

# HAWAI'I MEDICAL JOURNAL

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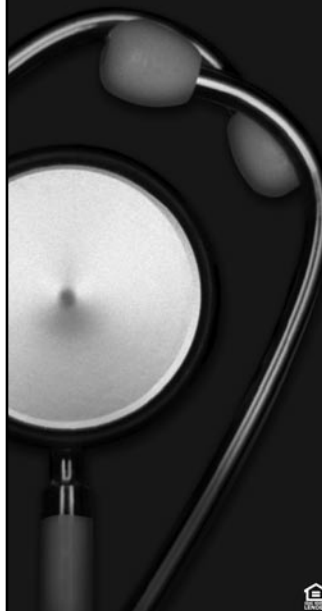
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# Hydroxycut® (herbal weight loss supplement) Induced Hepatotoxicity: A Case Report and Review of Literature

Tarun Sharma MD; Linda Wong MD; Naoky Tsai MD and Russell D. Wong MD

## Abstract

*Use of supplement and alternative drugs continues to thrive and is becoming an increasing cause of concern since many of these substances may have unexpected or unexplained medical consequences. We present below the first reported case of hepatotoxicity from Hydroxycut® in Hawai'i.*

## Introduction

Use of dietary supplement is gaining increasing popularity in the United States as a quick fix remedy with allegedly no side effects. Nearly one in five adults in the United States admits to using herbal medications for their diseases or health improvement and 58% of those using these drugs fail to report such use to their primary care physicians.<sup>1</sup>

One such common drug is Hydroxycut® (Lovate Health Sciences Inc.) which has been touted as a safe remedy for weight loss as well as a fat burner. Though it was recalled by the manufacturer after an FDA issued warning on May 1, 2009, the side effect of hepatotoxicity was mentioned to be rare. The FDA warning is based on reports of 23 cases of liver damage including one fatality and a liver transplant.<sup>2</sup> We are presenting another case with severe liver toxicity in the setting of exposure to Hydroxycut® and extensive testing to rule out other causes of hepatotoxic disease as well as a biopsy indicative of drug induced hepatotoxicity.

## Case Report

A 19-year-old man with no significant past medical history presented to a community medical center with 2-day history of fever, severe fatigue, myalgia, arthralgias and an erythematous rash over his lower extremities. Patient had started using Hydroxycut® approximately one week prior to presentation for fat burning and muscle building. He denied any smoking or alcohol use and was on no other prescription or over the counter medication apart from Hydroxycut® and Myoflex® cream. His initial exam was notable for toxic appearance and marked icterus with fever up to 103 degrees Fahrenheit. His blood test revealed an Aspartate aminotransferase (AST/SGOT) level of 23 units/liter, Alanine aminotransferase (ALT/SGPT) of 81 units/liter, Alkaline phosphatase 298 units/liter (GGTP-250), white blood cell count of  $31 \times 10^9$ /liter, hemoglobin level of 12.7 gram/deciliter and normal platelet count. Total bilirubin was 7.3 milligram/deciliter, Prothrombin time of 16.7 seconds. Blood cultures, urine analysis, chest X-ray, abdominal ultrasound, Computed Tomography scan and Magnetic Resonance Cholangiopancreatography results were normal. His liver appeared normal in size and texture and there was no evidence of mass, vascular compromise, stone disease, ascites or biliary ductal dilatation. Patient continued to have rising bilirubin levels over the next 3 days and despite antibiotics (Piperacillin and Tazobactam) had persistent fever. On day 4, the patient was transferred to our hospital for possible urgent liver transplant evaluation due to rising total bilirubin of 12.7 milligram/deciliter and Prothrombin time of 21.7 seconds. At presentation he had low-grade fevers with marked icterus, mild right upper quadrant tenderness on deep palpa-

tion and a mild erythematous rash over the lower extremities which gradually started to desquamate. Rest of the physical examination including vitals signs was normal and he had no evidence of spider nevi, palmar erythema, gynecomastia or encephalopathy. Hepatic profile showed AST at 27 units/ liter, ALT at 24 units/liter, alkaline phosphatase at 152 units/liter, bilirubin at 12.4 milligram/deciliter, prothrombin time of 15.4 seconds, ammonia 38 microgram/deciliter, White blood cell count of  $34.8 \times 10^9$ /liter (71 neutrophils and 24 bands), hemoglobin level at 11.2gram/deciliter, platelet count of 237,000/microliter. Repeat blood cultures and sputum culture as well as urine analysis showed no evidence of infection. Serologies for Hepatitis A, Hepatitis B, Hepatitis C, Anti mitochondrial antibody, Anti nuclear antibody, Anti smooth muscle antibody, F actin IgG, Liver Kidney Microsomal antibody-1, Cytomegalovirus, Epstein-Baar virus, Herpes Simplex virus, Group A streptococcal antigen, Coxsackie virus, Monospot virus and Leptospirosis were negative. Ceruloplasmin and Alpha-1 anti trypsin levels were normal. Human immunodeficiency virus and Rapid plasma reagin tests were negative. Alpha-fetoprotein level was normal at 1 nanogram/milliliter. Iron studies were notable for mild iron deficiency and a Ferritin level of 463 nanogram/milliliter. A comprehensive urine toxicity screen was negative for any drugs except for opiates which he were administered at the hospital for pain management. Liver biopsy done on the 7th day of hospitalization showed acute cholangitis with scant micro vascular fatty changes (less than 5 percent) and no evidence of lobulitis, hepatocytes necrosis, cholestasis, fibrosis, parasite, ova, vasculitis, thrombosis, viral inclusions or neoplasm (Figure-1). Infectious disease consultation was obtained and Vancomycin was added to his antibiotic regimen. No infectious etiology could be determined and patient continued to have hyperbilirubinemia. He was started on Ursodiol 600 mg orally twice a day. His bilirubin level peaked at 18.6 milligram/deciliter, (direct at 10.2) and started to decrease after day 6 of hospitalization. Peak alkaline phosphatase was on day 3 of admission at 298 units/liter and peak AST/ALT levels were 110/142 units/liter respectively on days 11 and 13. All abnormal levels gradually started to decrease (Figure-2). Antibiotics were discontinued after a total 14 days of therapy. Patient was discharged from hospital on day 17 with a bilirubin level of 6.8 milligram/deciliter (direct at 3.2), AST level of 68 units/liter, ALT level of 108 units/liter, alkaline phosphatase level of 160 units/liter. Patient had gradual recovery of liver functions and at 14 weeks after initial onset of symptoms his liver function tests had returned to normal.

## Discussion

Use of alternative and herbal medication as dietary supplement is becoming increasingly popular in recent years owing to toxicity associated with most prescription medication and the presumed notion of safety with over the counter and so called natural weight loss therapies in the setting of our epidemic of obesity in the United States.

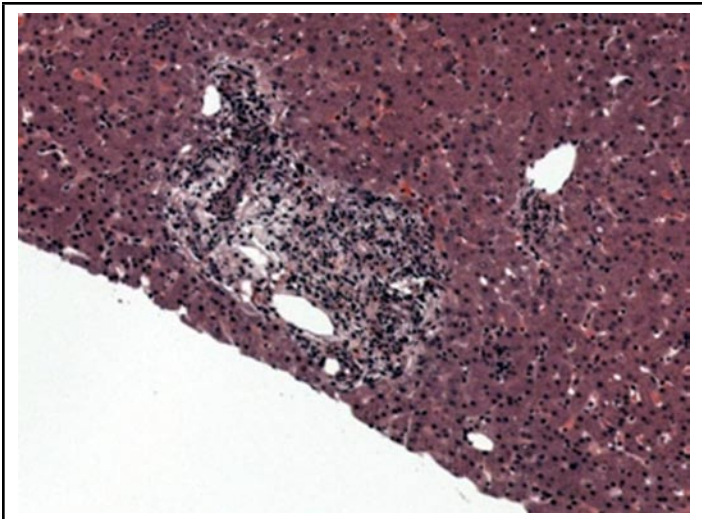


Figure 1.— Cholangitis on Liver Biopsy

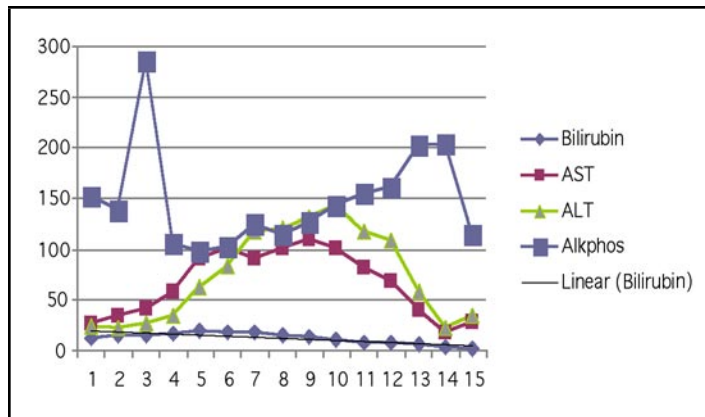


Figure 2.— Liver Test Results During Hospitalization

US Congress defined the term “dietary supplement” in the Dietary Supplement Health and Education Act (DSHEA) of 1994.<sup>3</sup> A dietary supplement is a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet. The “dietary ingredients” in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, soft gels, gel caps, liquids or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of “foods,” not drugs, and requires that every supplement be labeled a dietary supplement. Under DSHEA, once the product is marketed, the FDA has the responsibility for showing that a dietary supplement is “unsafe,” before it can take action to restrict the product’s use or removal from the marketplace.<sup>4</sup> In contrast, pharmaceutical companies that produce medications granted approval by the FDA must prove that their products are safe. In other words, with “medications,” the pharmaceutical company must prove their product is safe while in “dietary supplements” it is the FDA’s responsibility to prove that the product is unsafe.

Hydroxycut<sup>®</sup> was one of the most commonly used dietary supplement in the United States. Hydroxycut<sup>®</sup> ingredients include calcium, potassium, chromium and 2 blends known as hydroxagen plus and Hydroxy tea both of which are registered trademarks of Hydroxycut<sup>®</sup>. The former blend contains garcinia cambogia rind extract, *Gymnema sylvestre* leaf extract, Phosphatidylserine-enriched soy Lecithin and *rodiola rosea* root extract. The latter blend contains green tea leaf extract, anhydrous caffeine, oolong tea extract, ginger root extract, raspberry ketone and quercitine dehydrate.<sup>5</sup> The key ingredient of *Garcinia* is Hydroxy Citric Acid (HCA) and there has been a case report of its possible synergistic involvement with montelukast leading to fatal hepatotoxicity.<sup>6</sup>

The patient developed severe liver injury after use of Hydroxycut<sup>®</sup> and comprehensive serological and imaging for other causes were negative. The patient needed transport from a community medical

center to Hawai‘i Medical Center-East liver transplant center in the event that urgent transplant evaluation would be needed. Fortunately, the patient improved with supportive therapy. He had no other etiologies for possible liver injury. One of the components of Hydroxycut<sup>®</sup>, *Garcinia*, has been associated with both hepatocellular and cholestatic pattern of injury and our biopsy was suggestive of cholangitis likely secondary to infectious or drug mediated injury. Extensive evaluation for infectious disease by an infectious disease specialist failed to diagnose any infection and fevers can be associated with drug induced hepatotoxicity and can last weeks. The authors initially placed the patient on broad spectrum antibiotics while we waited for diagnostic studies to return. He also had severe leukocytosis with a left shift to suggest a bacterial etiology but did not have any significant improvement in jaundice with antibiotics and later gradually improved without them. While causation is difficult to prove in any drug induced injury, the temporal relationship after Hydroxycut<sup>®</sup> exposure and gradual improvement after withdrawing the involved medication plus absence of any other etiologies despite comprehensive testing would point to Hydroxycut<sup>®</sup> being the most likely possible cause for hepatotoxicity. Earlier reports from Dara et al with case series of 2 patients have shown a similar temporal relationship, also present histological data for possible association with drug toxicity.<sup>7</sup> A report of 2 cases from Stevens et al showed one with hepatocellular and the other with cholestatic liver toxicity secondary to Hydroxycut<sup>®</sup> use.<sup>8</sup> The latter is more similar to our case reports in terms of presentation, lab values and biopsy report. Shim et al and Jones et al have also reported a case of Hydroxycut<sup>®</sup> induced hepatotoxicity each.<sup>9-10</sup> These cases were reviewed by Lobb in a strong case for better post market surveillance and highlighting the significance of case reports in assisting such surveillance.<sup>11</sup>

Hydroxycut<sup>®</sup> was withdrawn by its manufacturer after a May 1, 2009 warning issued by FDA for its possible role in 23 cases of hepatotoxicity.<sup>12</sup>

## Conclusion

Obesity continues to be a major health care problem in the United States and adult Americans spend over \$30 billion a year in weight loss products and services.<sup>13</sup> Non-conventional products (“natural

products”) continue to be touted as “safe and effective” for treatment of various health conditions including weight reduction. However these products have not undergone rigorous scrutiny for effectiveness and safety and consequently drug induced toxicities do occur with some frequency. While some preparations of Hydroxycut® have been withdrawn from the market by its manufacturer, there still remain a substantial number of similar products on market which may have deleterious health effects. Also it is difficult to convincingly implicate any medication most of the times secondary to polypharmacy and to an extent lack of reporting.

The case also seeks to bring forth the fact that hypersensitivity hepatitis secondary to drugs can also have a superimposed fever, rash and leucocytosis, which may be confused with other viral infections or staphylococcal pharyngitis. Lee has reported similar findings in his review of drug induced hepatotoxicity.<sup>14</sup> Resolution occurs slowly and a high index of suspicion with immediate discontinuation of the offending drug is warranted. The authors hope this case report with temporal and histological evidence of toxicity from Hydroxycut® in absence of other causes will assist in further defining hepatotoxicity from Hydroxycut® as well as encourage health care professionals to be alert to the possibility of severe toxicity from the so called innocuous alternative medications.

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***Hawaiian proverb: “A heart as big as a house.”***

# Diffuse Plexiform Neurofibroma of the Back: Report of a Case

Ezella N. Washington DO; Timothy P. Plackett DO; Ronald A. Gagliano, Jr. MD; Jeffery Kavolius MD; and Donald A. Person MD

## Abstract

*Neurofibromatosis type 1 is an autosomal dominant disorder affecting the ras proto-oncogene. It is characterized by the overgrowth of nervous tissue and skin discoloration. While it is associated with a variety of phenotypic presentations, it is the plexiform variant that is particular concerning, as it can become extremely disfiguring and has a propensity for malignant degeneration.*

*A case of a Pacific Islander with a large plexiform type 1 neurofibroma is presented. The patient was ultimately treated with surgical resection, negative pressure wound therapy, and split-thickness skin grafting with good results. A review of the literature concerning the diagnosis and treatment of neurofibromatosis is included.*

## Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder affecting the ras proto-oncogene, resulting in growth of nervous and fibrotic tissues.<sup>1</sup> It has a variety of clinical presentations ranging from benign café-au-lait macules to malignant degeneration of plexiform neurofibromas. The hallmark neurofibromas can grow large in size and result in significant disfigurement. Currently, outside of clinical trials, treatment is limited to surgical resection.<sup>2</sup>

## Case Report

A 19-year-old man was referred to our institution from the Republic of the Marshall Islands via the Pacific Island Health Care Project for evaluation and treatment of a large mass of the back and buttock (Fig. 1).<sup>3</sup> The mass had been present since birth and had been progressively enlarging over the past several years. The patient reported embarrassment over the disfigurement caused by the mass.

Physical examination revealed a soft tissue mass of the back that extended from the tenth thoracic vertebra to the inferior gluteal clefts. The mass had hyperpigmentation, corrugations, and neovascularization. No additional neurofibromas or café-au-lait spots were noted. Neurological examination was normal. CT scan images demonstrated the mass to be confined to the subcutaneous tissues, without extension into the underlying musculature.

The patient underwent a radical resection of the mass. The superficial margins were the tenth thoracic vertebra superiorly, laterally to the anterior abdominal wall, and inferiorly to the gluteal clefts. The deep resection margin was the paravertebral fascia. The wound was initially managed with negative pressure wound therapy, and once a bed of healthy granulation tissue was created, autogenous skin was harvested from the upper back and grafted to the granulation bed. Two weeks later, excellent graft take was noted (Fig. 2) and the patient returned home.

## Discussion

Neurofibromatosis type 1, also known as von Recklinghausen's disease, is an autosomal dominant disease with an incidence of 1 in 2,600 to 3,000 individuals. It has equal distribution between men and women and in one half of patients there is a family history of neurofibromatosis.<sup>4,5</sup>

The disease results from a mutation of the NF1 gene on chromosome 17q. The gene codes for neurofibromin, a 260 kDa ubiquitously expressed protein found throughout the body.<sup>6</sup> The protein has both structural and functional similarity to guanosine triphosphatase-related proteins that are involved in the regulation of the proto-oncogene ras. Therefore, it has been speculated that the function of the NF-1 gene may be related to its ability to modify ras-mediated cell proliferation.<sup>6</sup> Mutations of the gene have highly variable phenotypic expression, resulting in a heterogeneous presentation.<sup>7</sup> The hallmark of NF1 is the hyperpigmented cutaneous lesions. Diagnostic criteria were developed by a National Institutes of Health consensus conference in 1987 and refined by a second conference in 1997 (Table 1).<sup>8</sup> Few if any patients, however, will manifest all of the clinical features. In fact, for nearly one-third of patients the clinical diagnosis will be made based on a family history and the presence of only one of the six characteristic physical features.<sup>8</sup>

Various subtypes of neurofibromas have been described based on histologic appearance and location. These include the cutaneous, subcutaneous, nodular, and diffuse plexiform variants.<sup>19</sup> The former two arise from the distal end of the nerve and are localized to the cutaneous and subcutaneous skin layers respectively. Nodular neurofibromas arise from the proximal nerve root and are often found growing within organs. Finally, the diffuse plexiform variant involves long segments of multiple nerves. This is in contrast to the other 3 types which rarely if ever involve long segments of the nerve or the axon itself. Additionally, this variant can be found in any histologic layer of tissue where nerves are present.

The plexiform variant of neurofibromatosis represents a major cause of morbidity and disfigurement. Approximately 20-44% of individuals with neurofibromatosis type 1 develop plexiform neurofibromas.<sup>9</sup> Plexiform variants are slow-growing tumors, which may be present at birth or develop later in life. These lesions are composed of an overgrowth of neural elements of tumor and connective tissue that infiltrate normal tissue. They can be superficial (affecting the skin and subcutaneous tissue) or deep (affecting visceral and adjacent tissues through occluding or obstructive mechanisms). They arise in various regions of the body, including the trunk, limbs, head, and neck. In a study of 126 individuals 16 years of age or older with NF1, plexiform neurofibromas were found in the chest of 20% of patients and in the abdomen and pelvis of 44%.<sup>9</sup> This particular variant of neurofibromatosis is especially concerning as it has a 20% risk for malignant degeneration into peripheral nerve sheath tumor.<sup>1,10</sup> Furthermore, these spindle cell sarcomas tend to be poorly responsive to therapy, are frequently metastatic at the time of diagnosis, and are associated with a 28% 5-year survival.<sup>11</sup>

No specific treatment for plexiform neurofibromas currently exists, aside for surgical resection. Clinical trials examining conventional chemotherapeutic agents, antifibrotic agents, and other biologic therapies have had mixed results. Pirfenidone, an antifibrotic agent, has been shown to inhibit survival of human neurofibroma xenografts



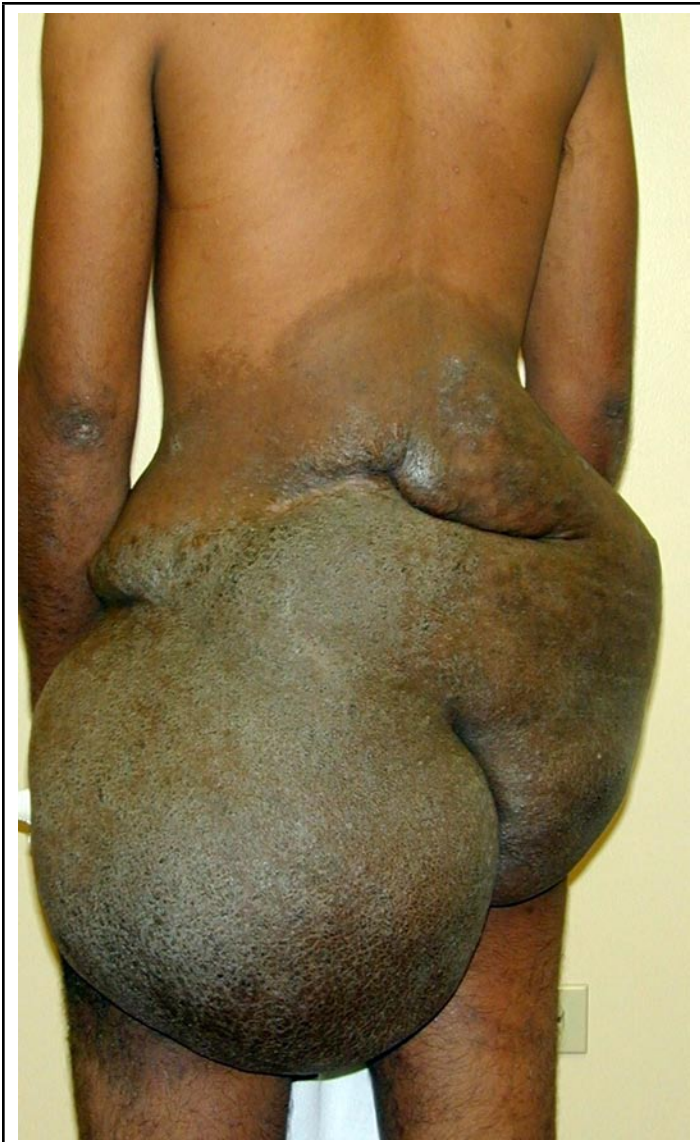


Figure 1



Figure 2

in mice, but human trials have been less promising.<sup>12</sup> In adults, pirfenidone has been shown to decrease the size of the neurofibroma by up to 15% in a minority of patients, however, these results were not sustained at 24 month follow up.<sup>13</sup> A phase one trial in pediatric patients had similar disappointing results.<sup>14</sup> Thalidomide, a Tumor Necrosis Factor-alpha inhibitor, has also been tested with poor results. In a trial of 20 patients, 67% showed no change in tumor size after 1 year of treatment and the remaining patients had a less than 25% reduction in tumor size.<sup>15</sup>

In light of the poor results from medication trials, primary therapy continues to be complete surgical excision of the neurofibroma. This can be a challenging procedure as the lesion may involve multiple nerve fascicles, with serpiginous growth and significant vascularity.<sup>16</sup> Indications for resection of plexiform neurofibromas include cosmesis, intractable pain, neurologic deficit, suspected malignant transformation, and progressive enlargement with compressive effects.<sup>17</sup> Even with surgical excision, plexiform neurofibromas have a recurrence rate of 20%.<sup>18</sup>

In summary, there are several types of neurofibromas including: cutaneous, subcutaneous, nodular, and diffuse plexiform. The cutaneous neurofibromas are benign soft, fleshy lesions that are most concerning for cosmetic reasons. In contrast, subcutaneous neurofibromas are firm and tender lesions that can cause pain and neurological deficits. However, the plexiform variant is the major cause of morbidity and disfigurement. Unlike the other variants, plexiform neurofibromas carry an increase risk of malignant peripheral sheath tumors. These tumors typically arise from pre-existing plexiform lesions, metastasize widely, and present with poor outcomes. The treatment for this variant of neurofibromatosis is complete excision of the malignant peripheral sheath tumor with palliative chemotherapy.

*The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.*

**Table 1.— National Institutes of Health Diagnostic Criteria for Neurofibromatosis Type 1**

**Two or more of the following clinical features must be present:**

Six or more café-au-lait macules (> 5 mm in greatest diameter in prepubertal individuals or > 15 mm in greatest diameter in postpubertal individuals)

Two or more neurofibromas of any type or one plexiform neurofibroma

Freckling in the axillary or inguinal regions

Optic glioma

Two or more iris hamartoma (Lisch nodules)

Distinctive bony lesion such as sphenoid dysplasia, or thinning of the long bone cortex with or without pseudoarthrosis

A first-degree relative (parent, sibling, or offspring) with NF 1 based on the above criteria.

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*Hawaiian proverb: “Dip your paddle in and join the effort.”*

# Racial/Ethnic Differences in the Incidence of Kawasaki Syndrome among Children in Hawai'i

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## Abstract

**Objective:** To describe the occurrence of Kawasaki syndrome (KS) among different racial/ethnic groups in Hawai'i.

**Methods:** Retrospective analysis of children <18 years of age, with a focus on children <5 years of age, living in Hawai'i who were hospitalized with KS using the 1996-2006 Hawai'i State Inpatient Data.

**Results:** Children <5 years of age accounted for 84% of the 528 patients <18 years of age with KS. The average annual incidence among this age group was 50.4 per 100,000 children <5 years of age, ranging from 45.5 to 56.5. Asian and Pacific Islander children accounted for 92% of the children <5 years of age with KS during the study period; the average annual incidence was 62.9 per 100,000. Within this group, Japanese children had the highest incidence (210.5), followed by Native Hawaiian children (86.9), other Asian children (84.9), and Chinese children (83.2). The incidence for white children (13.7) was lower than for these racial/ethnic groups. The median age of KS admission for children <5 years of age was 21 months overall, 24 months for Japanese children, 14.5 months for Native Hawaiian children and 26.5 months for white children.

**Conclusions:** The high average annual KS incidence for children <5 years of age in Hawai'i compared to the rest of the United States population reflects an increased KS incidence among Asian and Pacific Islander children, especially Japanese children. The incidence for white children was slightly higher than or similar to that generally reported nationwide.

## Introduction

Kawasaki syndrome (KS) cases were first reported in the United States in Hawai'i in 1976.<sup>1</sup> The KS incidence among children <5 years of age in Hawai'i has been much higher than that for children in the continental United States (9 to 19 cases per 100,000 children <5 years of age).<sup>2-8</sup> The incidence of KS in Hawai'i was 47.7 and 45.2 per 100,000 children <5 years of age during the mid-1990s and 1996-2001, respectively.<sup>4,5</sup> Furthermore, the occurrence of KS has been reported in community-wide outbreaks within Hawai'i and the continental United States.<sup>9,11,12</sup> In both Hawai'i and the continental United States, the incidence of KS has been reported to be high among children with Japanese and other Asian ancestry.<sup>4,5,7,9</sup> A large proportion of children living in Hawai'i have ancestral origins in Asia, which contributed to the overall high rate of KS among children in Hawai'i compared to rate estimates for the continental United States.<sup>2-6,9</sup>

In the present study, we analyzed records for patients <18 years of age hospitalized with KS during 1996 through 2006 using Hawai'i hospital discharge data to describe recent trends of KS and better understand the racial/ethnic-specific incidence of KS among children living in Hawai'i.

## Methods

Hospital discharge records with KS listed as a diagnosis from 1996 through 2006 for patients <18 years of age living in Hawai'i were obtained from the Hawai'i State Inpatient Database (SID).<sup>13</sup> The

Hawai'i Health Information Corporation (HHIC) partners with the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (AHRQ) to produce the Hawai'i SID.<sup>13,14</sup> The HHIC is a non-profit corporation that was established in 1994 to collect all inpatient data submitted from Hawai'i's 25 acute-care hospitals, representing 100% of the hospitalizations in Hawai'i.<sup>13,14</sup> The KS hospital discharge data obtained on October 2008 included hospitalizations with KS reported by both community hospitals and military/Department of Defense hospitals for the study period.

All hospitalizations for children with an International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM)<sup>14</sup> code for KS (446.1) listed as any one of up to 20 diagnoses on the discharge record were selected for our analysis. Multiple hospitalizations for patients during the study period were identified internally by AHRQ and HHIC through matching admissions by date of birth, sex, and residential zip code (no unique identifiers were available). The records for patients with more than one KS hospitalization were further examined to estimate a rate of KS recurrence. To analyze records by patient, the first KS hospitalization during the study period was selected for analysis; therefore, the patient's age was derived from their first admission with KS and the number of hospitalization days for each patient was summed from all of their KS hospitalizations. Race/ethnicity was described by using the race/ethnicity classification of the children from the hospital discharge records; for those records with missing race/ethnicity, appropriate hospital staff were contacted to review the medical records. Race/ethnicity was not available for 118 (22.3%) children <18 years of age. Race/ethnicity for patients recorded as "mixed or other race" and patients with a missing race/ethnicity was recorded as "other/unknown" by some of the hospitals (54 children <5 years of age had a recorded race of "mixed or other", and 42 patients had a missing race/ethnicity), therefore "mixed or other race" and "other/unknown race" were both considered as unknown for this study. Due to the small number of patients with race/ethnicity coded as either Black or as Hispanic, analysis of these racial/ethnic groups is not provided separately in this study. Thus, for the present study, race/ethnicity was examined for Asian and Pacific Islander and white children; Asian and Pacific Islander children were further analyzed by specific racial/ethnic classifications.

The average annual KS-associated incidence rates were estimated by age group for children <18 years of age, and by sex and race/ethnicity for children <5 years of age. The incidence estimate was calculated as the number of children hospitalized with KS per 100,000 of the corresponding population. In addition, the average annual KS-associated hospitalization rate for children <5 years of age was calculated by using the total number of KS hospitalizations for children <5 years of age per 100,000 children <5 years of age. The KS-associated incidence is reported unless otherwise indicated. The National Center for Health Statistics Bridged Race Vintage

population estimates for the population of children <18 years of age in Hawai'i for 1996 through 2006 were used for the denominator for overall rates, rates by age group, general race group (white and Asian/Pacific Islander), and sex.<sup>16,17</sup> The average annual incidence rate for each detailed racial/ethnic group was estimated for the 11-year study period; the denominator for each of these groups was calculated by summing the 2000 Census with the corresponding census data for each of the other study years (the population for each detailed race group was based on the Census 2000 proportion of each detailed race group).<sup>18</sup> Census 2000 is the most recent census data that provides the population classified by race listed alone or in combination with other races, which was not available in earlier census race classifications.<sup>19</sup> The listed-alone race categories were used for race/ethnicity-specific denominators. Persons indicated as part-Native Hawaiian were considered Native Hawaiian, as reported by the census.<sup>19</sup> Incidence rates were compared using Poisson regression analysis, and age in months for groups was compared using the Wilcoxon rank-sum test.

## Results

During 1996 through 2006, 528 children < 18 years of age accounted for 582 hospitalizations with KS. The 1996-2006 average annual KS-associated incidence rate for children <18 years of age was 16.3 patients per 100,000 children (Table 1). The average annual incidence rate for children <5 years of age (50.4) was significantly higher than those for children 5-9 and 10-17 years of age (8.6 and 0.7, respectively;  $p < 0.001$ ). The incidence for children <1 year of age was significantly higher than that for children 1-4 years of age (77.4 and 43.6, respectively;  $p < 0.001$ ). The median age of admission for children <18 years of age hospitalized with KS was 2 years of age.

Of the 528 children < 18 years of age, 441 (83.5%) were <5 years of age and accounted for 487 hospitalizations. Forty-four patients <5 years of age (10%) had more than one KS hospital stay, accounting for 9.4% of the hospitalizations. Approximately 1.1% of all KS patients <5 years of age had a second hospitalization with KS as the primary diagnosis occurring  $\geq 3$  months after the first KS hospitalization during the study period.

The 1996-2006 average annual KS-associated incidence rate for children <5 years of age was 50.4 patients per 100,000 children (Table 1). The annual incidence was relatively stable during the study period and ranged from 45.5 to 56.5. The average annual KS-associated hospitalization rate was 55.7 hospitalizations per 100,000 children.

For children <5 years of age, the incidence for boys was higher than the incidence for girls (55.2 and 45.3, respectively;  $p = 0.04$ ; Table 1). Among infants, the KS incidence rate was significantly higher for boys than that for girls ( $p = 0.001$ ); there was no significant rate difference by sex among children in the 1-4 year old age group.

Asian and Pacific Islander children <5 years of age accounted for 91.6% of the children <5 years of age for whom race information was available; the KS incidence was 62.9 per 100,000. Among Asian and Pacific Islander children, the incidence was higher for infants than that for children 1-4 years of age. The Asian and Pacific Islander infant incidence was higher than that for white infants (104.6 and 4.8 per 100,000 children, respectively,  $p < 0.0001$ ). Among all racial/ethnic groups <5 years of age in Hawai'i, Japanese children

| Characteristic                     | Number of Patients (%) <sup>a</sup> | Incidence (per 100,000) <sup>b</sup> |
|------------------------------------|-------------------------------------|--------------------------------------|
| <b>Total (&lt;18 years of age)</b> | 528 (100)                           | 16.3                                 |
| Age group (years) <1               | 136 (25.8)                          | 77.4                                 |
| Age group (years) 1–4              | 305 (57.8)                          | 43.6                                 |
| Age group (years) 5-9              | 77 (14.6)                           | 8.6                                  |
| Age group (years) 10-17            | 10 (1.9)                            | 0.7                                  |
| <b>Gender</b>                      |                                     |                                      |
| Boys                               | 306 (58.0)                          | 18.3                                 |
| Girls                              | 222 (42.0)                          | 14.2                                 |
| <b>Children &lt;5 years of age</b> |                                     |                                      |
| <b>Gender</b>                      |                                     |                                      |
| Boys                               | 249 (56.5)                          | 55.2                                 |
| <1 year                            | 89 (35.7)                           | 98.2                                 |
| 1–4 years                          | 160 (64.3)                          | 44.4                                 |
| Girls                              | 192 (43.5)                          | 45.3                                 |
| <1 year                            | 47 (24.5)                           | 55.3                                 |
| 1–4 years                          | 145 (75.5)                          | 42.8                                 |

<sup>a</sup> Proportion of patients is based on the primary group of patients with known data. Percentages may not add to 100% due to rounding.

<sup>b</sup> Average annual incidence rate is the number of children hospitalized with KS per 100,000 children from the corresponding group in the census data during the study period.<sup>16</sup>

had the highest incidence (210.5), followed by Native Hawaiian children (86.9), other Asian children (84.9), and Chinese children (83.2; Table 2). The KS incidence for Japanese children was more than twice that for Native Hawaiian children ( $p = 0.01$ ) and much greater than that for white children (13.7;  $p < 0.0001$ ).

The median age for children <5 years of age was 21 months (25th and 75th percent quartiles of 10 and 36 months, respectively; Figure 1). The median age of admission for Japanese children <5 years of age was 24 months, and was significantly higher than the median age of Native Hawaiian children (14.5 months;  $p = 0.03$ ) and not statistically different from that for white children (26.5 months).

No clear seasonal pattern in KS hospital admissions for children <5 years of age was observed; admissions occurred throughout the study period with a small peak seen in December/January. The median length of hospital stay was 2 days (quartiles = 2 and 3.5 days). No in-hospital deaths were reported among children hospitalized with KS.

## Discussion

The average annual KS-associated incidence among children <5 years of age in Hawai'i for 1996-2006 was 50.4 per 100,000 children. This relatively high KS incidence reflects the high incidence among Asian and Pacific Islander children, especially Japanese children. This incidence was approximately 2.5 times higher than the upper range of the reported incidence for the continental United States (9 to 19 cases per 100,000 children <5 years of age).<sup>2-8</sup> As reported

Table 2.— Race/ethnicity of children hospitalized with Kawasaki syndrome (KS) and KS incidence rate estimates among children <18 and <5 years of age, Hawai'i, 1996–2006.

| Race/ethnicity <sup>a</sup>         | <18 years of age                    |                                      | <5 years of age                     |                                      |
|-------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|
|                                     | Number of Patients (%) <sup>b</sup> | Incidence (per 100,000) <sup>c</sup> | Number of Patients (%) <sup>b</sup> | Incidence (per 100,000) <sup>c</sup> |
| Japanese                            | 131 (32.4)                          | 57.8                                 | 104 (30.8)                          | 210.5                                |
| Native Hawaiian                     | 75 (18.6)                           | 27.7                                 | 60 (17.8)                           | 86.9                                 |
| Chinese                             | 21 (5.2)                            | 23.8                                 | 18 (5.3)                            | 83.2                                 |
| Filipino                            | 81 (20.0)                           | 19.0                                 | 70 (20.7)                           | 64.5                                 |
| Other Asian <sup>d</sup>            | 57 (14.1)                           | 25.0                                 | 52 (15.4)                           | 84.9                                 |
| Other Pacific Islander <sup>e</sup> | 12 (3.0)                            | 8.5                                  | 12 (3.6)                            | 8.6                                  |
| White                               | 27 (6.7)                            | 5.0                                  | 22 (6.5)                            | 13.7                                 |

<sup>a</sup> Race/ethnicity was not reported for 118 patients <18 years of age and 96 patients <5 years of age, therefore the rates and percentages are based on patients with reported race. Incidence rates are not presented for the Black and Hispanic race/ethnic groups, as there were few children reported in these categories. Percentages may not add to 100% due to rounding.

<sup>b</sup> Proportion of patients is based on the primary group of patients with known data.

<sup>c</sup> The average annual incidence rate is the number of children hospitalized with KS during the study period per 100,000 children from the corresponding group. This incidence was estimated by using the 2000 Census for detailed race data, and the census data for the other study years as the proportion of the detailed race groups for the Census 2000 data.<sup>17</sup>

<sup>d</sup> Census for other Asians includes persons who provide a response of Korean, Vietnamese, Cambodian, Hmong, Laotian, Asian Indian, and others, or other Asian not specified.<sup>18</sup>

<sup>e</sup> Census for Other Pacific Islanders includes persons who provide a response of Pacific Islander groups, such as Samoan, Tongan, Guamanian or Chamorro, Fijian, Polynesian and others, or Pacific Islander not specified.<sup>18</sup>

in previous studies, the KS incidence approximates 90% of the KS hospitalization rate; this percentage takes into account multiple KS hospitalizations.<sup>3,20</sup> Although the KS incidence in Hawai'i was strikingly higher than in the continental United States, the median age of children <5 years of age with KS in Hawai'i (22 months) and in the overall US population (23–24 months) was similar.<sup>7,8</sup> The incidence of KS varies by race/ethnicity; studies have described a particularly high KS incidence among Asian children.<sup>4,7-9</sup> The high KS incidence among children <5 years of age in Hawai'i is likely due to the large population of Asian children in Hawai'i. The incidence for white children was lower than the incidence for the other reported racial/ethnic groups in Hawai'i and was slightly higher than or similar to those estimated for white children in the general US population.<sup>7,8</sup> The reported KS hospitalization rate for non-Hispanic white children in the general US population was 11.4 (95% CI=10.5–12.4) for 2000 and 12.0 (95% CI=10.2–13.8) for 2006.<sup>7,8</sup> The observed average annual KS incidence for Japanese-American children <5 years of age remains the highest among children of racial/ethnic groups living in Hawai'i, and appears to be slightly higher than or similar to that reported for children <5 years of age living in Japan where the KS incidence rate was 184.6 cases per 100,000 children <5 years of age for 2005–2006.<sup>21</sup>

The observed differences in KS incidence by race/ethnicity in Hawai'i likely reflect important racial/ethnic differences in genetic susceptibility to KS. Other factors such as environmental factors, access to health care, the index of suspicion and awareness of physicians for KS, and geographic location or culture among Asian populations may affect KS incidence.<sup>4</sup> At the Ninth International Kawasaki Disease Symposium, several investigators reported on progress in identifying genetic susceptibility factors for KS.<sup>22, 23</sup>

Approximately 10% of the hospitalizations represented multiple admissions for KS. A small number of patients were admitted for a hospitalization with KS as the primary diagnosis at least three months after an initial KS hospitalization, representing an estimated recurrence rate of 1.1%. This rate falls close to previously reported recurrence rates in North America (1%) and Japan (approximately 3%).<sup>24</sup>

This study used statewide hospital discharge data with KS listed as a diagnosis and has some limitations. These data are physician diagnosis-based and likely include patients that may not meet the epidemiologic KS case definition.<sup>3,25</sup> In addition, incompleteness of records and diagnostic miscoding may have occurred. Patients' race/ethnicity was classified at the hospital into one racial/ethnic group, where a patient may be of more than one race/ethnicity. Incompleteness of patient's race/ethnicity on hospital records (21.8%), which includes the classification of other and unknown race together, may have led to underestimation of the KS incidence among some of the race/ethnic groups. The 2000 Census data for Hawai'i were used to estimate the incidence of KS for the racial/ethnic groups; population estimates for each racial/ethnic group alone were used, which does not account for persons of mixed race/ethnicity. Furthermore, the assignment of patients' race/ethnicity by the hospitals in Hawai'i might differ from the race/ethnicity of the census denominator and thereby alter the incidence in some racial/ethnic groups. Overall, differences between the incidence determined in the present study with incidences reported for Asian countries and the United States may be partially influenced by differences in reporting, diagnosis, and study design.<sup>4, 10</sup>

The incidence of KS in Hawai'i remains high, reflecting the high incidence among Asian and Pacific Islander children, especially Japanese children. White children, compared to Asian and Native Hawaiian children, had a lower incidence in Hawai'i, which was similar to or slightly higher than the rates reported for white children in the continental United States. Further efforts in the study of KS, and the monitoring of the occurrence of KS among children in Hawai'i, including racial/ethnic incidence differences, remain important.

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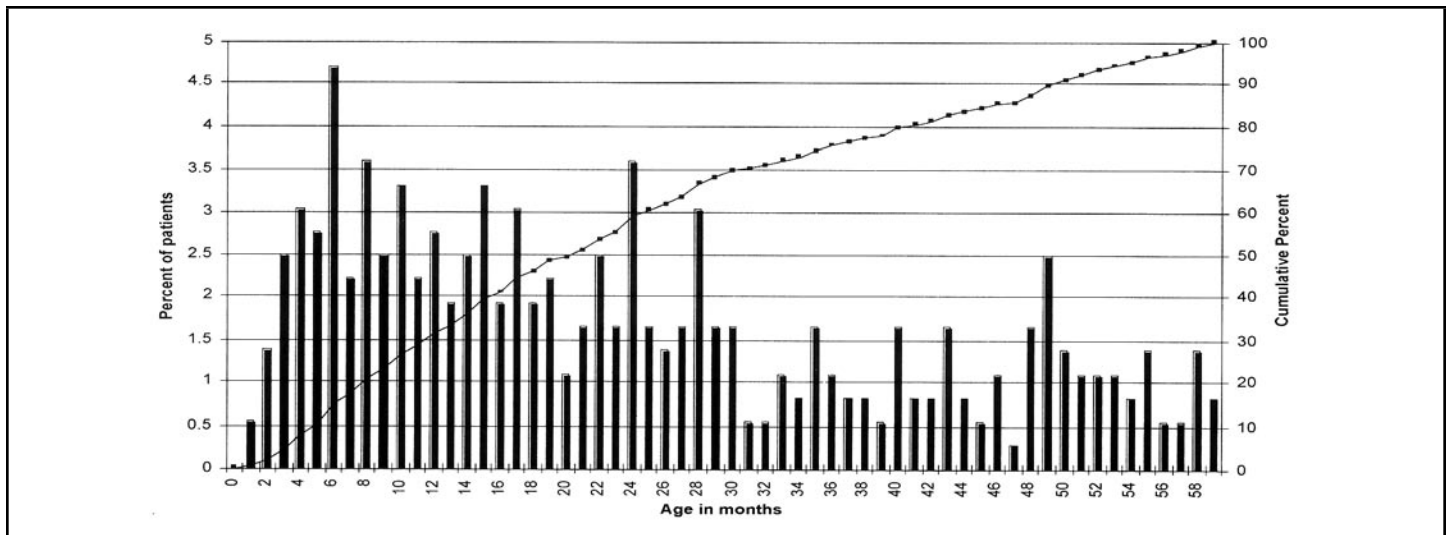


Figure 1.— Proportion of Children <5 Years of Age Hospitalized with KS by Month of Age, Hawai'i, 1996-2006.

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# MEDICAL SCHOOL HOTLINE

SATORU IZUTSU PHD, CONTRIBUTING EDITOR

## University Clinical, Education, and Research Associates (UCERA)

**Patricia Lanoie Blanchette MD, MPH; Chief Operating Officer, UCERA**

In addition to its academic and research missions, medical schools also have a mission to provide highly skilled clinical care services. These clinical services are usually organized in one or more faculty practice plans. Hawai'i is particularly challenged by circumstances that have resulted in an overall physician shortage with more serious shortages in certain specialties, and with problems related to geographical difficulties in access to care. As a state school, the John A. Burns School of Medicine (JABSOM) shares in the land grant responsibilities of the University to provide community service. To help fulfill this mission, JABSOM looks to its clinical departments and to faculty practice plans to attract, retain, and support new physicians and to develop needed clinical services. For JABSOM, those faculty practice plans now include UCERA, staffed by members of all clinical departments except Pediatrics, and Kapiolani Medical Specialists staffed by members of the Department of Pediatrics.

While JABSOM was a relatively new school, of necessity it first needed to focus on its teaching and later its research missions. With increasing maturity, the school is now expanding its clinical service mission, especially in areas of the state's greatest needs.

UCERA is a non-profit 501(c) 3 organization affiliated with the University of Hawai'i. It is aligned with the mission of the John A. Burns School of Medicine and UCERA's clinical departments mirror those of the medical school. In keeping with the School's vision of Attaining Lasting Optimal Health for All (ALOHA), and its mission to be part of the fabric of Hawai'i, the School is committed to excellence and leadership in: educating current and future healthcare professionals and leaders; delivering high-quality healthcare; conducting research and translating discoveries into practice; establishing community partnerships and fostering multidisciplinary collaboration; pursuing alliances unique to Hawai'i and the Asia-Pacific region; acting with forethought regarding right relationships, respect, and moral action, i.e. "pono."

UCERA's principal purpose is to provide the vehicle by which the School fulfills or supports its mission of education and clinical service. UCERA administers the clinical practice of participating faculty members and aims to provide funding to build and sustain the infrastructure of the School and its departments. In its role as a faculty practice plan, UCERA contracts with insurance companies and is authorized to bill, collect and disburse patient care and other revenues earned by participating faculty members and to enter into contracts for the generation and collection of such revenues.

The principal activities of UCERA include:

- a) Managing the clinical practice of the faculty, including, without limitation, billing, collection, and other financial aspects of clinical practice;
- b) Entering into contractual arrangements, which may include affiliations or joint ventures, with hospitals, managed care organizations, networks of health care providers, government agencies or other healthcare organizations or entities;
- c) Securing, in cooperation with JABSOM, appropriate sites for faculty to provide patient care;
- d) Establishing, managing and operating one or more networks of academic healthcare providers;
- e) Providing high-quality clinical teaching and clinical research environments for the JABSOM faculty.

Of particular importance to the Hawai'i Medical Journal (HMJ), UCERA became the parent corporation of the HMJ when the journal's founder and long-time sustainer, the Hawai'i Medical Association, decided it could no longer do so. HMJ helps to fulfill the School's mission to educate current and future healthcare professionals, to improve healthcare, to foster research and to highlight new research findings, especially as they relate to issues of importance to Hawai'i and the Asia-Pacific region. Over the years, many faculty members have worked alongside community physicians for HMJ, providing members to the editorial board, serving as reviewers, and writing for publication. In fact, the Journal's editor at the time of the transition to UCERA is now the Interim Chair of the School's Department of Native Hawaiian Health.

UCERA is governed by a voluntary Board of Directors. JABSOM's Dean Jerris Hedges is the Chairperson of the Board of Directors, and board membership includes both the clinical department chairs and a number of community members. Current board members include: Dr. Elizabeth Tam, Vice-Chair who is also Chair of the Department of Internal Medicine; Dr. Danny Takanishi, Treasurer and Chair of the Department of Surgery; Judge James A. Burns, Secretary and Community Member; Sandra Tsuruda, Assistant Secretary (non-voting); Dr. Kheng See Ang, Community Member; Kathryn Inkinen, Community Member; Mr. John Holzman, designee of the UH Board of Regents; Dr. Kalani Brady, Interim Chair of the Department of Native Hawaiian Health; Dr. Roseanne Harrigan, Chair of the Department of Complementary and Alternative Medicine; Dr. Jeffrey Killeen, Acting Chair of the Department of Pathology; Dr. Earl Hishinuma, Department of Psychiatry; Dr. Satoru Izutsu, JABSOM Vice-Dean; Dr. Kamal Masaki, Acting Chair of the Department of

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Geriatric Medicine; Dr. Neal Palafox, Chair of the Department of Family Medicine and Community Health; Dr. Raul Rudoy, Chair of the Department of Pediatrics; and, Dr. Lynnae Sauvage, Chair of the Department of Obstetrics, Gynecology and Women's Health. Dr. Roy Magnusson, UCERA's Chief Medical Officer and JABSOM Associate Dean for Clinical Affairs, and Dr. Patricia Blanchette, UCERA's Chief Operating Officer, serve in an ex-officio capacity to the UCERA board.

UCERA currently has over one hundred and twenty physician providers and an equal number of support staff members whose central services include Medical Billing, Revenue Cycle Management, Contracting, Compliance, Finance, Human Resources, Inhouse Counsel, Compensation Management, and Information Technology and Security. In addition to the central office staff, UCERA staff members also work in many clinical departments providing clinic staffing and department clinical administrative support.

UCERA has had many success stories over the past few years, including the following examples:

- The Department of Obstetrics, Gynecology and Women's Health is providing a great deal of clinical service and faculty support to stem the serious decline of specialists and subspecialists in this field in Hawai'i. The department operates many clinics, provides services in underserved areas, and also provides shortage specialty services in hospitals and clinics, including emergency coverage.
- Supporting the efforts of the Department of Family Medicine and Community Services and Hilo Medical Center, the UCERA central staff provided the organizing logistical work and financial management for the establishment of the new Hawai'i Island Family Health Center in Hilo to serve as the base of a planned new rural Family Medicine residency program in Hilo.

- UCERA worked with its Department of Surgery to contract with the Queen's Medical Center to recruit and retain new trauma surgeons and to provide 24/7 coverage for these services to the state's major trauma center.

- UCERA supports the work of the Department of Psychiatry in its provision of most of the psychiatric professional services at the Queen's Medical Center.

- UCERA provides the central billing service for the Department of Geriatric Medicine's Teaching Nursing Home Program (TNH) whereby faculty geriatricians and geriatric medicine fellows provide service in over twenty nursing homes. This is greatly needed care in a critical shortage field.

- The Department of Native Hawaiian Health provides culturally competent clinical services on O'ahu and at Kalaupapa on Moloka'i.

These are only some examples of how UCERA serves to assist the School in its community service efforts. All of the examples cited underscore how the focus of UCERA's efforts with the School have been targeted on areas of serious community need, and where the shortages have been the most acute, and where clinical services have been needed both to provide patient care and to serve as a base for the school's clinical teaching activities.

It is said that the best medical care is that provided when a medical student or resident is looking over your shoulder to learn. If this is true, JABSOM's clinical faculty and its faculty practices certainly provide some of the best medical care in Hawai'i.

### ***Hawaiian proverb:***

***“In the end... we will take care of only what we love; We will love only what we understand; We will understand only what we are taught.”***





## Induction of Breast Cancer in Wild Type p53 Cells by BRCA1-IRIS Overexpression

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### Abstract

*Cells ability to evade cell death and to proliferate post geno-/cell-toxic stresses, likely leads to formation of cancer. Activation of p38MAPK and p53 following these stresses help protect cells against cancer development by initiating apoptosis. The duration of p38MAPK and p53 activation is regulated by the WIP1 phosphatase. BRCA1-IRIS triggers WIP1 expression in p53-dependent and -independent manner. BRCA1-IRIS triggers the expression and cytoplasmic localization of the mRNA stabilization and translation inducer, HuR that binds p53 and PPM1D mRNA. Hence, BRCA1-IRIS overexpression inactivates p38MAPK and/or p53 by upregulating WIP1 expression. BRCA1-IRIS abrogation of the homeostatic balance maintained by p38MAPK-p53-WIP1 pathway suppressed cell death induced by a lethal dose of UVC, high dosages of etoposide or H<sub>2</sub>O<sub>2</sub>, and allowed cells to survive and proliferate post geno-/cell-toxic stresses. This mechanism represents a new link between geno-/cell-toxic stress and aggressive breast cancer formation in p53 wild-type cells.*

### The Tumor Suppressor p53 and the Cell Death Inducer p38MAPK.

The tumor suppressor p53 is activated in response to a variety of mitogenic and stressful stimuli.<sup>1</sup> Following geno-/cell-toxic stresses p53 expression increases primarily through modulation of the steady-state level of the protein through phosphorylation and acetylation.<sup>2</sup> Stabilized p53 induce transcription of many cell cycle arrest and apoptosis genes, such as Gadd45 and p21 WAF1, Bcl-2, Bax, PUMA, and MDM2.<sup>1</sup> P38MAPK is serine/threonine kinase, member of the mitogen-activated protein kinases (MAPK) family that includes the extracellular signal-regulated protein kinases (ERKs), and the stress-activated c-Jun N-terminal kinases (JNKs).<sup>3</sup> Following geno-/cell-toxic stresses p38MAPK is activated by phosphorylation of threonine 180/Tyrosine 182 (T180/Y182).<sup>3</sup> Activated p38MAPK then activates p53 by phosphorylating its serine 15, 33 and 46 thereby inducing cell cycle arrest or apoptosis. The stabilizing factor, HuR binds and stabilizes p53 mRNA following UV irradiation.<sup>4</sup> HuR is a nucleocytoplasmic shuttling protein that binds to AU-rich element in the 3' UTR of mRNAs of many genes, such as *VEGF*, *p21*, *Cyclin A* and *B1*, *c-fos*, *p27*.<sup>5</sup>

### The Inactivator of p53 and p38MAPK, WIP1.

The Protein phosphatase magnesium-dependent 1, delta (*PPM1D*), the gene encoding for the serine/threonine phosphatase WIP1 (for wild-type p53-induced phosphatase 1) is located on human chromosome 17q23–24.<sup>6</sup> *PPM1D* amplification and overexpression is associated with poor clinical outcomes in neuroblastoma, breast and ovarian clear cell carcinomas.<sup>7</sup> WIP1 is expressed under various geno-/cell-toxic stress conditions in a p53-dependent manner, where it inactivates p38MAPK and p53 itself.<sup>8</sup>

### The Activator of WIP1, BRCA1-IRIS.

Despite its original discovery as a product of the tumor suppressor BRCA1 locus, and despite sharing 1365 from its 1399 residues with the tumor suppressor protein product of this locus BRCA1/p220, BRCA1-IRIS has oncogenic properties. BRCA1-IRIS promotes DNA replication during S phase, in part through suppressing the inhibitory function of the DNA replication suppressor, Geminin,<sup>9</sup> and cell proliferation through upregulating Cyclin D1 expression, directly by binding to its promoter through c-Jun/AP1 transcription complex and activates its transcription<sup>10</sup> or indirectly by suppressing the expression of the JNK-specific inactivating phosphatase DUSP3/VHR.<sup>11</sup> In this recent study, we examined the mechanisms governing the production of breast cancer in wild-type p53 cells. We found that geno-/cell-toxic stresses, e.g., irradiation, such as short wavelength UV light (UVC), chemotherapy drugs, such as etoposide or the free-radical generate, such as H<sub>2</sub>O<sub>2</sub> exposure triggered BRCA1-IRIS expression in normal as well as breast cancer cell lines, which triggered WIP1 expression by p53-dependent and -independent manner. Independently, BRCA1-IRIS promoted the expression and cytoplasmic localization of HuR that binds p53 and *PPM1D* mRNAs and enhanced their stability and translation. Accordingly, BRCA1-IRIS silencing induced apoptosis in breast cancer cells exposed to UVC, etoposide or H<sub>2</sub>O<sub>2</sub>, and p53 silencing or p38MAPK inactivation augmented that. Whereas, BRCA1-IRIS overexpression in normal human mammary epithelial (HME) cells suppressed cell death induced by UVC, etoposide or H<sub>2</sub>O<sub>2</sub>, and these damaged cells continued to proliferate, especially when p53 was silenced or p38MAPK was inactivated in them. We propose that this mechanism accounts, at least in part, for the initiation of breast cancers in patients with wild-type p53 gene.

### Conclusion

Our data together show that BRCA1-IRIS overexpression inactivates p38MAPK and p53 by inducing expression of their phosphatase WIP1, that BRCA1-IRIS triggers p53 and WIP1 expression is posttranscriptional, that BRCA1-IRIS induced *PPM1D* and p53 mRNA stabilization and translational by promoting the expression and cytoplasmic availability of the mRNA binding protein, HuR. In keeping with its ability to induce WIP1 expression in mutant as well as wild type p53 cells. While HuR binding and stabilization of p53 mRNA has been reported earlier,<sup>4</sup> we are the first to show post-transcriptional control of WIP1 expression by BRCA1-IRIS-induced HuR. We propose that Targeting BRCA1-IRIS with a drug will enhance the efficacy of drugs aimed at inducing cell death in tumor cells through induction of geno-/cell-toxic stresses. Studies aiming at identifying such a pharmacological inhibitor are underway in our laboratory.

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## ❖ IT WASN'T CHEATING. THEY JUST HAD THE QUESTIONS AHEAD OF TIME.

Almost all physicians in active practice sat for a board certification examination at least once in their careers and before taking the test, signed a pledge not to reveal questions. The American Board of Internal Medicine (ABIM) has brought a law suit against Arora Board Review and five physicians. The suit alleges that five physicians infringed the organization's copyright on the test questions. ABIM is seeking an injunction and monetary relief for the more than \$75,000 it has cost the board in developing its questions. The board is sanctioning the five physicians along with 134 others for what it deemed ethical breaches involving disclosure of test questions which are not to be repeated, copied or reproduced. Arora course instructors told class members that the review questions were from the actual exam, and allegedly solicited examinees to provide additional questions which they remembered. Depending on the offense, sanctioning may involve one year suspension of board certification or having it yanked indefinitely.

## ❖ YES, BUT THERE IS STILL THE PROBLEM WITH THE COLD NOSE.

In Paris, France, researchers at the Hospital Tenon spent a year training Belgian Malinois shepherd dogs to tell the difference between urine from 33 men with prostate cancer and urine from a group that was cancer-free. When the dogs identified a cancerous sample by running to their trainer they got a reward. After the training, the dogs correctly identified 63 out of 66 samples as cancerous or not. Dr. Anthony Smith, prostate cancer expert from the American Urological Association, saw the research presented at their annual meeting. He stated, "These data suggest prostate cancer tumors may excrete volatile organic compounds that turn up in a patient's urine and that this scent may be specific to prostate cancer."

## ❖ GENDER EQUALITY WITH THE HELP OF TOBACCO.

Lung cancer is the most common fatal malignant neoplasm in the United States. Over the past 30 years the rate of death among males has substantially decreased, but the interesting finding is that lung cancer deaths in women have gradually increased. Tobacco is still cited as the primary culprit, but an unexplained finding is that one in five women with lung cancer has never smoked compared with one in twelve never-smoking men. While breast cancer will kill about 40,000 women in 2010, lung cancer deaths are projected to hit 71,000. Some cancer researchers believe the rise in lung cancer in women is simply due to differences in male/female smoking patterns with women starting smoking later and being slower to quit. That is too simple according to a research team at the Fox Chase Cancer Center in Philadelphia. Publishing in Cancer Prevention Research, this team's research is focusing on estrogen as a factor noting higher hormone levels before menopause and that some women take drugs to boost estrogen including replacement therapy and birth control pills.

## ❖ AND NOW PLAYING ON THE JUMBO-TRON - INVASION OF THE BODY SCANNERS!

The Transportation Security Administration (TSA) has rolled out the new body-screening machines in 27 airports around the country. The TSA has a goal of 450 scanners screening travelers around the nation, and many of the flying public have come to accept the body-peeking device without complaint. One man who travels two or three times a week stepped into the scanner at Chicago's O'Hare airport and was told to remove his belt and his wallet, then told to hold his hands above his head. When he tried to hold up his pants the agent shouted at him to keep his hands up so the machine could get a clear picture. Swell! Hey, if you have to drop your pants why bother with a scanner?! Still, public opinion polls reveal widespread acceptance of the technology in the U.S. because travelers believe tighter security more than outweighs inconvenience. The Christmas Day 2009 "crotch bomber" attempt to blow up the Delta Air Lines flight into Detroit really brought the value of the scanner into play. At some airports, TSA screeners randomly assign people to the machines, and they can refuse, but then must undergo a pat-down search. A female infertility-expert physician in Chicago refused the scanner and asked how many rads she would receive. TSA screener had no answer, so she said, "I don't appreciate being touched all over, but I prefer that to adding to my cancer risk." Apparently, travelers are willing to forget the fourth amendment right about unreasonable searches.

## ❖ KOOL ISN'T COOL. AS YE SMOKE, SO SHALL YE REEK!

Menthol cigarettes are becoming increasingly popular and now make up one-quarter of all cigarettes sold in the United States. In 2009 the Food and Drug Administration was given the authority to regulate tobacco products and banned fruit or chocolate flavored cigarettes which would be tempting

to kids. Menthol was not mentioned Tobacco experts say the menthol-flavored cigarettes are advertised as cool, soothing and smooth, have greater appeal for young people, and are more addictive and harder to quit than regular cigarettes. Philip Gardiner, researcher at the University of California tobacco-related research program in Oakland, claims that menthol is the "ultimate candy flavoring." The FDA has a hearing scheduled in July, but to date has not planned a ban on menthol.

## ❖ A FIVE DAY WINDOW? PLENTY TIME TO COME AND GO.

Although birth control pills have been available for a half century, 50% of pregnancies are still unplanned. The Bush administration fought for five years to prevent plan B medication before it finally became available over the counter. The FDA is currently studying a new "morning after" pill called Ella, made by Pharma, which is already marketed in Europe. The one-dose drug will prevent ovulation for five days, extending the time for safe and effective pregnancy prevention by from three to five days. The FDA panel of advisors unanimously recommended approval. The drug is less effective in obese women, and does not prevent pregnancy in repeated sexual contact in the five day period.

## ❖ HAWAI'I CONVENTION CENTER MANNING THE ECONOMIC PUMP.

Searching for jobs and dollars is a statewide struggle, but the Hawai'i Convention Center is looking good. Five major medical meetings are in the hopper. Recent HMA past president Pat Blanchette had a hand in bringing the Alzheimer's Association International Congress due in July with 5,500 delegates and 44,200 room nights scheduled for local hotels. In October the Annual Meeting of the American Academy of Periodontology will bring 6,000 delegates and occupy 48,240 room nights, followed in December by the American Chemical Society 2010 International Congress of Pacific Basin Societies and with a great crowd of 11,620 delegates scheduled to occupy 93,425 room nights. For May 2011 Hawai'i's own Jeffrey Akaka, M.D. encouraged the American Psychiatric Association to hold their Annual Meeting at the Hawai'i Convention Center bringing 18,500 delegates to occupy 148,470 rooms. Later in 2011 the American College of Chest Physicians will bring their Annual Meeting and another 5,000 attendees for 40,200 room nights.

## ❖ "HOLY SMOKE!" THE PREACHER SHOUTED.

In Monroe, Ohio, a 60 foot statue of Jesus was erected in 2004 at the evangelical Solid Rock Church along interstate highway 75. The statue was made of plastic foam and fiberglass over a steel frame and featured the torso of Jesus with both arms raised similar to the mural that overlooks the Notre Dame stadium. It was nicknamed "touchdown Jesus." Alas, a bolt of lightning stuck the statue about 11:30 P.M. recently, and it burned to the ground. Pastor Darlene Bishop said, "This meant a lot to a lot of people," and she said it will be rebuilt of non-flammable material.

## ❖ IN LOS ANGELES THE CITY COUNCIL MOVES SOME TOKES OVER THE LINE.

In Los Angeles, California, 400 new marijuana stores sprang up after the Obama administration fulfilled a campaign promise to cease federal prosecution of marijuana laws. Now the LA City Council has approved a new ordinance that will close hundreds of clinics. Those that remain will be banished to industrial areas forcing their clientele to travel longer distances. The new dispensaries must close their doors promptly and the older ones can be grand-fathered in, but they will locate at least 1,000 feet away from schools, public parks, public libraries and religious institutions.

## ❖ WANT TO REDEEM YOUR FREQUENT FLIER MILES? FUGGETTA-BOUDIT!

If you want to score a free air line ticket with those miles you have built up with flights and charge card credits, a few airlines, Southwest and Air Canada, are ready to help about 95% of the time. Others, especially Delta and US Air honor only 10 or 15% of requests All the airlines are tied to credit card companies, and miles build up for any and all purchases from grocery stores to theater tickets, even to auto buys. Worldwide, the estimate is that 10 trillion frequent flyer miles have accumulated with the result that a ticket request for six months in the future may well be refused.

## ADDENDA

- ❖ The great white shark is the only shark that can hold its head above water to observe activity on the surface.
- ❖ The first quarter of 2010 attracted 90,000 honeymooners to Hawai'i, up 8% over 2009.
- ❖ Seven out of ten women surveyed said they are turned on by men who help with household chores.
- ❖ Always eat safely. Use condiments.

# UPCOMING CME EVENTS

Interested in having your upcoming CME Conference listed? Please contact Nathalie George at (808) 536-7702 x103 for information.

| Date                  | Specialty | Sponsor  | Location                                      | Meeting Topic  | Contact   |
|-----------------------|-----------|--|---|--|---|
| <b>September 2010</b> |           |  |   |  |   |
| 9/3-9/4               | Multi     | Cancer Research Center of Hawai'i and Hawai'i Consortium for Continuing Medical Education    | Four Seasons Resort Hualalai, Kona, Hawai'i   | 13th Annual West Hawai'i Cancer Symposium  | Tel: (808) 987-3707   |
| 9/28-10/2             | NRN       | Western Neuroradiological Society  | Fairmont kea Lani, Maui                       | 42nd Annual Meeting  | Web: www.wnrs.org   |
| <b>October 2010</b>   |           |  |   |  |   |
| 10/3-10/7             | PMM       | Ironman Sports Medicine Conference   | Royal Kona Resort, Kailua-Kona, Hawai'i       | 22nd Annual Ironman Sports Medicine Conference   | Tel: (877) 843-8500<br>Web: www.cmtravel.com                    |
| 10/17-10/22           | Multi     | Scripps Conference Services & CME  | Kaua'i Marriott Resort & Beach Club, Kaua'i   | 9th Annual Destination Health: Renewing Mind, Body and Soul<br>Email: med.edu@scrippshealth.org  | Tel: (858) 652-5400<br>Web: www.scripps.org/conferenceservices  |
| 10/23-10/29           | U         | Western Section of the American Urological Association                                       | Hilton Waikoloa Village                       | 86th Annual WSAUA Meeting  | Web: http://www.wsaua.org/hawaii2010/2010.htm                   |
| 10/31-11/5            | R         | University of California, San Francisco  | The Fairmont Kea Lani, Wailea, Hawai'i        | Abdominal and Thoracic Imaging on Maui   | Tel: (415) 476-4251<br>Web: www.cme.ucsf.edu                    |
| <b>November 2010</b>  |           |  |   |  |   |
| 11/1-11/5             | AN        | California Society of Anesthesiologists  | Mauna Lani Resort & Spa, Kailua-Kona, Hawai'i | 2010 CSA Fall Hawaiian Seminar   | Web: www.csaqh.org  |
| 11/7-11/10            | R         | Department of Radiology, Duke University   | Hyatt Regency Maui, Ka'anapali Beach, Maui    | A Comprehensive Review of Musculoskeletal MRI  | Web: www.radiology.duke.edu                                     |
| 11/15-11/17           | PD        | Lucile Packard Children's Hospital   | Mauna Lani Bay Hotel, Kohala Coast, Hawai'i   | Popular Pediatric Clinical Topics  | Web: www.lpch.org/CME Courses                                   |
| 11/20                 | Multi     | Hepatitis Support Network of Hawai'i and Hawai'i Consortium for Continuing Medical Education | Queen's Conference Center                     | Viral Hepatitis in Hawai'i - 2010  | Tel: (808) 538-2881<br>Web: www.hepatitis.IDLinks/symposium2010 |
| <b>January 2011</b>   |           |  |   |  |   |
| 1/16-1/19             | ORS       | Vindico Medical Education  | Grand Hyatt Kaua'i                            | Orthopedics Today Hawai'i 2011   | Web: www.othawaii.com   |
| 1/16-1/21             | OPH       | Vindico Medical Education  | Hyatt Regency Maui, Ka'anapali Beach, Maui    | Retina 2011  | Web: www.retinameeting.com                                      |
| 1/16-1/21             | OPH       | Vindico Medical Education  | Hyatt Regency Maui, Ka'anapali Beach, Maui    | Hawaiian Eye 2011  | Web: www.osnhawaiianeye.com                                     |
| 1/24-1/28             | AN        | California Society of Anesthesiologists  | Mauna Lani Resort & Spa, Kailua-Kona, Hawai'i | 2011 CSA Winter Hawaiian Seminar   | Web: www.csaqh.org  |
| <b>February 2011</b>  |           |  |   |  |   |
| 2/13-2/18             | R         | University of California San Francisco School of Medicine                                    | Fairmont Orchid, Kohala Coast, Hawai'i        | Neuro and Musculoskeletal Imaging  | Web: www.cme.ucsf.edu/cme                                       |
| 2/16-2/20             | EM        | University of California San Francisco School of Medicine                                    | Marriott Ihilani Resort & Spa, O'ahu          | High Risk Hawai'i 2011   | Web: www.retinameeting.com                                      |
| 2/19-2/20             | OTO       | University of California San Francisco School of Medicine                                    | Moana Surfrider Hotel, Waikiki, O'ahu         | American College of Surgeons Thyroid and Parathyroid Ultrasound Skills-Oriented Course           | Web: www.osnhawaiianeye.com                                     |
| 2/19-2/22             | OTO       | University of California San Francisco School of Medicine                                    | Moana Surfrider Hotel, Waikiki, O'ahu         | Pacific Rim Otolaryngology Head and Neck Surgery Update  | Web: www.csaqh.org  |
| 2/20-2/25             | IM        | University of California San Francisco School of Medicine                                    | Fairmont kea Lani, Maui                       | Infectious Diseases in Clinical Practice: Update on Inpatient and Outpatient Infectious Diseases | Web: www.csaqh.org  |