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Ed's List

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Prepared by Ed Pavlik (Ed's List) --- University of Kentucky Medical Center *

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August

Pan-cancer prediction of radiotherapy benefit using genomic-adjusted radiation dose (GARD): a cohort-based pooled analysis. JG Scott, G Sedor, P Ellsworth, JA Scarborough, KA Ahmed, DE Oliver, SA Eschrich, MW Kattan, JF Torres-Roca. Lancet Oncology, 2021, 22(9) 1221-1229, /doi.org/10.1016/ S1470-2045(21)00347-8 https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1470204521003478?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1470204521003478%3Fshowall%3Dtrue&referrer=

Background Despite advances in cancer genomics, radiotherapy is still prescribed on the basis of an empirical one-size-fits-all paradigm. Previously, we proposed a novel algorithm using the genomic-adjusted radiation dose (GARD) model to personalise prescription of radiation dose on the basis of the biological effect of a given physical dose of radiation, calculated using individual tumour genomics. We hypothesise that GARD will reveal interpatient heterogeneity associated with opportunities to improve outcomes compared with physical dose of radiotherapy alone. We aimed to test this hypothesis and investigate the GARD-based radiotherapy dosing paradigm.

Methods We did a pooled, pan-cancer analysis of 11 previously published clinical cohorts of unique patients with seven different types of cancer, which are all available cohorts with the data required to calculate GARD, together with clinical outcome. The included cancers were breast cancer, head and neck cancer, non-small-cell lung cancer, pancreatic cancer, endometrial cancer, melanoma, and glioma. Our dataset comprised 1615 unique patients, of whom 1298 (982 with radiotherapy, 316 without radiotherapy) were assessed for time to first recurrence and 677 patients (424 with radiotherapy and 253 without radiotherapy) were assessed for overall survival. We analysed two clinical outcomes of interest: time to first recurrence and overall survival. We used Cox regression, stratified by cohort, to test the association between GARD and outcome with separate models using dose of radiation and sham-GARD (ie, patients treated without radiotherapy, but modelled as having a standard-of-care dose of radiotherapy) for comparison. We did interaction tests between GARD and treatment (with or without radiotherapy) using the Wald statistic.

Findings Pooled analysis of all available data showed that GARD as a continuous variable is associated with time to first recurrence (hazard ratio [HR] 0·98 [95% CI 0·97–0·99]; p=0·0017) and overall survival (0·97 [0·95–0·99]; p=0·0007). The interaction test showed the effect of GARD on overall survival depends on whether or not that patient received radiotherapy (Wald statistic p=0·011). The interaction test for GARD and radiotherapy was not significant for time to first recurrence (Wald statistic p=0·22). The HR for physical dose of radiation was 0·99 (95% CI 0·97–1·01; p=0·53) for time to first recurrence and 1·00 (0·96–1·04; p=0·95) for overall survival. The HR for sham-GARD was 1·00 (0·97–1·03; p=1·00) for time to first recurrence and 1·00 (0·98–1·02; p=0·87) for overall survival.

Interpretation The biological effect of radiotherapy, as quantified by GARD, is significantly associated with time to first recurrence and overall survival for patients with cancer treated with radiation. It is predictive of radiotherapy benefit, and physical dose of radiation is not. We propose integration of genomics into radiation dosing decisions, using a GARD-based framework, as the new paradigm for personalising radiotherapy prescription dose.

Video Abstract

YouTube URL: https://youtu.be/gvyiNOPJ-14

Cell therapies in ovarian cancer. A Sarivalasis, M Morotti, A Mulvey, M Imbimbo, G Coukos. Ther Adv Med Oncol. 2021 Apr 22;13:17588359211008399. doi: 10.1177/17588359211008399. Ther Adv Med Oncol. 2021;13 1-17
Epithelial ovarian cancer (EOC) is the most important cause of gynecological cancer-related mortality. Despite improvements in medical therapies, particularly with the incorporation of drugs targeting homologous recombination deficiency, EOC survival rates remain low. Adoptive cell therapy (ACT) is a personalized form of immunotherapy in which autologous lymphocytes are expanded, manipulated ex vivo, and re-infused into patients to mediate cancer rejection. This highly promising novel approach with curative potential encompasses multiple strategies, including the adoptive transfer of tumor-infiltrating lymphocytes, natural killer cells, or engineered immune components such as chimeric antigen receptor (CAR) constructs and engineered T-cell receptors. Technical advances in genomics and immuno-engineering have made possible neoantigen-based ACT strategies, as well as CAR-T cells with increased cell persistence and intratumoral trafficking, which have the potential to broaden the opportunity for patients with EOC. Furthermore, dendritic cell-based immunotherapies have been tested in patients with EOC with modest but encouraging results, while the combination of DC-based vaccination as a priming modality for other cancer therapies has shown encouraging results. In this manuscript, we provide a clinically oriented historical overview of various forms of cell therapies for the treatment of EOC, with an emphasis on T-cell therapy.

Immune checkpoint inhibitors in ovarian cancer: where do we stand? REVIEW A Leary, D Tan, J Ledermann. Therapeutic Advances in Medical Oncology13, 1-13, 2021 https://doi.org/10.1177/17588359211039899 https://journals.sagepub.com/doi/full/10.1177/17588359211039899?utm_medium=email&utm_content=1A01195&utm_campaign=not+tracked&utm_term=&em=1823c8e8baebcbaf1c9586fc7535683553a72b53dcd33cb86b9c268e9a00b88b&utm_source=adestra&
Numerous retrospective studies have demonstrated that the density of intra-tumoral immune cell infiltration is prognostic in epithelial ovarian cancer (OC). These observations together with reports of programmed death ligand-1 (PD-L1) expression in advanced OC provided the rationale for investigating the benefit of programmed death-1 (PD1) or PD-L1 inhibition in OC. Unfortunately clinical trials to date evaluating PD1/PD-L1 inhibition in patients with relapsed OC have been disappointing. In this review we will discuss early results from single agent PD1/PD-L1 inhibitors and the strategies to enhance benefit from immune-oncology agents in OC, including proposing anti-PD-L1 in combination with other agents (cytotoxics, anti-angiogenics, poly(ADP-ribose) polymerase. (PARP) inhibitors, targeted therapies or other immunotherapies), as well as evaluating these agents earlier in the disease course, or in biomarker selected patients.

Connections between prolactin and ovarian cancer.
A Alkharusi , A AlMuslahi, N AlBalushi, R AlAjmi, S AlRawahi, A AlFarqani, G Norstedt, F Zadjali
PLOS One 16(8): e0255701, 2021 https://doi.org/10.1371/journal.pone.0255701 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0255701
Ovarian cancer (OC) is characterized by a high morbidity and mortality, highlighting a great need for a better understanding of biological mechanisms that affect OC progression and improving its early detection methods. This study investigates effects of prolactin (PRL) on ovarian cancer cells, analyzes PRL receptors (PRLR) in tissue micro arrays and relates PRLR expression to survival of ovarian cancer. A database, composed of transcript profiles from OC, was searched for PRLR expression and results were put in relation to survival. Expression of PRLR in OC tissue sections and OC cell lines SKOV3, OV2008 and OVSAHO was assessed using immunohistochemistry, western blots and quantitative real-time PCR. The biological function of PRLR was evaluated by proliferation, colony formation and wound healing assays. Levels of PRLR mRNA are related to survival; in epithelial OC a high PRLR mRNA expression is related to a shorter survival. Analysis of a tissue micro array consisting of 84 OC showed that 72% were positive for PRLR immuno-staining. PRLR staining tended to be higher in OC of high grade tumors compared to lower grades. PRLR mRNA and protein can further be detected in OC cell lines. Moreover, in vitro treatment with PRL significantly activated the JAK/STAT pathway. PRLR expression is associated with OC survivals. PRL and its receptor may play an onco-modulatory role and promote tumor aggressiveness in OC. Alternatively, increased PRLR levels may form a base for the development of PRLR antagonist or PRLR antagonist-drug conjugate to increase selective uptake of anti-cancer drugs.

Chlamydia trachomatis, Pelvic Inflammatory Disease, and Epithelial Ovarian Cancer. J Paavonen, RT Fortner, M Lehtinen, A Idahl, The Journal of Infectious Diseases, Volume 224, Issue Supplement_2, 15 August 2021, Pages S121–S127, https://doi.org/10.1093/infdis/jiab017 https://academic.oup.com/jid/article/224/Supplement_2/S121/6352166?login=true
Epidemiologic, clinical, molecular and translational research findings support an interrelationship between Chlamydia trachomatis, pelvic inflammatory disease (PID), and epithelial ovarian cancer (EOC). Overall, the link between C. trachomatis, PID, and EOC seems to be relatively weak, although nondifferential misclassification bias may have attenuated the results. The predominant tubal origin of EOC and the role of chronic inflammation in tumorigenesis suggest that the association is biologically plausible. Thus, C. trachomatis and PID may represent potential risk factors or risk markers for EOC. However, many steps in this chain of events are still poorly understood and need to be addressed in future studies.

Research gaps include time of exposure in relation to the long-term consequences and lag time to EOC. Data of differential risk for EOC between chlamydial and nonchlamydial PID is also needed. Another major research gap has been the absence of high-performance biomarkers for C. trachomatis, PID, and EOC, as well as EOC precursors. Biomarkers for C. trachomatis and PID leading to increased risk of EOC should be developed. If the association is confirmed, C. trachomatis and PID prevention efforts may play a role in reducing the burden of EOC.

Mutation- and methylation-profiles of ectopic and eutopic endometrial epithelium. L Li, MF Antero, M Zhang, T Chu, T Seckin, A Ayhan, T Pisanic, T-L Wang, L Cope, J Segars, I-M Shih. Journal of Pathology 2021 https://doi.org/10.1002/path.5778 https://onlinelibrary.wiley.com/doi/abs/10.1002/path.5778

Adenomyosis and peritoneal endometriosis are common gynecologic lesions; they are characterized by aberrant locations of normal-appearing endometrium in myometrium and peritoneal surface, respectively. Both ectopic lesions are speculated to originate from uterine eutopic endometrium, which is composed of epithelium and stroma, but how these two different tissue types co-evolve in ectopic locations remain unclear. Here, we analyzed exome-wide mutations and global methylation in microdissected epithelium and stroma separately in paired adenomyosis, peritoneal endometriosis, and endometrium to investigate their relationship. Analyses of somatic mutations and their allele frequencies indicate mono-clonal development not only in epithelium but also in the stroma of adenomyosis and peritoneal endometriosis. Our preliminary phylogenetic study suggests a plausible clonal derivation in epithelium and stroma of both ectopic and eutopic endometrium from the same founder epithelium-stroma progenitor cells. While a patient-specific methylation landscape is evident, adenomyosis epithelium and stroma can be distinguished from normal-appearing eutopic endometrium and epigenetically less homogenous. In summary, endometrial stroma, like its epithelial counterpart, could be clonal and both ectopic and eutopic endometrium following divergent evolutionary trajectories. Our data also warrant future investigations into the role of endometrial stroma in the pathobiology of endometrium-related disorders.

Human papillomavirus vaccination history and diagnosis of cervical intraepithelial neoplasia grade ≥2 severe lesions among a cohort of women who underwent colposcopy in Kaiser Permanente Southern California. NM.Lonky, L Xu, DM Da Silva, JC Felix, C Chao. Amer J Obstetrics & Gynecology DOI:https://doi.org/10.1016/j.ajog.2021.07.006 https://www.ajog.org/article/S0002-9378(21)00792-4/fulltext

Background The risk of a high-grade lesion in women undergoing colposcopy following an abnormal screening result may be different by human papillomavirus vaccination status, because women who are vaccinated are presumably less likely to harbor human papillomavirus types 16 and 18.

Objective This study aimed to evaluate whether the risk of high-grade cervical lesion diagnosed through colposcopy is lower in women with human papillomavirus vaccination than in women without vaccination referred to colposcopy based on equal abnormal screening findings.

Study Design Kaiser Permanente Orange County female patients between ages 21 and 38 years were included following an abnormal screening if they had ≥1 colposcopies between July 2017 and August 2018 and had at least 1 pathology diagnosis from the colposcopy visits. Data on demographic characteristics, clinical and sexual histories, and human papillomavirus vaccination were collected using a colposcopy registry smart form and from electronic medical records. Human papillomavirus genotyping was performed for tissues from confirmed cervical intraepithelial neoplasm grade 2+ diagnoses. A multilevel generalized linear model with a logic function was used to evaluate the association between human papillomavirus vaccination history and the outcome of a cervical intraepithelial neoplasm grade 2+ diagnosis and for human papillomavirus type 16- or 18-positive cervical intraepithelial neoplasm grade 2+ as an alternative outcome, adjusting for screening results and potential confounders.

Results Of 730 women included in the study, 170 had a histologic diagnosis of cervical intraepithelial neoplasm grade 2+ (23.2%). Moreover, 68 cases (40.0%) were histologically human papillomavirus type 16 and/or 18 positive. Of the 730 women, 311 (43%) were vaccinated for the human papillomavirus before colposcopy. Most women (206 [66.2%]) with human papillomavirus vaccination received the vaccine between the ages 18 and 26 years. A history of human papillomavirus vaccination overall, before sexual debut, before the age of 18 years, or with complete dosing was not associated with lower odds of a cervical intraepithelial neoplasm grade 2+ diagnosis (odds ratio, 1.07 [95% confidence interval, 0.70–1.64]; odds ratio, 1.11 [95% confidence interval, 0.55–2.24]; odds ratio, 0.96 [95% confidence interval, 0.49–1.91]; and odds ratio, 0.84 [95% confidence interval, 0.53–1.35], respectively, in reference to no vaccination). Human papillomavirus vaccination history was not significantly associated with the odds of a human papillomavirus type 16- or 18-positive cervical intraepithelial neoplasm grade 2+ diagnosis (P=.45). Notably, 8 cases (4.8% of all cervical intraepithelial neoplasm grade 2+ cases) showed a human papillomavirus type 16 on a cervical intraepithelial neoplasm grade 2+ histologic polymerase chain reaction analysis despite reported or documented human papillomavirus vaccination before sexual debut, including 2 cases who started vaccination before the age of 13 years.

Conclusion Our study did not support modifying the colposcopy management guidelines for abnormal screening results for women with human papillomavirus vaccination, especially those vaccinated in the catch-up age range. Our findings on the 8 cases of human papillomavirus 16-positive cervical intraepithelial neoplasm grade 2+ vaccination before sexual debut

suggested that lowering the recommended age for human papillomavirus vaccination may have additional benefits for preventing human papillomavirus infection that could occur early in life in some women.

A machine learning approach to identify predictive molecular markers for cisplatin chemosensitivity following surgical resection in ovarian cancer. NB Shannon, LLY Tan, QX Tan, J W-S Tan, J Hendrikson, WH Ng, G Ng, Y Liu, X-YS Ong, R Nadarajah, JS M Wng, GHC Tan, KC Soo, MCC Teo, CS Chia, C-A Johnny. OngSci Rep 11, 16829 (2021). https://doi.org/10.1038/s41598-021-96072-6 https://www.nature.com/articles/s41598-021-96072-6

Ovarian cancer is associated with poor prognosis. Platinum resistance contributes significantly to the high rate of tumour recurrence. We aimed to identify a set of molecular markers for predicting platinum sensitivity. A signature predicting cisplatin sensitivity was generated using the Genomics of Drug Sensitivity in Cancer and The Cancer Genome Atlas databases. Four potential biomarkers (CYTH3, GALNT3, S100A14, and ERI1) were identified and optimized for immunohistochemistry (IHC). Validation was performed on a cohort of patients (n = 50) treated with surgical resection followed by adjuvant carboplatin. Predictive models were established to predict chemosensitivity. The four biomarkers were also assessed for their ability to prognosticate overall survival in three ovarian cancer microarray expression datasets from The Gene Expression Omnibus. The extreme gradient boosting (XGBoost) algorithm was selected for the final model to validate the accuracy in an independent validation dataset (n = 10). CYTH3 and S100A14, followed by nodal stage, were the features with the greatest importance. The four gene signature had comparable prognostication as clinical information for two-year survival. Assessment of tumour biology by means of gene expression can serve as an adjunct for prediction of chemosensitivity and prognostication. Potentially, the assessment of molecular markers alongside clinical information offers a chance to further optimise therapeutic decision making.

Incidence and Types of Human Papillomavirus Infections in Adolescent Girls and Young Women Immunized With the Human Papillomavirus Vaccine. NF Schlecht, A Diaz, A Nucci-Sack, K Shyhalla, V Shankar, M Guillot, D Hollman, HD Strickler, RD Burk. JAMA Netw Open. 2021;4(8):e2121893. doi:10.1001/jamanetworkopen.2021.21893

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2783300?guestAccessKey=e4174bbf-1f9a-4d87-9992-ce8dcd0ecd65&utm_source=silverchair&utm_campaign=jama_network&utm_content=onc_weekly_highlights&cmp=1&utm_medium=email

Key Points

Question Has the introduction of the vaccine for human papillomavirus (HPV) been associated with changes in infection rates among sexually active adolescent girls and young adult women?

Findings This cohort study assessed HPV infection rates of vaccinated adolescent and young adult women at a large adolescent-specific health center in New York City. Age-adjusted cervical HPV detection of vaccine-related types were lower year over year, while the prevalence of nonvaccine high-risk HPV types remained flat or higher.

Meaning These results indicate the real-world effectiveness of the HPV vaccines in female youth in New York City; nevertheless, rates of some nonvaccine high-risk HPV types were higher.

Abstract

Importance Rates of human papillomavirus (HPV) infection have decreased since the introduction of HPV vaccines in populations with high vaccine uptake. Data are limited for adolescent and young adult populations in US metropolitan centers.

Objective To determine HPV infection rates in adolescent girls and young women aged 13 to 21 years in New York City following HPV vaccination.

Design, Setting, and Participants This cohort study of type-specific cervical HPV detection was conducted at a large adolescent-specific integrated health center in New York City between October 2007 and September 2019. Participants included an open cohort of adolescent girls and young adult women who received the HPV vaccine (Gardasil; Merck & Co) over a 12-year period following HPV vaccination introduction. Data analysis was concluded September 2019.

Exposures Calendar date and time since receipt of first vaccine dose.

Main Outcomes and Measures Temporal associations in age-adjusted postvaccine HPV rates.

Results A total of 1453 participants, with a mean (SD) age at baseline of 18.2 (1.4) years, were included in the cohort (African American with no Hispanic ethnicity, 515 [35.4%] participants; African American with Hispanic ethnicity, 218 [15.0%] participants; Hispanic with no reported race, 637 [43.8%] participants). Approximately half (694 [47.8%] participants) were vaccinated prior to coitarche. Age-adjusted detection rates for quadrivalent vaccine types (HPV-6, HPV-11, HPV-16, and HPV-18) and related types (HPV-31, and HPV-45) decreased year over year, with the largest effect sizes observed among individuals who had been vaccinated before coitarche (adjusted odds ratio [aOR], 0.81; 95% CI, 0.67-0.98). By contrast, detection was higher year over year for nonvaccine high-risk cervical HPV types (aOR, 1.08; 95% CI, 1.04-1.13) and anal HPV types (aOR, 1.11; 95% CI, 1.05-1.17). The largest effect sizes were observed with nonvaccine types HPV-56 and HPV-68.

Conclusions and Relevance Whereas lower detection rates of vaccine-related HPV types were observed since introduction of vaccines in female youth in New York City, rates of some nonvaccine high-risk HPV types were higher. Continued monitoring of high-risk HPV prevalence is warranted.

Association Between Human Papillomavirus Vaccination and Primary Ovarian Insufficiency in a Nationwide Cohort. A Hviid, E Myrup Thiesson. JAMA Netw Open. 2021;4(8):e2120391. doi:10.1001/jamanetworkopen.2021.20391
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2783512?guestAccessKey=32508539-d74f-4b34-97f7-03bcbbfeb64e&utm_source=silverchair&utm_campaign=jama_network&utm_content=onc_weekly_highlights&cmp=1&utm_medium=email

Key Points

Question Is human papillomavirus vaccination associated with primary ovarian insufficiency among Danish girls and women?

Findings In this cohort study of 996 300 girls and women, vaccination was not associated with primary ovarian insufficiency.

Meaning This finding suggests that human papillomavirus vaccination is unlikely to be associated with moderate to large increases in the risk of primary ovarian insufficiency.

Abstract

Importance Anecdotal case reports have suggested an association between human papillomavirus (HPV) vaccination and primary ovarian insufficiency, but observational studies of HPV and primary ovarian insufficiency are rare, and their findings do not support an association. However, available studies have been limited by statistical power, and concerns about infertility after vaccination are associated with lower levels of uptake of the cancer-preventing vaccine in many countries.

Objective To evaluate the risk of primary ovarian insufficiency after quadrivalent human papillomavirus (4HPV) vaccination.

Design, Setting, and Participants This retrospective cohort study with follow-up from 2007 to 2016 used nationwide data for 996 300 Danish-born girls and women aged 11 to 34 years. Cox proportional hazards regression was used to estimate hazard ratios (HRs) of primary ovarian insufficiency diagnoses by 4HPV vaccination status with adjustment for age, calendar period, and a propensity score summarizing health care use. Data were analyzed from October 2020 to January 2021.

Exposures Receiving 4HPV vaccination compared with receiving no vaccination.

Main Outcomes and Measures The main outcome was hospital contacts for primary ovarian insufficiency, and the main outcome measures were HRs comparing rates of primary ovarian insufficiency among vaccinated and unvaccinated individuals.

Results During 6 781 166 person-years of follow-up among 996 300 girls and women aged 11 to 34 years (505 829 vaccinated individuals [50.8%] and 490 471 unvaccinated individuals [49.2%]), 144 individuals were diagnosed with primary ovarian insufficiency, including 54 individuals diagnosed after 4HPV vaccination. The median (interquartile range) age of primary ovarian insufficiency diagnosis was 26.94 (12.68) years. The adjusted HR of primary ovarian insufficiency comparing 4HPV vaccination to no vaccination was 0.96 (95% CI, 0.55-1.68).

Conclusions and Relevance This study found no association between HPV vaccination and primary ovarian insufficiency. However, given the rarity of the outcome in this study, the presence of a clinically relevant increase in rate of diagnosis cannot be excluded.

Human papillomavirus load and genotype analysis improves the prediction of invasive cervical cancer. M Hortlund, T van Mol, F Van de Pol, J Bogers, J Dillner. Int. J. Cancer. 2021; 149: 684– 691. https://doi.org/10.1002/ijc.33519 https://onlinelibrary.wiley.com/doi/10.1002/ijc.33519

Human papillomavirus (HPV)-based cervical screening is a globally recommended health policy. Different HPV types have different risk for cervical cancer. For optimal HPV screening, the sensitivity and specificity for each HPV type at different viral loads should be known in a screening setting. HPV test results in about 1 million cervical samples analyzed during 2006 to 2014 were compared for 319 women who had developed invasive cervical cancer up to 8.5 years later and for 1911 matched control women. Detection including low viral loads resulted in markedly increased sensitivity for cervical cancer only for HPV types 16 and 18. Testing for HPV types 31, 33, 45 and 52 also increased the sensitivity for prediction of cervical cancer, but for these viruses, detection of low viral load did not further increase sensitivity. HPV types 35, 39, 51, 56, 58, 59, 66 and 68 only predicted occasional additional cervical cancer cases. Testing for HPV16/18 at low viral load plus testing for HPV31, 33, 45 and 52 at >3000 copies/μL predicted 86.5% of cancers occurring within a year after testing, similar to the 89.4% that were predicted by testing for 14 HPV types. By contrast, the type and viral load-restricted testing greatly increased specificity: 6.3% of healthy women tested positive as compared to 11.7% of healthy women testing positive for the 14 HPV types commonly screened for today. Adequate HPV screening sensitivity, with considerable increase in specificity, can be obtained by testing only for HPV16/18/31/33/45/52, with detection of low viral load required only for HPV16/18.

A Simple, Novel Prognostic Score in Platinum Sensitive Relapsed Ovarian Cancer, American Journal of Clinical Oncology. L Goenka, T Nakka, B Dubashi, S Kayal, P Penumadu, L Chaturvedula, P Veena, J Durairaj, P Ganesan. August 2021 - Volume 44 - Issue 8 - p 434-441 doi: 10.1097/COC.0000000000000830 https://journals.lww.com/amjclinicaloncology/Fulltext/2021/08000/A_Simple,_Novel_Prognostic_Score_in_Platinum.10.aspx

Objectives: Epithelial ovarian cancer is one of the commonest gynecologic cancers and one with the highest mortality. This retrospective cohort study was done to identify predictors of outcomes in platinum-sensitive relapsed ovarian cancer patients (PS-ROC).

Methods: Data regarding baseline characters, laboratory findings, therapeutic details and survival outcomes was obtained from the medical records of PS-ROC patients presented between January 2015 and December 2019. Prognostic score was constructed using factors which were significant on multivariate analysis to predict survival outcomes.

Results: A total of 71 (PS-ROC) patients were included in the study with a median age of 50 years. Relapse treatment was either chemotherapy alone (n=53, 75%) or chemotherapy plus surgery (n=18, 25%). The estimated progression-free survival (PFS) and overall survival were 10 and 29 months, respectively. The overall response rate after treatment of relapse was 59%. Prognostic score was created with the 3 factors (each scoring 1 point) which were predictive of PFS (higher lymphocyte-monocyte ratio, longer platinum-free interval and secondary cytoreduction). Patients with low score (0,1) had better PFS than those with higher score (2,3) (13 vs. 7 mo [P=0.0001]).

Conclusions: A composite prognostic score could predict outcomes in PS-ROC and potentially identify a subgroup with very poor prognosis. Future studies with a greater number of patients are needed to validate these findings. This information could help tailor more intense therapies to the high-risk patients and attempt to improve outcomes and serve as stratification factors for prospective trials.

FTO-Dependent N6-Methyladenosine Modifications Inhibit Ovarian Cancer Stem Cell Self-Renewal by Blocking cAMP Signaling

H Huang, Y Wang, M Kandpal, G Zhao, H Cardenas, Y Ji, A Chaparala, EJ Tanner, J Chen, R V. Davuluri, Daniela Matei. Cancer Res August 15 2020 (80) (16) 3200-3214; DOI: 10.1158/0008-5472.CAN-19-4044 https://cancerres.aacrjournals.org/content/80/16/3200

N6-Methyladenosine (m6A) is the most abundant modification of mammalian mRNAs. RNA methylation fine tunes RNA stability and translation, altering cell fate. The fat mass- and obesity-associated protein (FTO) is an m6A demethylase with oncogenic properties in leukemia. Here, we show that FTO expression is suppressed in ovarian tumors and cancer stem cells (CSC). FTO inhibited the self-renewal of ovarian CSC and suppressed tumorigenesis in vivo, both of which required FTO demethylase activity. Integrative RNA sequencing and m6A mapping analysis revealed significant transcriptomic changes associated with FTO overexpression and m6A loss involving stem cell signaling, RNA transcription, and mRNA splicing pathways. By reducing m6A levels at the 3′UTR and the mRNA stability of two phosphodiesterase genes (PDE1C and PDE4B), FTO augmented second messenger 3′, 5′-cyclic adenosine monophosphate (cAMP) signaling and suppressed stemness features of ovarian cancer cells. Our results reveal a previously unappreciated tumor suppressor function of FTO in ovarian CSC mediated through inhibition of cAMP signaling.

Significance: A new tumor suppressor function of the RNA demethylase FTO implicates m6A RNA modifications in the regulation of cyclic AMP signaling involved in stemness and tumor initiation.

The Ratio of Toxic-to-Nontoxic miRNAs Predicts Platinum Sensitivity in Ovarian Cancer. M Patel, Y Wang, ET Bartom, R Dhir, KP Nephew, D Matei, AE Murmann, E Lengyel, ME Peter. Cancer Res August 1 2021 (81) (15) 3985-4000; DOI: 10.1158/0008-5472.CAN-21-0953 https://cancerres.aacrjournals.org/content/81/15/3985

Ovarian cancer remains one of the deadliest gynecologic malignancies affecting women, and development of resistance to platinum remains a major barrier to achieving a cure. Multiple mechanisms have been identified to confer platinum resistance. Numerous miRNAs have been linked to platinum sensitivity and resistance in ovarian cancer. miRNA activity occurs mainly when the guide strand of the miRNA, with its seed sequence at position 2–7/8, is loaded into the RNA-induced silencing complex (RISC) and targets complementary short seed matches in the 3′ untranslated region of mRNAs. Toxic 6mer seeds, which target genes critical for cancer cell survival, have been found in tumor-suppressive miRNAs. Many siRNAs and short hairpin RNAs (shRNA) can also kill cancer cells via toxic seeds, the most toxic of which carry G-rich 6mer seed sequences. We showed here that treatment of ovarian cancer cells with platinum led to increased RISC-bound miRNAs carrying toxic 6mer seeds and decreased miRNAs with nontoxic seeds. Platinum-tolerant cells did not exhibit this toxicity shift but retained sensitivity to cell death mediated by siRNAs carrying toxic 6mer seeds. Analysis of RISC-bound miRNAs in tumors from patients with ovarian cancer revealed that the ratio between miRNAs with toxic versus nontoxic seeds was predictive of treatment outcome. Application of the 6mer seed toxicity concept to cancer relevant miRNAs provides a new framework for understanding and predicting cancer therapy responses.

Significance: These findings demonstrate that the balance of miRNAs that carry toxic and nontoxic 6mer seeds contributes to platinum resistance in ovarian cancer.

Therapeutic Implications of Germline Testing in Patients With Advanced Cancers. ZK Stadler, A Maio, D Chakravarty, Y Kemel, M Sheehan, E Salo-Mullen, K Tkachuk, CJ Fong, B Nguyen, A Erakky, K Cadoo, Y Liu, MI Carlo, A Latham, H Zhang, R Kundra, S Smith, J Galle, C Aghajanian, N Abu-Rustum, A Varghese, EM O'Reilly, M Morris, W Abida, M Walsh, A Drilon, G Jayakumaran, A Zehir, M Ladanyi, O Ceyhan-Birsoy, DB Solit, N Schultz, MF Berger, D Mandelker, LA Diaz Jr, K Offit, ME Robson. Journal of Clinical Oncology 2021 39:24, 2698-2709 DOI: 10.1200/JCO.20.03661 https://ascopubs.org/doi/full/10.1200/JCO.20.03661

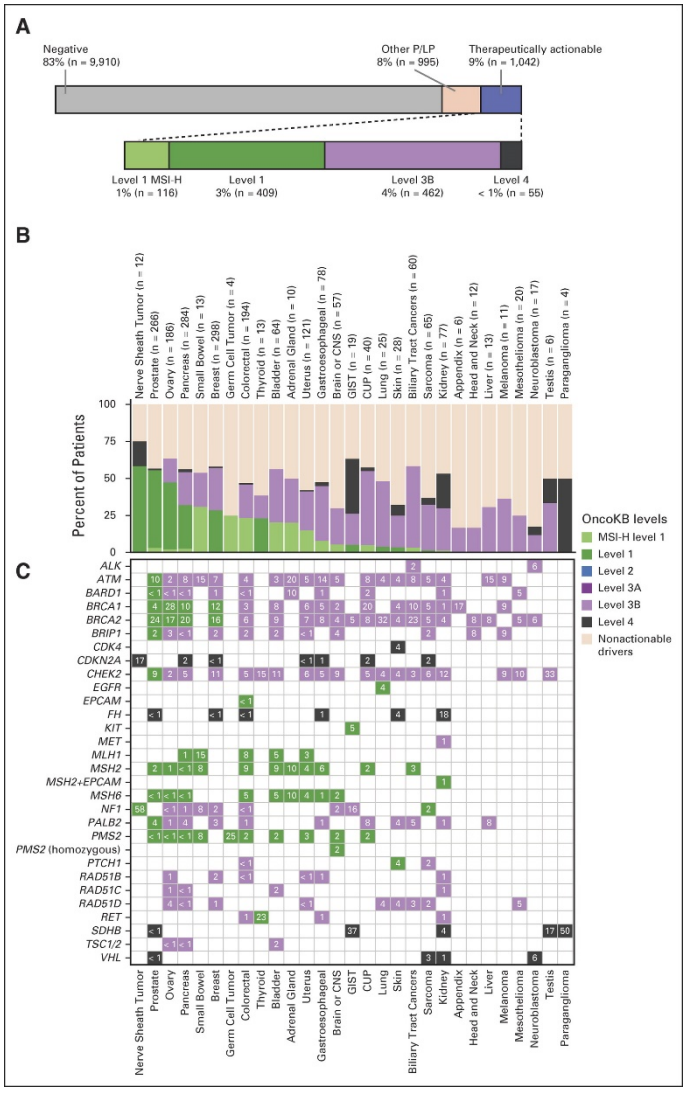
PURPOSE Tumor mutational profiling is increasingly performed in patients with advanced cancer. We determined the extent to which germline mutation profiling guides therapy selection in patients with advanced cancer.

METHODS

Patients with cancer undergoing tumor genomic profiling were prospectively consented for germline cancer predisposition gene analysis (2015-2019). In patients harboring germline likely pathogenic or pathogenic (LP/P) alterations, therapeutic actionability was classified using a precision oncology knowledge base. Patients with metastatic or recurrent cancer receiving germline genotype–directed therapy were determined.

RESULTS Among 11,947 patients across > 50 malignancies, 17% (n = 2,037) harbored a germline LP/P variant. By oncology knowledge base classification, 9% (n = 1042) had an LP/P variant in a gene with therapeutic implications (4% level 1; 4% level 3B; < 1% level 4). BRCA1/2 variants accounted for 42% of therapeutically actionable findings, followed by CHEK2 (13%), ATM (12%), mismatch repair genes (11%), and PALB2 (5%). When limited to the 9,079 patients with metastatic or recurrent cancer, 8% (n = 710) harbored level 1 or 3B genetic findings and 3.2% (n = 289) received germline genotype–directed therapy. Germline genotype–directed therapy was received by 61% and 18% of metastatic cancer patients with level 1 and level 3B findings, respectively, and by 54% of BRCA1/2, 75% of mismatch repair, 43% of PALB2, 35% of RAD51C/D, 24% of BRIP1, and 19% of ATM carriers. Of BRCA1/2 patients receiving a poly(ADP-ribose) polymerase inhibitor, 45% (84 of 188) had tumors other than breast or ovarian cancer, wherein the drug, at time of delivery, was delivered in an investigational setting.

CONCLUSION In a pan-cancer analysis, 8% of patients with advanced cancer harbored a germline variant with therapeutic actionability with 40% of these patients receiving germline genotype–directed treatment. Germline sequence analysis is additive to tumor sequence analysis for therapy selection and should be considered for all patients with advanced cancer.



Secondary Cytoreduction and Carboplatin Hyperthermic Intraperitoneal Chemotherapy for Platinum-Sensitive Recurrent Ovarian Cancer: An MSK Team Ovary Phase II Study. O Zivanovic, DS Chi, Q Zhou, A Iasonos, JA Konner, V Makker, RN Grisham, AK Brown, S Nerenstone, JP Diaz, ED Schroeder, CL Langstraat, V Paroder, Y Lakhman, K Soldan, K Su, G J. Gardner, V Andikyan, J Guo, EL Jewell, KL Roche, T Troso-Sandoval, SM Lichtman, LA Moukarzel, K Dessources, NR Abu-Rustum, C Aghajanian, WP Tew, J Beumer, Y Sonoda, RE O'Cearbhaill

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PURPOSE The purpose of this phase II study was to evaluate hyperthermic intraperitoneal chemotherapy (HIPEC) with carboplatin for recurrent ovarian cancer during secondary cytoreductive surgery.

MATERIALS AND METHODS Patients were intraoperatively randomly assigned to carboplatin HIPEC (800 mg/m2 for 90 minutes) or no HIPEC, followed by five or six cycles of postoperative IV carboplatin-based chemotherapy, respectively. Based on a binomial single-stage pick-the-winner design, an arm was considered winner if ≥ 17 of 49 patients were without disease progression at 24 months post-surgery. Secondary objectives included postoperative toxicity and HIPEC pharmacokinetics.

RESULTS Of 98 patients, 49 (50%) received HIPEC. Complete gross resection was achieved in 82% of the HIPEC patients and 94% of the standard-arm patients. Bowel resection was performed in 37% of patients in the HIPEC arm compared with 65% in the standard (P = .008). There was no perioperative mortality and no difference in use of ostomies, length of stay, or postoperative toxicity. At 24 months, eight patients (16.3%; 1-sided 90% CI, 9.7 to 100) were without progression or death in the HIPEC arm and 12 (24.5%; 1-sided 90% CI, 16.5 to 100) in the standard arm. With a medium follow-up of 39.5 months, 82 patients progressed and 37 died. The median progression-free survival in the HIPEC and standard arms were 12.3 and 15.7 months, respectively (hazard ratio, 1.54; 95% CI, 1 to 2.37; P = .05). There was no significant difference in median overall survival (52.5 v 59.7 months, respectively; hazard ratio, 1.39; 95% CI, 0.73 to 2.67; P = .31). These analyses were exploratory.
CONCLUSION HIPEC with carboplatin was well tolerated but did not result in superior clinical outcomes. This study does not support the use of HIPEC with carboplatin during secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer.

High-risk endometrial cancer proteomic profiling reveals that FBXW7 mutation alters L1CAM and TGM2 protein levels. M Ellen Urick, E-J Yu, DW Bell. https://doi.org/10.1002/cncr.33567 https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.33567
Background FBXW7 is frequently somatically mutated in grade 3 endometrioid endometrial cancers (G3EECs) and serous endometrial cancers (SECs), which are high-risk cancers associated with poor outcomes and in need of novel treatment options. The aim of this study was to determine the proteomic effects of 3 FBXW7 mutations in high-risk endometrial cancers (ECs).
Methods Clustered regularly interspaced short palindromic repeats (CRISPR) editing was used to generate 3 HEC-50B G3EEC derivative cell lines, each of which harbored 1 FBXW7 mutation, and to revert an endogenous FBXW7 mutation in HEC-1-B grade 2 endometrioid endometrial cancer (G2EEC) cells to the wild-type genotype. Proteomic profiling based on liquid chromatography–tandem mass spectrometry was used to determine protein differences between the HEC-50B derivative lines and parental cells. Western blot analysis was performed to assess differential protein levels of CRISPR-edited derivative lines originating from HEC-50B, ARK1 (SEC), ARK4 (SEC), HEC-1-B, and JHUEM-1 (G2EEC) cell lines in comparison with parental cells.
Results Results of this study demonstrated the effects of FBXW7 mutations on the proteome and phosphoproteome of HEC-50B G3EEC cells and highlighted proteins that also exhibited altered levels in FBXW7-mutated ARK1 and ARK4 SEC cells, including 2 potentially druggable proteins: L1 cell adhesion molecule (L1CAM) and transglutaminase 2 (TGM2). Furthermore, they demonstrated that reversion of an endogenous FBXW7 mutation to the wild-type genotype in JHUEM-1 and HEC-1-B G2EEC cells resulted in decreased L1CAM and TGM2 protein levels.
Conclusions L1CAM and TGM2 protein levels are affected by FBXW7 mutations in ECs.

Antimullerian Hormone as a Serum Biomarker for Risk of Chemotherapy-Induced Amenorrhea. KJ Ruddy, DJ Schaid, A Batzler, RS Cecchini, AH Partridge, A Norman, L Fehrenbacher, EA Stewart, E Trabuco, E Ginsburg, FJ Couch, PA Fasching, C Vachon, PA Ganz, JNCI: 113, Issue 8, 2021, 1105–1108, https://doi.org/10.1093/jnci/djaa160 https://academic.oup.com/jnci/article-abstract/113/8/1105/5959958?redirectedFrom=fulltext
Antimullerian hormone (AMH) is a promising biomarker for ovarian reserve. In this study, we assessed AMH before and 1 year after initiation of adjuvant chemotherapy on National Surgical Adjuvant Breast and Bowel Project (NSABP)/NRG Oncology B-47 in female participants aged 42 years and younger (median age = 39 years). At baseline, median AMH was 1.2 ng/mL; 13 (4.7%) values were less than 0.1 ng/mL (the threshold for detectable levels, in the perimenopause and menopause range), and 57 values (20.6%) were less than 0.5 ng/mL. At 1 year, 215 (77.6%) were less than 0.1 ng/mL, and 264 (95.3%) were less than 0.5 ng/mL. Postchemotherapy menses were reported by 46.2% of participants. Multivariable logistic regression found that the odds of having postchemotherapy menses increased with younger age, higher body mass index, and higher prechemotherapy AMH, but not by trastuzumab administration or by the choice of chemotherapy (doxorubicin-cyclophosphamide followed by paclitaxel vs docetaxel-cyclophosphamide). We conclude that higher prechemotherapy AMH predicts a lower risk of chemotherapy-induced amenorrhea and that AMH 1 year after chemotherapy initiation is not informative in this setting because it is likely to be very low.

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[*] ***In The Know*** (aka *Ed's List*) is prepared for the education of our fellows & candidate fellows on a monthly basis. It's purpose and intent is to make those involved in training aware of significant contributions to the field of Gynecologic Oncology. Two successive months of literature are put

together to accommodate on line vs print appearances and to compensate for delays in a publication (i.e. the March material is not available until June).