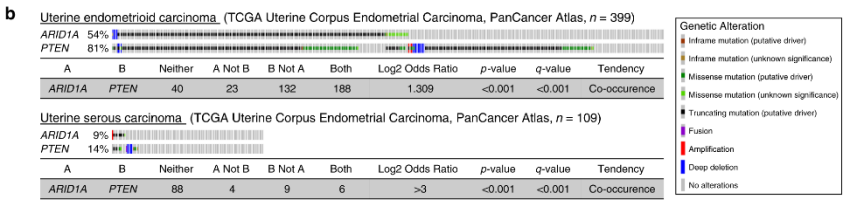
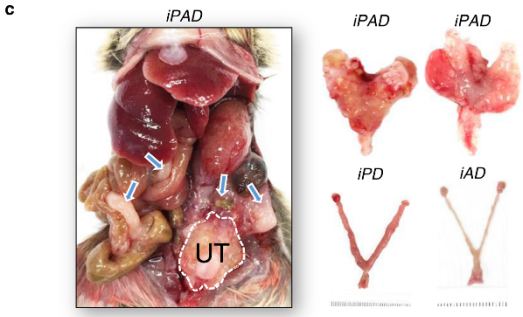
Inactivation of Arid1a in the endometrium is associated with endometrioid tumorigenesis through transcriptional reprogramming.

YS Rahmanto, W Shen, X Shi, X Chen, Y Yu, Z-C Yu, T Miyamoto, M-H Lee, V Singh, R Asaka, G Shimberg, MI Vitolo, SS Martin, D Wirtz, R Drapkin, J Xuan, T-i Wang, & I-M Shih. Nat Commun 11, 2717 (2020). https://doi.org/10.1038/s41467-020-16416-0 https://www.nature.com/articles/s41467-020-16416-0#citeas







Somatic inactivating mutations of *ARID1A*, a SWI/SNF chromatin remodeling gene, are prevalent in human endometrium-related malignancies. To elucidate the mechanisms underlying how *ARID1A* deleterious mutation contributes to tumorigenesis, we establish genetically engineered murine models with *Arid1a* and/or *Pten* conditional deletion in the endometrium. Transcriptomic analyses on endometrial cancers and precursors derived from these mouse models show a close resemblance to human uterine endometrioid carcinomas. We identify transcriptional networks that are controlled by Arid1a and have an impact on endometrial tumor development. To verify findings from the murine models, we analyze $ARID1A^{WT}$ and $ARID1A^{KO}$ human endometrial epithelial cells. Using a system biology approach and functional studies, we demonstrate that *ARID1A*-deficiency lead to loss of TGF-β tumor suppressive function and that inactivation of ARID1A/TGF-β axis promotes migration and invasion of *PTEN*-deleted endometrial tumor cells. These findings provide molecular insights into how *ARID1A* inactivation accelerates endometrial tumor progression and dissemination, the major causes of cancer mortality.

Financial conflicts of interest among National Comprehensive Cancer Network clinical practice guideline panelists in 2019. AP Desai, Madhuri Chengappa, Ronald S. Go, Thejaswi K Poonacha. Cancer
https://doi.org/10.1002/cncr.32997
https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/cncr.32997?campaign=wolearlyview

Background Clinical practice guidelines (CPGs) are evidence-based guidelines that serve as a standard of care in oncology practice, reimbursements, and quality improvement initiatives. To our knowledge, the extent of financial conflicts of interest (FCOIs) in National Comprehensive Cancer Network (NCCN) guidelines have not been systemically evaluated. The current study evaluated the extent of FCOIs in the NCCN CPGs for the most common malignancies in the United States.

Methods The authors examined the latest 2019 versions of the NCCN CPGs for the 10 most common cancers by incidence in the United States. Using disclosure lists, they catalogued the FCOIs for the panelists under various categories outlined in the CPG. The authors also tabulated the companies and institutions involved in each panel disclosure. An "episode" describes 1 instance of participation of a panelist in 1 company in 1 category of each guideline. "Affiliation" describes an industrial, commercial, or institutional affiliation reported by a panelist in each episode.

Results Of the 491 panelists on the CPG panel, 483 (98.3%) completed FCOI disclosures. A total of 224 (46.4%) reported at least 1 FCOI episode. A total of 1103 episodes were disclosed with an average of 4.9 episodes reported per panelist with FCOIs. Acting as part of scientific advisory boards, as a consultant, or as an expert witness was the most common FCOI category (19.9%). A total of 191 companies were associated with 1103 episodes of FCOI. The top companies were Bristol-Myers Squibb, Merck, Genentech, and AstraZeneca. Among cancers, the prevalence of FCOIs was highest for lung cancer (56%), bladder cancer (52%), pancreatic cancer (52%), non-Hodgkin lymphoma (50%), kidney cancer (49%), colorectal cancer (43%), breast cancer (42%), melanoma (40%), prostate cancer (38%), and uterine cancer (32%). Among the panelists with FCOIs, 26%, 17%, and 57%, respectively, reported 1, 2, and >3 episodes. There were 127 episodes noted among the CPG chairs and/or vice chairs who reported FCOIs (mean, 6.4 episodes). The chairs and/or vice chairs of CPGs for uterine cancer, pancreatic cancer, melanoma, and prostate cancer were not found to have any FCOIs.

Conclusions FCOIs are very prevalent among NCCN CPG panelists. In nearly one-half of the CPGs, the majority of the panelists had at least 1 FCOI. Greater than one-half of the CPG chairs and/or vice chairs reported multiple FCOIs. Further research studies are necessary to determine the impact of these FCOIs.

In vivo modeling of metastatic human high-grade serous ovarian cancer in mice. O Kim, EY Park, DL Klinkebiel, SD Pack, Y-H Shin, Z Abdullaev, RE Emerson, DM Coffey, SY Kwon, CJ Creighton, S Kwon, EC Chang, T Chiang, AN Yatsenko, J Chien, D-J Cheon, YYang-Hartwich, H Nakshatri, KP Nephew, RR Behringer, Facundo M. Fernández, C-Heum Cho, B Vanderhyden, R Drapkin, RC Bast Jr, KD. Miller,
AR Karpf, J Kim. PLOS Genetics https://doi.org/10.1371/journal.pgen.1008808
https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1008808

Abstract Metastasis is responsible for 90% of human cancer mortality, yet it remains a challenge to model human cancer metastasis *in vivo*. Here we describe mouse models of high-grade serous ovarian cancer, also known as high-grade serous carcinoma (HGSC), the most common and deadliest human ovarian cancer type. Mice genetically engineered to harbor *Dicer1* and *Pten* inactivation and mutant p53 robustly replicate the peritoneal metastases of human HGSC with complete penetrance. Arising from the fallopian tube, tumors spread to the ovary and metastasize throughout the pelvic and peritoneal cavities, invariably inducing hemorrhagic ascites. Widespread and abundant peritoneal metastases ultimately cause mouse deaths (100%). Besides the phenotypic and histopathological similarities, mouse HGSCs also display marked chromosomal instability, impaired DNA repair, and chemosensitivity. Faithfully recapitulating the clinical metastases as well as molecular and genomic features of human HGSC, this murine model will be valuable for elucidating the mechanisms underlying the development and progression of metastatic ovarian cancer and also for evaluating potential therapies.

Author summary Rarely does an experimental model fully replicate the clinical metastases of a human malignancy. Faithfully representing the clinical metastases of human high-grade serous ovarian cancer with complete penetrance, coupled with histopathological, molecular, and genomic similarities, these mouse models, particularly one harboring mutant p53, will be vital to elucidating the underlying pathogenesis of human ovarian cancer. In-depth understanding of the development and progression of ovarian cancer is crucial to medical advances in the early detection, effective treatment, and prevention of ovarian cancer. Also, these robust mouse models, as well as

cell lines established from the mouse primary and metastatic tumors, will serve as useful preclinical tools to evaluate therapeutic target genes and new therapies in ovarian cancer.

Limitations in Clinical Trials Leading to Anticancer Drug Approvals by the US Food and Drug Administration. T Hilal, M Gonzalez-Velez, V Prasad. JAMA Intern Med. 2020. doi:10.1001/jamainternmed.2020.2250
https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2767107

Key Points
Question How often are anticancer drugs approved by the US Food and Drug Administration (FDA) based on clinical trials with the following limitations: nonrandomized design, lack of demonstrated survival advantage, inappropriate use of crossover, or the use of suboptimal control arms?

Findings In this observational study, 187 trials leading to anticancer drug approvals between June 30, 2014, and July 31, 2019, were reviewed. A total of 125 (67%) trials leading to anticancer drug indications had limitations in at least 1 of the 4 domains of interest.

Meaning Despite the increase in the number of drug approvals by the FDA, a substantial number of drugs are authorized based on data that do not demonstrate efficacy over established standards of care.

Abstract
Importance While there have been multiple assessments of clinical trials leading to anticancer drug approvals by the US Food and Drug Administration (FDA), the cumulative percentage of approvals based on trials with a limitation remains uncertain.

Objective To assess the percentage of clinical trials with limitations in 4 domains—lack of randomization, lack of significant overall survival advantage, inappropriate use of crossover, and use of suboptimal control arms—that led to FDA approvals from June 30, 2014, to July 31, 2019.

Design, Setting, and Participants This observational analysis included all anticancer drug indications approved by the FDA from June 30, 2014, through July 31, 2019. All indications were investigated, and each clinical trial was evaluated for design, enrollment period, primary end points, and presence of a limitation in the domains of interest. The standard-of-care therapy was determined by evaluating the literature and published guidelines 1 year prior to the start of clinical trial enrollment. Crossover was examined and evaluated for optimal use. The percentage of approvals based on clinical trials with any or all limitations of interest was then calculated.

Main Outcomes and Measures Estimated percentage of clinical trials with limitations of interest that led to an anticancer drug marketing authorization by the FDA.

Results A total of 187 trials leading to 176 approvals for 75 distinct novel anticancer drugs by the FDA were evaluated. Sixty-four (34%) were single-arm clinical trials, and 123 (63%) were randomized clinical trials. A total of 125 (67%) had at least 1 limitation in the domains of interest; 60 of the 125 trials (48%) were randomized clinical trials. Of all 123 randomized clinical trials, 37 (30%) lacked overall survival benefit, 31 (25%) had a suboptimal control, and 17 (14%) used crossover inappropriately.

Conclusions and Relevance Two-thirds of cancer drugs are approved based on clinical trials with limitations in at least 1 of 4 essential domains. Efforts to minimize these limitations at the time of clinical trial design are essential to ensure that new anticancer drugs truly improve patient outcomes over current standards.

Development and validation of the gene-expression Predictor of high-grade-serous Ovarian carcinoma molecular subTYPE (PrOTYPE). Ovarian Tumor Tissue Analysis Consortium. Clinical Cancer Research DOI: 10.1158/1078-0432.CCR-20-0103 https://clincancerres.aacrjournals.org/content/early/2020/06/17/1078-0432.CCR-20-0103
Purpose: Gene-expression-based molecular subtypes of high-grade serous tubo-ovarian cancer (HGSOC), demonstrated across multiple studies, may provide improved stratification for molecularly targeted trials. However, evaluation of clinical utility has been hindered by non-standardized methods which are not applicable in a clinical setting. We sought to generate a clinical-grade minimal gene-set assay for classification of individual tumor specimens into HGSOC subtypes and confirm previously reported subtype-associated features.

Experimental Design: Adopting two independent approaches, we derived and internally validated algorithms for subtype prediction using published gene-expression data from 1650 tumors. We applied resulting models to NanoString data on 3829 HGSOCs from the Ovarian Tumor Tissue Analysis Consortium. We further developed, confirmed, and validated a reduced, minimal gene-set predictor, with methods suitable for a single patient setting.

Results: Gene-expression data was used to derive the Predictor of high-grade-serous Ovarian carcinoma molecular subTYPE (PrOTYPE) assay. We established a de facto standard as a consensus of two parallel approaches. PrOTYPE subtypes are significantly associated with age, stage, residual disease, tumor infiltrating lymphocytes, and outcome. The locked-down clinical-grade PrOTYPE test includes a model with 55 genes that predicted gene-expression subtype with >95% accuracy that was maintained in all analytical and biological validations.

Conclusions: We validated the PrOTYPE assay following the Institute of Medicine guidelines for the development of omics-based tests. This fully defined and locked-down clinical-grade assay will enable trial design with molecular subtype stratification and allow for objective assessment of the predictive value of HGSOC molecular subtypes in precision medicine applications.

A healthy lifestyle and survival among women with ovarian cancer Jessy M. Hansen, Christina M. Nagle, Torukiri I. Ibiebele, Peter T. Grant, Andreas Obermair, Michael L. Friedlander, Anna DeFazio, Penelope M. Webb, Ovarian Cancer Prognosis and Lifestyle Study Group. International Journal of Cancer https://doi.org/10.1002/ijc.33155 https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.33155?af=R

Ovarian cancer has a poor survival rate and, understandably, women often want to know whether there is anything they can do to improve their prognosis. Our goal was to investigate the association between a healthy lifestyle prediagnosis and postdiagnosis and survival in a cohort of Australian women with invasive epithelial ovarian cancer. We calculated a healthy lifestyle index (HLI) based on women's self-reported smoking status, height, weight, physical activity, diet and alcohol consumption before diagnosis (n = 678) and after completing primary treatment (n = 512). Clinical data and vital status for each woman were ascertained through medical records. Cox proportional hazards regression was conducted to calculate hazard ratios (HR) and 95% confidence interval (CI) for all-cause mortality. There was a suggestive association between a more healthy lifestyle before diagnosis and better survival (HR 0.79, 95% CI: 0.59-1.04), however, the association was stronger for lifestyle after diagnosis, with women in the highest tertile having significantly better survival than women in the lowest tertile (HR 0.61, 95% CI: 0.40-0.93; *P*-trend = .02). Current smoking, particularly postdiagnosis, was associated with higher mortality (HR 1.68, 95% CI: 1.17-2.42; HR 2.82, 95% CI: 1.29-6.14, for prediagnosis and postdiagnosis smoking, respectively), but women who quit after diagnosis had survival outcomes similar to nonsmokers (HR 0.99, 95% CI: 0.57-1.72). Higher physical activity after diagnosis was associated with better survival (HR 0.60, 95% CI: 0.39-0.92; *P*-trend = .02). A healthy lifestyle after diagnosis, in particular not smoking and being physically active, may help women with ovarian cancer improve their prognosis.

Subsequent Development of Epithelial Ovarian Cancer After Ovarian Surgery for Benign Ovarian Tumor: A Population-Based Cohort Study. C-Y Huang, W-H Chang, H-Y Huang, CY Guo, Y-J Chou, N Huang, W-L Lee, P-H Wang. Clinical Epidemiology 2020; 2020:12:637—649 DOI https://doi.org/10.2147/CLEP.S199349 https://www.dovepress.com/subsequent-development-of-epithelial-ovarian-cancer-after-ovarian-surg-peer-reviewed-fulltext-article-CLEP

Purpose: The goal of the current study is to determine the risk of subsequent development of epithelial ovarian cancer (EOC) in women after ovarian surgery for benign ovarian tumors.
Patients and Methods: We conducted the nationwide population-based historic cohort study using the National Health Insurance Research Database (NHIRD) of Taiwan. Eleven thousand six hundred twenty women who underwent ovarian surgery for ovarian benign diseases were analyzed. The collected data included age, types of ovarian surgery, medical history by Charlson comorbidity index (CCI), infertility (yes/no), pelvic inflammatory disease (PID) (yes/no), tubal ligation (yes/no), total/subtotal hysterectomy (TH/STH) (yes/no), and endometrioma (yes/no). We used the Kaplan–Meier method and the Log-rank test to evaluate the risk factors. Cox proportional hazard methods were used to evaluate risk factors for the subsequent development of EOC. Multivariate analysis using Cox stepwise forward regression was conducted for the covariate selected in univariate analysis. Hazard ratio (HR) and 95% confidence interval (CI) were calculated using the Wald test.

Results: Subsequent EOC incidence rate (IR, incidence per 10,000 person-years) of women after ovarian surgery for benign ovarian tumors was 2.98. Separating into four groups based on different age, IR of EOC was 1.57 (< 30 years), 4.71 (30– 39 years), 3.59 (40– 49 years) and 0.94 (≥ 50 years), respectively. Univariate and multivariate analyses

identified only high level of CCI (≥ 2 or more) as an independent risk factor for subsequent development of EOC in women after ovarian surgery for benign ovarian tumors (HR 59.17, 95% CI 7.50– 466.80 in women with CCI level of 2 and HR 190.68, 95% CI 24.33– 2494.19, in women with CCI level ≥ 3, respectively).

Conclusion: Our results, if confirmed, suggest that women with other comorbidities (CCI) should be well informed that they may have a higher risk of subsequent development of EOC when ovarian surgery is planned even though the final pathology showed a benign ovarian tumor.

Molecular and functional e xtracellular vesicle analysis using nanopatterned microchips monitors tumor progression and metastasis. P Zhang, eX Wu, G Gardashova, Y Yang, Y Zhang, L Xu, Y Zeng. Science Translational Medicine 2020:12, (547), eaaz2878 DOI: 10.1126/scitranslmed.aaz2878
https://stm.sciencemag.org/content/12/547/eaaz2878

Probing plasma with patterned chips Liquid biopsy of blood or other biofluids has shown promise for cancer detection and monitoring response to treatment. Zhang *et al.* used colloidal inkjet printing to create nanopatterned polydimethylsiloxane/glass microfluidic chips to analyze extracellular vesicles (EVs) in plasma. The chips captured EVs expressing different surface markers of interest and measured the expression and activity of EV-bound MMP14. EVs derived from cancer cell lines in vitro and breast cancer tumors in mouse models and patients analyzed using chips revealed differential expression and activity of EV-bound MMP14 with metastasis or cancer stage. These chips provide a useful platform for characterizing EVs with implications for noninvasive cancer diagnosis and surveillance.

Abstract Longitudinal cancer monitoring is crucial to clinical implementation of precision medicine. There is growing evidence indicating important functions of extracellular vesicles (EVs) in tumor progression and metastasis, including matrix remodeling via transporting matrix metalloproteases (MMPs). However, the clinical relevance of EVs remains largely undetermined, partially owing to challenges in EV analysis. Distinct from existing technologies mostly focused on characterizing molecular constituents of EVs, here we report a nanoengineered lab-on-a-chip system that enables integrative functional and molecular phenotyping of tumor-associated EVs. A generalized, high-resolution colloidal inkjet printing method was developed to allow robust and scalable manufacturing of three-dimensional (3D) nanopatterned devices. With this nanochip platform, we demonstrated integrative analysis of the expression and proteolytic activity of MMP14 on EVs to detect in vitro cell invasiveness and monitor in vivo tumor metastasis, using cancer cell lines and mouse models. Analysis of clinical plasma specimen showed that our technology could be used for cancer detection including accurate classification of age-matched controls and patients with ductal carcinoma in situ, invasive ductal carcinoma, or locally metastatic breast cancer in a training cohort (n = 30, 96.7% accuracy) and an independent validation cohort (n = 70, 92.9% accuracy). With clinical validation, our technology could provide a useful liquid biopsy tool to improve cancer diagnostics and real-time surveillance of tumor evolution in patients to inform personalized therapy.

Identification of novel epithelial ovarian cancer loci in women of African ancestry A Manichaikul, LC Peres, X-Q Wang, ME Barnard, D Chyn, X Sheng, Z Du, J Tyrer, J Dennis, AG Schwartz, ML Cote, E Peters, PG Moorman, M Bondy, JS Barnholtz-Sloan, P Terry, AJ Alberg EV Bandera, Funkhouser, AH Wu, CL Pearce, M Pike, VW Setiawan, CA. Haiman the African American Breast Cancer Consortium (AABC), the African Ancestry Prostate Cancer Consortium (AAPC), JR Palmer, L LeMarchand, LR Wilkens, A Berchuck,, JA Doherty F Modugno, R Ness, K Moysich, BY Karlan, AS Whittemore, V McGuire, W Sieh, K Lawrenson, S Gayther, TA Sellers, P Pharoah, JM Schildkraut, on behalf of the African American Cancer Epidemiology Study (AACES) and the Ovarian Cancer Association Consortium (OCAC. International J Cancer 146, (11) 2020, 2987-2998 https://doi.org/10.1002/ijc.3265
https://onlinelibrary.wiley.com/doi/10.1002/ijc.32653

Women of African ancestry have lower incidence of epithelial ovarian cancer (EOC) yet worse survival compared to women of European ancestry. We conducted a genome-wide association study in African ancestry women with 755 EOC cases, including 537 high-grade serous ovarian carcinomas (HGSOC) and 1,235 controls. We identified four novel loci with suggestive evidence of association with EOC ($p < 1 \times 10^{-6}$), including rs4525119 (intronic to AKR1C3), rs7643459 (intronic to LOC101927394), rs4286604 (12 kb 3′ of UGT2A2) and rs142091544 (5 kb 5′ of WWC1). For HGSOC, we identified six loci with suggestive evidence of association including rs37792 (132 kb 5′ of follistatin [FST]), rs57403204 (81 kb 3′ of MAGEC1), rs79079890 (LOC105376360 intronic), rs66459581 (5 kb 5′ of PRPSAP1), rs116046250 (GABRG3 intronic) and rs192876988 (32 kb 3′ of GK2). Among the identified variants, two are near genes known to regulate hormones and diseases of the ovary (AKR1C3 and FST), and two are linked to cancer (AKR1C3 and MAGEC1). In follow-up studies of the 10 identified variants, the GK2 region SNP, rs192876988, showed an inverse association with EOC in European ancestry women ($p = 0.002$), increased risk of ER positive breast cancer

in African ancestry women (p = 0.027) and decreased expression of GK2 in HGSOC tissue from African ancestry women (p = 0.004). A European ancestry-derived polygenic risk score showed positive associations with EOC and HGSOC in women of African ancestry suggesting shared genetic architecture. Our investigation presents evidence of variants for EOC shared among European and African ancestry women and identifies novel EOC risk loci in women of African ancestry.

Brain Metastases From Gynecologic Malign ancies. D Nasioudis, A Persaud, N Taunk, NA Latif. American Journal of Clinical Oncology: 2020, 43 (6) 418-421 doi: 10.1097/COC.0000000000000689
https://journals.lww.com/amjclinicaloncology/Fulltext/2020/06000/Brain_Metastases_From_Gynecologic_Malignancies_.6.aspx

Objective: The objective of this study was to investigate the prevalence, clinicopathologic characteristics, management, and outcomes of patients with brain metastasis (BM) from gynecologic malignancies in a large hospital-based database.

Materials and Methods: The National Cancer Database (NCDB) was accessed and patients with ovarian, uterine, or cervical cancer and BM were identified. We identified those who received radiation therapy (RT) as whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS). Kaplan-Meier curves were generated to determine median overall survival (OS) and compared with the log-rank test.

Results: A total of 853 patients with BM were identified. The rate of BMs upon diagnosis was 0.4% (211/57,160) for patients with cervical cancer, 0.2% (498/243,785) for patients with uterine, and 0.2% (144/92,301) for ovarian malignancies. Only 30.4% had isolated BM, while 52.2% had lung metastasis. Approximately half of the patients (50.1%) received chemotherapy, while brain RT was administered to 324 (38%) patients. Among patients who received brain RT, only 60 (18.5%) had SRS, while 264 (81.5%) had WBRT. Patients who underwent SRS had a better survival (n=47, median OS=9 mo) than those who received WBRT (n=201, median OS=4.73 mo, P=0.018), or those who did not receive any brain RT (n=370, median OS=4.01 mo, P=0.007).

Conclusions:

The incidence of BM among patients with gynecologic malignancies is rare and associated with poor survival. For select patients, SRS may be associated with prolonged survival.

Association Between Breastfeeding and Ovarian Cancer Risk

A Babic, N Sasamoto, BA Rosner, SS Tworoger, SJ Jordan, HA Risch, HR Harris, MA Rossing, JA Doherty, RT Fortner, J Chang-Claude, MT Goodman, PJ Thompson, KB Moysich, RB Ness, SK Kjaer, A Jensen, JM Schildkraut, LJ Titus, DW Cramer, EV Bandera, Bo Qin, W Sieh, V McGuire, R Sutphen, CL Pearce, AH Wu, M Pike, PM Webb, F Modugno, KL Terry. JAMA Oncol. 2020;6(6):e200421. doi:10.1001/jamaoncol.2020.0421

https://jamanetwork.com/journals/jamaoncology/article-abstract/2763398

Question Is breastfeeding associated with risk of ovarian cancer overall and by histotype?

Findings In this pooled analysis including 9973 women with ovarian cancer and 13 843 controls from 13 case-control studies, breastfeeding was associated with a 24% reduced risk of invasive epithelial ovarian cancer. Longer breastfeeding duration and shorter time since last breastfeeding episode were associated with a further decrease in risk.

Meaning This large study with extensive information on breastfeeding provides epidemiological evidence that breastfeeding, a potentially modifiable factor, may confer significant reduction in ovarian cancer risk, including high-grade serous, the deadliest subtype.
Abstract

Importance Breastfeeding has been associated with a reduced risk of epithelial ovarian cancer in multiple studies, but others showed no association. Whether risk reduction extends beyond that provided by pregnancy alone or differs by histotype is unclear. Furthermore, the observed associations between duration and timing of breastfeeding with ovarian cancer risk have been inconsistent.

Objective To determine the association between breastfeeding (ie, ever/never, duration, timing) and ovarian cancer risk overall and by histotype.

Design, Setting, and Participants A pooled analysis of parous women with ovarian cancer and controls from 13 case-control studies participating in the Ovarian Cancer Association Consortium was performed. Odds ratios (ORs) and 95% CIs of the overall association were calculated using multivariable logistic regression and polytomous logistic regression for histotype-specific associations. All data were collected from individual sites from November 1989 to December 2009, and analysis took place from September 2017 to July 2019.

Exposures Data on breastfeeding history, including duration per child breastfed, age at first and last breastfeeding, and years since last breastfeeding were collected by questionnaire or interview and was harmonized across studies.

Main Outcomes and Measures Diagnosis of epithelial ovarian cancer.

Results A total of 9973 women with ovarian cancer (mean [SD] age, 57.4 [11.1] years) and 13 843 controls (mean [SD] age, 56.4 [11.7] years) were included. Breastfeeding was associated with a 24% lower risk of invasive ovarian cancer (odds ratio [OR], 0.76; 95% CI, 0.71-0.80). Independent of parity, ever having breastfed was associated with reduction in risk of all invasive ovarian cancers, particularly high-grade serous and endometrioid cancers. For a single breastfeeding episode, mean breastfeeding duration of 1 to 3 months was associated with 18% lower risk (OR, 0.82; 95% CI, 0.76-0.88), and breastfeeding for 12 or more months was associated with a 34% lower risk (OR, 0.66; 95% CI, 0.58-0.75). More recent breastfeeding was associated with a reduction in risk (OR, 0.56; 95% CI, 0.47-0.66 for <10 years) that persisted for decades (OR, 0.83; 95% CI, 0.77-0.90 for ≥30 years; *P* for trend = .02).

Conclusions and Relevance Breastfeeding is associated with a significant decrease in risk of ovarian cancer overall and for the high-grade serous subtype, the most lethal type of ovarian cancer. The findings suggest that breastfeeding is a potentially modifiable factor that may lower risk of ovarian cancer independent of pregnancy alone.

Comment 1 Comment for this article

June 22, 2020

Backwards figures

Jenny Allen | As usual the results are backwards, citing a reduced risk due to breastfeeding. However, breastfeeding is the biological norm, and should be used as the baseline, not breastfeeding is the deviation from the biological norm, so these results should be written as the increased risk of cancer from not breastfeeding.

Ovarian Cancer After Prophylactic Salpingectomy in a Patient With Germline BRCA1 Mutation. L Santiago, E Smith, M Cox, C Wan, NE Tchabo, I Awowole, V Broach, DS Chi. Obstetrics & Gynecology: 2020 135 (6) 1270-1274 doi: 10.1097/AOG.0000000000003864
https://journals.lww.com/greenjournal/Fulltext/2020/06000/Ovarian_Cancer_After_Prophylactic_Salpingectomy_in.6.aspx

BACKGROUND: Women with germline *BRCA1* or *BRCA2* mutations have a lifetime risk of ovarian cancer of up to 46%. Opportunistic salpingectomy has been advocated as a risk-reducing strategy owing to increasing recognition of tubal origin, yet evidence of efficacy in this high-risk population is limited.

CASE: This is the case of a woman with a *BRCA1* mutation who underwent prophylactic mastectomy and bilateral salpingectomy with ovarian retention before the age of 40 years. She did not undergo oophorectomy and subsequently developed stage IV high-grade serous ovarian cancer 4 years after her initial surgery.

CONCLUSION: More research is needed to determine the role of prophylactic salpingectomy with delayed oophorectomy, optimal timing of completion oophorectomy, and the risks and benefits compared with up-front risk-reducing salpingo-oophorectomy.

Pelvic fractures and changes in bone mineral density after radiotherapy for cervical, endometrial, and vaginal cancer: A prospective study of 239 women. MP Salcedo, AK Sood, A Jhingran, PJ Eifel, AH Klopp, RB Iyer, BM Fellman, C Jimenez, KM Schmeler. Cancer, (2020) 126: 2607-2613. doi:10.1002/cncr.32807 https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.32807

Background Advances in radiotherapy (RT) have led to improved oncologic outcomes for women with gynecologic cancers; however, the long-term effects and survivorship implications need further evaluation. The purpose of this study was to determine the incidence of pelvic fractures and changes in bone mineral density (BMD) after pelvic RT.

Methods Two hundred thirty-nine women who had pelvic RT for cervical, endometrial, or vaginal cancer between 2008 and 2015 were prospectively studied. BMD scans and biomarkers of bone turnover were obtained at the baseline and 3 months, 1 year, and 2 years after RT. Imaging studies were assessed for pelvic fractures for up to 5 years. Patients with osteopenia, osteoporosis, or pelvic fractures at any point were referred to the endocrinology service for evaluation and treatment.

Results The median age at diagnosis was 51 years; 132 patients (56%) were menopausal. The primary diagnoses were cervical (63.6%), endometrial (30.5%), and vaginal cancer (5.9%). Sixteen patients (7.8%; 95% confidence interval, 4.5%-12.4%) had pelvic fractures with actuarial rates of 3.6%, 12.7%, and 15.7% at 1, 2, and 3 years, respectively. Fractures were associated with baseline osteoporosis ($P < .001$), higher baseline bone-specific alkaline phosphatase ($P < .001$), and older age ($P = .007$). The proportion of patients with osteopenia/osteoporosis increased from 50% at the baseline to 58%, 59%, and 70% at 3 months, 1 year, and 2 years, respectively.

Conclusions A high proportion of women had significant decreases in BMD after pelvic RT, with 7.8% diagnosed with a pelvic fracture. BMD screening and pharmacologic intervention should be strongly considered for these high-risk women.

Transformation of naked mole-rat cells. F. Hadi, Y Kulaberoglu, KA Lazarus, *et al. Nature* 583, E1–E7 (2020). https://doi-org.ezproxy.uky.edu/10.1038/s41586-020-2410-x

The naked mole rat (NMR), *Heterocephalus glaber*, is a mouse-sized subterranean rodent that is native to East Africa and is used in research for the potential development of therapeutics because of its unusual physiology1,2, long lifespan3 and cancer resistance2,4. In a previous study, Tian et al.5 reported that the cancer resistance of NMRs is mediated by high-molecular-mass hyaluronan produced by NMR cells and showed that wild-type NMR cells, but not cells in which hyaluronan expression is perturbed, are resistant to transformation by SV40 large T antigen (encoded by *SV40LT*) and oncogenic HRAS ($HRAS^{G12V}$)—a combination of oncogenes that is sufficient to transform mouse and rat fibroblasts6,7. Here we developed a number of lentiviral vectors to deliver both of these oncogenes and generated 106 different cell lines from 5 different tissues and 11 different NMRs and show that, in contrast to the previous study5, NMR cells are susceptible to oncogenic transformation by *SV40LT* and $HRAS^{G12V}$. Our data thus suggest that a non-cell autonomous mechanism underlies the remarkable cancer resistance of NMRs and that identifying this non-cell autonomous mechanism could have important implications for our understanding of cancer development in humans.

See also,

https://medicalxpress.com/news/2020-07-secrets-naked-mole-rat-cancer-resistance.html

Until now, it was thought that naked mole-rats almost never got cancer because their healthy cells were resistant to being converted into cancer cells. However, researchers at the University of Cambridge have shown for the first time that genes known to cause cancer in cells of other rodents can also lead naked mole-rat cells to become cancerous. This finding suggests that what sets naked mole-rats apart is the microenvironment—the complex system of cells and molecules surrounding a cell, including the immune system. The researchers believe interactions with this microenvironment are what stops the initial stages of cancer from developing into tumors, rather than a cancer resistance mechanism within healthy cells as previously thought.

Circulating Lysophosphatidylcholines, Phosphatidylcholines, Ceramides, and Sphingomyelins and Ovarian Cancer Risk: A 23-Year Prospective Study. OA Zeleznik, CB Clish, P Kraft, J Avila-Pacheco, AH Eliassen, SS Tworoger. *JNCI* 112, (6), 2020, 628–636, https://doi.org/10.1093/jnci/djz195

https://academic.oup.com/jnci/article-abstract/112/6/628/5583767?redirectedFrom=fulltext

Background Experimental evidence supports a role of lipid dysregulation in ovarian cancer progression. We estimated associations with ovarian cancer risk for circulating levels of four lipid groups, previously hypothesized to be associated with ovarian cancer, measured 3–23 years before diagnosis.

Methods Analyses were conducted among cases (N = 252) and matched controls (N = 252) from the Nurses' Health Studies. We used logistic regression adjusting for risk factors to investigate associations of lysophosphatidylcholines (LPCs), phosphatidylcholines (PCs), ceramides (CERs), and sphingomyelins (SMs) with ovarian cancer risk overall and by histotype. A modified Bonferroni approach (0.05/4 = 0.0125, four lipid groups) and the permutation-based Westfall and Young approach were used to account for testing multiple correlated hypotheses. Odds ratios (ORs; 10th–90th percentile), and 95% confidence intervals of ovarian cancer risk were estimated. All statistical tests were two-sided.

Results SM sum was statistically significantly associated with ovarian cancer risk (OR = 1.97, 95% CI = 1.16 to 3.32; *P* = .01/permutation-adjusted *P* = .20). C16:0 SM, C18:0 SM, and C16:0 CERs were suggestively associated with risk (OR = 1.95–2.10; *P* = .004–.01; permutation-adjusted *P* = .08–.21). SM sum, C16:0 SM, and C16:0 CER had stronger odds ratios among postmenopausal women (OR = 2.16–3.22). Odds ratios were similar for serous/poorly differentiated and endometrioid/clear cell tumors, although C18:1 LPC and LPC to PC ratio were suggestively inversely associated, whereas C18:0 SM was suggestively positively associated with risk of endometrioid/clear cell tumors. No individual metabolites were associated with risk when using the permutation-based approach.

Conclusions Elevated levels of circulating SMs 3–23 years before diagnosis were associated with increased risk of ovarian cancer, regardless of histotype, with stronger associations among postmenopausal women. Further studies are required to validate and understand the role of lipid dysregulation in ovarian carcinogenesis.

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https://www.sciencedirect.com/journal/gynecologic-oncology/vol/158/issue/1

In the Know (aka Ed's List) is prepared by Dr. Edward Pavlik for the education of the fellows & candidate fellows at the University of Kentucky on a monthly basis. Dr. Pavlik extends this resource to members of the International Gynecologic Cancer Society to promote continued learning and increase awareness of the latest significant research findings in the field of gynecologic oncology on a global level.

Two successive months of literature are put together to accommodate online vs print appearances and to compensate for delays in a publication (i.e. the March material is not available until June).

See more of Ed's Lists at https://igcs.org/in-the-know/