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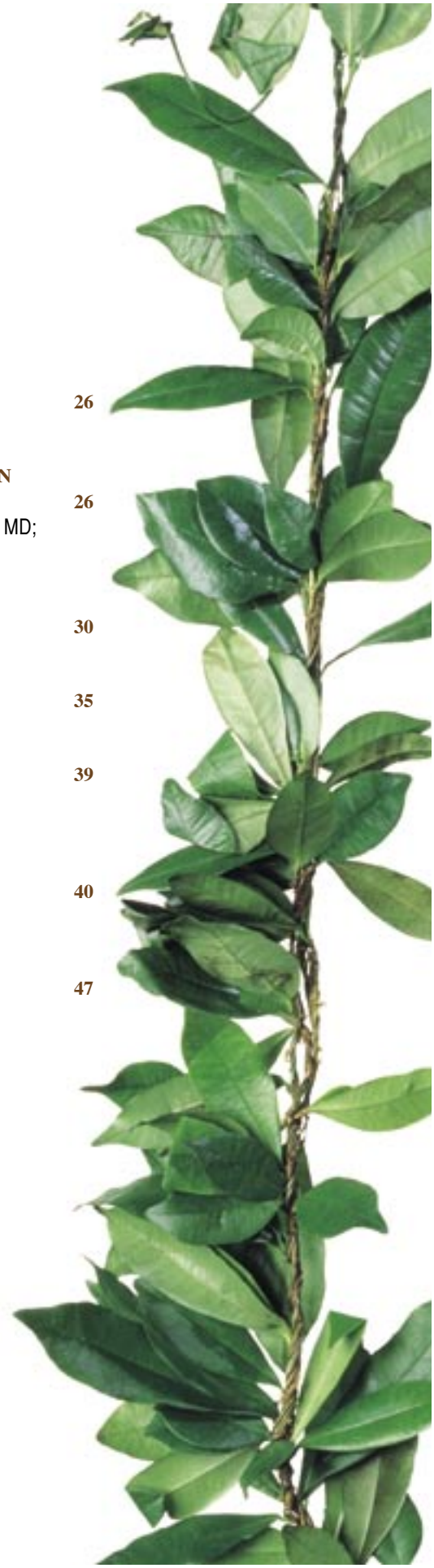

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EDITORIAL
From the Editor Emeritus

In 1941, Harry L. Arnold, Jr. MD, established and edited the Hawai'i Medical Journal under the auspices of the Hawai'i Medical Association. When Dr. Arnold retired to the mainland in 1985, J. I. Frederick Reppun MD, served as Editor through 1993. Upon becoming Editor in January 1994, I hoped to publish the Journal with "a new skin." In 1996, cover art by Dietrich Varez began, and was used for the following ten years. As stated in the Journal editor's aloha message of January 2006, "Smooth sailing is never assured, but with Kalani Brady MD, as Editor at the helm; Russ Stodd's insightful Weather Vanes, Drake Chinen keeping us on course, Michael Roth providing the staple of advertising revenue, and through the support of Pat Blanchette MD, President of the Hawai'i Medical Association, the USS Hawai'i Medical Journal is set to embark on an exciting course. We wish the crew Bon Voyage".

Dr. Kalani Brady, the Board of Directors, and the HMA, have kept the Journal afloat magnificently through unexpected squalls, like the 2009 budgetary constraints of the Hawai'i Medical Association, which can no longer buoy the Journal. However, HMA is continuing to provide moral support to HMJ through editorial board service from HMA President Gary A. Okamoto MD, and Executive Director April Troutman Donahue. Former HMA President Pat Blanchette MD, is now CEO of UCERA, the University of Hawai'i School of Medicine 501(c)3 division, that will financially support the Journal as the Hawai'i Medical Association has done through 68 years of determined dedication to educate and inform.

When Dr. Brady requested that I return to active editorial service on the Board, I agreed, since my compass is not yet pointing south. Contributing Editor, Russ Stodd MD, on Maui, has also agreed to stay on top of his column, Weather Vanes. Other members continuing onboard include Al Morris MD, Satoru Izutsu PhD, Myron Shirasu MD, and John Breinich, former Director of the Hawai'i Medical Library. Returning to service are Douglas Massey MD, and Ben Berg MD.

Alan Tice MD, continuing as Associate Editor, is guiding the Journal transformation from a bound vessel of information, to launch HMJ as an electronic medical cyberspacecraft of the 21st century. HMA physician members as well as non-members, students, paramedical specialists —and indeed, everyone in Hawai'i and through-out the world, may come aboard to learn of advancements in science by viewing Journal articles on the web. Hard copies will also be available. Editorial intern Janessa Ruckle joins Drake Chinen in day-to-day operations. The prototype online Journal of 2009 covered January & February. Now you can expect monthly editions. Many thanks to the Board of Directors, contributing authors, peer reviewers, and loyal readers of the Hawai'i Medical Journal.

Norman Goldstein MD
HMJ Editor Emeritus

Hansen's Disease with HIV: A Case of Immune Reconstitution Disease

Dominic Chow MD, MPH; Leila Okinaka MD; Scott Souza PharmD; Cecilia Shikuma MD; and Alan Tice MD

Abstract

Immune reconstitution inflammatory syndrome (IRIS) is an acute symptomatic expression of a latent infection during the recovery of the immune system usually as a response to antiretroviral therapy (ART). Opportunistic infections can trigger IRIS. Hansen's disease is an infection caused by Mycobacterium leprae (M. leprae). There have been a limited number of case reports reporting the presentation of the co-infection of HIV and M. leprae. We report an unique case of IRIS in a patient co-infected with HIV and M. leprae presenting as an exacerbation of his Hansen's Disease where the patient's skin lesions progressed from borderline tuberculoid to lepromatous leprosy following ART administration.

Introduction

Immune reconstitution inflammatory syndrome (IRIS) is an acute symptomatic expression of a latent infection during the recovery of the immune system, usually as a response to antiretroviral therapy (ART). This syndrome usually affects human immunodeficiency virus (HIV)- infected individuals at advanced stages of HIV disease (CD4 lymphocyte counts <200 cells/μL).[1] Clinical signs of inflammation appear mostly in association with opportunistic infection such as *Mycobacterium tuberculosis* (TB), cytomegalovirus and herpes infections when ART triggers a generalized immune activation during the transition phase of HIV viral load suppression and CD4 lymphocyte increase.[1,2] Hansen's disease is an infection caused by *Mycobacterium leprae*. There have been a limited number of case reports reporting the presentation of the co-infection of HIV and M. *leprae*.[3] We report a unique case of IRIS in a patient co-infected with HIV and *M. leprae* presenting as an exacerbation of Hansen's Disease where the patient's skin lesions progressed from borderline tuberculoid to lepromatous leprosy following ART administration.

Case Report

The patient is a 25-year-old Micronesian man with a history of Hansen's disease and HIV co-infection who presented to our outpatient clinic with an one month history of worsening skin rash on his arms and torso. The patient was initially diagnosed with borderline tuberculoid leprosy 6 years prior and treated with clofazimine, rifampin and dapsone for 11months before he returned to Micronesia where he was lost to follow up. See Table for timeline of events. His skin lesions were griscent when he returned to Hawai'i 3 years later and was diagnosed with HIV. He was started on an ART regimen of efavirenz, lamivudine, and zidovudine (CD4 lymphocyte count of 320 cells/μL). After 6 months of taking his antiretroviral medications the patient stopped his medications because of personal and financial reasons and returned back home to Micronesia. Upon return to Hawai'i his CD4 progressively declined to 144 cells/μL. He was started on a protease inhibitor based antiretroviral medication regimen (due to the presence of the K103N mutation) of once daily tenofovir, emtricitabine, and atazanavir/ritonavir three months prior to his current presentation.

On review of systems, the patient reported feeling overall well but complained of progressive skin rash over his arms and torso for the past month which he described as painless, non-pruritic white spots. He denied any fever, chills, numbness, tingling, or hair loss over the eyebrows or lashes. He also had not had any recent cough, abdominal pain, vomiting, diarrhea or dysuria. On physical exam, the patient was afebrile with normal vital signs and appeared comfortable. His head and neck were without any palpable lymph nodes or prominent pre-auricular nerves and his heart, lung and abdomen exam were within normal limits. His skin exam was remarkable for numerous 2-3cm hypopigmented macules scattered on his torso and bilateral upper and lower extremities in addition to a 3-4cm erythematous plaques over both anterior surfaces of the forearms (Figure). There was no ulnar nerve enlargement palpated but he did have decreased pinpoint sensation over the areas of hypopigmentation.

Given the new skin lesions found on exam, there was concern for reactivation of the patient's M. leprae infection and he was referred to dermatology clinic in addition to infectious disease clinic. Skin biopsies of the lesions showed vacuolated macrophages (foam cells) with predominantly superficial perivascular distribution and numerous well-preserved acid fast bacilli in clumps consistent with lepromatous leprosy (Figure). The diagnosis of lepromatous leprosy was confirmed by the Hansen's Disease Center in Louisiana. A regimen of dapsone, clofazimine and azithromycin was started. On follow-up 9 months later, the patient's skin lesions were still present but improved. Patient's laboratory findings showed an undetectable HIV viral load and a CD4 lymphocyte count of 266 cells/μL.

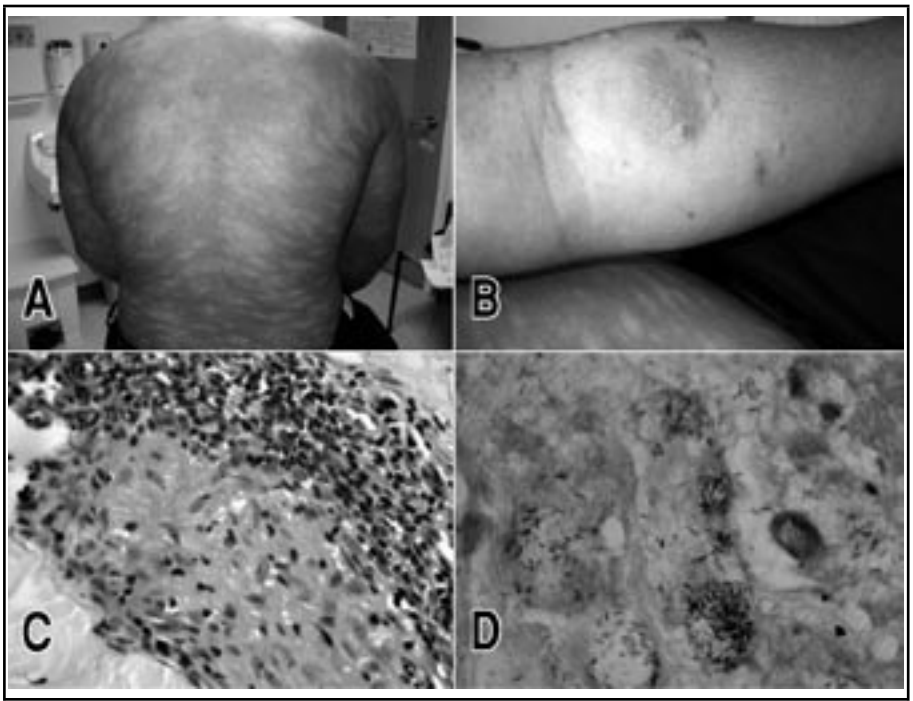
Discussion

The clinical presentation of Hansen's disease is chiefly dependent upon the host response to the organism, where skin lesions and neuropathy are most common. Those with more robust cellular immunity tend to present with fewer skin lesions in a more asymmetric pattern and few to no bacilli on tissue smear. This has been referred to historically as tuberculoid leprosy. In contrast, lepromatous leprosy typically manifests as widespread skin lesions including nodules and plaques with more severe nerve involvement and is attributed to those with a less vigorous cellular immune response as noted in our case.[4]

Given the essential role of cellular immunity in the clinical course of *M. leprae*, it would reasonably follow that HIV-positive individuals would be at greater risk for progression of disease as is the case with tuberculosis (TB). Indeed, it has been well documented that TB patients with HIV suffer more reactivation as well as reinoculation TB.[5] One of the proposed mechanisms is a relative decreased production of interferon by T1 lymphocytes in HIV-positive patients, which increases susceptibility to the Mycobacterium. Conversely, it has also been reported that TB infection appears to worsen HIV by increasing HIV replication. This has been proposed to occur secondary to a Mycobacterium-induced production of tumor necrosis

Table.— Timeline of Events

Variable	7/2000	6/2001-1/2004	1/2004	2004-2006	10/2006	1/2007	7/2007
Clinical Course	- Noted to have 2 hypopigmented lesions over torso and upper extremities - 1 area of erythematous, raised plaque over the anterior torso - Enlarged nerves of bilateral greater auriculars - Negative Tinel's and Phalen's signs - First diagnosis of Hansen's disease	- Lost to follow-up - Living in Miconesia - No therapy for Hansen's Disease	- Returned to Honolulu - First diagnosis of HIV - No skin lesions - Treatment for Hansen's Disease not continued	- Lost to follow-up - Living in Miconesia - No therapy for Hansen's Disease - No therapy for HIV infection	- Return to Honolulu - No skin lesions noted - Not on antiretroviral medication	- 3 months after restarting ART, patient presented with numerous hypopigmented lesions over the torso and extremities - Plaques and nodules over both forearms - Had decreased pinpoint sensation over the areas of hypopigmentation and nodules - No ulnar nerve enlargement	- 9 months after restarting ART, skin lesions improved - Neurologic status unchanged (decreased pinpoint sensation over the areas of hypopigmentation and nodules)
Pathologic Course - Skin Biopsy	Tuberculoid Leprosy					Lepromatous Leprosy	
CD4 count, cells/μL			320 cells/μL		144 cells/μL		266 cells/μL
HIV RNA viral load, copies / ml				Prior to leaving to Micronesia, HIV RNA viral load was undetectable	20,000 copies/ml		Undetectable
Treatment for Hansen's Disease	Clofazimine, rifampin and dapsone for 11months					Dapsone, clofazimine and azithromycin	Dapsone, clofazimine and azithromycin continued
Treatment for HIV			Efavirenz, lamivudine, and zidovudine for 7 months		Tenofovir, emtricitabine, and atazanavir/ritonavir started 1 month after CD4 count obtained (delay in initiating ART was secondary to problems securing health insurance)	Tenofovir, emtricitabine, and atazanavir/ritonavir	Tenofovir, emtricitabine, and atazanavir/ritonavir



Figure

Legend: Skin lesions noted on patient who is dually infected with HIV and Hansen's Disease.

a) Multiple hypopigmented to erythematous macules with diminished sensation;

b) Papular and nodular lesions of left forearm;

c) Initial skin biopsy (2000) showing epithelioid granulomas of lymphocytes and nonspecific chronic inflammation consistent with tuberculoid leprosy;

d) Skin biopsy (2007) from left forearm showing vacuolated macrophages (foam cells) with predominantly superficial perivascular distribution and numerous well-preserved acid fast bacilli in clumps consistent with lepromatous leprosy.

factor, interleukin-1 and interleukin-6 by macrophages.[5] Although there have been several case reports on HIV patients co-infected with leprosy, unlike TB, there has been no evidence to show that M. leprae infection is associated with worse outcomes as compared to non-HIV infected individuals.[5,6] Several studies have also documented no significant alteration in ratio of lepromatous to tuberculoid disease in HIV-positive versus negative patients.[5] However, over the past few years, there have been more than 10 cases of documented leprosy presenting as IRIS.[5,6] Several possible underlying mechanisms of IRIS and Hansen's Disease have been proposed by Ustianowski, et al. They propose that initiation of HAART allows recovery of the body's own cellular immunity which leads to a usual presentation of leprosy that would otherwise be dormant.[5] Alternatively, IRIS could possibly serve as a trigger for a more aggressive type I reaction to the Mycobacterium explaining the severe reactions seen as in our case.[7] Our case is the first case where there was a documented change in skin lesion from borderline tuberculoid to lepromatous leprosy following ART administration.

In summary, IRIS can present as worsening of leprosy in co-infected patients. Leprosy may be "unmasked" in the context of IRIS and treating physicians, particularly in highly endemic areas for Hansen's Disease, need to be cognizant to this possibility.

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Racial Disparities in Pacific Islanders Undergoing Renal Transplant Evaluation

Linda L. Wong MD; Kelly Kindle RN; and Blair Limm

Abstract

Pacific Islanders currently comprise 35% of all end-stage renal disease patients in Hawai'i but a much smaller proportion of those who undergo renal transplant. The purpose of this study to determine the reasons for such a disparity. In this retrospective review of 207 patients who were referred for renal transplant evaluation, 18.8% were Pacific Islanders. Patients attended a kidney transplant class, were offered evaluation and were placed on the waiting list if deemed appropriate. Of patients that were eventually placed on the list, 18.6% were Pacific Islander. There was no difference in age, gender, body mass index, presence of diabetes, number with potential living donors, dialysis status, time from the referral to attending class and the time from the class to listing between Pacific Islanders and other ethnic groups. Pacific Islanders who are referred to our transplant program are able to make it through the evaluation and be listed with the same success as other patients. The problem in racial disparities in Hawai'i involves referral to the transplant center. Whether the problem of referral is due to other medical comorbidities or noncompliance is not clear and will require further investigation.

Introduction

The number of patients undergoing renal replacement therapy for end-stage renal disease (ESRD) has continued to grow over the past two decades. In the US, approximately 106,000 new patients had dialysis therapy initiated in 2005 and the prevalence of ESRD in 2005 was 341,000. Hawai'i is the state with the third highest incidence of ESRD in 2005 at 404.9 per million population and lags only slightly behind West Virginia (425 per million) and Texas (413.4 per million). At the end of 2005, over 2800 people in Hawai'i were on some type of dialysis for ESRD.[1]

Renal transplantation is clearly the most effective and cost-effective therapy. Transplantation allows a longer life expectancy and quality of life in addition to a decrease in healthcare costs, however limited donor kidneys continue to be the major barrier to optimal therapy.[2-4] As of May 2008, over 75,000 patients are on the United Network for Organ Sharing (UNOS) waiting list for potential deceased-donor kidneys. In 2007, transplant centers across the US performed 10,587 deceased-donor and 6,037 living donor renal transplants.[5] The remaining patients continue to wait on this ever-growing list, as the burden of ESRD continues to challenge the US health care system.

Census data from 2006 indicate that there are about 426,000 Pacific Islanders living in the United States, most of whom reside in Hawai'i, Utah, Alaska, California and Nevada. An estimated 8.7% of Hawai'i's population is listed as Native Hawaiian/Pacific Islander.[6] Pacific Islanders (PI) who live in the United States have a high incidence of diabetes, hypertension, cardiovascular disease, stroke and obesity.[7] The prevalence of diabetes is 2.5 times higher in Native Hawaiians compared to White residents in Hawai'i.[8] With PI having many of the disease processes that lead to ESRD, it is no surprise that 35% of the current dialysis patients in Hawai'i are PI.[9] The purpose of this study is to determine if PI with ESRD had similar access to renal transplant as non-PI patients.

Methods and Materials

This is a retrospective study of the renal transplant program at Hawai'i Medical Center – East (formerly St. Francis Medical Center) between July 2005 and September 2007. Hawai'i Medical Center-East is a tertiary facility with the only transplant center in the State and is the major referral center for renal transplant for American territories of the Pacific Basin (including American Samoa, Guam, Saipan, Micronesia and the Marshall Islands). Foreign nationals from Asian countries such as Japan, Korea, and the Philippines who desired medical care in the United States have also been referred. This transplant program has been in operation continuously since 1969 and has performed over 1000 such transplants.

Potential renal transplant candidates were referred from dialysis units and nephrologists throughout the State and the Pacific Basin. Prior to 2004, transplant candidates met with a transplant nurse coordinator, a social worker, and a transplant surgeon before completing the testing for the evaluation. During these meetings, patients were individually evaluated and educated on renal transplant.

Beginning in 2004, all potential transplant candidates were required to attend a 2 hour "Kidney Transplant Class". They were given a presentation explaining the evaluation process, transplant operation, use of immunosuppression, results and specifics about our center. They were introduced to our transplant coordinators, social worker and financial coordinator. Interactive discussions about living donation also occurred and patients were encouraged to bring their caregiver and any potential donors to this class. Patients also underwent financial screening and body mass index (BMI) was calculated. Only patients with BMI of 35 or less were allowed to complete the formal evaluation. Those with BMI greater than 35 were counseled and referred to appropriate weight reduction programs. Interested living donors were given a packet of information regarding living donation and a short video with donor testimonials. Patients from Hawaiian Islands other than Oahu were able to attend class via videoteleconference. Residents of other Pacific Islands outside of Hawai'i underwent evaluation on an individual basis as done before 2004.

After completing the class and initial screening, patients proceeded with the formal evaluation which consisted of meeting with a transplant surgeon, dental clearance, laboratory testing, chest x-ray, electrocardiogram (EKG), echocardiogram and Human Leukocyte Antigen (HLA) typing. They also met individually with the social worker, nurse coordinator and nutritionist. Evaluation by a cardiologist was performed in all patients older than 50 years and all patients with diabetes. Additional medical and psychology consultations were done as deemed necessary by the transplant team. All cases were presented to the Renal Transplant Selection Committee for the final decision regarding listing for transplant.

The following data were collected on the potential renal transplant candidates who attended class: demographics, ethnicity, etiology of ESRD, dialysis status, BMI, possibility of living donation. The dates of referral to the transplant center, attendance at "Kidney Transplant

Class", and listing for transplant were noted. Final status of patients with at least one year of follow-up after referral included (1) listed for transplant vs (2) not listed for transplant due to one of the following: expired, rejected by patient or physician, transplanted at another center, listed at another center, BMI >35, pending cardiac clearance, pending dental clearance, or incomplete evaluation as of the current date.

General data on ethnicity were also collected from several other sources: (1) All patients on dialysis in Hawai'i from the ESRD Network 17, Annual Report 2004,[9] (2) Those patients awaiting deceased-donor renal transplant (DDRT) at Hawai'i Medical Center-East in 2006 and 2007, (3) All patients who underwent living renal transplant (LRT) 1999-2005, (4) All patients who underwent DDRT at our center 2002-2007, (5) All patients with ESRD on dialysis in the United States.[1]

Demographic data were analyzed for descriptive statistics using SPSS version 14.0 software. Chi-square analyses were used to compare ethnicity for ESRD between various groups.

Results

During the period noted, 207 patients attended Kidney Transplant Class. The mean age was 53.3 years with a range 5-79 years and median age of 56 years. Male to female ratio was 115:92 and 18.8% of patients were PI (see table 1 for race distribution) In this group, 59.3% had diabetes (86/145), BMI was >35 in 8.6% (16/185) and the mean time from referral to attendance in this class was 52 days.

Of the 207 patients who attended class, 86 (41.5%) were eventually placed on the deceased donor waiting list. Among the listed patients, mean age was 54 years, men:women was 51:35 and 18.6% were PI (table 1). Approximately 57.7% (41/71) were diabetics and 34.5% (30/86) claimed to have a potential living donor. The mean time from referral to attending class was 48 days and mean time from attending class to completing evaluation and listing was 246 days.

Of the 121 patients (58.5%) who were not placed on the list during the 13 months of observation, mean age was 52.7 years, men:women was 64:57 and 19% were PI. About 61% were diabetics and the mean time from referral to the Kidney Class was 52 days. Most patients (89 of 121) who were not listed had not completed the evaluation process in the time studied. Thirty-five patients were not listed for various reasons including: BMI >35, expired during evaluation, declined completion of the evaluation, were listed or transplanted at another center, or found medically unsuitable for transplant. Table 2 shows the disposition and specific reasons for non-listing. There was no difference in age, gender, presence of diabetes, potential living donors, dialysis status and time from referral to attendance at class between those patients who were listed versus not listed.

In comparing PI (n=39) versus non-PI(n=168), there was no difference in mean age, gender, presence of diabetes, BMI >35, potential living donors, or dialysis status. There was also no difference in the time between referral and attendance at Kidney Class, time between attendance at Kidney Class and listing and the proportion of patients that eventually were placed on the transplant list (see table 3).

Data for Hawai'i from the ESRD Network 17 for 2006 indicates that 622 patients were newly diagnosed with ESRD, 2328 were living with ESRD on dialysis and 441 patients died while on dialysis. Of these, 34.8% patients currently on dialysis were PI.[9]

Table 1.— Distribution of ethnicities for all patients referred for renal transplant and those patients eventually listed or not listed for renal transplant

Ethnicity	All patients (n = 207)	Listed patients (n = 86)	Patients not listed (n = 121)
Asian	125 (60.4%)	55 (64.0%)	70 (57.9%)
Pacific Islander	39 (18.8%)	16 (18.6%)	23 (19.0%)
Caucasian	11 (5.3%)	3 (3.5%)	8 (6.6%)
Afro-Americans	1 (0.5%)	1 (1.1%)	0
Hispanic	1 (0.5%)	0	0
2 or more ethnicities	25 (12.1%)	10 (11.6%)	15 (12.4%)
Unknown	5 (2.4%)	1 (1.1%)	4 (3.3%)

Table 2.— Specific reasons for non-listing of patients who underwent evaluation (n=121)

		#Patients
FINAL STATUS	32	
BMI >35		16
Expired		6
Rejected by MD or patient		6
Transplant at other center		2
Listed at other center		2
PENDING STATUS	89	
Cardiac		49
Considering kidney/pancreas trantransplant		3
Dental clearance		2
Awaiting other clearance		5
Incomplete/pending		30

In 2007, our center had 309 patients on the renal transplant UNOS waiting list, of which 10% were PI. From 2002-2007, there were 281 DDRTs of which 7.5% were PI. From 1999-2005, 110 LRT were performed and 9.1% were PI (table 4).

In summary, PI comprise 34.8% of all patients on dialysis in Hawai'i. This is significantly different from the proportion of PI patients referred for transplant (18.8%, p <0.0001), newly listed (18.6%, p=0.0016), on the DDRT waiting list (10%, p<0.0001), who underwent LRT (9.1%, p<0.0001) and who underwent DDRT (7.5%, p<0.0001).

Discussion

Disparities in medical care are increasingly described in the literature. Stolzman et al showed that ESRD patients with the highest level of income and education, patients living at a farther distance from the transplant center and males (compared to females) were more likely to receive kidney transplants.[10] Another study showed that women were less likely to finish the evaluation process for transplant. Those of lower socioeconomic status were less likely to be medically suitable, interested in transplant and complete the work-up.[11]

Ethnic disparities in renal transplant for African-Americans (AfA) have been well documented. The incidence of ESRD is over 4 times higher in AfA, yet AfA are much less likely to be referred to a trans-

Table 3.— Comparing Pacific Islanders vs non-Pacific Islanders for all referred patients who attended the Kidney Transplant Class			
	Pacific Islanders (n = 39)	**NonPacific Islanders (n = 168)**	
Age	52.1	53.5	NS
Gender (M:F)	23:16	94:75	NS
Diabetes	22/31 (71%)	64/115 (55.6%)	NS
BMI >35	5/35 (14.3%)	11/156 (7.1%)	NS
With potential living donor	10/22 (45.5%)	51/95 (53.7%)	NS
Currently on dialysis	21/25 (84%)	77/96 (80.2%)	NS
Time between referral and class	56 days	51 days	NS
Time between class and listing	217 days	254 days	NS
Patients listed	16/39 (41%)	70/169 (41.4%)	NS

Table 4.— Current United Network for Organ Sharing (UNOS) renal transplant waiting list and all patients who underwent deceased-donor renal transplant (DDRT) or living donor renal transplant (LRT) in Hawai'i				
Ethnicity	**UNOS list 2006 (n=326)**	**UNOS list 2007 (n=309)**	**DDRT 2002-2007 (n=281)**	**LRT 1999-2005 (n=110)**
Asian	210 (64.4%)	213 (68.9%)	153 (54.5%)	56 (50.9%)
Caucasian	11 (3.4%)	9 (2.9%)	33 (11.7%)	17 (15.5%)
2 or more ethnicities	70 (21.5%)	51 (16.5%)	70 (24.9%)	22 (20.0%)
Pacific Islanders	33 (10.1%)	31 (10.0%)	21 (7.5%)	10 (9.1%)
Afro-Americans	2 (0.6%)	5 (1.6%)	4 (1.4%)	3 (2.7%)
Hispanic	0	0	0	2 (1.8%)

plant center and to undergo renal transplant.[12] A 10-year study of 8816 patients in the US Renal Data System showed that AfA were less likely to be placed on the waiting list even after adjustment for sociodemographic characteristics and health status.[13] In 23,797 ESRD patients in Wisconsin , AfA were 35% less likely to receive transplant than whites and this discrepancy increased over time with AfA 74% less likely to receive transplants by 2005. Specific reasons for the disparity have included: AfA are less likely to be interested in transplants, [10] AfA are less likely to be rated as appropriate candidates and completion of the evaluation process slower among AfA .[14,15] In a survey of 1857 prospective living donors, AfA had more incompatible blood types and ineligible recipients. More AfA donor referrals were lost to follow-up and more AfA non-donation was due to high BMI. [16]

Issues in disparities may be related to physician referral of patients to transplant centers. Two surveys of nephrologists on this topic have been performed to address this. Ayanian et al showed that physicians (n = 278) were less likely to believe that transplant improves survival for AfA than Whites. Some of the reasons for referral disparity between AfA and Whites included: patient preference for transplantation (66%), living donor availability (66%), noncompletion of recommended patient transplant assessment (53%), clinical appropriateness or comorbid illness (52%), social support for assessment and post transplant care (48%) and expected patient adherence following transplant (47%). [17] A second survey of 271 nephrologists showed that white males were 2.5 times more likely than White females to be recommended for transplant, but there was no difference between Whites and AfA in terms of recommendations for transplant.[18]

Ethnic disparities in renal transplant other than AfA have not been as well described. Sequist et al studied 1335 ESRD patients in Arizona and New Mexico. There were no differences in referral for transplant, but American Indians and Hispanics were less likely to be placed on the transplant waiting list and to receive a transplant once listed.[19] Little is known about ethnic disparities in Asians and Pacific Islanders as these groups are frequently categorized as "other". One study stated that Asian-Americans or Native Americans did not fare as poorly as AfA in terms of access to renal transplant though another study indicated that there was an excess burden of ESRD in all minorities for referral/initiation of dialysis and access to kidney transplant.[20-21] Unfortunately, because PI are a relatively small group in the United States, they are combined with Asian Americans and no prior studies on access to transplant in only PI have been done.

There are inherent barriers to access of renal transplant to PI. Minimum requirements for renal transplant in the United States include adequate cardiovascular function to tolerate the operation and anesthesia, no active malignancy, no active infection, and compliance. Many programs also consider obesity as a relative or absolute contraindication. Morbid obesity (BMI >35) has been shown to increase the risk for delayed graft function, acute rejection, prolonged hospitalization and overall graft failure in renal transplant.[22] PI frequently have cardiovascular and cerebrovascular problems, and Native Hawai'ians have been reported to have the worst health and socioeconomic indicators in the state of Hawai'i.[23] Obesity and poor diet are also a major concern in PI. Focus groups have indicated that PI consider obesity to be "beautiful" and "a sign of wealth" and the first seven of the world's most overweight (BMI> 30) countries are

in Pacific Island nations (Nauru, Micronesia, Cook Islands, Tonga, Niue, Samoa and Palau). [24-27] Trying to overcome these genetic and cultural issues to qualify for transplant may be difficult.

This study is limited in that 43% of the patients were unable to complete this process in the 12 month observation period. Many were waiting for additional tests, especially cardiac studies. PI may require more time to complete the evaluation process and we would need to follow these patients for longer periods to determine if this is a factor. Also 12.1% of the patients are listed as having more than one ethnicity and many of these patients are PI in combination with another ethnicity. The effect of having PI partially in one's ethnic background is not addressed.

PI who are referred to our transplant program are able to make it through the evaluation and be listed with the same success as a non-PI patient. The problem in racial disparities in Hawai'i is primarily one of referral of PI to the transplant center. Perhaps these patients are not referred due to medical comorbidities, obesity or noncompliance. There is also some disparity in PI newly listed and actual deceased-donor transplants, though this may represent a lag due to waiting time. There are also fewer living renal transplants performed in the PI and further studies will need to be done to determine if this is due to the absence of medically suitable donors or if PI have other barriers to donation. Our transplant center is making efforts to be culturally-sensitive and conduct our kidney transplant classes in hopes of offering renal transplant available to as many appropriate ESRD patients as possible.

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Post-Infant Circumcision Amongst Children in Hawai'i

Leah Y. Nakamura MD and Loren G. Yamamoto MD, MPH, MBA

Abstract

Background: *The purpose of this study is to determine the frequency of circumcision in children older than 12 months of age in US born versus non-US born children in Hawai'i from 1996-2005.*
Methods: *Aggregate circumcision data from a children's hospital was obtained from medical records. Birth place was also identified for circumcisions (ICD9 code 64.0) in children 12 months to 18 years of age. Birth place is a surrogate marker of immigration status.*
Results: *During the 1996-2005 study period, there were 29,408 male births with an average newborn circumcision rate of 89%. The rate of circumcisions has declined from 93% in 1997 to 88% in 2005. There were 552 circumcisions performed on children 12 months to 18 years of age during this study period. Of these, 45 were performed in 1996 and 81 cases were performed in 2005. Birthplace data was missing from 25% of these cases. For those with birthplace data available, 60% of the circumcisions were amongst those born in Hawai'i, 15% were born in the other 49 states and US territories, and 24% were born in a foreign country.*
Conclusion: *In a community in which newborn circumcision rates are high, the frequency of circumcision is declining, while the number of circumcisions performed in children aged 1-18 is increasing. The number of circumcisions performed in non-US born children is disproportionately higher than what would be expected suggesting that the post-infant circumcision rates for this age group is higher in immigrants.*

Introduction

Circumcision is one of the most common surgical procedures done in the United States.[1,2] A study using data from the Nationwide Inpatient Sample1988 found that newborn circumcision rates increased nationwide from 48% to 61% between 1988-2000 despite the controversy of its medical benefits.[1] Contrary to the rest of the United States, Hawai'i's newborn circumcision rates have been decreasing over the past few years.[3] However, Hawai'i's average newborn circumcision rate still remains well above the national average at 88% in 2005.[1,3]

While newborn circumcision rates have been declining, circumcisions amongst children 1-18 years of age might be increasing, and anecdotally many of these children undergoing circumcision are immigrants. The importance of this study is to describe the frequency and characteristics of circumcision in children older than 12 months of age in US born versus non-US born children in Hawai'i from 1996-2005, to determine if there are any trends or identifiable factors that account for the changes in post-infant circumcision frequency.

Methods

Data was obtained from hospital medical records between the years 1996-2005 from Kapiolani Medical Center For Women And Children (KMCWC), a tertiary pediatric and obstetrics/gynecology medical center in Honolulu, Hawai'i. This study was approved by the Institutional Review Board (IRB) of Hawai'i Pacific Health. The International Classification of Disease (ICD)-9 procedure code 64.0 was used to identify patients who underwent circumcision. These patients were then grouped by age with <365 days representing newborn and infant circumcisions. Newborn/infant circumcision rates were calculated using the total number of live male births at KMCWC. Males who had no record of (ICD)-9 code 64.0 were assumed to be uncircumcised. For patients aged 1-18 years, ethnicity as well as birthplace (both self-reported during patient registration) were extracted from their medical record. Birthplace served as a surrogate marker for immigration status.

Data from the US Census Bureau was used to estimate the proportion of foreign born people in Hawai'i.

Results

During the 1996-2005 study period, there were 29,048 male births at KMCWC with an average newborn/infant circumcision rate of 89%. The rate of newborn/infant circumcisions declined from 93% in 1997 to 88% in 2005. The yearly numbers are listed in Table 1.

The 552 post-infant (patients age 1 to 18 years) circumcisions performed in patients are stratified in Table 2. The average age in the ten year period was 5 years of age. Birthplace data was missing from 25% of these cases. For those with birthplace data available, 57% of the circumcisions were amongst those born in Hawai'i. 17% were born in the other 49 United States and US territories, and 26% were born in a foreign country. The average age for a Hawai'i born child to receive a post-infant circumcision was 4.3 years of age. Those born in the other 49 states and US territories had an average age of 5.1 years. This table shows an increasing number of foreign born post-infants who are being circumcised.

Tables 3 and 4 stratify post-infant circumcisions by ethnicity.

Table 5 stratifies post-infant circumcisions by birth country and age. There was an estimated 149,977 foreign-born residents (all ages) in Hawai'i in 1990 which increased to 212,229 or 17.5% of the Hawai'i population by the year 2000.[4] The proportion remained steady with 212,404 foreign-born residents in 2005 or 17.2% of the Hawai'i population.[4] Of these foreign-born residents, it is estimated that 174,455 people immigrated from Asia. There has been an average of 5908 new legal permanent residents added per year from foreign countries in Hawai'i over 2001-2005.[4] Of these an average 2781 legal permanent residents per year or 47% are from the Philippines.[4]

Discussion

Circumcision is a topic of debate and its potential medical benefits are still not completely clear. Some studies that claim to have shown reduced risk of UTI in neonatal boys with circumcision.[2] Despite this information, the AAP Task Force concluded that the data was insufficient to recommend routine circumcision.[2] Other studies have shown that circumcision may have a reduced risk of genital ulcerative disease, HIV (human immunodeficiency virus) transmission, HPV (human papilloma virus) infection, and penile cancer.[2]

The incidence of complications associated with circumcision is estimated to be between 0.2-3 percent. Some of these include bleeding, infection, phimosis, adhesions, meatitis, meatal stenosis, chordee, urethrocutaneous fistula, necrosis, amputation, hypospadias, and even death.[5]

In the United States, circumcision rates are difficult to estimate.

Data from the Nationwide Inpatient Sample estimated that an average of 61.1% of newborns underwent circumcision from 1997-2000 in the United States.[1] The NIS database contained data from 1000 hospitals or about 20% of the nation's public and academic hospitals. It's estimated that <1% of males in several countries in Europe and Asia such as China and Japan are circumcised.[6] Countries such as South America and Central America also have low circumcision rates.[7]

Kapiolani Medical Center For Women And Children is the major center for births in Hawai'i (approximately 32% of births in the state of Hawai'i). This high circumcision rate is not limited to this hospital. Tripler Army Medical Center, a large general military hospital in Honolulu, Hawai'i, had an average 90% circumcision rate over the years 1973-1981.[3]

Phimosis and balanitis are two of the most common medical reasons to undergo circumcision after the neonatal period. Balanitis can often be treated with separation of preputial adhesions using topical anesthetic and circumcision should only be reserved for those with recurrent troublesome infections.[8] Physiologic phimosis is often mistaken for pathologic phimosis. The prepuce begins to develop at 8 weeks and is complete by 16 weeks. During this time the prepuce and glans are contiguous. Over time, desquamation of the epithelial tissue gradually pushes the surfaces apart and is usually complete by the age of three.[5] Surgery is not necessary for physiologic phimosis.[9] Pathologic phimosis also doesn't necessarily require surgery and can also be treated with topical corticosteroids and preputioplasty.[8] The incidence of true pathologic phimosis is believed to be only 0.6% and is rare in those under the age of five.[10] Almost two-thirds of the post-infant circumcisions performed in Hawai'i were amongst those age 5 and under. Many of these operations were probably elective given that these children probably had physiologic rather than pathologic phimosis; however we did not review medical records and cannot determine whether these circumcisions were done for medical reasons or non-medical reasons.

In this study, 552 non-infant circumcisions were performed and of these, 24% were performed on foreign-born children. 17.2% of Hawai'i's population is foreign born.[4] There is a proportionally higher rate of circumcision amongst those foreign born compared to those who are Hawai'i-born.

Reasons for higher post-infant circumcision rates in foreign born children are not likely to be physiologic, but rather cultural. For example in the Philippines, circumcision is seen as a rite of passage towards manhood and is often done between the ages of 10-14.[11] This cultural tradition still seems to be carried out by both the local born Filipinos as well as the immigrants. The average age for post-infant Filipino males to be circumcised in our study was 6.8 years of age. When just taking into account the Filipino immigrant males, the average is even higher at 7.9 years. In a community where there is an average of 2781 new legal permanent residents from the Philippines per year, this cultural custom could play a significant role in these circumcision rates.

Table 1.— KMCWC Newborn Circumcision Data

	Male Births	Circumcisions Performed	Circumcision Rate
1996	2,375	2,183	92%
1997	2,726	2,530	93%
1998	2,947	2,610	89%
1999	2,879	2,579	90%
2000	3,051	2,650	87%
2001	2,894	2,587	89%
2002	3,194	2,827	89%
2003	3,230	2,907	90%
2004	3,079	2,705	88%
2005	3,031	2,656	88%
Total	**29,406**	**26,234**	**89%**

Table 2.— Post-Infant KMCWC Circumcision Data

	Hawai'i Born	Non-Hawai'i US Born	Foreign Born	Birth place not recorded	Total
1996	11	1	1	32	45
1997	9	2	3	25	39
1998	24	9	14	1	48
1999	28	6	12	2	48
2000	18	7	12	3	40
2001	23	7	9	4	43
2002	29	11	9	8	57
2003	33	14	16	8	71
2004	42	3	11	24	80
2005	24	6	20	31	81
Total	**241**	**66**	**107**	**138**	**552**

Parents may choose elective circumcision so that their child will resemble his peers.[12] In a community based study in the Philippines, the most common reason for males to obtain circumcision was to avoid being called "supot" (uncircumcised) and that it was part of the tradition to undergo circumcision.[11] In societies where circumcision rates are high, those who are uncircumcised are often made to feel unequal and abnormal.[13] In a community with high circumcision rates, parents in Hawai'i may want their children to fit in with everyone else. Immigrants may face even higher pressure because of the desire to assimilate into society.

Circumcision rates can and have changed in the past. In South Korea, circumcision was practically unheard of in the past. Whether it was Western influence or some other phenomenon, by the 1960's there was a surge in the amount of circumcisions performed. Most boys were circumcised between the ages of 9-14 years and the current circumcision rate is estimated to be 60%.[14] Physicians claimed they were performing the operations to prevent sexually transmitted diseases, improve hygiene, prevent cervical cancer (75%), and to oblige parental requests (18%).[14] Ninety-nine percent of physicians polled recommended circumcision regardless of age.[14] In a nationwide poll in South Korea, parents revealed that they were strongly influenced by peer pressure. About 40% felt that

Table 3.— Post-Infant Circumcisions stratified by ethnicity and age						
	Age 1-5	Age 6-12	Age 13-18	Total	Average age	Ethnicity proportion of state population*
African Americans	1	1	1	3	8.3	1.8%
Caucasian	36	9	2	47	4.0	24.2%
Chinese	17	9	0	26	4.5	4.7%
Multiple ethnicities	6	2	1	9	4.5	N/A
Filipino	49	62	8	119	6.4	14%
Hawaiian	2	0	0	2	2.0	6.6%
Hispanic	4	2	0	6	5.0	7.2%
Japanese	30	9	5	44	4.7	16.6%
Korean	5	2	4	11	6.1	1.9%
Laotian	2	0	1	3	6.7	0.2%
Asian Mix	14	5	1	20	3.9	N/A
Asian/Caucasian	16	11	0	27	4.7	N/A
Other/Pacific Isle	21	8	1	30	4.2	0.1%
Other/unknown	38	15	5	58	4.9	N/A
Part Hawaiian	67	9	0	76	2.7	N/A
Samoan	30	19	5	54	6.2	1.3%
Vietnamese	6	10	1	17	6.7	0.7%
All	344	173	35	552	5.0	

* These numbers are used for comparison purposes, but it should be noted that the circumcisions listed above are not statewide numbers. Thus, an accurate circumcision rate cannot be calculated using the ethnicity proportion of the state population since the age distribution is not necessarily the same for each ethnic group and some hospitals serve disproportionately different ethnic distributions (e.g., military hospitals or hospitals that serve a lower portion of medicaid patients). Data was obtained from 2000 US Census.

Table 4.— Post-Infant Circumcisions Stratified by Ethnicity and Birthplace					
	Hawai'i Born	Non-Hawai'i US Born*	Foreign Born	Birth place not recorded	Total
African Americans	1	1	0	1	3
Caucasian	25	8	2	12	47
Chinese	11	1	7	7	26
Multiple ethnicities	7	2	0	0	9
Filipino	39	1	43	36	119
Hawaiian	0	1	0	1	2
Hispanic	3	2	1	0	6
Japanese	24	1	11	8	44
Korean	2	0	5	4	11
Laotian	2	0	0	1	3
Oriental Mix	9	1	4	6	20
Oriental/Caucasian	13	1	4	9	27
Other/Pacific Isle	8	8	13	1	30
Other/unknown	19	8	9	21	57
Part Hawaiian	57	6	1	12	76
Samoan	12	28	3	11	54
Vietnamese	9	2	4	2	17
All	241	71	107	132	551

*Includes American Samoa and Guam

their child would be ridiculed by his peers if he wasn't circumcised.[15] In England, circumcision rates have been declining with a 20% decrease from 2.6/1000 boys in 1997 to 2.1/1000 boys in 2003.

In Hawai'i it appears that the declining neonatal circumcision rate is being partially offset by an increase in circumcisions amongst those aged 1-18. Better education and the new policies regarding circumcision have probably contributed to the decline.[7] The same kind of education is needed for parents who want to circumcise their older child. This will help to prevent an unnecessary procedure for a physiologic process or to help their child "fit in".

Limitations of this study include a limited sampling at only one hospital in Hawai'i and 25% of the study group did not provide their country of birth.

In conclusion, neonatal circumcision rates still remain high in Hawai'i despite the slow decline over the past few years. While neonatal circumcision rates are slightly decreasing, circumcisions in non-infants is increasing, and a disproportionately high portion of these are being done on immigrant children.

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Table 5.— Post-Infant Circumcisions Stratified by by Country of Birth and Age

	Age 1-5	Age 6-12	Age 13-18	Total	Average age
Hawai'i Born	169	59	13	241	4.3
Guam	2	2	0	4	4.3
American Samoa	14	12	1	27	6.0
US Mainland Born*	26	12	2	40	4.5
Asia	1	0	0	1	1.0
Brazil	0	1	0	1	11.0
China	2	1	0	3	4.7
Fiji	1	0	0	1	3.0
Germany	0	1	1	2	12.5
Hong Kong	2	1	0	3	5.0
Iceland	1	0	0	1	3.0
Japan	9	4	2	15	5.6
Kazakhstan	3	0	0	3	1.3
Korea	5	2	1	8	5.6
Macau	1	0	0	1	4.5
Marshall Islands	4	4	0	8	5.1
Micronesia	2	1	0	3	4.7
New Zealand	2	1	0	3	5.7
Philippines	14	27	4	45	7.9
Saipan	2	0	0	2	1.7
Western Samoa	2	1	0	3	4.0
Tonga	1	0	0	1	1.0
Vietnam	2	1	0	3	5.3
Foreign Born total	54	45	8	107	6.1

*Excludes Hawai'i, American Samoa, and Guam born.

Medical Student Research at John A. Burns School of Medicine (JABSOM), University of Hawai'i

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Introduction

The Association of American Medical Colleges (AAMC) institutions in the United States have invested approximately $15 billion into new research facilities between 1999-2007, compared to $3.2 billion between 1990-1998.[1] The National Institutes of Health (NIH) budget doubled from $13.67 billion in 1998 to $27.07 billion in 2003, and is currently $29.46 billion in 2008.[2] In Hawai'i, the State Legislature, despite an economic slump, invested $150 million* into the JABSOM Kaka'ako campus, which includes an 180,000 square-foot research building.[3] During this time, research awards from NIH to JABSOM have increased from $1.9 million in 1999 to $20 million in 2005.[4] For medical students, these resources, both in Hawai'i and nationally, allow for a rich diversity of research opportunities in addition to the foundational knowledge provided to every student. The curriculum regarding research has recently changed to better enable students to utilize these invaluable opportunities.

Learning about Research and Medical Student Research at JABSOM

Every medical student at JABSOM is introduced to the basic principles of clinical and translational research in their first curricular unit, which covers study design, research ethics and clinical trials. Their second year curriculum includes "Introduction to Evidence-Based Medicine" during which students discover more about study design, analyzing clinical trials and related biostatistics. Throughout their four-year curriculum, students have opportunity to learn about issues related to clinical and translational research through their patient cases in the problem-based learning (PBL) curriculum, and through their required and elective clinical clerkships. The month prior to graduation, a "Research in Residency and Beyond" presentation is incorporated into their Senior Seminar course.

Since the institution of PBL curricula at JABSOM in 1989, all medical students have been required to complete a student research project of their choice in the summer between their first and second year of medical school, concurrent with a local primary care preceptorship. All students developed a research plan and submitted a final written project summary to the Office of Medical Education. The dissemination of such research to a larger audience was provided by the Annual Biomedical Research Symposium, held each spring for undergraduate, graduate and medical student participants, as well as resident physicians, post-doctoral fellows and faculty. By joining national societies in their field of interest, students also had opportunities to present at local, national, or international meetings. Medical students were encouraged to submit their research or scholarly work for publication in local or national journals.

The productivity of the medical students under the curriculum described above was determined by surveying the graduating class of 2008. Fifty of 57 students replied, for a response rate of 88%. Thirty-two of the respondents (64%) had research or scholarly work that was either presented and/or published, submitted for presentation or publication, or had abstracts or manuscripts in progress. Eleven students (22%) had both presentations and publications.

A total of 47 presentations involved twenty of the respondents (40%), at a variety of venues listed below.

- Within University of Hawai'i (17 presentations)
  - JABSOM Biomedical Sciences Symposium
  - JABSOM Community Health Fair
  - UH Pediatrics Residency Grand Rounds Conference
- Locally (9 presentations)
  - Hawai'i Chapter Meeting of the American College of Physicians
- Nationally (17 presentations) at the annual meetings of the:
  - American Academy of Neurology
  - American Academy of Pediatrics
  - American College of Physicians
  - American College of Radiation Oncology
  - American Geriatric Society
  - American Roentgen Ray Society
  - Orthopaedic Research Society
  - Radiologic Society of North America
  - Society for Interventional Radiologists
  - Society for Pediatric Radiologists
  - Society of Photo-Optical Instrumentation Engineers (SPIE) Medical Imaging
- Internationally (4 presentations)
  - Annual meeting of the American College of Obstetrics and Gynecology (Germany)
  - Annual meeting of the International Society for Magnetic Resonance (Canada)
  - International Congress of Parkinson's Disease and Movement Disorders (Japan)
  - Honorary symposium for Dr. Anthony Tu (Okinawa)

Thirteen journal publications were co-authored by nine of the respondents (18%) within the journals listed below.

- Hawai'i Medical Journal
- Clinical Autonomic Research
- Consultant
- Journal of Clinical Laboratory Analysis
- Journal of Medical Case Reports
- Journal of Neuroscience Research
- Journal of Neurovirology
- Journal of Rheumatology
- Journal of Toxicology
- Journal of Vascular and Interventional Radiology
- Mitochondrion

An additional 3 students (6%) had 5 abstracts submitted or in progress, and an additional 17 students (34%) had 22 manuscripts and 4 book chapters submitted or in progress.

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Ovarian Cancer: Risks

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Ovarian cancer is the deadliest gynecologic cancer. The American cancer society estimates 21,650 new cases of ovarian cancer will be diagnosed in the United State during 2008 with 16,000 deaths.[1] In general, a women's risk of getting invasive ovarian cancer during her lifetime is about 1 in 71. Fortunately, 3 of 4 women diagnosed with ovarian cancer survive at least 1 year after diagnosis. Unfortunately, 3 of 4 women will die of their disease in 5 years. Overall, woman's lifetime chance of dying from invasive ovarian is about 1 in 95.

The incidence of ovarian cancer is highest in Westernized industrialized countries, particularly in Europe, Canada, and North America.[2] Several risk factors have been associated as increasing the risk of ovarian cancer including low parity, infertility, early age of menarche, and late age of menopause.[3] The pathogenesis of ovarian carcinoma remains unclear. Several theories have been proposed to explain the epidemiology of ovarian cancer including:

1. Incessant ovulation, whereby, with repeated damage and trauma to the ovarian epithelium during each ovulatory cycle, there is an increased potential for genetic mutation and ovarian neoplasm during the repair process.[4,5]
2. The pituitary gonadotropin hypothesis, which postulates that high level of gonadotropins increase stimulation of estrogen, which can cause ovarian epithelial cells to become entrapped in inclusion cysts and undergo malignant change.[2,6]
3. The androgen/progesterone hypothesis, which suggests that androgens may stimulate ovarian cancer formation, whereas progestins are protective.[2,6,7]
4. The inflammation hypothesis, which proposes that factors that predispose to inflammation, such as endometriosis, pelvic inflammatory disease, perineal talc use, and hyperthyroidism, may stimulate ovarian cancer formation.[2,8]
5. The ovarian stromal hypothesis, which states that there may be a failure of apoptosis of granulosa and theca cells after ovulation, these cells continue to produce steroid hormones, thereby stimulating the formation of cancer.[2,9]

Associated risk factors for ovarian cancer support many of these hypothesis. For example, oral contraceptive use is consistently associated with a decreased risk of ovarian cancer and may operate through preventing the trauma from repeated ovulation as well as by lowering exposure to gonadotropins. No one theory, however, explains all the associated risk factors.

This article will review factors that increase or decrease risk of ovarian cancer. These factors are categorized into reproductive factors, exogenous hormones, gynecology related conditions, environmental factors, and genetic factors.

Reproductive Factors

Parity and Pregnancy

A consistent finding in ovarian cancer epidemiology is the protection from EOC(Epithelial Ovarian Cancer) observed among parous compared with nulliparous women. The association was observed in both case-control and cohort studies.[10-17] The odds ratios (ORs) of EOC for parous compared to nulliparous women in several case-control studies ranged from 0.3 to 0.7.[14,18] Increasing parity also seems to reduce EOC risk further. Significantly reduced risks of EOC were demonstrated in a pooled analysis of 12 US-based case-control studies, with a 40% lower risk after the first birth, while each additional birth incurred another 14% risk reduction.[14] An OR for EOC of 0.32(95% CI 0.18-0.56) was reported among women who had given birth to five or more children compared to nulliparous. Parous women also seem to be at reduced risks of BOT (Borderline Ovarian Tumor), although the protection seems to be weaker than that seen for EOC.[12,19-23] Histology-specific risk estimates indicate a protective effect of parity against all types of EOC and BOT[13,19] except possibly for mucinous tumors, where positive, inverse[10,13,19,20] and absent associations have been reported.[23] Several case-control studies also found positive association between a late age at first birth and the risk of EOC.[14,17,18] In the Swedish study each 5-year increment in age at first birth appeared to reduce EOC risk by 10% and the effects were stronger for EOC than BOT.[12]

A Swedish population-based cohort in 2008 also found relation of a high placental weight to increase risk of developing invasive epithelial ovarian cancer at a young age.[24] This is consistent with prior study from the same institution that reported low birth weight baby adjusted for gestational age to be associated with a reduce risk of developing epithelial ovarian cancer at an early age (mean age at diagnosis was 43 years).[25]

For miscarriage or abortion, most studies found slightly reduced risk[13,14,17] or no associations to EOC.[10,15,16] In general incomplete pregnancies seem to confer some protection from EOC, although the protection is weaker than that from full-term pregnancies. Incomplete pregnancies also seem to reduce the risk of BOT in some[19,22] but not all investigations.[20]

The biological mechanism explaining the protective effect of pregnancy has not been identified. Pregnancy leads to anovulation thereby reducing gonadotropin secretion and increasing endogenous estrogen and progesterone levels. Furthermore, pregnancy temporarily interrupts the retrograde transportation of exogenous substances or menstrual blood through the fallopian tubes, and presumably provides time for apoptosis. Progesterone has also been suggested to have a protective role in ovarian cancer development by suppressing epithelial proliferation, promoting cellular differentiation and apoptosis, thus removing premalignant cells from ovaries[26] Experimental studies in animals and human cell lines have shown that administration of progestins up-regulates expression of the p53 tumor

suppressor gene and induces apoptosis.[27] These data suggest that apoptosis resulting from high progesterone levels during pregnancy or from exogenous hormone could clear transformed cells in the ovarian epithelium. The postulated protective role of progesterone, however, may be outweighed by the influence of other hormonal factors during pregnancy. One concern is exposure to IGF-I which is strongly associated with risk of premenopausal ovarian cancer.[28] IGF-I, made in the placenta, increase with placental weight and rises significantly in late pregnancy.[24]

Lactation

It is well known that breastfeeding lowers a women's risk of breast cancer. Similarly, most studies indicate that breastfeeding slightly lowers the risk of EOC. Risk estimates between 0.6 and 0.9 have been observed for parous women who have breastfed their children compared with those who never breastfed.[14,15,24] According to some studies, lactation during the initial months after delivery conferred stronger protection from EOC than lactation at later time periods.[14] Data from two prospective cohorts, with up to 391 epithelial ovarian cancer cases among 149,693 parous women, revealed risk reduction, although non significant, in ever breastfeeding compared to never breast feeding with a median duration of breastfeeding of nine months (RR = 0.86,95%CI 0.70-1.06).[29] However, breastfeeding of 18 or more months was associated with a significant decrease in ovarian cancer risk compared to never breastfeeding (RR = 0.66, 95%CI 0.46-0.96). For each month of breastfeeding the relative risk decreased by 2% (RR = 0.98, 95%CI 0.97-1.00). A protective effect of lactation on EOC risk would support hypotheses linked to incessant ovulation, excess gonadotropins, retrograde transportation and apoptosis.

Age at Menarche and Menopause

A large number of epidemiological studies have examined age at menarche and menopause in relation to the risk of EOC, and generally these factors appear to be weak predictors of risk. Moderately elevated risks of EOC were reported among women whose menarche occurred before 12 years of age, compared to those who were older than 14,[17,30] although many of the ORs were not statistically significant. A population-based case control analysis from North Carolina revealed young age at menarche was statistically significantly associated with premenopausal but not postmenopausal risk of ovarian cancer.[31] A positive association between age at natural menopause and EOC risk appears in several case-control studies, with risk estimates across studies from 1.5 to 2.9 for the oldest menopause category compared with younger referents[17-19] supporting the incessant ovulation hypothesis but contradicting a gonadotropin hypothesis. Late age at menopause also was associated with an increased risk of BOT in some[19,21,22] but not other studies.[20]

Exogenous hormones

Oral contraceptives

The contraceptive effect of combined oral contraceptives (OCs), which contain both weak estrogens and more potent progestins, is mediated by suppression of the midcycle gonadotropin surge with a consequent inhibition of ovulation. Based on numerous epidemiological studies, it is now accepted that OCs protect against EOC. Ever-users of OCs compared with never-users have been at consistently lower risk of EOC in almost all case-control studies[13,14,15,16,17] and prospective studies,[30] where this association was examined. One meta-analysis study also showed relative risk (RR) for EOC of 0.64 (95% CI 0.57-0.73) among ever-users compared with never-users of OCs[32] and similar findings were reported in other analyses.[14]

A longer duration of OC used seems to enhance the protection against EOC risk. Most studies have observed reduced risks of EOC after several years of OC use,[13-17,33,34] however a risk reduction has also been found with short-term use (<1year) in some studies.[14,34] In a recent review, a 50% decrease in the risk of EOC was estimated after 5 years on the pill,[35] and a similar effects was seen in a meta-analysis where each year of OC use contributed to a 10-12% risk reduction.[32] The protective effect of OCs continues for a long time after cessation of OC use. Several studies have demonstrated a 40-70% reduced risk of EOC even after 10 years had elapsed since last use.[13,14,17,33,34] In a pooled analysis based on three European case-control studies, a 50% risk reduction still persisted after 15 years off the pill.[36] A recent population-based cohort study from North Carolina revealed an inverse association of ovarian cancer with longer duration of oral contraceptive use, later age at last use, and more recent use among premenopausal women. Contrary to overwhelming currently published data, one recent study reported no significant protective effect of contraceptive use in postmenopausal women that developed ovarian cancer.[31] Only a few studies have evaluated progestin-only contraceptives in relation to EOC risk, and although these data are sparse, a protective effect seems plausible.[33,34] The use of OCs appear to have no effect on mucinous cancers in some studies.[11,13,23,34] For BOT, OCs also appears to reduce risk when separate analysis was performed.[20-23,34]

Suggesting a co-effect of NSAIDS and OCP's, a population-based case control study from Wisconsin and Massachusetts found an inverse association of ever users of NSAIDs in women that never use oral contraceptives with OR = 0.58 (95%CI 0.42-0.80) but not for women that ever use oral contraceptives (OR = 0.98, 95%CI 0.71-1.35). A reduced risk with NSAID use was also noted in nulliparous women but not among parous women.[37]

Fertility Medication

Nulliparity is an established risk factor for EOC and BOT. Fertility drugs such as climiphene citrate, human menopausal gonadotropin(hMG) and human chorionic gonadotropin(hCG) were epidemiologically linked to BOT and EOC in initial studies raising concerns about the use of these drugs and the association with elevated risk of these malignancies.[38,39] A number of studies have addressed the central question of whether nulliparity, infertility and the use of fertility agents independently are associated with the risk of EOC and BOT. However, there were many confounding factors limiting studies among women who used infertility medications, including inconsistent definitionions of infertility or subfertility, poor recall of infertility agents used by physicians and patients, the poor selection of appropriate control groups, associated endometriosis and small numbers.[40]

Infertility apart from nulliparity appeared to increase the risk of EOC in most[10,11,15,17,40,41] but not all studies.[42,43] Some studies observed that the increased EOC risk from infertility was restricted to women who remained childless, while temporary fertility problems among women who eventually gave birth were not related to an increased

risk.[14,15,17,44] A positive association between infertility and BOT also has been reported.[20]

Studies that examined infertility type in relation to EOC risk report conflicting and often statistically nonsignificant results. Elevated risks of EOC have been observed for anovulatory,[45,46] nonhormonal[47] and unexplained infertility types.[41] The most important question regarding infertility and BOT/EOC is whether the widespread use of fertility agents in assisted reproductive technology increases risk. The findings of studies where this question was addressed are conflicting. Several studies demonstrated an increased risk of EOC among those exposed to clomiphene,[46] hMG[45,46] or any ovulatory stimulants[14,41] compared with nonexposed, whereas this was not observed by others evaluating EOC risk in relation to ovulatory stimulation.[15,14,16,19] In a combined analysis evaluating the use of fertility agents and the risk of BOT and EOC separately, the risk of BOT was stronger than that for EOC,[14,22] and this was also observed elsewhere.[41] Because there are not consistent findings in the literature and because of the complexity separating various factors causing infertility, it is unlikely that fertility agents alne contribute a large increased risk for the development of EOC.

Ovarian epithelial dysplasia was also described after prophylactic oophorectomies for genetic risk and was linked to be risk factor for EOC through incessant ovulation theory. The reported from France revealed higher ovarian dysplasia score in the ovulation induction group than in the control group, although the number of cases in this study is low. They also found a relationship between the number of ovulation-induced cycles and the severity of ovarian dysplasia(dose-effect) and a relationship between time after the end of ovulation induction (over 7 years) and the severity of ovarian dysplasia(time-effect).[48]

Hormone Replacement Therapy (HRT)

HRT is mainly indicated to alleviate climacteric symptoms as well as strengthen bone. Previous epidemiological findings on HRT and the risk of EOC are contradictory. In a few studies HRT appeared to reduce the risk of EOC,[49,50] whereas other studies demonstrated no associations,[14,16,51] or moderately increased risks of EOC among HRT users.[10,13,17,18,23] In several studies where a positive association between HRT ever-use and EOC risk was seen, no clear trends with duration appeared.[17,18] However, other studies indicated elevated EOC risks after longer durations of HRT use,[10,23,52-54] and excess risk that declined after discontinuation of use.[54,55]

In a recent well-conducted cohort study of 44241 US women, a RR for ovarian cancer of 1.6 (95%CI 1.2-2.0) was reported among ever-users compared with never-users of estrogen replacement therapy (ERT),[56] and the largest risk was seen among those who had used ERT for 20 years or more (RR 3.2; 95%CI 1.7-5.7).

One of the studies evaluated risk of EOC in relation to sequential or continuous progestin regimens in HRT.[57] This study demonstrated an increased risk of EOC among ever-users compared with never-users of HRT containing estrogens opposed by sequential progestins (OR 1.53; 95%CI 1.15-2.05), and the highest risks were observed among those who had used this type of HRT in excess of 10 years. Ever-use of estrogens continuously combined with progestins was unrelated to EOC risk (OR 1.02; 95%CI 0.73-1.43). In the Women's Health Initiative (WHI) study, the hazard ratio of ovarian cancer was 1.58 (95%CI 0.74-3.24) in women who were randomly assigned to either a fixed combination of 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate or the placebo.[58] The risk estimate was based upon 32 incident ovarian cancers (20 in the treatment group and 12 in the placebo group) that occurred during a mean follow-up time of 5.6 years. Although statistically not significant, the WHI authors suggested that the risk of ovarian cancer is increased among users of this type of HRT regimen. In a population-based study in Washington State, 812 women with ovarian cancer and 1313 controls were interviewed about the use of HRT and other characteristics. The risk of epithelial ovarian cancer was increased among current or recent (within the last 3 years) users of unopposed estrogen for 5 or more years (OR 1.6, 95%CI 1.1-2.5 and OR 1.8, 95%CI 0.8-3.7, respectively). However, no increase in risk was noted among women who used combined estrogen and progestins therapy regardless of duration (OR 1.1, 95%CI 0.8-1.5).[59]

Some studies suggest that the effect of ERT on EOC risk is modified by hysterectomy, with an excess risk of EOC among ERT users present only among women with an intact uterus but not in hysterectomized women.[14,55,57] However, the US cohort data reported an elevated risk of EOC among both hysterectomized and nonhysterectomized subjects.[56] The responsiveness to HRT may differ depending on the histological type of EOC, seous being the most common, followed by mucinous and then endometroid and clear cell. Elevated risks of the less common endometrioid EOC, in particular, have been reported by most[10,23,52,55,57,60] but not all studies[14,17,49-51] examining this association. Some[23,52,57] but not other[49-51,55] studies indicated an elevated risk of serous EOC among ERT users, while most previous research indicates that HRT is unrelated to the risk of mucinous EOC,[23,49,52,55] although positive associations have been observed.[51,57]

In one of these studies, based on a cohort of more than 200,000 postmenopausal women, an RR of 2.20 (95%CI 1.53-3.17) for fatal EOC appeared among those who had used ERT longer than 10 years compared with nonusers.[54] However, it has also been reported that HRT is not related to the risk of recurrent EOC.[61] Only a handful of studies have reported no association between the use of HRT and the risk of BOT.[19,20,22,23]

The potential carcinogenic effect of HRT compounds could be explained by retrograde bleeding through the fallopian tubes.[62,63] This suggestion is supported by the absence of an elevated risk of EOC among hysterectomized women using ERT.[55,57,60] Additional perhaps more likely mechanisms to explain an increased risk of EOC among HRT users include a direct hormonal action on steroid receptors.[7] Estrogen is a well-known endometrial-lining carcinogen. Although the explanation for the increased risk with HRT/ERT is not clear, this should nevertheless be considered as part of the overall discussion of risk and benefits of treatment.

Gynecologic Related Condition

Gynecologic surgery

Bilateral oophorectomy will reduce the risk of ovarian cancer almost completely, but for obvious reasons, this is not performed routinely. In the case of genetic predisposition such as inherited BRCA-1, BRCA-2 or HNPCC mutations, prophylactic oophorectomy is lifesaving as the risk of future ovarian cancer is as high as 50%. In the case of routine hysterectomy for benign indications, the question always arises: should the ovaries be removed. The benefit would be

a nearly complete elimination of risk of future ovarian cancer and future operation for benign adnexal conditions. As women approach menopause, it seem reasonable to consider removal of the ovaries at the time of hysterectomy. However, some studies suggest other medical benefits to leaving the ovaries even at the time of menopause that may outweigh the reduction in cancer and future operation risks. This may be due to hormones. Although menses ceases at menopause, there continues to be an ever diminishing secretion of hormones that may have a beneficial effect.

Almost all epidemiological studies that examined the association between tubal ligation and EOC risk support a protective effect with observed risk reductions from 10% to 80%.[11,13,17,23,17,64-66] Prospective data from the Nurses Health Study on a cohort of 121,700 female nurses (30-55 years) showed a statistically significant 67% reduced risk of EOC among nurses who had tubal ligation compared to those without this procedure.[66] The reduced risks of EOC after tubal ligation also persisted across all levels of parity in this study. Furthermore, the protective effect after tubal ligation has been reported to persist up to 20 years after the surgery.[64,65] It appears that most common surgical sterilization methods are equally protective.[65] Tubal ligation has also been observed to reduce the risk of BOT, although because of a limited number of cases these results are often statistically not significant.[20,22] The majority of studies where hysterectomy was assessed in relation to EOC risk have demonstrated an inverse association.[13,17,33,65,66] The magnitude of the protection against EOC seems somewhat weaker compared with the protection afforded by tubal ligation. In the Nurses Health study the risk of EOC decreased by 33% after hysterectomy.[66] In contrast with tubal ligation and hysterectomy, fewer reports have examined unilateral oophorectomy in relation to EOC and BOT risks. A reduced risk of EOC appeared after unilateral oophorectomy in some investigations,[13,33,49,67] whereas the opposite was found in another study,[68] and no associations were reported by others.[17] Population-based case control study from Washington US with personal phone interview of ovarian cancer patients found increase risk of borderline mucinous ovarian tumor associated with a history of an ovarian cyst (OR = 1.7, 95%CI 1.0-2.8), but did not vary notably according to receipt of subsequent ovarian surgery. The risk of invasive epithelial ovarian cancer, in this study, was slightly increased among women with a cyst who had no subsequent ovarian surgery, it was reduced when a cyst diagnosis was followed by surgery (OR = 0.6, 95%CI 0.4-0.9).[69]

Endometriosis

Endometriosis is a common medical condition where endometrial tissue is present outside the uterine cavity, preferentially in the cul-de-sac and on the ovarian surface.[70] The hormonally regulated lesions of endometriosis may trigger a local inflammatory reaction with activation of macrophages, release of cytokines and elevation of growth factors.[70] Several studies have linked endometriosis to an increased risk of EOC.[70,71] Several clinical series also reported the coexistence of endomtriosis and EOC,[72] particularly endomtrioid[71,72] and clear-cell EOC.[71] One study reported three fold increase risk of endometrioid and clear cell invasive tumors in women with a history of endometriosis, with a lesser risk increase among women who underwent subsequent ovarian surgery.[69] Endometriosis is also linked to elevated risks for ovarian cancer with standardized incidence ratios (SIR) of 1.37, endocrine tumors, renal cancer, thyroid cancer, brain tumors, malignant melanoma and breast cancer, as well as reduced risk of cervical cancer in National Swedish Inpatient Data.[73] Endogenous or exogenous hyperestrogenism was positively related to the risk of development of cancer from endometriosis.[70,74]

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) includes endometritis, salpingo-oophoritis and tubo-ovarian abscess formation. A limited number of epidemiological studies have focused on the associations between PID and the risk of EOC.[75,76] Some of these studies found positive associations between PID and the risk of EOC[76] while others found no effects.[16,65,77] A Canadian Study reported an increased EOC risk among women with one compared to no episodes of PID (OR 95% CI 1.0-2.1)[76] and the positive association between PID and EOC risk was stronger if PID had occurred at an early age, if the women were nulliparous, infertile, or had experienced recurrent PID episodes. This study also reported similar risk estimates for EOC and BOT in relation to PID.

Polycystic ovarian syndrome

Common clinical presentations of polycystic ovarian syndrome (PCOS) include obesity, hirsutism, infertility and menstrual abnormalities. Obese women with PCOS are at an increased risk of uterine endometrial cancer,[77] but the relationship between PCOS and EOC risk is less extensively evaluated. Elevated risks of EOC appeared among women with PCOS (OR 2.5; 95%CI 1.1-5.9) and the associations were stronger among those who had not used OCs or were lean.[78] Other study found PCOS unrelated to EOC.[77]

Environmental risk factors

Genital use of talcum powder has been extensively investigated as a potential risk factor for ovarian cancer. A Meta-analysis study reported an approximately 30% increase in risk of total epithelial ovarian cancer with regular genital exposure to talc,[79] and several studies have suggested a stronger association with the serous or serous invasive histologic subtype.[80-81] Talc is structurally similar to asbestos, and studies have suggested that there are histologic similarities between serous adenocarcinomas and the mesotheliomas seen in asbestos exposure. These facts may explain findings of increased risk of serous tumors in talc powder users.[82] Talc also can induced granulomas and other inflammatory response in vivo[83] and a recent study found that exposing human ovarian stromal and epithelial cells to talc resulted in increased cell proliferation and neoplastic transformation of cells.[84] Talc also appears to increase cellular production of reactive oxygen species. Animal studies also demonstrated that talc migrates from the vagina through the peritoneal cavity to the ovaries. Talc then may stimulate the entrapment of the ovarian surface epithelium, causing a reaction similar to the reaction that occurs during ovulation. New study tries to relate genetic factor such as variant of the glutathione S-transferase M1 (GSTM1) and N-acetlytransferase 2 (NAT2) to the association between talc exposure and ovarian cancer risk.[85] Although there was no clear evidence of the interaction of these genes, these results suggest that women with certain genetic variants may have a higher risk of ovarian cancer associate with genital talc use.

Cigarette smoking may be a risk factor for ovarian cancer, although its role is controversial. Some studies reported smoking to increase the risk of mucinous tumor[86,87] but some study failed to find significant correlation to ovarian cancer.[88] Although smoking

doubles risk of mucinous ovarian cancer in meta-analysis study, this study showed that smoking cessation returned the risk to that of never having smoked within 20 to 30 years.[89]

Dietary factors may also relate to risk of ovarian cancer, but the evidences still controversy. There was a study reviewed intake of red meat which showed increases risk of ovarian cancer with an odds ratio of 1.53 for highest intake compare to women at lowest quintile.[90] Study from Italy reported diet containing with bread and pasta associated with increase risk of breast and ovarian cancer (OR 1.21 for ovarian cancer). In contrast to women consume fruits and vegetables was protective against ovarian cancer with OR = 0.81.[91] Dietary high in fiber, carotene, and vitamins seem to be protective.[92,93] Vitamins A,C,D, and E has, for the most part, shown some reduced risk of ovarian cancer.[94,95] There was pros and cons of fruit and vegetable consumption in associate with reduced risk of ovarian cancer[94] versus no effect on risk reduction.[96,97]

Several studies reported inverse association between dietary vitamin D,[98] sunlight exposure[99] and ovarian cancer. The observations that vitamin D and its synthetic analogues inhibit growth and induce apoptosis in ovarian cells in culture and in animal models of ovarian cancer[100-102] provide further plausibility to this hypothesis. The proposed mechanism for the role of vitamin D in carcinogenesis involves regulation of differentiation and proliferation of cancer cells possibly by influencing cell cycle regulatory proteins.[103] Down-regulation of telomerase activity by vitamin D might be another component of the ovarian cancer cells growth suppression.[101] The vitamin D receptor (VCR) is a nuclear transcription factor that mediates most of the actions of vitamin D.[104] In animal study, VDR-null mice exhibit gonadal insufficiency, reduced aromatase gene expression, low aromatase activity, and elevated serum levels of luteinizing and follicle-stimulating hormones.[105] In human, there was a study revealed evidence of polymorphisms in VDR gene might influence ovarian cancer susceptibility.[104]

Studies on the influence of alcohol intake showed conflicting data, with several studies reported no association between total intake and ovarian cancer.[106,107] Although one reported note the association between heavy consumption of alcohol to risk of mucinous ovarian cancer.[108]

Caffeine intake has also been reported to increase risk of ovarian cancer in premenopausal women[109] as well as no association[110] and decrease risk of ovarian cancer.[111] The consumption of tea, specifically green and black tea, has been shown to reduce the risk of epithelial ovarian cancer in a dose-response manner.[112] The propose mechanism of protection include antioxidant activity, changes in cell signaling pathways, induction of apoptosis, and the possibility of the modulation of endogenous hormones.[113]

Overweight (BMI 25-29.9) and Obesity (BMI ≥ 30) in early adulthood was also associated with an increased risk of ovarian cancer with pooled OR = 1.5 among case-control analysis from meta-analysis study from Australia.[114] There was no evidence that the association varied for the different histological subtypes of ovarian cancer.

Genetic Risk Factors

Considering all the factors mentioned above, none contributes more to the future risk of EOC as does genetic, specifically hereditary, factors.

Mutated high-penetrance genes such as the breast-ovarian cancer genes 1/2 (BRCA1/2) have been shown to increase the risk of epithelial ovarian cancer, particularly serous carcinoma. Approximately 10% of ovarian cancers are hereditary, with BRCA1 and BRCA2 explaining the majority (approximately 90%) of hereditary ovarian cancer cases. The lifetime risk varies between 15 and 66%, suggesting the existence of modifying genetic or environmental factors.[115] Ovarian cancer has also been associated strongly with Lynch Syndrome, (HNPCC), and less so with basal cell nevus (Gorlin) syndrome, and multiple endocrine neoplasia type 1 (MEN1).[116]

Low-penetrance susceptibility genes have been shown to influence the risk of different histologic types of epithelial ovarian cancers. For example, the glutathione S-transferase M1 (GSTM1) null genotype has been associated with an increased risk of endometrioid or clear cell invasive cancer.[76,117,118] In addition, while possession of the A2 variant of P450c17 alpha gene (CYP17) appeared to increase risk for all types of ovarian cancer, possession of the Val/Met variant of catechol-o-methyltransferase (COMT) decreased the risk for mucinous tumors.[118] There are also data related risks of epithelial ovarian cancer to a difference in DNA sequence among individuals, groups, or populations. For example, Paraoxonase I gene which involve in irradiation of oxygen free radical in cell[119] or estrogen receptor beta (ESR2)[120] which mediates estrogen-induced apoptosis, both of which show association with increase risk of ovarian cancer with defect of the genes in certain population. A small population-based case-control study from Hawai'i, also showed that genetic variation of CYP19A1 may influence susceptibility to ovarian cancer among Caucasian and Japanese women, by 10-20% increases in estrogen production among postmenopausal women.[121]

Conclusion

Epidemiologic studies are among the first clues in the effort to detect risk factors associated with cancers thus forming the scientific foundation leading to theory development, hypothesis testing and ultimately a better understanding and treatment of cancer. The pathogenesis of ovarian cancer is a complex process, which certainly involves host genetic factors influenced by hormones, inflammation, pregnancy and other environmental factors. At this point in time, the most important modifiable protective factors include identifying a hereditary cancer syndrome with subsequent prophylaxis, avoidance of genital talc, as well as the use of oral contraceptives.

For more information on the Cancer Research Center of Hawai'i, visit www.crch.org.

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Medical School Hotline from p. 39

Current and future curriculum for medical student research at JABSOM

Beginning in the summer of 2008, the curriculum regarding research has been restructured. Students will continue to learn about the basic principles of clinical and translational research as described above, but the required research experience is an elective. The summer between the first and second year of medical school is composed of two 4-week curricular sessions, during which the students are required to take at least one of several electives offered, including clinical preceptorships, basic sciences and research.

In this revised curriculum, students interested in research are able to approach a faculty member whose work interests them, without competing with 60 other students in need of a required research project. The faculty, in turn, can feel confident that the students they accept into their project will be dedicated, contributing members of the research team. This optimal situation would lead to medical student involvement in high quality research projects of value to that field. In addition, requirements for the research elective are determined by the faculty mentor, instead of a universal standard applied to all medical students. Previously, a research report was required of all medical students, and although it was a good experience in writing about their research, that time and effort may be of more benefit to the research group if it were applied to working on the research project. This would allow the medical student to participate as a member of the research team, to have the opportunity to gain a deeper understanding and appreciation of the research environment, and to extend their involvement in research beyond the elective time if they so choose. Also, with the transition from required local preceptorships and research projects to elective courses, students have an opportunity to accept research experiences in other institutions for elective credit. In the summer of 2008, five medical students were involved in independent research at Case-Western Reserve University, Fred Hutchinson Cancer Research Center, Medical University of South Carolina (MUSC), St. Jude and the University of Medicine and Dentistry of New Jersey (UMDNJ). An additional 13 students were involved in research programs in Hawai'i with nine different faculty and physician mentors, for a total of 29% of the current second year class that chose research electives.

This restructured curriculum will allow students who are truly passionate about research to have invaluable opportunities with dedicated faculty members, both locally and nationally. Their involvement in medical research, whether basic, clinical or translational, will contribute to our understanding of human disease, the diagnostic tools we employ, the pharmaceutical therapies we prescribe and various other facets of the practice of medicine.

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THE WEATHERVANE

RUSSELL T. STODD MD, CONTRIBUTING EDITOR

❖ CERTIFICATE OF NEED LAW: LET US DEFEND AND PROTECT MEDIOCRITY.

According to a joint statement by the Federal Trade Commission (FTC) and the Dept. of Justice, "Illinois' certificate of need law and similar statutes in other states (e.g. Hawai'i) stifle innovation and generally have failed to keep health care costs down." The American Medical Association and the Hawai'i Medical Association have long opposed CON restrictions and the Illinois Medical Society wants to see the law repealed. Moreover, the AMA and the government report emphasized that recent growth in specialty hospitals, ambulatory surgery centers and other physician-owned facilities have brought patient and doctor convenience, lower costs, better technology and prodded hospitals to improve services. As everyone on Maui knows, the dedicated effort by Dr. Ronald Kwon with his excellent plan to bring a second hospital to the island was endorsed by the Governor, the Mayor of Maui County, most Maui physicians, and a team of citizen supporters, but was turned down by the single signature of the state health planning director, David Sakamoto MD, (He subsequently resigned his post.). The denial was based upon the apparent fear of patient choice and financial protection of the existing hospital. To many Maui citizens his action was an endorsement of status quo with the understanding that creative ideas, competition and modernization are to be avoided in health care.

❖ HIPAA –A HUGE SECURITY LAW MANAGED BY PIGMIES.

The Health Insurance Portability and Accountability Act (HIPAA) is intended to allow patients to have more control over their medical records. However, in the matter of litigation there is dispute as to what HIPAA does or does not protect. In Georgia, previous state law gave plaintiffs a chance to object to any defense requests for interviews of prior or subsequent treating doctors, and if there were no dispute the treating doctor would release information. The Georgia Supreme Court gave a unanimous thumbs down, and stated that HIPAA preempted the Georgia statute. "Patients' privacy rights must come first." Defense attorneys claim that HIPAA was not intended to block them from accessing crucial evidence in a claim while plaintiffs have complete access to all treating physicians. Defendants are one down before any trial or settlement discussion.

❖ IN PHARMACEUTICAL ETHICS HONESTY IS SITUATIONAL.

Senators Charles Grassley (R-Iowa) and Herb Kohl (D-Wisconsin) have proposed the *Physician Payments Sunshine Act* which would create a national registry of payments to physicians by pharmaceutical companies and medical device makers for providing speaking and advisory service. Eli Lilly and Merck announced that they would prepare a list of physicians in early 2009, but to date AstraZeneca, Abbott, and Pfizer did not offer to propose a registry. Johnson and Johnson did not reply to an inquiry. All gave lip service endorsing the legislation, but pharmaceutical lobbyists are trying to head off the legislation. It appears that they fear the Sunshine Act will influence doctors' willingness to act as a professional shill.

❖ WHEN ALL ELSE FAILS, READ THE INSTRUCTION MANUAL.

Few people are familiar with the Ecri Institute, an independent organization which conducts patient-safety research and investigates medical-device incidents. The company has prepared a list of the top ten hospital technology hazards that can be harmful to patients: (1) Alarm hazards -- lack of appropriate response to a warning device, (2) Needle stick or sharp object injuries, (3) Air embolism from contrast media injections, (4) Retained tools or devices or fragments left in patients, (5) Surgical fires, (6) Anesthesia hazards due to inadequate pre-use inspection, (7) Misleading displays, (8) CT radiation dose, (9) MR imaging burns, (10) Fiberoptic light-source burns. Personnel may fail to read a manual or even have one after first day use, or trained people may be moved or are busy elsewhere. Patient safety depends on each person to act responsibly in the chain of medical and surgical care to prevent any problem.

❖ IT'S AMAZING! YOU CAN CREATE A HUMAN BEING WITH THINGS YOU HAVE AROUND THE HOUSE.

It has long been a premise of obstetrics that having a caesarean section or inducing labor after 34 weeks gestation posed little or no risk since beyond that time all the baby has to do is grow. Pre-term births before 37 weeks have risen 31% in the United States since 1981, but it's unclear how many are for non-medical reasons. A study in the Journal of Pediatrics of nearly 15,000 children found that those born between 32 and 36 weeks had lower reading and math scores in first grade than babies born at full term. Another study revealed that pre-term infants are at higher risk for lower I.Q.s and mild cognitive defects than full term babies. Research reported in the American Journal of Obstetrics and Gynecology found that for each week a baby stayed in utero between 32 and 39 weeks there is a 23% decrease in problems, e.g.. respiratory distress, seizures, brain hemorrhage and jaundice. Too often obstetricians respond to pressure from women who are "tired of being pregnant" or who urge delivery for financial reasons or for timing home assistance. It all adds up to a downside for electing to shorten gestation. Yet another example of don't fool around with mother nature.

❖A MASTER OF CEREMONIES WAS TURNED INTO PIECES.

Many of us remember the urbane and engaging Alistair Cooke who for many years was the host for the PBS production Masterpiece Theater. He died of cancer at age 95 and wanted his remains to be cremated. His family was stunned and enraged to learn that rather than cremation a consent form for removal of tissue was forged and his body parts were removed and sold for transplantation. Theft of body parts by unscrupulous ghouls in funeral parlors and other locations is an enlarging billion dollar business. Pharmaceutical and medical industries pay very well for skin, scalp, tendons, bones, heart valves and even fingernails. Underground traders may use a university as a "front" for freezing or marketing tissue, often with knowledge of highers up as revealed by the investigation at UCLA medical center in 2004. Innocent transplant recipients are now at risk for HIV/AIDS, syphilis, hepatitis B and C, as well as other infectious, chronic or fatal diseases. As one health official said, the transplant tissue industry is so poorly regulated that anyone with a chain-saw and a pick up truck can get into it.

❖ THE BEST MIND ALTERING DRUG IS TRUTH.

In 2006, worldwide sales of the type 2 anti-diabetic drug Avandia reached $2.5 billion for GlaxoSmithKline. Sadly for Glaxo, sales plummeted in 2007 after the New England Journal of Medicine (NEJM) reported the high risk of heart attack tied to use of Avandia. The embarrassing, if not criminal, part for the pharmaceutical company is that they had been informed of problems dating back to 2000 when Mary Money MD, a Maryland internist and one of her colleagues, raised questions. The company disclaimed their anxiety and even wrote to Dr. Money's hospital demanding that she stop sharing her concerns.. A spokeswoman for Glaxo said Dr. Money's theories were unsubstantiated and she was misinterpreting journal articles to support her case. The Food and Drug Administration (FDA) responded to Dr.Money's complaint with a form letter and took no action. Last year Duke research scientist Dr. John Buse voiced similar problems with Avandia and Glaxo went so far as to threaten him with a lawsuit and characterized him as a liar. The Justice Department is already investigating GlaxoSmithKline for its marketing methods about Paxil and presumably Avandia also, and a grand jury in Boston is asking for witnesses.

❖ CAN YOU GET AN EAR INFECTION FROM PHONE SEX?

In Arkansas, a man inadvertently forgot his cell phone when he left a McDonald's restaurant. Store employees promised to secure it until he returned. No big deal except that he had nude photos of his wife recorded on the phone and the photo-art ended up on-line. He is suing the franchise owner, McDonald's Corp. and the store manager for suffering embarrassment sufficient to force him to relocate to a new home. He wants a jury trial and three million dollars. Moral: always wear a gorilla mask for nude photography.

❖ ACCORDING TO THE ADA LAW HE IS WITHIN HIS RIGHTS.

In Dallas, Texas a man in a wheelchair came into a 7-eleven convenience store. He rolled directly up to the cash register and beat it open with a baseball bat. Surprisingly, he did not steal any cash, but grabbed ten boxes of condoms and a bottle of an energy drink. He was believed to be intoxicated. With ten boxes of condoms he will definitely need more than one bottle of gatorade.

ADDENDA

❖ Each year 2500 BB gun injuries involve the eye and approximately 40% cause loss of eyesight.

❖ According to a study at the University of Colorado women have a greater variety of bacteria on their hands than men have.

❖ In Laurel, Massachusetts, John Henry has invented a vibrating toilet seat. "The invention is designed to stimulate and to make you feel good while you are there."

❖ In Dorset, England disgruntled customers at a Christmas tree theme park were angry about the long lines and poor quality attractions, so they beat up three elves and Father Christmas was punched in his grotto.

❖ It's OK to laugh in your own bedroom so long as you don't point.

ALOHA AND KEEP THE FAITH — **rts**■

Editorial comment is strictly that of the writer.