

## Journal Watch

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### **Distribution of subsequent primary invasive melanomas following a first primary invasive or *in situ* melanoma - Queensland, Australia, 1982-2010**

Youlten DR, Youl PH, Soyer HP, Aitken JF, Baade PD.

[JAMA Dermatol 2014;150:526-34.](#)

Melanoma survivors are faced with an increased likelihood of developing subsequent melanomas. It was reported that patients with a first primary invasive melanoma had a six- to seven-fold higher risk of developing a second invasive melanoma compared with the general population in Australia. This current study examined the effects of the body site, sex, age group, and time since diagnosis on the probability of developing subsequent invasive primary melanomas following a first invasive or *in situ* primary melanoma in a high risk population.

This is a retrospective cohort study of 39,668 cases of first primary invasive melanoma and 22,845 cases of first primary *in situ* melanoma from the Queensland Cancer Registry, Queensland, Australia. It was found that both patients with invasive or *in situ* melanoma had a substantially higher risk of developing a subsequent primary invasive melanoma. Subsequent primary invasive melanomas were more likely to occur at the same body site as the initial invasive or *in situ* melanoma. It was noted that female patients with primary invasive melanoma on the head had a high risk of developing a subsequent primary invasive melanoma at the same site.

The authors highlighted the need for vigilant inspection around the site where the first primary melanoma appeared during subsequent follow-

up of melanoma survivors. Continued surveillance is paramount not only for patients with invasive melanoma but also for those with an *in situ* melanoma.

### **Effect of host, tumor, diagnostic, and treatment variables on outcomes in a large cohort with Merkel cell carcinoma**

Asgari MM, Sokil MM, Warton EM, Iyer J, Paulson KG, Nghiem P.

[JAMA Dermatol. Published online May 07, 2014. doi:10.1001/jamadermatol.2013.8116.](#)

Merkel cell carcinoma (MCC) is a rare, aggressive, neuroendocrine-derived skin cancer. Data on the recurrence and survival of patients with MCC are lacking. This was a retrospective cohort study of 218 patients with MCC from the cancer registry of an integrated healthcare system in Northern California from 1995 to 2009. The effects of the host characteristics, the tumour characteristics, the diagnostic methods used and the treatment modalities employed on disease recurrence and survival were examined.

It was found that immunosuppression was associated with higher MCC-specific mortality. Tumour extent including local, regional and distant extent of the disease was significantly associated with all outcomes of MCC. An unknown primary site was associated with a lower risk of distant metastasis and improved survival. Pathological nodal evaluation was associated with improved survival and lower risk of metastasis. Patients who underwent sentinel lymph node biopsy alone had a reduction in all-cause mortality. Sentinel lymph node biopsy combined with lymphadenectomy

was also associated with reductions in all-cause and MCC-specific mortality and with reduction in the risk for metastasis of borderline significance. Radiation therapy was associated with a decreased risk of loco-regional recurrence. Chemotherapy was not associated with any alteration in outcome.

The findings of this study have certain clinical implications. Pathological nodal evaluation should be used in prognostic evaluation since it is associated with improved outcomes. Radiation therapy may be the preferred adjuvant treatment modality in view of the decreased risk of loco-regional recurrence of MCC. Adjuvant chemotherapy is not associated with survival benefit despite its important role in palliation.

### **Field evaluation of the CRT and ACON chlamydia point-of-care tests in a tropical, low resource setting**

Hurly DS, Buhler-Skinner M, Badman SG, Bulu S, Tabrizi SN, Tarivonda L, et al.  
*Sex Transm Infect* 2014;90:179-84.

Chlamydial infection is a common sexually transmitted infection (STI). Although DNA-based laboratory test provides high sensitivity and specificity, it requires the patients to return for the result that may cause default and delay in treatment. A well performed point-of-care (POC) test can offer the test and treatment within a visit that not only improves compliance but also decreases the default rate. The aim of the study is to evaluate two commercial available POC tests – "Chlamydia Rapid Test (CRT) and ACON Chlamydia Rapid Test Device (ACON) by comparing them with standard nucleic acid amplification test (NAAT). Both of these POC tests are immunoassay-based tests.

In this study, 379 individuals (156 men and 223 women) had valid CRT + NAAT. The sensitivity and specificity of the CRT in men were 41.4% (95% CI 23.5%-61.1%) and 89.0% (95% CI 82.2%-93.8%) respectively. In women, the sensitivity of CRT was 74.2% (95% CI 61.5%-84.5%) and the specificity was 95.7% (95% CI 91.3%-98.2%). A total of 207 individuals (132 men and 75 women) had ACON + NAAT. The sensitivity in men was 43.8% (95% CI 19.8%-70.1%) and the specificity

was 98.3% (95% CI 93.9%-99.8%). In women, the sensitivity of ACON was 66.7% (95% CI 22.3%-95.7%) and the specificity was 91.3% (95% CI 82.0%-96.7%).

The authors concluded that the high false-positive results would cause overtreatment and social labelling whereas genuine cases would be missed due to the high proportion of false negatives. The performance of both commercially available POC tests is well below the level stated by the manufacturer and is unlikely to be helpful in the clinic setting.

### **Sleep quality in efavirenz-treated Chinese HIV patients – comparing between GT and GG genotype of CYP2B6-516 G/T polymorphisms**

Lee SS, To KW, Lee MP, Wong NS, Chan DP, Li PC, et al.

*Int J STD AIDS* 2014;25:193-200.

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor used in highly active anti-retroviral therapy. It can be conveniently given in single daily dose but neuropsychiatric side effects are common especially affecting the sleeping quality such as insomnia, reduced sleep efficiency and vivid dreams. These adverse effects are more prominent shortly after the initiation of the EFV and often resolved at week four. Though such toxicity is short-lived, discontinuation and switching treatment may be needed. The aim of the present study is to assess the pattern of sleep problems in EFV treated Chinese HIV patients in an one-year observational period by using Pittsburgh sleep quality index (PSQI) focussing on the associations with plasma EFV levels and CYP2B6-516 G/T genotype. The PSQI has an overall score from 0 to 21 with the higher mark indicating poorer sleep quality. The authors deliberately excluded TT genotype since it is associated with a very high plasma level of EFV and TT only accounts for a small proportion of all EFV-treated patients in any population because of the low allelic frequency.

A total of 72 treatment naive HIV-positive Chinese patients were recruited. All were male except five. The mean age was 39.2±10.3 years at diagnosis. None of them had neuropsychiatric disorders or were put on neuropsychiatric medications. The

seven components of sleep quality could be differentiated in this study: duration of sleep; sleep disturbance; sleep latency; day dysfunction; sleep efficiency; perceived overall sleep quality and the need for sleeping medications. Overall, 47% patients had a worsened PSQI at week four when compared with that at baseline. Comparing between GT and GG genotype, the median PSQI was higher for GT than GG at 6 months (6 vs 4,  $p < 0.05$ ) while there was no difference in baseline, week four and 12 months. Also, a higher proportion of GT patients had significant poorer score for day dysfunction at week four (13% vs 7%) and 6 months (8% vs 0%) when compared with GG. Although the GT group had a higher EFV level (defined as  $>4$  mg/L), there was no difference between sleep quality and plasma EFV level.

In conclusion, this study showed that the plasma level of EFV was higher and there was a tendency to cause sleep problems in the GT genotype. Although high plasma level and sleep problems are harmless, patients should be well informed of these side effects before starting EFV containing regimen so as to reduce the chance of treatment withdrawal.

### **Effect of psoriasis activity on epidermal growth factor (EGF) and the concentration of soluble EGF receptor in serum and plaque scales**

Flisiak I, Sztetling-Jaworowska M, Baran A, Rogalska-Taranta M.

Clin Exp Dermatol 2014;39:461-7.

Upon binding to epidermal growth factor receptors (EGFR), epidermal growth factors (EGF) act by regulating keratinocytic cell growth, proliferation and differentiation and are known to be over-expressed in the keratinocytes of psoriatic skin. The present study aimed to investigate the serological levels of EGF and soluble EGFR in the lesional scales of patients with severe psoriasis. Their association with the clinical disease activities was also analysed. Fifty-one patients with severe chronic plaque psoriasis and 15 healthy controls were included in this study. Serum samples and plaque scales from the patients were collected. Concentrations of EGF

and EGFR in both serum and lesional scales were measured. The mean serum EGF concentration in patients appeared to be higher than that in the controls ( $701 \pm 72$  vs  $586 \pm 63$  pg/mL), but the difference did not reach statistical significance. The mean serum concentration of EGFR was significantly lower than that in the controls ( $40.8 \pm 1.4$  vs  $86.4 \pm 11.3$  ng/mL) ( $p < 0.001$ ). The serological levels of EGF showed a positive correlation and EGFR showed a negative correlation with PASI ( $p < 0.05$ ). Serological EGF had the highest mean level ( $914 \pm 138$  pg/mL) in patients with PASI  $> 20$ . However, no correlation was observed between PASI and EGF content in scales. The authors concluded that patients with psoriasis had increased serological levels of EGF and decreased EGFR levels and that EGF and EGFR levels correlated with disease severity. In practice, the authors suggested that measurement of the serological levels of EGF and EGFR could be considered as an objective assessment of disease severity in patients with psoriasis. Also, there might be a possible role of EGFR inhibitors in the treatment of psoriasis.

### **Patch testing for vulval symptoms: our experience with 282 patients**

Al-Niaimi F, Felton S, Williams J.

Clin Exp Dermatol 2014; 39:439-42.

Allergic contact dermatitis (ACD) of the vulva can be primary or secondary to underlying vulval dermatoses. There is a lack of knowledge on the allergens responsible for the condition. The present study analysed the incidence of vulval ACD and the responsible allergens in 282 patients over a 6-year period. A retrospective review of all patients with vulval symptoms in a tertiary centre was carried out. In the study, 282 patients underwent patch tests. Patients aged between 14 to 89 years and the incidence of vulval ACD was found to be 54%. Seventeen percent of patients had vulval symptoms for over 10 years. Pruritus was the commonest presenting complaint. Thirty-nine percent of patients had positive reactions to two to four allergens and 8% to more than four allergens. Forty-nine percent of the positive allergens correlated to clinical presentation. Among the positive allergens, nickel was the commonest positive finding. However, it was often

not clinically relevant based on history. Clinically important and common allergens included fragrances, topical antibiotics and anaesthetics (in descending order: neomycin, fragrance mix, Balsam of Peru). Predictors for positive reactions in patch tests included having long-standing symptoms and/or usage of multiple hand products in the affected areas. The authors concluded that patch testing should always be considered when evaluating patients with pruritus or non-specific vulval symptoms. Detailed history and physical examination are essential to identify clinically relevant allergens.

### **Simvastatin as a novel therapeutic agent for venous ulcers: a randomized, double-blind, placebo-controlled trial**

Evangelista MT, Casintahan MF, Villafuerte LL.  
*Br J Dermatol* 2014;170:1151-7.

This single centre randomised double-blind controlled trial was conducted at a dermatology centre in Manila from February 2012 to May 2013 to assess the efficacy and safety of simvastatin in venous ulcer healing. Patients aged 18-85 years who had received therapy for their venous ulcers during the study period were recruited. All patients were given simvastatin or placebo for a maximum of 10 weeks on top of standardised local management of ulcers. Sixty-six cases were finally included and randomised to treatment (simvastatin, n=32) and control (placebo, n=34) groups. The study showed that 90% of patients had complete ulcer closure in the simvastatin group compared with 34% of patients in the control group (RR 0.158, 95% CI 0.053-0.474). For ulcers  $\leq 5$  cm, subgroup analysis showed that all ulcers healed in the simvastatin group compared with only 50% of patients had closed ulcers in the control group (RR 0.10, 95% CI 0.0141-0.707) and the average healing times were 6.89 weeks and 8.40 weeks for the simvastatin and control groups respectively (p=0.001). For ulcers over 5 cm, 67% had closure with a mean healing time of 9.17 weeks in the simvastatin group, whereas none of these ulcers healed in the control group (RR 0.33, 95%

CI 0.132-0.840). The author thus concluded that the combination therapy of simvastatin and standard wound care was associated with a significant improvement in healing rate and time, as well as an improved patient quality of life in the management of venous ulcers.

### **Risk factors for morphea disease severity: a retrospective review of 114 paediatric patients**

Pequet MS, Holland KE, Zhao S, Drolet BA, Galbraith SS, Siegel DH, et al.  
*Br J Dermatol* 2014;170:895-900.

This single-centre retrospective study was conducted in USA to describe the natural history of morphea and isolated clinical features that could help predict disease severity. Patients who had onset of morphea prior to 18 years of age and received treatment at the study centre from 2000 to November 2011 were recruited. One hundred and fourteen subjects were finally included in the study. Among them, 55 patients (48%) had linear morphea, 38 patients (33%) had circumscribed morphea, 12 patients (11%) had generalised morphea and nine patients (8%) had mixed morphea. The median age of onset was seven years and the female: male ratio was 2.6:1. Extracutaneous manifestations were present in 27 subjects (24%) and joint involvement (17 subjects) was the most common manifestations followed by neurological involvement (10 subjects). Thirty-eight per cent of subjects with linear morphea had extracutaneous involvement compared with 15% with generalised morphea and 3% with circumscribed morphea (p=0.0001). Thirty-six per cent of children with onset of morphea prior to 10 years of age and 5% of children with morphea onset after 10 years of age had extracutaneous manifestations (p=0.0002). Extracutaneous involvement was significantly associated with linear morphea and early-onset disease in a multivariable model. The authors thus concluded that children with linear morphea and disease onset before 10 years of age should be followed closely for extracutaneous manifestations and require early systemic medication to prevent disease complications.

### **Herpes zoster infection associated**

### **with acute coronary syndrome: a population-based retrospective cohort study**

Wang CC, Lin CL, Chang YJ, Wang GJ, Sung FC, Kao CH.

Br J Dermatol 2014;170:1122-9.

This population-based cohort study was carried out in Taiwan to determine the risk of acute coronary syndrome (ACS) associated with herpes zoster infection. Patients with herpes zoster under National Health Insurance Research Database between 1999 and 2010 in Taiwan were included and were followed up until the end of 2010 to measure the incidence of ACS and 57 958 patients with herpes zoster and 231 832 control patients were finally included. Kaplan-Meier analyses and Cox proportional-hazards regression were used to measure the cumulative incidence of ACS and the hazard ratios (HR) respectively. There were 1053 patients with herpes zoster and 3318 control patients who were diagnosed with ACS over the 12-year follow-up period. The incidence rates for the herpes zoster and the control groups were 36.8 and 29.6 per 10 000 person-years respectively and the overall adjusted HR (aHR) of ACS was 1.15 for patients with herpes zoster (95% CI 1.07-1.24). The herpes zoster group had a significantly higher risk of ACS than the non-herpes zoster group (aHR 1.10, 95% CI 1.02-1.19) after the 1-year follow-up period as shown by analysis by the time lag. The authors therefore concluded that herpes zoster infection was associated with an increased risk of ACS.

### **Prognostic value of BRAF mutations in localized cutaneous melanoma**

Nagore E, Requena C, Traves V, Guillen C, Hayward NK, Whitman DC, et al.

J Am Acad Dermatol 2014;7:858-62.

BRAF mutations are frequently detected in melanoma. Despite various *in vitro* studies demonstrating its enhanced oncogenic effects, its prognostic implications on survival in localised melanoma is not fully understood.

In this retrospective study, the authors aimed at

evaluating the prognostic value of BRAF mutations in localised cutaneous melanoma. This study reviewed the database from Instituto Valenciano de Oncologia in Spain and patients with localised cutaneous melanoma over the extremities and trunk were selected. Those who presented with metastatic melanomas, multiple primary invasive melanomas, acral lentiginous melanomas and Spitzoid or naevoid lesions were excluded. Eligible patients were included only if sufficient DNA could be extracted for molecular analysis. All studied subjects were then tested for the presence of BRAF and NRAS mutation. Other confounding variables including age, sex, location of lesions, Breslow thickness, presence of ulcerations and tumour mitotic rate were recorded. The primary endpoint was overall survival and disease-free survival.

A total of 147 patients were included, with the median follow-up period of 49 months. Most tumours occurred over the trunk (63%), with a median thickness of 1 mm (0.6-2 mm). Seventy-five percent of cases were superficial spreading type melanomas followed by nodular type (17.7%) and lentigo maligna (2.7%). The remainders had unclassified histology. Twenty-six percent of cases showed mutated BRAF and 18% with mutated NRAS, which were mutually exclusive. A total of 13 patients relapsed (6 BRAF-mutant, 3 NRAS-mutant, 4 without mutations) and 17 died (7 BRAF-mutant, 4 NRAS-mutant, 6 without mutations). Patients with BRAF-mutant melanomas showed a poorer disease-free survival than those with BRAF-wild type (adjusted hazard ratio 2.2, CI 1.1-4.3), but the overall survival was not significantly worsened (HR 1.5, CI 0.5-4.4).

The authors concluded that BRAF mutation was a poor prognostic predictor for relapse and death in patients with localised cutaneous melanoma. Hence, adjuvant treatment with BRAF inhibitors may improve the prognosis in these patients.

This study was limited by the short follow-up period and small sample size.

### **Lack of efficacy with 1064-nm**

### **neodymium:yttrium-aluminum-garnet laser for the treatment of onychomycosis: a randomized controlled trial**

Hollmig ST, Rahman Z, Henderson MT, Rotatori RM, Gladstone H, Tang JY.

*J Am Acad Dermatol* 2014;70:911-7.

There are different treatment modalities for onychomycosis. Laser treatment had been a recent focus and it was also approved by the Food and Drug Administration for temporary nail plate clearance. Although the exact mechanism is still not fully understood, it is believed that light energy penetrates through the nail plate and reaches a temperature that kills the colonised fungus. However, there is only limited data supporting the use of laser in onychomycosis and its long-term efficacy is not known. Hence, in this randomised controlled study, the authors aimed at evaluating the clinical and mycological outcome using 1064-nm Nd:YAG laser in patients with onychomycosis at three and 12 months.

Twenty-seven patients with both clinical and mycological confirmed onychomycosis were included. They were randomised into laser or control group at 2:1 ratio (laser 17, control 10). Patients in the treatment arm received two courses of laser treatments separated by two weeks, at the setting recommended by laser manufacturer (fluence 5 J/cm<sup>2</sup>, pulse width 0.3 ms, spot size 6 mm, rate 6 Hz, 2-3 passes), while all patients in the control group were also offered a single laser treatment at the end of a three-month observation period. Both groups were assessed at three months for mycological clearance, clinical proximal nail plate clearance and complete clinical clearance. Cases who had received laser treatment but not controls were assessed 12 months later for long-term efficacy.

At the end of the study, 12 patients with 57 clinically involved toenails were treated with laser treatment while 12 patients with 68 affected toenails were assigned to the control group.

After three months, 33% of the laser group and 20% of the control group showed negative culture, which was not significantly different ( $p=0.49$ ). Moreover, there was no significant difference in

terms of proximal nail plate clearance and complete clinical clearance at three months in both groups. Furthermore, there was no statistically significant difference in clinical clearance in the treatment group at 12 months when compared to baseline.

The authors concluded that 1064-nm Nd:YAG device was not effective for onychomycosis, but these results could not be generalised to other devices and treatment parameters. Further well-conducted studies on other devices are warranted to evaluate the role of laser treatment on onychomycosis. This study was limited by the small sample size, which was underpowered to detect clinically less obvious improvement and to allow stratification by different types of causative organisms and severity of the diseased nail.

### **Thymic stromal lymphopoietin variation, filaggrin loss of function, and the persistence of atopic dermatitis**

Margolis DJ, Kim B, Apter AJ, Gupta J, Hoffstad O, Papadopoulos M, et al.

*JAMA Dermatol* 2014;150(3):254-9.

Atopic dermatitis (AD) is known to be associated with loss-of-function mutations in the filaggrin (FLG) gene. Thymic stromal lymphopoietin (TSLP) was also reported to be associated with AD. TSLP promotes the differentiation of naive T cells into type 2 helper T cells, a cell type associated with atopic diseases. Increased expression of TSLP is strongly associated with atopic diseases including AD, asthma, allergic rhinitis and food allergy. It is postulated that patients with diminished TSLP expression, even in the setting of skin barrier dysfunction due to a FLG loss-of-function mutation, would be less likely to exhibit active symptoms of AD. The objective of this study is to evaluate the association between TSLP variation and the persistence of the symptoms of AD.

This was a prospective cohort study investigating the self-reported outcome of whether a child's skin had no symptoms of AD and required no medications for six months at six-month intervals. A total of 796 children enrolled in the Paediatric

Eczema Elective Registry were recruited. DNA genotyping were performed and fourteen variants of TSLP were evaluated.

Among the 14 variants of TSLP, it was found that the variant rs1898671 was significantly associated with the outcome in white children. Within the sub-cohort of individuals with a FLG

loss-of-function mutation, those with TSLP variation were more likely to have less persistent disease. The authors suggested that inhibition or diminution of the effect of TSLP may be a potential therapeutic target for the treatment of AD, especially in individuals with diminished barrier function due to FLG mutations.