Ed's List March 2021

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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(https://academic.oup.com/jnci/article/113/1/1/5859629)

Characterization of ascites- and tumor-infiltrating γδ T cells reveals distinct repertoires and a beneficial role in ovarian cancer. Emelie Foord, Lucas C. M. Arruda, Ahmed Gaballa, Charlotte Klynning and Michael Uhlin. Science Translational Medicine 13 (577) 2021 eabb0192

DOI: 10.1126/scitranslmed.abb0192 https://stm.sciencemag.org/content/13/577/eabb0192

An innate response to ovarian cancer

Favorable outcomes for patients with epithelial ovarian cancer have been associated with infiltration of immune cells into tumors. In this study, Foord et al. investigated the contribution of a subset of immune cells, γδ T cells, to clinical outcomes in these patients. The authors demonstrated that tumor-infiltrating γδ T cells isolated from patients with ovarian cancer have distinct T cell receptors and exhibit more innate-like functions compared to blood- or ascites-derived γδ T cells. Furthermore, γδ T cell infiltration into tumors was associated with increased survival in patients with ovarian cancer. These findings suggest that promoting γδ T cell responses may be a therapeutic option for ovarian cancer.

Abstract

The role of γδ T cells in antitumor immunity has been under investigation for the past two decades, but little is known about their contribution to clinical outcomes in patients. Here, we set out to define the clonotypic, phenotypic, and functional features of γδ T cells in peripheral blood, ascites, and metastatic tumor tissue from patients with advanced epithelial ovarian cancer. T cell receptor (TCR) sequencing of the γ chain revealed that tumor-infiltrating γδ T cells have a unique and skewed repertoire with high TCR diversity and low clonality. In contrast, ascites-derived γδ T cells presented a lower TCR diversity and higher clonality, suggesting a TCR-dependent clonal focusing at this site. Further investigation showed that tumor samples had abundant γδ T cells with a tissue-resident, activation-associated phenotype, less usage of Vγ9 and an impaired response to adaptive-associated stimuli, implying an innate-like activation pathway, rather than an adaptive TCR-engaging pathway, at these tumor sites. Furthermore, high γδ T cell cytokine responsiveness upon stimulation was associated with a favorable outcome for patients in terms of both overall survival and reduced residual tumor burden after primary surgery. Last, the functionality of γδ T cells and patient survival were negatively affected by the proportions of CD39-expressing T cells, highlighting the potential of CD39 as a target to improve γδ T cell responses and unleash their antitumor capabilities.

Gene Sequencing for Pathogenic Variants Among Adults With Breast and Ovarian Cancer in the Caribbean

SHL. George, T Donenberg, C Alexis, V DeGennaro Jr, H Dyer, S Yin, J Ali, R Butler, SN Chin, D Curling, D Lowe, J Lunn, T Turnquest, G Wharfe, D Cerbon, P Barreto-Coelho, MP Schlumbrecht, MR Akbari, SA Narod, JE Hurley. JAMA Netw Open. 2021;4(3):e210307. doi:10.1001/jamanetworkopen.2021.0307
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776805?guestAccessKey=7fb18015-eb01-

4812-b8e9-dbc328802abd&utm_source=silverchair&utm_campaign=jama_network&utm_content=onc_weekly_highlights&cmp=1&utm_medium=email

Key Points

Question What proportion of patients in the Caribbean who develop breast or ovarian cancer carry deleterious variants?

Findings This genetic association study included 1018 adult women and men with breast and ovarian cancer, of which 144 individuals had a pathogenic variant in a moderate- to high-risk gene. This finding was consistent with high rates of premenopausal breast cancer in Black women with Caribbean ancestry.

Meaning Results of this study suggest that in people with Caribbean ancestry diagnosed with breast or ovarian cancer, 1 in 7 will have an actionable pathogenic variant, which may lead to use of targeted therapies and precision prevention approaches.

Abstract

Importance Rates of breast and ovarian cancer are high in the Caribbean; however, to date, few published data quantify the prevalence of inherited cancer in the Caribbean population.

Objective To determine whether deleterious variants in genes that characterize the hereditary breast and ovarian cancer syndrome are associated with the development of breast and ovarian cancer in the English- and Creole-speaking Caribbean populations.

Design, Setting, and Participants This multisite genetic association study used data from germline genetic test results between June 2010 and June 2018 in the Bahamas, Cayman Islands, Barbados, Dominica, Jamaica, Haiti, and Trinidad and Tobago. Next-generation sequencing on a panel of 30 genes and multiplex ligation-dependent probe amplification (*BRCA1* and *BRCA2*) were performed. Medical records were reviewed at time of study enrollment. Women and men diagnosed with breast and ovarian cancer with at least 1 grandparent born in the participating study sites were included; 1018 individuals were eligible and consented to participate in this study. Data were analyzed from November 4, 2019, to May 6, 2020.

Exposures Breast and/or ovarian cancer diagnosis

Main Outcomes and Measures Rate of inherited breast and ovarian cancer syndrome and spectrum and types of variants.

Results Of 1018 participants, 999 (98.1%) had breast cancer (mean [SD] age, 46.6 [10.8] years) and 21 (2.1%) had ovarian cancer (mean [SD] age, 47.6 [13.5] years). Three individuals declined to have their results reported. A total of 144 of 1015 (14.2%) had a pathogenic or likely pathogenic (P/LP) variant in a hereditary breast and ovarian cancer syndrome gene. A total of 64% of variant carriers had P/LP variant in *BRCA1*, 23% in *BRCA2*, 9% in *PALB2* and 4% in *RAD51C*, *CHEK2*, *ATM*, *STK11* and *NBN*. The mean (SD) age of variant carriers was 40.7 (9.2) compared with 47.5 (10.7) years in noncarriers. Individuals in the Bahamas had the highest proportion of hereditary breast and ovarian cancer (23%), followed by Barbados (17.9%), Trinidad (12%), Dominica (8.8%), Haiti (6.7%), Cayman Islands (6.3%), and Jamaica (4.9%). In Caribbean-born women and men with breast cancer, having a first- or second-degree family member with breast cancer was associated with having any *BRCA1* or *BRCA2* germline variant (odds ratio, 1.58; 95% CI, 1.24-2.01; $P < .001$). A *BRCA1* vs *BRCA2* variant was more strongly associated with triple negative breast cancer (odds ratio, 6.33; 95% CI, 2.05-19.54; $P = .001$).

Conclusions and Relevance In this study, among Caribbean-born individuals with breast and ovarian cancer, 1 in 7 had hereditary breast and ovarian cancer. The proportion of hereditary breast and ovarian cancer varied by island and ranged from 23% in the Bahamas to 4.9% in Jamaica. Each island had a distinctive set of variants.

Assessment of Clinical Benefit of Integrative Genomic Profiling in Advanced Solid Tumors

Erin F. Cobain, Yi-Mi Wu, Pankaj Vats, Rashmi Chugh, Francis Worden, David C. Smith, Scott M. Schuetze, Mark M. Zalupski, Vaibhav Sahai, Ajjai Alva, Anne F. Schott, Megan E. V. Caram, Daniel F. Hayes, Elena M. Stoffel, Michelle F. Jacobs, Chandan Kumar-Sinha, Xuhong Cao, Rui Wang, David Lucas, Yu Ning, Erica Rabban, Janice Bell, Sandra Camelo-Piragua, Aaron M. Udager, Marcin Cieslik, Robert J. Lonigro, Lakshmi P. Kunju, Dan R. Robinson, Moshe Talpaz, Arul M. Chinnaiyan. JAMA Oncol. Published online 2021. doi:10.1001/jamaoncol.2020.7987
https://jamanetwork.com/journals/jamaoncology/fullarticle/2776760?guestAccessKey=a801e653-2ce4-41a0-9c72-f548fc2dc720&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jamaoncology&utm_term=mostread&utm_content=olf-widget_03092021

Key Points

Question What is the clinical utility of genomic profiling for patients with advanced solid tumors?

Findings In this cohort study of 1015 patients who underwent integrative genomic profiling, a high rate of pathogenic germline variants and a subset of patients who derive substantial clinical benefit from sequencing information were identified.

Meaning These findings support (1) directed germline testing for inherited cancer predisposition in all patients with advanced cancer and (2) use of integrative genomic profiling as a component of standard of care for patients with cancer of unknown origin and other rare malignant neoplasms.

Abstract

Importance Use of next-generation sequencing (NGS) to identify clinically actionable genomic targets has been incorporated into routine clinical practice in the management of advanced solid tumors; however, the clinical utility of this testing remains uncertain.

Objective To determine which patients derived the greatest degree of clinical benefit from NGS profiling.

Design, Setting, and Participants Patients in this cohort study underwent fresh tumor biopsy and blood sample collection for genomic profiling of paired tumor and normal DNA (whole-exome or targeted-exome capture with analysis of 1700 genes) and tumor transcriptome (RNA) sequencing. Somatic and germline genomic alterations were annotated and classified according to degree of clinical actionability. Results were returned to treating oncologists. Data were collected from May 1, 2011, to February 28, 2018, and analyzed from May 1, 2011, to April 30, 2020.

Main Outcomes and Measures Patients' subsequent therapy and treatment response were extracted from the medical record to determine clinical benefit rate from NGS-directed therapy at 6 months and exceptional responses lasting 12 months or longer.

Results During the study period, NGS was attempted on tumors from 1138 patients and was successful in 1015 (89.2%) (MET1000 cohort) (538 men [53.0%]; mean [SD] age, 57.7 [13.3] years). Potentially clinically actionable genomic alterations were discovered in 817 patients (80.5%). Of these, 132 patients (16.2%) received sequencing-directed therapy, and 49 had clinical benefit (37.1%). Exceptional responses were observed in 26 patients (19.7% of treated patients). Pathogenic germline variants (PGVs) were identified in 160 patients (15.8% of cohort), including 49 PGVs (4.8% of cohort) with therapeutic relevance. For 55 patients with carcinoma of unknown primary origin, NGS identified the primary site in 28 (50.9%), and sequencing-directed therapy in 13 patients resulted in clinical benefit in 7 instances (53.8%), including 5 exceptional responses.

Conclusions and Relevance The high rate of therapeutically relevant PGVs identified across diverse cancer types supports a recommendation for directed germline testing in all patients with advanced cancer. The high frequency of therapeutically relevant somatic and germline findings in patients with carcinoma of unknown primary origin and other rare cancers supports the use of comprehensive NGS profiling as a component of standard of care for these disease entities.

Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial

T Shi, J Zhu, Y Feng, D Tu, P Zhang, H Jia, X Huang, Y Cai, S Yin, R Jiang, W Tian, W Gao, J Liu, H Yang, X Cheng, R Zang. Lancet Oncology 22, (4) 439-449 2021 DOI:https://doi.org/10.1016/S1470-2045(21)00006-1
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00006-1/fulltext?rss=yes

Background The benefits of secondary cytoreduction for platinum-sensitive relapsed ovarian cancer are still widely debated. We aimed to assess the efficacy of secondary cytoreduction plus chemotherapy versus chemotherapy alone in this patient population.

Methods This multicentre, open-label, randomised, controlled, phase 3 trial (SOC-1), was done in four primarily academic centres in China (two in Shanghai, one in Hangzhou, and one in Guangzhou). Eligible patients were women aged 18 years and older with platinum-sensitive relapsed epithelial ovarian cancer with a platinum-free interval of at least 6 months after the end of first-line platinum-based chemotherapy and were predicted to have potentially resectable disease according to the international model (iMODEL) score and PET-CT imaging. iMODEL score was calculated using six variables: International Federation of Gynecology and Obstetrics stage, residual disease after primary surgery, platinum-free interval, Eastern Cooperative Oncology Group performance status, serum level of cancer antigen 125 at recurrence, and presence of ascites at recurrence. An iMODEL score of 4·7 or lower predicted a potentially complete resection. As per a protocol amendment, patients with an iMODEL score of more than 4·7 could only be included if the serum level of cancer antigen 125 was more than 105 U/mL, but the principal investigators assessed the disease to be resectable by PET-CT. Eligible participants were randomly assigned (1:1) via

a permuted block design (block size of six) and stratified by study centre, iMODEL score, residual disease at primary surgery, and enrolment in the Shanghai Gynecologic Oncology Group SUNNY trial, to undergo secondary cytoreductive surgery followed by intravenous chemotherapy (six 3-weekly cycles of intravenous paclitaxel [175 mg/m2] or docetaxel [75 mg/m2] combined with intravenous carboplatin [area under the curve of 5 mg/mL per min]; surgery group) or intravenous chemotherapy alone (no surgery group). Primary endpoints were progression-free survival and overall survival, analysed in all participants randomly assigned to treatment, regardless of treatment received (intention-to-treat [ITT] population). Here, we report the final analysis of progression-free survival and the prespecified interim analysis of overall survival. Safety was assessed in all participants who received their assigned treatment and had available adverse event data. This study is registered with ClinicalTrials.gov, NCT01611766, and is ongoing but closed to accrual.

Findings Between July 19, 2012, and June 3, 2019, 357 patients were recruited and randomly assigned to the surgery group (182) or the no surgery group (175; ITT population). Median follow-up was 36·0 months (IQR 18·1–58·3). In the no surgery group, 11 (6%) of 175 participants had secondary cytoreduction during second-line therapy while 48 (37%) of 130 participants who had disease progression crossed-over and had surgery at a subsequent recurrence. Median progression-free survival was 17·4 months (95% CI 15·0–19·8) in the surgery group and 11·9 months (10·0–13·8) in the no surgery group (hazard ratio [HR] 0·58; 95% CI 0·45–0·74; p<0·0001). At the interim overall survival analysis, median overall survival was 58·1 months (95% CI not estimable to not estimable) in the surgery group and 53·9 months (42·2–65·5) in the no surgery group (HR 0·82, 95% CI 0·57–1·19). In the safety population, nine (5%) of 172 patients in the surgery group had grade 3–4 surgical morbidity at 30 days, and no patients in either group had died at 60 days after receiving assigned treatment. The most common grade 3–4 adverse events during chemotherapy were neutropenia (29 [17%] of 166 patients in the surgery group vs 19 [12%] of 156 patients in the no surgery group), leucopenia (14 [8%] vs eight [5%]), and anaemia (ten [6%] vs nine [6%]). Four serious adverse events occurred, all in the surgery group. No treatment-related deaths occurred in either group.

Interpretation Secondary cytoreduction followed by chemotherapy was associated with significantly longer progression-free survival than was chemotherapy alone in patients with platinum-sensitive relapsed ovarian cancer, and patients should be counselled about the option of secondary cytoreduction in specialised centres. Long-term survival outcomes will be assessed using mature data on overall survival.

Endometrial Cancer Risk in Women with Germline BRCA1 or BRCA2 Mutations: Multicenter Cohort Study. MM de Jonge, CD de Kroon, DJ Jenner, J Oosting, JA de Hullu, JM Collée, K van Engelen, I van de Beek, HEBON group, VTHBM Smit, Matti A Rookus, GH de Bock, FE van Leeuwen, T Bosse, OM Dekkers, CJ van Asperen.

JNCI: Journal of the National Cancer Institute, 2021;, djab036, https://doi.org/10.1093/jnci/djab036
https://academic.oup.com/jnci/advance-article/doi/10.1093/jnci/djab036/6169002?rss=1

Background Endometrial cancer (EC) risk in BReast CAncer gene 1/2 (*BRCA1/2)* mutation carriers is uncertain, therefore we assessed this in a large Dutch nationwide cohort study.

Methods 5,980 *BRCA1/2* (3,788 *BRCA1*, 2,151 *gBRCA2*, 41 both *BRCA1/BRCA2)* and 8,451 non-*BRCA1/2* mutation carriers were selected from the HEBON-cohort. Follow-up started at date of nationwide PALGA coverage (January 1, 1989) or at the age of 25 years (whichever came last), and ended at date of EC diagnosis, last follow-up or death (whichever came first). EC risk in *BRCA1/2* mutation carriers was compared to: 1) general population, estimating standardized incidence ratios (SIRs) based on Dutch population-based incidence rates; and 2) non-BRCA1/2 mutation carriers, using Cox-regression analyses, expressed as hazard ratio (HR). Statistical tests were two-sided.

Results Fifty-eight *BRCA1/2* and 33 non-*BRCA1/2* mutation carriers developed EC over 119,296 and 160,841 person-years, respectively (SIR = 2.83, 95% confidence interval (CI) = 2.18–3.65; and HR = 2.37, 95% CI = 1.53–3.69, respectively). *gBRCA1* mutation carriers showed increased risks for EC overall (SIR = 3.51, 95% CI = 2.61–4.72; HR = 2.91, 95% CI = 1.83–4.66), serous-like EC (SIR: 12.64, 95% CI = 7.62–20.96; HR = 10.48, 95% CI = 2.95–37.20), endometrioid EC (SIR = 2.63, 95% CI = 1.80–3.83; HR = 2.01, 95% CI = 1.18–3.45) and *TP53*-mutated EC (HR = 15.71, 95% CI = 4.62–53.40). For *BRCA2* mutation carriers, overall (SIR = 1.70, 95% CI = 1.01–2.87), and serous-like EC risks (SIR = 5.11, 95% CI = 1.92–13.63) were increased when compared to the general population. Absolute risks by 75 years remained low (overall EC = 3.0%; serous-like EC = 1.1%).

Conclusions

BRCA1/2 mutation carriers have a 2- to 3-fold increased risk for EC, with highest risk observed for the rare subgroups of serous-like and p53-abnormal EC in *BRCA1* mutation carriers.

Effectiveness of Sequential Chemoradiation vs Concurrent Chemoradiation or Radiation Alone in Adjuvant Treatment After Hysterectomy for Cervical Cancer. The STARS Phase 3 Randomized Clinical Trial. Huang, Y-L Feng, T Wan, Y-N Zhang, X-P Cao, Y-W Huang, Y Xiong, X Huang, M Zheng, Y-F Li, J-D Li, G-D Chen, H Li, Y-L Chen, L-G Ma, H-Y Yang, L Li, S-Z Yao, W-J Ye, H Tu, Q-D Huang, L-Z Liang, F-Y Liu, Q Liu, J-H Liu. JAMA Oncol. 2021;7(3):361-369. doi:10.1001/jamaoncol.2020.7168 https://jamanetwork.com/journals/jamaoncology/article-abstract/2774871?guestAccessKey=f9cb8d8b-46af-46ff-a4af-517882d8d70b&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jamaoncology&utm_content=etoc&utm_term=031821

Key Points

Question When compared with radiation alone, does sequential chemoradiation or concurrent chemoradiation improve disease-free survival (DFS) in patients with early-stage cervical cancer after radical hysterectomy?

Findings In this phase 3 randomized clinical trial of 1048 eligible women, sequential chemoradiation improved 3-year DFS and distant DFS compared with concurrent chemoradiation or radiation alone, with tolerable toxic effects, especially in patients with high-risk factors. However, no substantial improvements in survival were seen among patients receiving concurrent chemoradiation compared with radiation alone.

Meaning Sequential chemoradiation may be an optimal adjuvant treatment after radical hysterectomy for early-stage cervical cancer.

Abstract

Importance There is no current consensus on the role of chemotherapy in addition to radiation for postoperative adjuvant treatment of patients with early-stage cervical cancer with adverse pathological factors.

Objective To evaluate the clinical benefits of sequential chemoradiation (SCRT) and concurrent chemoradiation (CCRT) compared with radiation alone (RT) as a postoperative adjuvant treatment in early-stage cervical cancer.

Design, Setting, and Participants After radical hysterectomy at 1 of 8 participating hospitals in China, patients with FIGO (International Federation of Gynecology and Obstetrics) stage IB to IIA cervical cancer with adverse pathological factors were randomized 1:1:1 to receive adjuvant RT, CCRT, or SCRT. Data were collected from February 2008 to December 2018.

Interventions Patients received adjuvant RT (total dose, 45-50 Gy), CCRT (weekly cisplatin, 30-40 mg/m^2), or SCRT (cisplatin, 60-75 mg/m^2, plus paclitaxel, 135-175 mg/m^2) in a 21-day cycle, given 2 cycles before and 2 cycles after radiotherapy, respectively.

Main Outcomes and Measures The primary end point was the rate of disease-free survival (DFS) at 3 years.

Results A total of 1048 women (median [range] age, 48 [23-65] years) were included in the analysis (350 in the RT group, 345 in the CCRT group, and 353 in the SCRT group). Baseline demographic and disease characteristics were balanced among the treatment groups except that the rate of lymph node involvement was lowest in the RT group (18.3%). In the intention-to-treat population, SCRT was associated with a higher rate of DFS than RT (3-year rate, 90.0% vs 82.0%; hazard ratio [HR], 0.52; 95% CI, 0.35-0.76) and CCRT (90.0% vs 85.0%; HR, 0.65; 95% CI, 0.44-0.96). Treatment with SCRT also decreased cancer death risk compared with RT (5-year rate, 92.0% vs 88.0%; HR, 0.58; 95% CI, 0.35-0.95) after adjustment for lymph node involvement. However, neither DFS nor cancer death risk was different among patients treated with CCRT or RT.

Conclusions and Relevance In this randomized clinical trial, conducted in a postoperative adjuvant treatment setting, SCRT, rather than CCRT, resulted in a higher DFS and lower risk of cancer death than RT among women with early-stage cervical cancer.

Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. A Poveda, A Floquet, JA Ledermann, R Asher, RT Penson, AM Oza, J Korach, T Huzarski, S Pignata, M Friedlander, A Baldoni, T-W Park-Simon, GS Sonke, A Lisyanskaya, J-H Kim, EA Filho, T Milenkova, ES Lowe, P Rowe I Vergote, E Pujade-Lauraine, theSOLO2/ENGOT-Ov21 investigators.

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https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00073-5/fulltext?rss=yes&utm_campaign=update-lanonc&utm_medium=email&_hsmi=117189311&_hsenc=p2ANqtz-9EPxLwC5YpwNQYlbMUc4tRi_ulFQ4cs7FqzXTK4qT62KVsbWFMwEv0SOFbOP4bGKtGIUNSSCe92qVZrq9dK-8XaSH1_A&utm_content=117189311&utm_source=hs_email

Background Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, has previously been shown to extend progression-free survival versus placebo when given to patients with relapsed high-grade serous or endometrioid ovarian cancer who were platinum sensitive and who had a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation, as part of the SOLO2/ENGOT-Ov21 trial. The aim of this final analysis is to investigate the effect of olaparib on overall survival.

Methods This double-blind, randomised, placebo-controlled, phase 3 trial was done across 123 medical centres in 16 countries. Eligible patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status at baseline of 0–1, had histologically confirmed, relapsed, high-grade serous or high-grade endometrioid ovarian cancer, including primary peritoneal or fallopian tube cancer, and had received two or more previous platinum regimens. Patients were randomly assigned (2:1) to receive olaparib tablets (300 mg in two 150 mg tablets twice daily) or matching placebo tablets using an interactive web or voice-response system. Stratification was by response to previous chemotherapy and length of platinum-free interval. Treatment assignment was masked to patients, treatment providers, and data assessors. The primary endpoint of progression-free survival has been reported previously. Overall survival was a key secondary endpoint and was analysed in all patients as randomly allocated. Safety was assessed in all patients who received at least one treatment dose. This trial is registered with ClinicalTrials.gov, NCT01874353, and is no longer recruiting patients.

Findings Between Sept 3, 2013 and Nov 21, 2014, 295 patients were enrolled. Patients were randomly assigned to receive either olaparib (n=196 [66%]) or placebo (n=99 [34%]). One patient, randomised in error, did not receive olaparib. Median follow-up was 65·7 months (IQR 63·6–69·3) with olaparib and 64·5 months (63·4–68·7) with placebo. Median overall survival was 51·7 months (95% CI 41·5–59·1) with olaparib and 38·8 months (31·4–48·6) with placebo (hazard ratio 0·74 [95% CI 0·54–1·00]; p=0·054), unadjusted for the 38% of patients in the placebo group who received subsequent PARP inhibitor therapy. The most common grade 3 or worse treatment-emergent adverse event was anaemia (which occurred in 41 [21%] of 195 patients in the olaparib group and two [2%] of 99 patients in the placebo group). Serious treatment-emergent adverse events were reported in 50 (26%) of 195 patients receiving olaparib and eight (8%) of 99 patients receiving placebo. Treatment-emergent adverse events with a fatal outcome occurred in eight (4%) of the 195 patients receiving olaparib, six of which were judged to be treatment-related (attributed to myelodysplastic syndrome [n=3] and acute myeloid leukaemia [n=3]).

Interpretation Olaparib provided a median overall survival benefit of 12·9 months compared with placebo in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation. Although statistical significance was not reached, these findings are arguably clinically meaningful and support the use of maintenance olaparib in these patients.

Sequencing chemotherapy before radiotherapy for women with stage IIIC endometrial cancer

D Narasimhulu, MS Block, ALWeaver, M McGree, A Kumar, C Langstraat, I Petersen A Mariani & G Glaser. International Journal of Gynecologic Cancer Published Online First: 26 March 2021. doi: 10.1136/ijgc-2020-002158

https://ijgc.bmj.com/content/early/2021/03/24/ijgc-2020-002158.abstract

Objective It is unclear how to best sequence adjuvant chemotherapy and radiotherapy for advanced endometrial cancer. We studied the outcomes for women treated with chemotherapy before radiotherapy in a chemotherapy-first (chemotherapy for 6 cycles followed radiotherapy) or 'sandwich' approach (chemotherapy for 3 cycles followed by radiotherapy and subsequently chemotherapy for 3 cycles).

Methods Women with stage IIIC endometrial cancer and no gross residual disease treated with chemotherapy before radiotherapy between April 2003 and April 2016 were included. The Kaplan-Meier method was used to estimate recurrence and survival. We performed a meta-analysis of endometrial cancer trials comparing chemotherapy and radiotherapy versus radiotherapy alone.

Results A total of 102 patients were included. The mean (SD) age was 63.8 (10.6) years; 84 patients received the chemotherapy-first approach and 18 patients received the 'sandwich' approach. Pelvic and para-aortic nodes were removed in 99% and 88.2%, respectively. Among all the patients, we observed 1 pelvic (1%), 1 para-aortic (1%), and 5 vaginal (4.9%) recurrences. At 3 years, for the 'sandwich' and chemotherapy-first approaches, the vaginal recurrence was 11.8% and 4.2%, pelvic recurrence was 0% and 1.5%, para-aortic recurrence was 0% and 1.2%, distant recurrence was 42.9% and 24.4%, and overall survival was 70.3% and 81.7%, respectively. With 'chemotherapy before radiotherapy' 94.9% completed 4+ chemotherapy cycles (vs 71–90% reported in the literature for 'radiotherapy before chemotherapy'). In a meta-analysis of endometrial cancer trials, distant recurrence rates were reduced with 4+ chemotherapy cycles but not with 3 cycles (p=0.01).

Conclusion Chemotherapy before radiation sequencing for stage IIIC endometrial cancer was associated with a high proportion of patients completing 4+ chemotherapy cycles and low locoregional lymphatic recurrence rate, despite delaying radiotherapy until after 3–6 cycles of chemotherapy and not administering concurrent cisplatin.

Point-of-Care Digital Cytology With Artificial Intelligence for Cervical Cancer Screening in a Resource-Limited Setting. O Holmström, N Linder, H Kaingu, N Mbuuko, J Mbete, F Kinyua, S Törnquist, M Muinde, La Krogerus, M Lundin, V Diwan, J Lundin. JAMA Netw Open. 2021;4(3):e211740. doi:10.1001/jamanetworkopen.2021.1740 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2777600

Key Points

Question Can point-of-care digital microscopy with artificial intelligence–based sample assessment be implemented at a clinic in a resource-limited setting where access to pathologists is limited and used to analyze Papanicolaou test results?

Findings In this proof-of-concept diagnostic study, Papanicolaou test results from 740 women were collected, digitized at a rural clinic in Kenya, and analyzed with a deep learning algorithm to detect atypical samples. The sensitivity for detection of atypia was high (96%-100%), with higher specificity for high-grade lesions (93%-99%) than for low-grade lesions (82%-86%), and no slides manually classified as high grade were incorrectly classified as negative.

Meaning The results of this study suggest that advanced digital microscopy diagnostics, supported by artificial intelligence, are feasible to use in rural, resource-limited settings for detection of abnormal cells in Papanicolaou tests.

Abstract

Importance Cervical cancer is highly preventable but remains a common and deadly cancer in areas without screening programs. The creation of a diagnostic system to digitize Papanicolaou test samples and analyze them using a cloud-based deep learning system (DLS) may provide needed cervical cancer screening to resource-limited areas.

Objective To determine whether artificial intelligence–supported digital microscopy diagnostics can be implemented in a resource-limited setting and used for analysis of Papanicolaou tests.

Design, Setting, and Participants In this diagnostic study, cervical smears from 740 HIV-positive women aged between 18 and 64 years were collected between September 1, 2018, and September 30, 2019. The smears were digitized with a portable slide scanner, uploaded to a cloud server using mobile networks, and used to train and validate a DLS for the detection of atypical cervical cells. This single-center study was conducted at a local health care center in rural Kenya.

Exposures Detection of squamous cell atypia in the digital samples by analysis with the DLS.

Main Outcomes and Measures The accuracy of the DLS in the detection of low- and high-grade squamous intraepithelial lesions in Papanicolaou test whole-slide images.

Results Papanicolaou test results from 740 HIV-positive women (mean [SD] age, 41.8 [10.3] years) were collected. The DLS was trained using 350 whole-slide images and validated on 361 whole-slide images (average size, 100 387 × 47 560 pixels). For detection of cervical cellular atypia, sensitivities were 95.7% (95% CI, 85.5%-99.5%) and 100% (95% CI, 82.4%-100%), and specificities were 84.7% (95% CI, 80.2%-88.5%) and 78.4% (95% CI, 73.6%-82.4%), compared with the pathologist assessment of digital and physical slides, respectively. Areas under the receiver operating characteristic curve were 0.94 and 0.96, respectively. Negative predictive values were high (99%-100%), and accuracy was high, particularly for the detection of high-grade lesions. Interrater agreement was substantial compared with the pathologist assessment of digital slides ($\kappa = 0.72$) and fair compared with the assessment of glass slides ($\kappa = 0.36$). No samples that were classified as high grade by manual sample analysis had false-negative assessments by the DLS.

Conclusions and Relevance In this study, digital microscopy with artificial intelligence was implemented at a rural clinic and used to detect atypical cervical smears with a high sensitivity compared with visual sample analysis.

Addressing cervical cancer screening disparities through advances in artificial intelligence and nanotechnologies for cellular profiling featured. Z Yang, J Francisco, AS Reese, DR Spriggs, H Im), CM Castro. Biophysics Rev. 2, 011303 (2021); https://doi.org/10.1063/5.0043089 https://aip.scitation.org/doi/10.1063/5.0043089

Almost all cases of cervical cancer are caused by the human papilloma virus (HPV). Detection of pre-cancerous cervical changes provides a window of opportunity for cure of an otherwise lethal disease when metastatic. With a greater understanding of the biology and natural course of high-risk HPV infections, screening methods have shifted beyond subjective Pap smears toward more sophisticated and objective tactics. This has led to a substantial growth in the breadth and depth of HPV-based cervical cancer screening tests, especially in developed countries without constrained resources. Many low- and middle-income countries (LMICs) have less access to advanced laboratories and healthcare resources, so new point-of-care (POC) technologies have been developed to provide test results in real time, improve the efficiency of techniques, and increase screening adoption. In this Review, we will discuss how novel decentralized screening technologies and computational strategies improve upon traditional methods and how their realized promise could further democratize cervical cancer screening and promote greater disease prevention.

Effective methylation triage of HPV positive women with abnormal cytology in a middle-income country. AT Ramírez, GI Sánchez, B Nedjai, MC Agudelo, AR Brentnall, K Cuschieri, KM Castañeda, J Cuzick, AT Lorincz. International Journal of Cancer 148 (5) 1383-1393. https://doi.org/10.1002/ijc.33314 https://onlinelibrary.wiley.com/doi/10.1002/ijc.33314

The S5-methylation test, an alternative to cytology and HPV16/18 genotyping to triage high-risk HPV-positive (hrHPV+) women, has not been widely validated in low-middle-income countries (LMICs). We compared S5 to HPV16/18 and cytology to detect cervical intraepithelial neoplasia Grade 2 or worse (CIN2+) and CIN3+ in hrHPV+ women selected from a randomized pragmatic trial of 2661 Colombian women with an earlier-borderline abnormal cytology. We included all hrHPV+ CIN2 and CIN3+ cases (n = 183) age matched to 183 <CIN2 hrHPV+. Baseline specimens were HPV-genotyped and tested by S5-methylation, blinded to cytology, histology and initial HPV results. We evaluated the test performance of predefined S5-classifier (cut-point 0.8) and a post hoc classifier at a different cut-point (3.1). S5 sensitivity for CIN2+ was 82% (95% confidence interval [CI] 76.4-87.5) and for CIN3+ 77.08% (95% CI 65.19-88.97). S5 sensitivity was higher than HPV16/18 sensitivity (48.1%, 95% CI 40.85-55.33) or cytology (31.21%, 95% CI 24.50-37.93) but with lower specificity (35%, 95% CI 28.1-42). At cut-point 3.1, S5 sensitivity for CIN2+ (55.2%, 95% CI 48-62.4) or CIN3+ (64.6%, 95% CI 51.0-78.1) was also superior to HPV16/18 (P < .05) or cytology (P < .0001). At this cut-point S5 specificity (76%, 95% CI 69.8-82.1 for <CIN2) was higher than HPV16/18 (67.21%, 95% CI 60.41-74.01, P = .0062) and similar to cytology (75.57%, 95% CI 69.34-81.79, P = 1). HPV16/18 plus cytology sensitivity was similar to S5 for CIN3+, however, false-positive rate was higher (50.27% vs. 24.04%). High sensitivity is crucial in LMICs, S5-methylation exceeded HPV16/18 or cytology sensitivity with comparable specificity for CIN2+ and CIN3+ in hrHPV-positive Colombian women. Furthermore, S5 triage had comparable sensitivity and significantly fewer false positives than cytology and HPV16/18 combination.

Specialist oncological surgery for removal of the ovaries and fallopian tubes in BRCA1 and BRCA2 pathogenic variant carriers may reduce primary peritoneal cancer risk to very low levels

EJ Crosbie, N Flaum, EF Harkness, RD Clayton, C Holland, P Martin-Hirsch, N Wood, P Keating, ER Woodward, F Lalloo, P Donnai, RJ Edmondson, DG Evans. International Journal of Cancer 148 (5) 1155-1163. https://doi.org/10.1002/ijc.33378 https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.33378

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is highly effective for the prevention of high-grade serous ovarian cancer (HGSOC) in BRCA1/2 pathogenic variant carriers (PVCs), but does not completely eliminate future risk of primary peritoneal cancer (PPC). The requirement to completely remove fallopian tubes at RRBSO and carefully exclude occult cancer/serous tubal intraepithelial carcinoma (STIC) lesions may not have been appreciated historically. We calculated rates of HGSOC and PPC in confirmed BRCA1/2 PVCs registered on the regional database in those who did (cases) and did not (controls) undergo RRBSO after genetic testing. Expected annual rates of ovarian/peritoneal cancer were 1% for BRCA1 ≥ 35 years and 0.5% for BRCA2 ≥ 45 years. Follow-up before 35/45 years was "risk free" and lead time excluded RRBSO <35 years and <45 years for BRCA1 and BRCA2, respectively. Women were followed from personal mutation report (controls) or RRBSO (cases) to death, ovarian/peritoneal cancer or last follow-up, whichever was sooner. In total, 891 cases (BRCA1 = 468, BRCA2 = 423) and 1302 controls had follow-up ≥35 years (BRCA1 = 736) and ≥45 years (BRCA2 = 566), respectively, over a total of 7261.1 risk eligible years (mean = 8.15 years). Twenty-one occult ovarian cancers were found at RRBSO (2.4%), 16 at stage 1. Post RRBSO, 56.97 ovarian/peritoneal cancers were expected but only 3 were observed (HR = 0.053; 95% CI = 0.013-0.14), with combined Kaplan-Meier analysis HR = 0.029 (95% CI = 0.009-0.100, P < .001). Risk reduction was greater in specialist (HR = 0.03; 95% CI = 0.001-0.13) compared to non-specialist centres (HR = 0.11; 95% CI = 0.02-0.37) (P = .07). In controls, 23.35 ovarian/peritoneal cancers were expected with 32 observed (HR = 1.37; 95% CI = 0.95-1.91). RRBSO <35/<45 years reduces the risk of ovarian/peritoneal cancer by 95% in BRCA1/2 PVCs and may be greater in specialist centres.

Discovery of a biomarker candidate for surgical stratification in high-grade serous ovarian cancer. H Lu, P Cunnea, K Nixon, N Rinne, EO Aboagye & C Fotopoulou. Br J Cancer 124, 1286–1293 (2021). https://doi.org/10.1038/s41416-020-01252-2 https://www.nature.com/articles/s41416-020-01252-2

Background Maximal effort cytoreductive surgery is associated with improved outcomes in advanced high-grade serous ovarian cancer (HGSOC). However, despite complete gross resection (CGR), there is a percentage of patients who will relapse and die early. The aim of this study is to identify potential candidate biomarkers to help personalise surgical radicality.

Methods 136 advanced HGSOC cases who underwent CGR were identified from three public transcriptomic datasets. Candidate prognostic biomarkers were discovered in this cohort by Cox regression analysis, and further validated by targeted RNA-sequencing in HGSOC cases from Imperial College Healthcare NHS Trust (n = 59), and a public dataset. Gene set enrichment analysis was performed to understand the biological significance of the candidate biomarker.

Results We identified ALG5 as a prognostic biomarker for early tumour progression in advanced HGSOC despite CGR (HR = 2.42, 95% CI (1.57–3.75), $p < 0.0001$). The prognostic value of this new candidate biomarker was additionally confirmed in two independent datasets (HR = 1.60, 95% CI (1.03–2.49), $p = 0.0368$; HR = 3.08, 95% CI (1.07–8.81), $p = 0.0365$). Mechanistically, the oxidative phosphorylation was demonstrated as a potential biological pathway of ALG5-high expression in patients with early relapse ($p < 0.001$).

Conclusion ALG5 has been identified as an independent prognostic biomarker for poor prognosis in advanced HGSOC patients despite CGR. This sets a promising platform for biomarker combinations and further validations towards future personalised surgical care.

Tumour-free distance: a novel prognostic marker in patients with early-stage cervical cancer treated by primary surgery. D Cibula, J Slama, L Dostálek, D Fischerová, A Germanova, F Frühauf, P Dundr, K Nemejcova, J Jarkovsky, S Sebestova, A Burgetová, M Borčinová & R Kocián. Br J Cancer 124, 1121–1129 (2021). https://doi.org/10.1038/s41416-020-01204-w https://www.nature.com/articles/s41416-020-01204-w

Background Models predicting recurrence risk (RR) of cervical cancer are used to tailor adjuvant treatment after radical surgery. The goal of our study was to compare available prognostic factors and to develop a prognostic model that would be easy to standardise and use in routine clinical practice.

Methods All consecutive patients with early-stage cervical cancer treated by primary surgery in a single referral centre (01/2007–12/2016) were eligible if assessed by standardised protocols for pre-operative imaging and pathology. Fifteen prognostic markers were evaluated in 379 patients, out of which 320 lymph node (LN)-negative.

Results The best predictive model for the whole cohort entailed a combination of tumour-free distance (TFD) ≤ 3.5 mm and LN positivity, which separated two subgroups with a substantially distinct RR 36% and 6.5%, respectively. In LN-negative patients, a combination of TFD ≤ 3.5 mm and adenosquamous tumour type separated a group of nine patients with RR 33% from the rest of the group with 6% RR.

Conclusions A newly identified prognostic marker, TFD, surpassed all traditional tumour-related markers in the RR assessment. Predictive models combining TFD, which can be easily accessed on pre-operative imaging, with LN status or tumour type can be used in daily practice and can help to identify patients with the highest RR.

Biomarkers for site-specific response to neoadjuvant chemotherapy in epithelial ovarian cancer: relating MRI changes to tumour cell load and necrosis. JM Winfield, JC Wakefield, JD Brenton, K AbdulJabbar, A Savio, S Freeman, E Pace, K Lutchman-Singh, K M. Vroobel, Y Yuan, S Banerjee, N Porta, SEA Raza & NM deSouza. Br J Cancer 124, 1130–1137 (2021). https://doi.org/10.1038/s41416-020-01217-5 https://www.nature.com/articles/s41416-020-01217-5

Background Diffusion-weighted magnetic resonance imaging (DW-MRI) potentially interrogates site-specific response to neoadjuvant chemotherapy (NAC) in epithelial ovarian cancer (EOC).

Methods Participants with newly diagnosed EOC due for platinum-based chemotherapy and interval debulking surgery were recruited prospectively in a multicentre study (n = 47 participants). Apparent diffusion coefficient (ADC) and solid tumour volume (up to 10 lesions per participant) were obtained from DW-MRI before and after NAC (including double-baseline for repeatability assessment in n = 19). Anatomically matched lesions were analysed after surgical excision (65 lesions obtained from 25 participants). A trained algorithm determined tumour cell fraction, percentage tumour and percentage necrosis on histology. Whole-lesion post-NAC ADC and pre/post-NAC ADC changes were compared with histological metrics (residual tumour/necrosis) for each tumour site (ovarian, omental, peritoneal, lymph node).

Results Tumour volume reduced at all sites after NAC. ADC increased between pre- and post-NAC measurements. Post-NAC ADC correlated negatively with tumour cell fraction. Pre/post-NAC changes in ADC correlated positively with percentage necrosis. Significant correlations were driven by peritoneal lesions.

Conclusions Following NAC in EOC, the ADC (measured using DW-MRI) increases differentially at disease sites despite similar tumour shrinkage, making its utility site-specific. After NAC, ADC correlates negatively with tumour cell fraction; change in ADC correlates positively with percentage necrosis.

Ovarian cancer prognosis in women with endometriosis: a retrospective nationwide cohort study of 32,419 women. M Hermens, AM van Altena, M van der Aa, J Bulten, HAAM. van Vliet, AG Siebers, RLM Bekkers. Amer J Obstet Gyn 224 (3), P284.E1-284.E10, 2021 DOI:https://doi.org/10.1016/j.ajog.2020.08.056 https://www.ajog.org/article/S0002-9378(20)30883-8/fulltext

Background Contradicting results regarding ovarian cancer prognosis in women with endometriosis have been reported in the literature. Owing to the small sample size of previous studies, larger studies are required to elucidate the role of endometriosis in ovarian cancer prognosis.

Objective This study aimed to evaluate the survival rate in women with ovarian cancer with or without histologically proven endometriosis in a Dutch population-based cohort.

Study Design

All women with ovarian cancer diagnosed between 1990 and 2015 were identified from the Netherlands Cancer Registry. We linked these women with the Dutch nationwide registry of histopathology and cytopathology (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief) to identify all women with histologically proven endometriosis. We compared the prognosis of patients with ovarian cancer with and without histologically proven endometriosis. Primary outcome was the overall survival with subgroup analyses stratified by histologic ovarian cancer subtype and stage. Multivariable Cox proportional hazard analysis was used to estimate hazard ratios with 95% confidence intervals.

Results We included 32,419 patients with ovarian cancer, of whom 1979 (6.1%) had histologically proven endometriosis. The median age of histologic endometriosis diagnosis was 53 years (interquartile range, 46–62). Of all women with ovarian cancer and endometriosis, 81.2% received a diagnosis of synchronous endometriosis and ovarian cancer. The endometriosis cohort was younger at ovarian cancer diagnosis, had more favorable tumor characteristics, and more often had surgical treatment for ovarian cancer than the women without endometriosis. These variables were included in the multivariable model as confounders. Women with histologically proven endometriosis had a significantly better prognosis in both crude and adjusted analyses (hazard ratio, 0.46; 95% confidence interval, 0.43–0.49; P<.0005, and adjusted hazard ratio, 0.89; 95% confidence interval, 0.83–0.95; P<.05, respectively).

Conclusion Women with ovarian cancer and histologically proven endometriosis had longer overall survival than women with ovarian cancer without endometriosis, even after adjustment for confounders. Future studies on ovarian cancer treatment and prognosis should consider stratifying by endometriosis status to elucidate its role. Furthermore, women diagnosed as having ovarian cancer and concurrent endometriosis should be explained the role of endometriosis in ovarian cancer survival.

Expanding Our Understanding of Ovarian Cancer Risk: The Role of Incomplete Pregnancies

AW Lee, S Rosenzweig, A Wiensch, the Australian Ovarian Cancer Study Group, SJ Ramus, U Menon, A Gentry-Maharaj, A Ziogas, H Anton-Culver, AS Whittemore, W Sieh, JH Rothstein, V McGuire, N Wentzensen, EV Bandera, B Qin, KL Terry, DW Cramer, L Titus, JM Schildkraut, A Berchuck, EL Goode, SK Kjaer, A Jensen, SJ Jordan, RB Ness, F Modugno, K Moysich, PJ Thompson, MT Goodman, ME Carney, J Chang-Claude, MA Rossing, HR Harris, JA Doherty, HA Risch, Lilah Khoja, Aliya Alimujiang, Minh Tung Phung, Katharine Brieger, Bhramar Mukherjee, Paul D P Pharoah, Anna H Wu, MC Pike, PM Webb, C Leigh Pearce. JNCI 113 (3) 2021, 301–308, https://doi.org/10.1093/jnci/djaa099 https://academic.oup.com/jnci/article-abstract/113/3/301/5885090?redirectedFrom=fulltext

Background Parity is associated with decreased risk of invasive ovarian cancer; however, the relationship between incomplete pregnancies and invasive ovarian cancer risk is unclear. This relationship was examined using 15 case-control studies from the Ovarian Cancer Association Consortium (OCAC). Histotype-specific associations, which have not been examined previously with large sample sizes, were also evaluated.

Methods A pooled analysis of 10 470 invasive epithelial ovarian cancer cases and 16 942 controls was conducted. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between incomplete pregnancies and

invasive epithelial ovarian cancer were estimated using logistic regression. All models were conditioned on OCAC study, race and ethnicity, age, and education level and adjusted for number of complete pregnancies, oral contraceptive use, and history of breastfeeding. The same approach was used for histotype-specific analyses.

Results Ever having an incomplete pregnancy was associated with a 16% reduction in ovarian cancer risk (OR = 0.84, 95% CI = 0.79 to 0.89). There was a trend of decreasing risk with increasing number of incomplete pregnancies (2-sided Ptrend < .001). An inverse association was observed for all major histotypes; it was strongest for clear cell ovarian cancer.

Conclusions Incomplete pregnancies are associated with a reduced risk of invasive epithelial ovarian cancer. Pregnancy, including incomplete pregnancy, was associated with a greater reduction in risk of clear cell ovarian cancer, but the result was broadly consistent across histotypes. Future work should focus on understanding the mechanisms underlying this reduced risk.

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p16/ki67 and E6/E7 mRNA Accuracy and Prognostic Value in Triaging HPV DNA-Positive Women. PG Rossi, F Carozzi, G Ronco, E Allia, S Bisanzi, A Gillio-Tos, L De Marco, R Rizzolo, D Gustinucci, A Del Mistro, H Frayle, M Confortini, A Iossa, E Cesarini, S Bulletti, B Passamonti, S Gori, L Toniolo, A Barca, L Bonvicini, P Mancuso, F Venturelli, M Benevolo, the New Technology for Cervical Cancer 2 Working Group. JNCI: Journal of the National Cancer Institute, Volume 113, Issue 3, March 2021, Pages 292–300, https://doi.org/10.1093/jnci/djaa105 https://academic.oup.com/jnci/article-abstract/113/3/292/5879994?redirectedFrom=fulltext

Background The study presents cross-sectional accuracy of E6 and E7 (E6/E7) mRNA detection and p16/ki67 dual staining, alone or in combination with cytology and human papillomavirus (HPV)16/18 genotyping, as a triage test in HPV DNA-positive women and their impact on cervical intraepithelial neoplasia (CIN2+) overdiagnosis.

Methods Women aged 25-64 years were recruited. HPV DNA-positive women were triaged with cytology and tested for E6/E7 mRNA and p16/ki67. Cytology positive women were referred to colposcopy, and negatives were randomly assigned to immediate colposcopy or to 1-year HPV retesting. Lesions found within 24 months since recruitment were included. All P values were 2-sided.

Results 40 509 women were recruited, and 3147 (7.8%) tested HPV DNA positive; 174 CIN2+ were found: sensitivity was 61.0% (95% confidence interval [CI] = 53.6 to 68.0), 94.4% (95% CI = 89.1 to 97.3), and 75.2% (95% CI = 68.1 to 81.6) for cytology, E6/E7 mRNA, and p16/ki67, respectively. Immediate referral was 25.6%, 66.8%, and 28.3%, respectively. Overall referral was 65.3%, 78.3%, and 63.3%, respectively. Cytology or p16/ki67, when combined with HPV16/18 typing, reached higher sensitivity with a small impact on referral. Among the 2306 HPV DNA-positive and cytology-negative women, relative CIN2+ detection in those randomly assigned at 1-year retesting vs immediate colposcopy suggests a -28% CIN2+ regression (95% CI = -57% to +20%); regression was higher in E6/E7 mRNA-negatives (Pinteraction = .29). HPV clearance at 1 year in E6/E7 mRNA and in p16/ki67 negative women was about 2 times higher than in positive women (Pinteraction < .001 for both).

Conclusions p16/ki67 showed good performance as a triage test. E6/E7 mRNA showed the highest sensitivity, at the price of too high a positivity rate to be efficient for triage. However, when negative, it showed a good prognostic value for clearance and CIN2+ regression.

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