

F055 - Late-breaking Research: Basic Science/Cutaneous Oncology/Pathology

Saturday, March 2 from 9:00 AM — 11:00 AM

Room 101

9:00 am - 9:10 am

11301 - Declining Incidence of Invasive Melanoma in Adolescents and Young Adults in the United States / Deepti Gupta, MD

BACKGROUND: Melanoma is epidemiologically linked to childhood Ultraviolet (UV) exposure. Data suggests public health campaigns are increasing sun-protective behavior in the United States. We sought to determine whether adolescent and young adult melanoma incidence is decreasing.

STUDY TYPE: Clinical study, Cutaneous Oncology and Pediatrics

METHODS: Registry data was extracted from the NPCR-SEER database, which captures >99% of US cancers for the years 2001-2015 including 988103 invasive melanomas. Analyses were stratified by sex, and incidence rates age-adjusted to the 2000 US standard population. Annual percentage change was calculated over the most recent decade (2006-2015) using the weighted least-squares method.

RESULTS: For all persons, melanoma cases in the US increased from 61,551 in the year 2006 to 83,362 in the year 2015 (+35%) with an associated significant rise in population-adjusted incidence. In contrast, among 10-19 year old adolescents and 20-29 year old young adults, the absolute number of cases (2,903 in 2006; 2,224 in 2015; -23%) and incidence rates declined, with a significant annual percentage change in incidence of -4.4% for adolescent males, -5.4% for adolescent females, and -3.7% and -3.6% for young adult males and females respectively ($p < 0.05$). Skin pigmentation and sun protective behavior information were unavailable; data are similar when limiting to non-Hispanic whites. Young adult women continue to have twice the risk of melanoma as men.

CONCLUSIONS: Invasive melanoma incidence in the US decreased in adolescents and young adults from 2006-2015, and this contrasted sharply with incidence trends in older populations. These incidence trends suggest public health efforts may be positively impacting melanoma incidence in the US.

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11260 - Relationship of Cutaneous and Noncutaneous Malignant Melanoma in Persons with Multiple Primary Tumors / Kourosh Beroukhi, MD

Background: The shared progenitor cell type among cutaneous and noncutaneous melanomas suggests that patients with a history of primary cutaneous melanoma may be at higher risk for subsequent noncutaneous melanoma. This has led some dermatologists to advocate periodic ophthalmologic, dental, and gynecologic examinations for patients with a history of cutaneous melanoma.

Purpose: To determine whether patients with primary cutaneous melanoma demonstrate an increased risk of second primary melanoma, including cutaneous, ocular, oral, vaginal/vulvar, and penile melanoma.

Design: Population-based retrospective cohort study.

Methods: Using the Surveillance, Epidemiology, and End Results database, we obtained standardized incidence ratios and excess absolute risks of second primary cutaneous, ocular, oral, vaginal/vulvar, and penile melanoma in patients with prior primary cutaneous melanoma diagnosed between 1973 and 2015.

Results: Patients with cutaneous melanoma (n=163,365) were more likely than the general population to develop a second primary cutaneous melanoma (observed to expected [O:E] ratio=8.2; 95% confidence interval [CI]=8.0-8.4), ocular melanoma (O:E=2.0; 95% CI=1.6-2.6), oral melanoma (O:E = 8.4; 95% CI=3.4-17.3), vaginal/vulvar melanoma (O:E=2.5; 95% CI=1.2-6.4), and penile melanoma (O:E=12.3; 95% CI=2.5-36.0). Risk for second primary melanoma was most increased among non-whites. The risk for second primary cutaneous, ocular, and oral melanoma was more pronounced in women compared to men.

Conclusions: Our research indicates that patients with cutaneous melanoma are at increased risk for subsequent primary cutaneous and noncutaneous melanoma. In caring for patients with a history of cutaneous melanoma, physicians should be vigilant not only about risk of recurrence, but also about second primary cutaneous and noncutaneous melanoma.

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11370 - Meta-analysis of the Prognostic 31-gene Expression Profile Test in 1261 Cutaneous Melanoma Cases / Bradley N. Greenhaw, MD

Background: The 31-gene expression profile (31-GEP) test for cutaneous melanoma stratifies the likelihood of developing metastasis within 5 years into low risk (Class 1A lowest risk) and high risk (Class 2B highest risk).

Type of Study/Methods: Using raw 31-GEP data from three published studies¹⁻³ (n=1261 total, n=989 Class 1A or 2B), we performed a meta-analysis evaluating the association of GEP class with recurrence-free (RFS), distant metastasis-free (DMFS), and melanoma-specific survival (MSS) using multivariate analysis in the following studies: Greenhaw¹ (1A: n=193;2B: n=16), Hsueh² (1A: n=206;2B: n=48), and Gastman³ (1A: n=312;2B: n=214).

Results: In each study, a Class 2B result from the 31-GEP was an independent predictor of risk. The hazard ratios (HR) for RFS were: 7.78(95%CI 1.00-60.47)¹, 3.11(95%CI 1.99-4.84)², and 5.60(95%CI 1.27-24.64)³, respectively. In the Hsueh and Gastman datasets, where DMFS was reported, the HRs were 5.78 (95%CI 0.49-68.10)² and 3.20 (95%CI 1.88-5.45)³. Meta-analysis revealed that the combined HRs across studies were 3.38 (95%CI 2.23-5.12; p<0.0001) and 3.29 (95%CI 1.95-5.53; p<0.0001) for RFS and DMFS, respectively. No melanoma-specific deaths were observed in the Class 1A subgroup of the prospective study reporting MSS¹ and thus prevented meta-analysis of MSS. In a meta-analysis of only the two prospective studies^{1,2}, the HR for RFS was 6.27 (95%CI 1.89-20.83; p<0.01).

Conclusion: This study represents the first-ever meta-analysis of a clinical GEP test, which represents the highest level of evidence for clinical prognostic tests, and its results indicate that the 31-GEP test is a robust and independent prognostic marker of RFS, DMFS, and MSS.

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11385 - Characterizing Trends in Utilization of Mohs Micrographic Surgery for Melanoma in the United States / Michael Lee

Mohs micrographic surgery (MMS) for melanoma has been increasingly utilized between 2003 and 2012 in the United States according to SEER data,^{1,2} but data from outside the SEER registries is lacking. Additionally, despite several case series demonstrating the utility of immunostaining with MMS for melanoma,^{3,4} it is unclear how the use of immunostaining has changed over time.

To further characterize the trends of MMS for melanoma and immunostaining, a cross-sectional analysis of surgical excision for melanoma was performed using the Optum© Clinformatics® DataMart de-identified commercial claims database from 2001-2016. Melanoma cases were identified by ICD 9th and 10th edition and linked to CPT codes for narrow excision, wide excision, MMS, and immunohistochemistry (IHC). Between 2001 and 2016, MMS for melanoma increased from 2.2% to 7.5% of all melanoma cases treated with surgical excision. MMS with IHC for melanoma also increased during this time from 10.8% to 40.2% of all melanoma cases treated with MMS. Variations across geographic census divisions were also seen through the years. For instance in 2016, 13% of melanoma cases treated with surgical excision were managed with MMS in East South Central Division in contrast to only 4.1% in the New England Division.

While utilization of MMS for melanoma continues to increase, large regional variations exist. Variations in practice patterns identify opportunities for standardizing care to improve patient outcomes. Prospective comparative studies are needed to better define the role of MMS in the surgical management armamentarium for melanoma.

REFERENCES

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11344 - The Brigham and Women's Hospital Tumor Classification System for Basal Cell Carcinoma / Frederick Morgan, BSPH

Background: Identification of basal cell carcinomas (BCC) having a risk of metastasis or death is challenging due to lack of staging criteria and rare poor outcomes.¹ The objective of this study was to identify risk factors independently associated with disease-related outcomes in large (≥ 2 cm) BCC and to develop a tumor (T) classification system for BCC.

Type of Study: Retrospective cohort study

Methods: Primary BCC diagnosed at two academic hospitals between 2000 and 2009 were retrospectively screened for tumor diameter. All large BCC and an equal number of randomly-selected small BCC were reviewed for disease-related outcomes (DRO: local recurrence [LR]; metastasis and/or death [M/D]).

Results: 248 large BCC and 248 small BCC were included. On multivariable logistic regression, three risk factors (RFs: head/neck location, tumor diameter ≥ 4 cm, and depth beyond fat) were found to be significant predictors of M/D in large BCC. A T classification system featuring three classifications (T1, T2, T3) was developed. T3 tumors (those ≥ 2 cm and with ≥ 2 RFs) accounted for just 25% of large BCCs but 82% of their DROs (71% of LR and 100% of M/D). The 10-year cumulative incidence of LR and M/D in the 49 T3 tumors was 47% (95% CI, 28-70%) and 37% (21-60%), respectively.

Conclusions: This study identifies a subset of BCC with significant risk of LR and M/D. The risk of metastasis may be high enough in T3 tumors to consider clinical trials of adjuvant therapy, particularly if these findings are validated in another cohort.

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11381 - Trends in Skin Cancer Treatment Costs in Massachusetts, 2012-2015 / Emily Ruiz, MD, MPH

Background: Skin cancer is the costliest cancer in the United States. Prior resource allocation studies have primarily focused on Medicare beneficiaries. However, there are no comprehensive cost analysis that evaluate skin cancer treatment costs in both Medicare and privately insured patients.

Type of Study: Cross-section study from 2012-2015

Methods: Massachusetts APCD was queried from 2012 to 2015 for claims filed for International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification codes for malignant melanoma (MM), squamous cell carcinoma (SCC), basal cell carcinoma (BCC), other malignant neoplasm of skin (OMN), carcinoma in situ (CIS), and actinic keratosis (AK). Claims associated with skin cancer-related diagnoses were analyzed by Current Procedure Terminology (CPT) code to determine how resources were allocated.

Results: In Massachusetts, total skin cancer related costs increased by 20% from \$131 million in 2012 to \$158 million in 2015. Similarly, the number of patients increased by 19% from 257,000 in 2012 to 305,000 in 2015. MM and OMN costs increased at a disproportionate rate compared to the number of patients treated (total cost: MM: 41%, OMN: 29% vs. number of patients: MM: 7%, OMN: 47%). The increase in treatment costs was primarily driven by increase in patients treated. For example, the per patient cost of Mohs surgery for SCC and BCC decreased by 10% and 3%, respectively, but the number of patients treated increased by 42% and 29%, respectively.

Conclusions: Although skin cancer related costs increased by 20% over the 4-year period, this was due to the rising skin cancer incidence.

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11228 - Cancer Risk in Patients with Keloids: A nationwide population-based cohort study / Kathy Chien-Hui Hong, MD, PhD

Background: Keloid is characterized by exaggerated scar formation, excessive fibroblast proliferation, and collagen deposition. Cancers commonly arise from a fibrotic microenvironment. As keloids are a prototypic fibroproliferative disease, this study investigated whether patients with keloids have an increased cancer risk.

Method: The Taiwan National Health Insurance Research Database was used to examine this association. 17,401 patients of keloids during 1998-2010 were matched by age and gender with 69,604 controls without keloids. The association between keloids and risk of subsequent cancer was estimated by logistic regression. Relative risk (RR) of cancer was determined by Cox proportional hazard regression models.

Results: In total, 893 first-time cases of cancer were identified in the 17,401 patients with keloids. The overall cancer risk was 1.51-fold higher in the keloids group compared to controls. Regarding specific cancers, the keloids group, had a significantly higher risk of skin cancer compared to controls (RR =1.73). The RR for skin cancer was higher for males with keloids (RR= 2.16). Further stratified analyses revealed a significantly higher risk of developing pancreatic cancer in female patients with keloids(RR=2.19) after adjustment for known risk pancreatic cancer risk factors such as chronic pancreatitis, liver cirrhosis and diabetes.

Conclusion: This study indicates that patients with keloids have a higher than normal risk for several cancer types, especially skin cancers (both genders) and pancreatic cancer (females). Therefore, patients with keloids should undergo regular skin examinations, and females with keloids should regularly undergo abdominal ultrasonography.

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11189 - Staphylococcus Dysbiosis Correlates of Success of Treatment of Atopic Dermatitis with the JAK/SYK Inhibitor ASN002 / Avidan U. Neumann, PhD

Background: Atopic dermatitis (AD) is a severe inflammatory skin disease, in which Staphylococcus aureus (S.aureus) dominated skin microbiome dysbiosis plays an important role. Recently [1], a novel oral JAK/SYK inhibitor, ASN002, demonstrated significant decreases in EASI scores over 4 weeks of treatment. However, the impact of JAK/SYK inhibition on AD-associated microbiome is still unknown.

Aim: Skin microbiome was analyzed in a clinical trial of ASN002 in AD patients to find its effect on S.aureus dysbiosis and investigate the microbiome correlates of success of treatment.

Methods: Moderate-to-severe AD patients received ASN002 for 28 days in a double-blind randomized phase-1b study with doses: 20, 40 and 80mg daily and placebo (N=9 per arm). Skin microbiome from lesional (LS) and non-lesional (NL) skin swabs at days 1, 29 and 43 were sequenced (16S V1-3).

Results: Higher S.aureus baseline frequency in LS was the major cause for microbiome dysbiosis and was significantly ($p < 0.001$) associated with higher EASI score at baseline. Moreover, lower S.aureus frequency at baseline predicts ($p = 0.03$) higher probability for a sustained EASI response 14 days after end-of-treatment, and in consequence significantly ($p < 0.001$) predicts lower EASI at day 43.

A significant ($p = 0.005$) dose-dependent decline in S.aureus frequency in LS was exhibited at day 29 in 86% of patients, in comparison to placebo (33%), and correlated with EASI decline ($R = 0.7$, $p = 0.003$).

Conclusions: JAK/SYK inhibition with ASN002 not only improves clinical scores [1] and Th2/Th22 inflammation markers [2] but also reduces S.aureus frequency in lesion. Conversely, lower baseline S.aureus frequency in lesion correlated with ASN002 sustained efficacy post-treatment.

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AAD 2018 Late Breaking Abstract presentation

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Authors: Robert Bissonnette M.D., M.Sc., FRCPC, Catherine Maaria M.D., Seth Formanb M.D., Neil Bhatia M.D., Mark Leed M.D., Joseph Fowlere M.D., Stephen Tyingf M.D., Ph.D, David Pariserg M.D., Howard Sofenh M.D., Sunil Dhawani M.D., Matthew Zookj M.D., David J Zammitk, Ph.D, MBA, Sarper Tokerk M.D. Niranjana Rao Ph.D., Emma Guttman-Yassky M.D. Ph.D.

2. ASN002, a dual oral inhibitor of JAK/SYK signaling, improves the lesional skin phenotype towards non-involved skin in moderate-to-severe atopic dermatitis patients, correlating with clinical outcomes

EADV 2018 Late Breaking Abstract presentation

Authors: Emma Guttman-Yassky MD PhD, Ana B. Pavel PhD, Teresa Song BSc, Hyun Je Kim MD PhD, Louis Denis MD, Niranjana Rao PhD, David J Zammit PhD MBA

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11289 - Whole Genome Sequencing Reveals Novel Rare Loss-of-function Variants in the Epidermal Differentiation Complex as Predisposing Factors to Atopic Dermatitis / Sandra Smieszek, PhD

The epidermal differentiation complex (EDC) includes over fifty genes encoding proteins involved in keratinocyte development. Of these fifty genes, filaggrin (FLG) located on chromosome 1 q21, a member of the SFTP family, is the most studied in the context of skin barrier dysfunction. We investigated the frequency and effect of rare loss-of-function (LOF) variants within the EDC in patients of a clinical study, (VP-VLY-686-2102) using 117 whole genome sequencing.

We have shown that 45/117 AD patients carry significantly more, rare loss-of-function (LOF) mutations in the SFTP family of genes as compared to 55/316 in a controls (p-value = 0.000004). This group of EDC LOF (stopgain, frameshift) rare variants (EDC-LR) consists of 20 variants observed in the 45 AD patients resulting in a calculated Odds Ratio of 2.96 and a Relative Risk of 2.38. Among the detected rare LOF variants, there are 25 cases of FLG LOF mutations as well as other members of the EDC.

Furthermore we examine the regional accumulation of rare LOF variants in 1) the FLG region alone and 2) the entire EDC region (LOF set), comparing AD with controls (WGS). For the entire EDC, we obtained a p-value of 4.7e-20, much lower than for FLG alone p-value of 4.5e-6, indicative of an even greater effect when analyzed jointly (entire family vs. FLG alone) in the AD context.

Whole genome sequencing of AD samples showed enrichment for rare variants in the entire EDC region in cases compared with controls, finding that helps delineate the genetic risk profile in AD.

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11185 - The Therapeutic Efficacy of BI 655130, an Anti-interleukin-36 Receptor Antibody, in Patients with Acute Generalized Pustular Psoriasis is Associated with the Downregulation of Inflammatory and Tissue Remodeling Genes in Lesional Skin / James G. Krueger, MD, PhD

Generalized pustular psoriasis (GPP) is a rare, life-threatening, difficult-to-treat disease, characterized by recurrent flares of pustular, erythematous rashes, with a strong genetic linkage to the interleukin (IL)-36 pathway.^{1–3}

The efficacy and safety of a single, open-label, intravenous dose of BI 655130 (10 mg/kg), an anti-IL-36 receptor monoclonal antibody, was assessed in a Phase I trial (NCT02978690) in seven patients presenting with a moderate-to-severe GPP flare. At baseline, all patients had a GPP Physician Global Assessment (GPPGA) score of 3 (moderate disease), and three had a loss-of-function mutation in the IL-36 receptor antagonist gene (IL36RN).

A rapid reduction in GPP Area and Severity Index was observed in all patients, and all patients achieved a GPPGA score of 0 (clear) or 1 (almost clear) by Week 4. At baseline, global transcriptome analysis identified 3276 differentially expressed genes in lesional and non-lesional skin; by Week 1, the expression of 1444 genes in lesional skin was strongly reduced, reaching near non-lesional levels. The genes regulated by BI 655130 were associated with a broad range of inflammatory processes, including the innate immune response (e.g. IL6, TNF, and CXCL1), Th1/Th17-mediated inflammation (e.g. IL1B, IL12B, and IL23A), and proinflammatory processes of keratinocyte activation (e.g. IL17C and IL24). In addition, immunohistochemical staining showed a marked reduction in neutrophil infiltration by Week 1.

Overall, blockade of the IL-36 pathway with BI 655130 was highly effective in patients with a moderate-to-severe GPP flare, and was associated with the downregulation of inflammatory and tissue remodeling genes in lesional skin.

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F055 - Late-breaking Research: Basic Science/Cutaneous Oncology/Pathology

Saturday, March 2 from 9:00 AM — 11:00 AM

Room 101

10:40 am - 10:50 am

11380 - Botulinum Toxin Blocks Mast Cells and Prevents Rosacea Like Inflammation / Tyler Werbel, MS

Background: The etiology of rosacea has been linked to mast cells (MCs) and the antimicrobial peptide cathelicidin LL-37. Onabotulinum toxin (BoNT) has demonstrated clinical benefit, but the mechanism is unknown. The SNARE proteins SNAP-25 and VAMP are known to be important for vesicle trafficking in neurons and are cleaved by BoNT A and B respectively. We hypothesized that BoNT improves rosacea lesions by cleaving SNARE proteins in MCs, thereby inhibiting degranulation.

Methods: Primary human and murine MCs were pretreated with BoNT A or B or control. Compound 48/80-induced MC degranulation was evaluated by β -hexosaminidase activity. Expression of BoNT receptor Sv2 was measured by qPCR of mouse MCs. Presence of SNAP-25 and VAMP2 was established by immunofluorescence. In vivo rosacea model was established by intradermally injecting LL-37 with or without BoNT A pretreatment. MC degranulation was assessed in vivo by histology. Rosacea biomarkers were analyzed by qPCR of mouse skin sections.

Results: BoNT A and B inhibited human and murine MC degranulation ($P < 0.001$). Expression of Sv2 was established in mouse MCs. BoNT A and B cleaved SNAP-25 and VAMP2 respectively in mouse MCs ($P < 0.05$). In mice, injection of BoNT A significantly reduced LL-37-induced skin erythema ($P < 0.05$), MC degranulation ($P < 0.001$), and mRNA expression of rosacea biomarkers ($P < 0.001$).

Conclusions: These findings suggest that BoNT reduces rosacea-associated skin inflammation by directly inhibiting MC degranulation. Since intradermal injections are invasive and require periodic office visits, a well-formulated topical BoNT may be appropriate for further study in the treatment of rosacea.

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F055 - Late-breaking Research: Basic Science/Cutaneous Oncology/Pathology

Saturday, March 2 from 9:00 AM — 11:00 AM

Room 101

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F055 - Late-breaking Research: Basic Science/Cutaneous Oncology/Pathology

Saturday, March 2 from 9:00 AM — 11:00 AM

Room 101

10:50 am - 11:00 am

11354 - Trichilemmal (Pilar) Cysts are Caused by Two “Hits” to the PLCD1 Gene: One inherited and one somatic / Sanjana Iyengar, MD

Background: Trichilemmal (pilar) cysts are common familial lesions that frequently require surgical treatment. However, the gene that causes the autosomal dominant inheritance and genesis of these lesions has remained unknown.

Type of Study: Case Series

Methods: We used whole exome sequencing to discover germline and somatic (tumor specific) mutation in patients with multiple trichilemmal cysts.

Results: Our approach identified a hemizygous c.2234G>A somatic mutation in exon 15 of phospholipase C delta 1 (PLCD1), a tumor suppressor gene, in 21/21 trichilemmal cysts sequenced. This mutation removes a serine phosphorylation site and exhibits a UV signature. 16 of the 17 patients in the study were also hemizygous for the c.1379G>A germline variant in exon nine of PLCD1 which is present in only about 6% of the US population and also eliminates a serine phosphorylation site. The one patient of 17 that did not show the c.1379G>A germline variant had a germline c.1363C>T mutation in exon nine of PLCD1. Five control subjects with epidermal inclusion cysts did not show any variation from the reference genome in exon nine of PLCD1.

Conclusion: Our results are consistent with familial trichilemmal cysts resulting from an inherited variant followed by a somatic mutation that presumably would involve both copies of the PLCD1 tumor suppressor gene. Our current research is investigating PLCD1 mutations in patients with presumed sporadic trichilemmal cysts and in proliferating trichilemmal cysts and trichilemmal carcinoma.

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