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Other Primary Neoplasms in Patients with Hepatocellular Cancer: Prognostic Implications?

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Abstract

Purpose: *Little is known about other primary neoplasms occurring in patients with hepatocellular cancer (HCC). This team attempted to characterize this cohort of patients to define incidence, risk factors, natural history, and potentially shared etiologies.*

Methods: *A retrospective analysis from an established, prospective database of patients with HCC during 1991-2004 was used to determine demographic data, risk factors, characteristics of the associated second primary neoplasm, and survival.*

Main Findings: *Of 306 patients with HCC, 23 patients (7.5%) were identified with a second neoplasm. Two of these patients had a third neoplasm. Mean age was 65.6 years and male:female ratio was 2.3:1. Risk factors included: hepatitis B (27.3%), hepatitis C (40.9%), smoking (17.4%), diabetes (26.1%), cirrhosis (63.6%), and family history of HCC (4.5%). Second associated primaries included 7 genitourinary (prostate--2, bladder--2, testicular--1, renal--1, ovarian--1), 7 gastrointestinal (colon--6, gastric--1), 3 breast, 2 skin, 2 lung, 2 hematologic, 1 tongue, and 1 desmoid. Four patients had HCC first, 1 patient had synchronous HCC and colon cancer, while 18 had the other primary first. Mean, 1 and 2-year survival after diagnosis of HCC was 1014.8 days, 75%, and 30%, compared to 782.6 days, 54.6%, and 41.1%, respectively, in the group with HCC only ($p>0.05$).*

Conclusion: *The incidence of other primary tumors in the setting of HCC is relatively common with a strong clustering of genitourinary and gastrointestinal malignancies. There was no statistically significant difference in overall survival compared to patients with HCC only, suggesting that the association of other primary tumors with HCC does not confer a worse prognosis.*

Introduction

HCC is the fifth most common cancer worldwide and is estimated to cause a half a million deaths per year. The incidence in the United States, although much less compared to Asian and African countries, has been increasing over the last decade and is currently estimated at 2.4 per 100,000.[1] Hepatitis C is likely responsible for much of this increase, as was demonstrated in a large group of US veterans. Rates of HCC related to hepatitis B and alcoholic liver disease are essentially unchanged.[2,3]

Due to recent changes in organ allocation practices and longer waiting times for all patients, more patients with HCC are undergoing liver transplant.[4,5] In parallel, new clinical and pathologic staging systems have provided for more precise stratification of patients, resulting in more appropriate selection of patients for resection, transplantation, or ablation techniques. During recent evaluations for liver transplant, a number of patients demonstrated a history of another cancer in addition to HCC. Should these patients be considered potential candidates for liver transplant and does their prognosis differ from those afflicted with HCC alone? Little has been reported on the natural history of those patients with HCC and a second primary neoplasm. The purpose of this descriptive analysis was to attempt to characterize this group of patients, to better understand their suitability for aggressive treatments and use of limited resources such as liver transplant. The authors report their experience with other primary tumors in the setting of HCC which, although relatively common, does not appear to portend a poorer prognosis.

Methods

This is a retrospective study of a prospectively collected database on HCC. A total of 306 cases were evaluated from August 1992 to March 2004. The Hawai'i Medical Center has the only clinic in Hawai'i dedicated to liver disease, the only transplant center in the state, and is the regional referral center for liver disease for the American territories of the Pacific Basin (American Samoa, Guam, Saipan, and the Marshall Islands). A number of patients were foreign nationals from Asian countries such as Japan, Korea, and the Philippines, who sought medical care in the United States.

HCC was diagnosed pathologically by percutaneous biopsy, liver biopsy done at the time of surgery, or from explanted liver at the time of transplant. Patients without histologic confirmation of HCC, but who had a history of chronic liver disease and one of the following: (1) discrete liver mass(es) and an alpha-fetoprotein (AFP) greater than 200 ng/dL, (2) discrete liver mass(es), which was (were) increasing in size, with AFP less than 200 ng/dL, (3) discrete liver mass with rising AFP for

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Table 1.— Patient Characteristics of the 23 Patients with HCC and Second Primary Tumors		
Characteristic	**Number of patients (%)**	
Ascites (n=23)	Present	3 (13.0%)
	Absent	20 (87%)
Encephalopathy (n=23)	Present	2 (8.7%)
	Absent	21 (91.3%)
Childs Class (n=23)	A	16 (69.6%)
	B	6 (26.1%)
	C	1 (4.3%)
CLIP score (n=16)*	0	6 (37.5%)
	1	4 (25%)
	2	4 (25%)
	3	2 (12.5%)

*CLIP scores were calculated only for those patient records that contained all variables necessary to calculate this variable.

Table 2.— Associated 25 Second Primary Tumors		
Type of tumor	**# tumors**	
Genitourinary (n=7)	Prostate	2
	Bladder	2
	Testicular	1
	Renal	1
	Ovarian	1
Gastrointestinal (n=7)	Colon	6
	Gastric	1
Other (n=11)	Breast	3
	Lung	2
	Skin	2
	Hematologic	2
	Tongue	1
	Desmoid	1
Order of Cancers (n=25)	HCC first	4
	Other primary first	20
	Synchronous	1
Time between HCC and second primary	0 years (synchronous)	1
	1-4 years	11
	5-9 years	3
	10 years or more	9
	unknown	1

3 consecutive values, or (4) discrete liver mass, with AFP less than 200 ng/dL, that is seen distinctly on Gallium scan or hepatic arteriogram, consistent with HCC, were included. This database contains comprehensive information on each consecutive patient's medical history, including the presence of another primary neoplasm. The type, location, and the approximate year of diagnosis was recorded for each additional primary tumor. Demographic data comprising age, sex, birthplace, and primary ethnicity (as identified by the patient) was collected. In addition, a history of diabetes, smoking, and family history of cancer was recorded. Risk factors for HCC, including viral hepatitis and significant alcohol usage (defined as two or more drinks/day for at least 10 consecutive years), and other chronic liver disease were identified.

With respect to the HCC, the size, number, and location of the tumor, in order to determine Tumor Node Metastases (TNM) stage (American Joint Commission on Cancer), was noted. Laboratory values for bilirubin, albumin, and prothrombin time were recorded, as was the presence or absence of ascites and encephalopathy, in order to calculate Child-Pugh-Turcotte (CPT) and Cancer of the Liver Italian Program (CLIP) scores. CLIP scores were calculated for 16 of these 23 patients for which all variables necessary to calculate this score was available. Serum AFP was also recorded. CPT scores were also expressed as Childs class A (CPT 5-6), B (CPT 7-9) or C (CPT >9). Finally, the type of treatment and dates of diagnosis and death were recorded in order to calculate the overall survival from establishment of diagnosis. The method of Kaplan and Meier was utilized to compare overall survival between groups.

Results

Of 306 consecutive cases of HCC, 23 patients were identified as having a second primary neoplasm, and this comprised the study group. In this group of 23 patients, the male to female ratio was 2.3:1 and mean age was 65.6 years. Ethnicity was primarily Asian (74%). Viral hepatitis B and C were present in 27.3% and 40.9%, respectively. Significant alcohol usage was noted in 17.4%, and 43.5% had a history of smoking. Six patients (26.1%) had diabetes and only 1 patient had a family history of HCC. More than half of the patients were born in Hawai'i and 25% were born in a foreign (Asian) country.

Underlying liver function was generally fairly well compensated (Table 1). Ascites was present in 13%, encephalopathy was present in 8.7% and a majority of patients were Childs A (69.6%). Fewer patients were Childs B (26.1%) or Childs C (4.3%). All CLIP scores were below 4, with nearly 88% of the scores ranging from 0 to 2. Mean bilirubin was 1.33 ± 0.90 mg/dl, mean albumin 3.53 ± 0.69 g/dl, and mean prothrombin time 13.46 ± 1.19 seconds. Mean AFP was 9155 ± 39,191 (range 2-180,000), with 11 patients (52.1%) having an AFP less than 20. Twenty-five second primary tumors were identified in these 23 patients. Twenty (80%) of these second primaries occurred prior to the establishment of diagnosis of HCC. Four HCCs occurred before the second primary and one patient had synchronous HCC and sigmoid colon cancer. Second primary tumors were primarily gastrointestinal (colon–6, gastric–1) or genitourinary (prostate–2, bladder–2, testicular–1,

renal–1, ovary–1). Other cancers included: breast–3, lung–2, skin–2, hematologic–2, tongue–1, desmoid–1. There was no definite pattern, in terms of interval between tumors, for HCC and the additional primary. About 40% of second primaries occurred 1-4 years apart and 36% occurred more than 10 years apart (Table 2).

Most of these patients with HCC had evidence of cirrhosis (65.2%). Of the pathology reports that recorded differentiation, 7 of 12 (58.3%) were of the well-differentiated type. Vascular invasion was noted in 4 of 13 reports (30.8%). Most tumors were single (65.2%). AJCC stage distribution was as follows: stage I–0, stage II–16 (69.6%), stage III–3 (13.0%), stage IV–4 (17.4%) (Table 3).

Of the 23 HCC patients with a history of second primary tumors, 10 underwent liver resection. Two of these patients had lung cancer develop after their liver transplant for HCC. Other treatments included: radiofrequency ablation–2 patients, transarterial chemoembolization–2 patients, cryosurgery–1 patient and cisplatin gel injection–1 patient. Five patients did not receive any treatment. One of these 5 patients was a candidate for liver resection, but committed suicide prior to scheduled surgery. Thus, more than half of all HCC patients with a second primary neoplasm were candidates for potentially curative treatments such as liver resection or transplant for their HCC.

Mean survival in these 23 patients was 1014.8 days following diagnosis of their HCC. Median survival was 792.0 days after diagnosis of HCC. One and 2-year overall survival were 75% and 30%, respectively. In the main database of 283 patients who did not have a second primary cancer, mean survival was 782.6 days, while median survival was 487.0 days. One and 2-year overall survival for this group with HCC only was 54.6% and 41.1%, respectively. Kaplan-Meier analysis demonstrates no significant difference in overall survival between both groups ($p>0.05$, log-rank test, Figure 1).

Table 3.— HCC Tumor Characteristics

Characteristic		# patients
Cirrhosis (n=23)		
	Present	15
	Absent	8
Differentiation (n=12)		
	Well	7
	Moderate	1
	Moderate/Poor	3
	Poor	1
Vascular invasion (n=23)		
	Present	4
	Absent	9
	Unknown	10
Number of tumors (n=23)		
	Single	15
	Multiple	8
Stage (n=23)		
	I	0
	II	16
	III	3
	IV	4

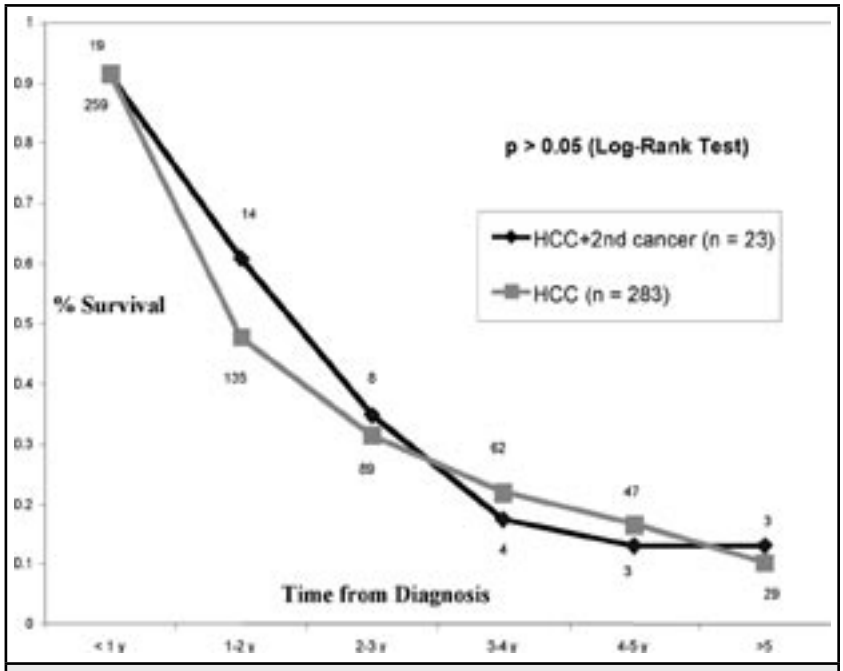

Figure 1.— Kaplan-Meier Analysis of Overall Survival in patients with HCC and associated Second Primary Tumors Compared to Patients with HCC Only

Discussion

In this study, the authors evaluated the characteristics of second primary tumors in the context of HCC, to define their incidence and type, risk factors, and their effect on overall survival. Although there are many reports documenting the occurrence of second malignancies with a number of solid tumors, particularly those that are treatment-related,[6-11] little is reported for HCC and second primaries. The majority of these consist of isolated case reports.[12-15] Perhaps the generally poor prognosis that a diagnosis of HCC carries limits the durable longevity and therefore diminishes the lead time necessary for the development of a subsequent, second malignancy. There were 4 such patients in this study, with the majority having their associated second primary tumors prior to the diagnosis of HCC.

Analysis of these types of data are important as the

development of subsequent second primaries constitute a significant "side-effect" of adjuvant therapy for prior cancers and this information may provide insight into shared common etiologies, both environmental and genetic, that advances understanding of cancer biology.[16,17] Also of major importance is the determination of the effects of second malignancies on overall survival. This will allow for more rational treatment planning and resource allocation with respect to appropriateness of liver transplant in such patients. Despite the relatively small cohort of patients identified, there are a number of observations that warrant discussion.

The incidence of second primaries in this investigation was relatively common, accounting for nearly 8% of HCC patients evaluated in this single institutional study. The risk factor profile of this group of patients demonstrates a significant proportion comprising smokers and alcohol abusers, with a larger proportion having either hepatitis B or C. This was further reflected in the high incidence of cirrhosis in this study population. All of these are features held in common with those patients with HCC only, and thus no discriminating variables were identified. Although the tumors were scattered among different sites of origin, there did appear to be clustering of the second primaries among gastrointestinal and genitourinary origin, perhaps suggesting a common etiology. In a nationwide cohort study in Denmark, alcohol and tobacco consumption in the setting of cirrhosis has been linked with a higher incidence of many solid tumors, particularly of the upper aerodigestive tract (lung, larynx, pancreas), genitourinary system (bladder and kidney), colon, and breast, substantiating the hypothesis of common etiology and environmental interaction.[17] Other epidemiologic studies have noted similar clustering patterns between HCC and other cancers.[16] Validation of shared etiology awaits molecular genetic analysis to identify the candidate gene(s) involved and to quantitatively determine their role in malignant transformation of the different tumor types.

In this study there appeared to be a bimodal distribution of time interval between the two primaries, of less than 4 years and greater than 10 years. The sample size is too small and lacks the statistical power necessary to accurately draw any definitive conclusion from this. However, patients who have a malignancy should not only undergo life-long surveillance for local recurrences and metastases, but consideration should also be given by physicians for observation for possible development of a second malignancy. Molecular biological analysis of these patients and their tumors may eventually help identify individuals at high risk for the development of specific metachronous cancers. This will provide major opportunities for closer surveillance, earlier diagnosis, and the development of novel prevention strategies and targeted therapies, as is being done for other cancers.[18]

Finally, the analysis of overall survival is most intriguing. It would have been intuitively expected that this cohort would have had better overall survival compared to the HCC only group for a number of reasons. The group with the second primaries appeared to have good physiologic reserve. Most did not have ascites or encephalopathy, reflected in a lower Childs classification and a lower CLIP score–all good prognostic indicators. Additionally, the HCC in these patients were of lower TNM stage, lower grade, single tumors, and without vascular invasion, which allowed more than half identified to undergo potentially curative therapies. It is possible that because these patients had a malignancy, surveillance follow-up was being undertaken by their physicians, allowing for lead time bias in the earlier diagnosis of the second primary. Statistical analysis did not demonstrate any conferred survival advantage in this group. This may have been attributable to a type II error due to the relatively small sample size of the study group. Nevertheless, it can be concluded is that the survival in this set of patients with second primary tumors is at least no worse than those with HCC only. Thus in terms of treatment planning, the history of a second malignancy should not be considered exclusionary criteria for additional aggressive therapeutic modalities. Patients undergoing liver transplant evaluation who have had a remote history of another cancer should be evaluated appropriately by that Transplant Center's practices in order to assure that there is no evidence of recurrent or metastatic cancer. Patients with current HCC should not be excluded from liver transplant evaluation merely because they have had a second primary cancer, as this study appears to indicate these patients fare as well as those with HCC alone.

Conclusion

The incidence of second primary tumors in HCC is relatively common with a strong clustering of genitourinary and other gastrointestinal malignancies, suggesting possible common underlying genetic-environmental interactions/etiologies. There was no statistically significant difference in overall survival compared to patients with HCC only, suggesting that a history of second primary tumors do not confer a worse prognosis and that physicians should not exclude them from aggressive therapies.

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The Cancer of the Liver Italian Program (CLIP) Score: Validation of a New Prognostic System for Hepatocellular Carcinoma

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Abstract

Purpose: *To determine the prognostic validity of a new staging system for hepatocellular carcinoma (HCC) proposed by the Cancer of the Liver Italian Program (CLIP) in the context of existing staging systems of known significance.*

Methods: *Retrospective analysis from an established prospective database of patients with HCC treated at a single, University-affiliated, community-based, tertiary center. All consecutively referred patients between 1991 and 2002 were eligible. Duration of follow up was 4 months to 11 years. CLIP score, Okuda, and American Joint Commission on Cancer Stage were determined for each case. Overall survival was the main endpoint measure.*

Main Findings: *Of 208 eligible patients, 8 were excluded due to lack of complete data necessary to determine CLIP, Okuda, and AJCC stage parameters. All three prognostication systems individually were predictive of overall survival. Logistic regression analysis demonstrated that AJCC staging was the best prognostic discriminator; however, when CLIP scores 3 through 6 were combined due to small sample size, the CLIP score was found to be the best index of prognosis.*

Conclusion: *The CLIP score may provide a more precise, quantitative method for improved prognostication of patients with HCC.*

Introduction

Hepatocellular Carcinoma (HCC) ranks among the most common malignancies worldwide. Advances in imaging modalities have impacted diagnostic evaluation by providing improved preoperative definition of the intrahepatic extent of these neoplasms. Additional gains will be realized concomitant with the development of immunization programs for Hepatitis B and C viruses, and by strategies that will decrease the incidence of cirrhosis from any origin. The role of transplantation continues to evolve and its place in the armamentarium of treatment options is gradually being refined.[1-6] Other modalities for locoregional treatment, such as transcatheter arterial embolization (TACE), percutaneous ethanol injection (PEI), and radiofrequency ablation (RFA), are being applied with mixed degrees of success.[1,5-8] Treatment planning has been a challenging endeavor, given the relatively high recurrence rates of these tumors and the associated physiologic derangements of hepatic metabolism associated with tumors of the hepatobiliary system that limit treatment options. This has made it difficult in clinical practice, despite the array of surrogate markers of prognosis, to accurately and quantitatively stratify patients into clearly defined prognostic categories. The ramifications have had profound influence on the difficult interpretation of responses to various treatment modalities and on the appropriate selection of candidates for surgical resection with curative intent.

To achieve the goal of improved prognostic stratification, many classification systems have been devised beyond the traditional American Joint Committee on Cancer (AJCC) staging system (Table 1). Many have sought to account for both tumor-related, known prognostic factors and hepatic functional reserve, to create a more sensitive and accurate prognostic index. The Cancer of the Liver Italian Program (CLIP) devised an innovative "scoring" system relevant to prognostic evaluation of patients with HCC in 1998.[9] This CLIP score consists of Child-Pugh stage, tumor morphology, alpha-fetoprotein levels, and the presence or absence of portal vein thrombosis (Table 2). Preliminary reports have indicated that this is a clinically feasible parameter to utilize and that it provides a more precise portrait of prognosis compared to other existing schemata.

For the purpose of this analysis the CLIP score was compared to existing prognostication systems of known significance, the standard AJCC staging system and another classification scheme that takes into consideration liver function, the Okuda staging system (variables – tumor size, presence of ascites, albumin level, and bilirubin level; Table 3), to attempt to validate this new staging system in our patient population.

Methods

This was a retrospective analysis from an established, prospective database of consecutively referred patients for treatment of HCC between 1991 and 2002.

Table 1.— AJCC Staging System for HCC	
Primary Tumor	
T1	Solitary tumor 2 cm or less; no vascular invasion
T2	Solitary tumor 2 cm or less with vascular invasion or more than 2 cm without vascular invasion; or multiple tumors 2 cm or less without vascular invasion limited to one lobe
T3	Solitary tumor > 2cm with vascular invasion; or multiple tumors 2 cm or less with vascular invasion limited to one lobe; or multiple tumors limited to one lobe with any > 2 cm with or without vascular invasion
T4	Multiple bilobar tumors; or tumor(s) involving major branch of portal or hepatic vein (s); adjacent organ involvement; or perforation of visceral peritoneum
Regional Lymph Nodes	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Stage Grouping	
I	T1N0M0
II	T2N0M0
III	T3N0M0; or T1-3, N1, M0
IV	T4, Any N, M0; or Any T, Any N, M1

Table 2.— CLIP Scorings System			
Variable	**Point Score**		
	0	1	2
Child-Pugh Class	A	B	C
Tumor Morphology	Uninodular Extension ≤50%	Multinodular Extension ≤50%	Massive or Extension >50%
AFP (ng/ml)	≤400	≥400	
Portal Vein Thrombosis	Absent	Present	

Table 3.— Okuda Staging System for HCC		
Variable	**Point Score**	
	0	1
Tumor Size	<50% of Liver	>50% of Liver
Ascites	Absent	Present
Albumin (g/dl)	≥3.0	<3.0
Bilirubin (mg/dl)	<3.0	≥3.0
Stage I	0 points	
Stage II	1 - 2 points	
Stage III	3 - 4 points	

All patients were treated in a University-affiliated, community-based, tertiary referral center. The following variables were obtained: age, gender, race, the presence of Hepatitis B or C viral infections, alcohol usage, date of diagnosis of HCC, tumor number and size, tumor morphology (uninodular, multinodular, diffuse), AJCC stage, portal vein thrombosis, the presence of cirrhosis (based on imaging studies or biopsy), ascites, encephalopathy, Child-Pugh classification, bilirubin level, albumin level, prothrombin time, and alpha-fetoprotein level at the time of diagnosis, type of therapy (locoregional or systemic); and date of death or vital status on latest follow up. Okuda stage and CLIP scores were calculated based on information from initial diagnosis of HCC.

Overall survival, which was defined as the time elapsed from date of diagnosis to date of last follow up or death, was the main outcome measure. To compare the three prognostic systems the 2-sided Pearson Chi square test was utilized. Logistic regression analysis was subsequently used to determine which classification schemata provided the most accurate prognostic discriminator.

Results

The database comprised 216 patients. Table 4 summarizes the patient characteristics. The median age was 61 years, nearly 70% were men, and approximately 14% were Caucasian, 77% Asian, and 9% Pacific Islander. A significant proportion had underlying cirrhosis and many (67.6%) were either chronic carriers of Hepatitis B or C viruses. Eleven (5.1%) were chronic carriers of both hepatitis B and C. Thirteen received systemic chemotherapy, while the majority (94%) did not receive any form of systemic therapy. AJCC staging information was available for 208 of these patients; however, the requisite data necessary for calculation of CLIP scores were available on 200 patients who therefore constituted the study group. Follow up was 4 months to 11 years.

All 3 prognostication systems were individually predictive of overall survival (see Table 5). Logistic regression analysis demonstrated that AJCC staging was the best prognostic discriminator ($p=0.001$); however, when CLIP scores 3 through 6 were combined due to small sample size, the CLIP score was found to be the best index of prognosis ($p<0.0001$).

Discussion

Many examples of staging systems exist for HCC, reflecting an attempt by investigators to develop a means to more accurately and precisely stratify patients who comprise a very heterogeneous group. This inherent prognostic heterogeneity has complicated our ability to design well-controlled clinical trials evaluating more innovative and novel treatment modalities for a generally lethal disease. Improved stratification of patients

will not only provide a mechanism to more accurately design and compare the results of clinical trials but will, by virtue of the improved discriminatory ability, result in more efficacious allocation of resources. Patients with less favorable prognoses, for example, might be considered for more aggressive treatment strategies in the context of clinical trials.

Additionally, in considering the feasibility and utility of staging or "scoring" systems it is imperative to evaluate gains in discriminant function in the context of applicability. The CLIP score is simple to calculate and comprises variables that are routinely assessed as part of the diagnostic workup of patients with HCC, hence has the potential for wide applicability.

In this cohort of patients, who represented a composite of Asian, Caucasian, and Pacific Islanders, the AJCC staging system was found to be the best prognosticator, in terms of overall survival. Due to the small sample size, however, when CLIP scores 3 through 6 were combined, the CLIP score was found to be the best indicator of prognosis. Although there is some disagreement in the literature regarding the utility and the validity of the CLIP scoring system in HCC,[10] our findings corroborate with similar studies from Italy,[9,11] Japan,[12] China,[13] Canada,[14] and the Middle East.[15] Many of these reports represent small, single Institutional studies, but nevertheless collectively provide added validation for this innovative tool.

Limitations of this study include its retrospective nature and the relatively small sample size.

Conclusion

The CLIP Score may provide a more precise, quantitative method for improved prognostication of patients with HCC and may also provide improved discriminant ability over the traditional AJCC staging system and the Okuda stage, if validated in larger, multi-center studies. The clinical implication is the added potential to provide improved stratification of patients for therapeutic clinical trials and this may serve to better identify patients who will benefit from more aggressive, innovative therapies.

Table 4.— Patient Characteristics

VARIABLE		n
Age (yr)-	Median	61
	Range	24 - 94
Gender-	Male	151
	Female	65
Race-	Caucasian	29
	Asian	164
	Pacific Islander	20
Etiology of parenchymal disorder-	Hepatitis B	81
	Hepatitis C	54
	Hepatitis B and C	11
	Cirrhosis	
	Present	148
	Absent	56
AFP (ng/dl)-	< 10	47
	11 - 400	79
	> 400	77
Tumor type-	Uninodular	107
	Multinodular	80
	Massive	20
Portal Vein Thrombosis-	Absent	186
	Present	30
Child-Pugh Class-	A	137
	B	61
	C	11
Systemic Therapy-	No	203
	Yes	13
AJCC Stage-	I	9
	II	102
	III	29
	IV	68
Okuda Score-	I	103
	II	88
	III	14
CLIP Score-	0	45
	1	60
	2	48
	3	33
	4	10
	5	3
	6	1

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Table 5.— Comparison of AJCC Stage, Okuda Stage, and CLIP Score in Predicting Overall Survival in Patients with Hepatocellular Carcinoma			
Staging System	Pearson Chi Square	df	p-Value
AJCC Stage	17.194	3	0.001
Okuda Stage	6.161	2	0.046
CLIP Score	16.186*	6	0.013
CLIP Score (3-6 Combined)	26.692	6	<0.0001

*5 cells (35.7%) had expected count less than 5. The minimum expected count is 0.37. Therefore Fischer's Exact Test also calculated (Value = 16.371, p=0.006).

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Survey of Methicillin–Resistant Staphylococcus aureus (MRSA) Carriage in Healthy College Students, Hawai'i

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Abstract

Currently, the carriage rate for Community-Acquired Methicillin Resistant Staphylococcus aureus *(CA-MRSA) is unknown in Hawai'i. This survey focuses on a healthy population of 95 college students and 5 faculty who completed a survey related to possible risk factors for colonization of* Staphylococcus aureus *and were sampled for S. aureus from their anterior nares. Thirty-three (33%) subjects were carrying S*taphylococcus aureus *and of those, 3 (3%) carried MRSA. There was no significant association between* Staphylococcus aureus *carriage and ethnicity, gender, exposure to seawater, prior* Staphylococcus aureus *infections, recent antibiotic use, or pets. Additional testing of a larger group of healthy individuals would be beneficial in assessing factors associated with CA-MRSA and Methicillin-susceptible* Staphylococcus aureus *(MSSA) carriage in Hawai'i.*

Introduction

Staphylococcus aureus is a growing problem with antimicrobial resistance and the spread of virulent strains in the community. Not only have an increasing number of infections been reported but hospital-associated strains have become increasingly resistant to penicillinase-resistant penicillins and cephalosporins, but also the mainstay of anti-staphylococcus therapy for the last few decades.[1] In addition, strains of a new community-acquired (CA) methicillin resistant *Staphylococcus aureus* (MRSA) have arisen, possibly from the Pacific Islands.[2] These strains have spread throughout the world and pose increasing challenges to the medical resources available to treat them.

Outbreaks of MRSA infections have been reported in healthy persons without risk factors including recent hospitalization or surgery, dialysis, residing in long-term care facilities, presence of an indwelling catheter, and use of injectable drugs.[3] The prevalence of CA-MRSA among children without identified risk factors has also been found to be increasing.[4,5] Although basically a human organism, its spread has also been associated with a variety of environmental factors, including athletic equipment, hot tubs, prisons, and other mammals which may carry the strains. The extent of CA-MRSA carriage in a healthy population has not been extensively studied.

In other countries such as Italy and the United Kingdom, the prevalence of MRSA nasal carriage ranged from 0.12% to 6%, respectively.[6,7] In New York City, the MRSA nasal colonization rate was as low as 0.2%.[8] Data obtained as part of the National Health and Nutrition Examination Survey, 2001-2002, reported a 0.8% prevalence of MRSA colonization in the United States. MRSA colonization was found to be associated with age ≥ 60 years and the female gender.[9,10] The problem with *Staphylococcus aureus* seems particularly acute in Hawai'i, where a rising incidence has been reported, especially among the Native Hawaiian population.[3,11] The recovery of methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA strains from the bathing beaches of Hawai'i emphasizes the need to explore the possible role of recreational seawater exposure to *Staphylococcus aureus* strains that may lead to colonization and infection.[11]

The purpose of this study was to determine the prevalence of nasal carriage rates of MSSA and MRSA in a healthy college population and to determine if gender, ethnicity, seawater exposure, pets, previous *Staphylococcus aureus* infections and recent or current antibiotic use were associated with MSSA or MRSA carriage.

Methods

During the spring semester of 2005, students and staff from 5 introductory-level microbiology labs and 2 biology labs at Kapi'olani Community College were asked to participate in the study. Of the 125 college students and 5 staff approached, 95 students and all 5 staff voluntarily agreed to participate. Participants verbally consented to have a culture taken from their anterior nares and to complete a 1-page survey of their activities over the previous 2 weeks. The study protocol and survey instrument were approved by the University of Hawai'i's Institutional Review Board.

Specimen collection and initial identification

After questionnaire completion, sterile dual swabs (BBL

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Microbiology systems, Becton Dickinson) were dipped into (0.85% NaCl) sterile saline and used to sample the subject's anterior nares (1 cm deep). The swabs were stored in sterile transport agar and streaked onto CHROMagar Staph aureus™ (CSA) within 24 hours of sampling. CSA plates were incubated at 37°C for 18-24 hours. Mauve-colored colonies were presumptively identified as target *Staphylococcus aureus*. Three to 5 mauve colonies were randomly chosen and subcultured onto Mannitol Salt Agar (MSA) plates and incubated at 37°C for 24-48 hours. Highly suspected *Staphylococcus aureus* colonies (yellow halos on MSA plates) were transferred to Tryptic Soy Agar (TSA) plates and incubated at 37°C for 24 hours.

Once pure cultures were confirmed on TSA, Gram staining and catalase testing (3% Hydrogen Peroxide) were performed to confirm the presence of Gram positive cocci and the enzyme catalase, respectively. Protein A and clumping factor, using fresh TSA cultures, were confirmed using *Staphylococcus aureus*-specific latex agglutination test (BBL™ Staphyloslide™). Coagulase testing was performed using rabbit plasma and coagulase-positive cultures were transferred to fresh TSA slants and incubated at 37°C for 18 hours.

Confirmation and resistance testing for MSSA and MRSA

ACCUPROBE *Staphylococcus aureus* culture identification test was performed to reconfirm the identification of *Staphylococcus aureus*. E Test was used to determine the Minimum Inhibitory Concentration (MIC) of oxacillin on all suspected MRSA using Mueller-Hinton agar supplemented with 2% NaCl. To confirm resistance to oxacillin, a latex test which detects the low-affinity penicillin-binding protein (PBP2'), encoded by the mecA gene, was used in this study (Oxoid). A fresh culture of highly suspected MRSA was used to prepare a very turbid suspension of cells in extraction reagent and then heated above 95°C for several minutes. Once cooled, a second extraction reagent was added, mixed, and then centrifuged. A small amount of supernatant was mixed with test and control latex on a test card.[12] Broad spectrum antibiotic testing was performed using standard NCCLS methods for antimicrobial disk susceptibility.[13] The antibiotics used in testing included: Erythromycin (15ug), Vancomycin (5 ug), Sulfamethoxazole (23.75 ug) Trimethoprim (1.25 ug), Ciprofloxacin (5 ug), Linezolid (30 ug), Ofloxacin (5 ug), Cefotaxime (30 ug), Tetracycline (30 ug), Rifampin (5 ug), Cefoxitin (30 ug), Ampicillin (10 ug), and Clindamycin (2 ug).

Statistical Analysis

Differences between colonized and noncolonized persons for variables with 2 categories (e.g., gender, seawater exposure, prior staph infections, recent/current antibiotic use, pets at home) were assessed by chi-square tests with Yate's correction. Ethnic differences in colonization status were assessed with ANOVA. All calculations were performed with EpiInfo version 3.3 (CDC, Atlanta, GA). P-values less than or equal to 0.05 were considered statistically significant. All tests were 2-tailed.

Results

The subjects' ages ranged from 19 to 67 years old; 29 were men and 71 were women. The sample was ethnically diverse, including 23 Caucasians, 19 Japanese, 15 Hawaiian or part-Hawaiian, 7 Filipino, 7 Korean, 3 Vietnamese, 2 Chinese, 18 persons of mixed Asian ancestry, 3 persons of mixed non-Asian ancestry, 1 Indian, 1 Haitian, and 1 Hispanic. The birthplaces of the subjects varied from different U.S. states to other countries such as Korea, Vietnam, Japan, China, Philippines, Haiti, Germany, and Guam.

Of the 100 subjects, 33 were tested positive for carriage of *Staphylococcus aureus*. None of the participants had any signs or symptoms of an infection in their nose or on their face at the time of sampling. By oxacillin testing, 6 students had more than one strain of *Staphylococcus* isolated.

The survey indicated that 14 of the 33 subjects (42%) colonized with *Staphylococcus aureus*, had seawater exposure within the 2 weeks prior to sampling. Seawater exposure included wading, swimming, paddling, windsurfing, surfing and/or diving. However 28 out of 67 subjects (42%) without colonization of *Staphylococcus aureus* also had seawater exposure. There was no apparent association with any of the specific water sports and colonization. In addition, there were no significant associations with gender, prior *Staphylococcus aureus* infections, antibiotic therapy during the last 3 months, nor with pets.

Of the 33 students and faculty that carried *Staphylococcus aureus* at the time of sampling, 3 carried MRSA. Of the 3 that carried MRSA, 2 (67%) had seawater exposure within 2 weeks, 2 (67%) were women, none of them had recently taken antibiotics, and none of them had prior *Staphylococcus aureus* infections (Table 1). The birth places of the 3 carrying MRSA were Hawai'i, California, and Korea.

Discussion

This study had the advantage of sampling a group of young, healthy college students and 5 faculty members outside of a hospital or clinical setting. They had no sign of *Staphylococcus* infection and they represented a wide range of ethnicities from various geographical locations in the world.

The percent of subjects colonized with *Staphylococcus aureus* was similar to recent studies. The finding of multiple different strains in the nares of the same person in 6 cases, however, was unusual and should be further evaluated.

No association could be demonstrated between

the carriage of *Staphylococcus aureus* and exposure to recreational seawater, pets, antibiotic use, or prior Staphylococcus aureus infections. However, the numbers are small and do not rule out a possible role or risk of transmission or colonization.

Further studies will be of value in determining whether the *Staphylococcus aureus* in the sea poses a risk to bathers. Although most of the strains in the sea appear to be simply shed by bathers, the possibility of transmission or acquisition is of some concern, especially with the concentrations of *Staphylococcus aureus* that can be recovered from popular beaches. Subsequent studies can be done in order to target a specific group of subjects such as canoe paddlers or surfers who are consistently exposed to seawater in Hawai'i. In addition, further analysis of virulence factors associated with infecting organisms would be helpful. To what extent seawater can serve as a vehicle to facilitate the transmission of virulence factors and/or antibiotic resistance is also unclear.

Additional testing of different and larger samples of people, strain typing, and virulence factor assays may be helpful in further assessing environmental risk factors related to *S. aureus* infections in Hawai'i.

Acknowledgements

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Table 1.— Survey of 100 subjects at the time of sampling

Characteristic	MRSA-colonized subject	MSSA-colonized subject	Subjects without Staphylococcus aureus colonization	P-value: colonized vs. noncolonized
Gender				0.97
Male (n = 29)	1 (3%)	9 (31%)	19 (66%)	
Female (n = 71)	2 (3%)	21 (30%)	48 (68%)	
Ethnicity				0.85
Caucasian (n = 23)	1 (4%)	5 (22%)	17 (74%)	
Japanese (n = 19)	0	7 (37%)	12 (63%)	
Hawaiian / Part Hawaiian (n = 15)	0	3 (20%)	12 (80%)	
Korean (of 7)	1 (14%)	2 (29%)	4 (57%)	
Filipino (n = 7)	0	2 (29%)	5 (71%)	
Vietnamese (n = 3)	0	2 (67%)	1 (33%)	
Chinese (n = 2)	0	1 (50%)	1 (50%)	
Mixed Asian (n = 18)	1 (6%)	6 (33%)	11 (61%)	
Mixed Non-Asian (n = 3)	0	1 (33%)	2 (67%)	
Other (n = 3)	0	1 (33%)	2 67%)	
Seawater Exposure*				0.88
Yes (n = 42)	2 (5%)	12 (29%)	28 (67%)	
No (n = 58)	1 (2%)	18 (31%)	39 (67%)	
Prior Staph Infections				0.88
Yes (n = 5)	0	2 (40%)	3 (60%)	
No (n = 95)	3 (3%)	28 (29%)	64 (67%)	
Recent/Current Antibiotic Use				0.56
Yes (n = 20)	0	5 (25%)	15 (75%)	
No (n = 80)	3 (4%)	25 (31%)	52 (65%)	
Pets at home				0.78
Yes (n = 49)	1 (2%)	14 (29%)	34 (69%)	
No (n = 51)	2 (4%)	16 (31%)	33 (65%)	
Total	3 (3%)	30 (30%)	67 (67%)	

*Seawater exposure includes wading, swimming, surfing, paddling, windsurfing or diving.

Senior Student Reflections on their Educational Experience at JABSOM

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A new trend in medical education is to foster reflection among students to maintain their connection to the humanistic elements of their medical school experience.[1] At Senior Seminars, a three-week course capping the four-year curriculum at JABSOM, students complete reflective in-class writing exercises on a variety of issues that are thematically linked to the topics presented that day. Selected essays are shared with the class on the last day of Senior Seminars. Examples of the instructions for some of the writing assignments are listed below:

1. Write a letter to a family member who supported you in medical school.

2. Write about an ethical issue you faced in medical school.

3. Write about a humorous incident in medical school.

4. Write a letter to incoming students.

Captured below are some of the reflections of the graduating seniors from the Class of 2006 and 2007. They show a side of our students and a snapshot of their educational experience not often seen by their teachers.

A Letter to a Family Member who Supported You in Medical School

Students most often chose to write to their parents, thanking them for their encouragement over the past four years. Many provided poignant tributes to family members no longer here or children who arrived while in medical school.

Dear Mom,
I have been faced with challenges throughout my life and medical school was no exception. The one thing I could always count on to get me through each obstacle was your love and support. No matter what I do or where I go, I know that I can always count on you to give me the encouragement I sometimes need…One of the main reasons I was able to finish med school was because you always told me that you would be proud of me no matter what I decided, even on those many days when I said I didn't want to be a doctor. So, although I'm fulfilling my long-time dream of being a physician, a big reason I'm doing it is to make you proud to know that all the love and encouragement you gave me paid off.

Dear Dad,
I wanted to thank you for all of your support throughout my life. Without your positive influence and guidance, I don't know if I would be where I am today. My only hope is that I have been able to make you proud and that you will be there when I graduate looking down from heaven at Mom and I.

My Dear Little One,

Thank you for understanding when Daddy had to work late and missed our goodnight kiss. Thank you for not complaining when Daddy couldn't take you to the park during final exam week. Thank for telling your friends that the reason Daddy wasn't at your May Day Program was because he was on-call at the hospital. You're the reason I survived working 36-hour shifts. You're the reason I stayed up nights reading and studying.

Ethical Issues in Medical School

Medical students found themselves immersed in life stories with unexpected twists and turns that challenged their belief systems and caused them to reevaluate what it means to be a physician.

I ran into a family member of one of my patients. The conversation took a serious turn when she said she intended to kill the patient…

A patient told me that she was raped by a family member…

A patient suffered a severe illness that left him neurologically devastated. In his advance directive, it was clear that he wanted to withdraw life support under these circumstances, but his power of attorney decided against this wish…

Humorous Incidents in Medical School

Humor, shared respectfully and at appropriate times, can have a very positive impact on the learning environment. While we must be mindful that negative humor may contribute to cynicism and breaches of professionalism, sharing those special moments that lighten our day without embarrassing others may bring a smile to the face of an exhausted student. And sometimes that is just what is needed to get through a busy day.

I was doing a preoperative exam on a bipolar patient who was humming a song that sounded familiar. When I was done, the surgeon came in and the patient started to sing aloud…"Like a surgeon…getting cut for the very first time…Like a surrrrrrrrgeon…"

Never say "oops" when doing any procedure – I did when giving an immunization to an adult who then proceeded to say "What?" then passed out.

During the end of my surgery clerkship, while looking through the laparoscopic camera, I became incredibly motion sick and had to be excused to throw up in the bathroom.

A resident from Japan was performing pelvic exams for the Gynecology Clinic and he kindly explained to his patients that they would feel some pressure during the exam. However, with his accent, it sounded as though he was telling them they were going to feel some "pleasure".

A Letter to Incoming Students

In choosing advice to share with those entering medical school,

senior students focused on several themes including the importance of studying hard, getting to know your classmates, maintaining personal balance, and having faith in your school and faculty. But first and foremost they wanted the freshman class to persevere and recognize that the four years ahead of them will be among the best of their lives.

> *Stick to it, pick yourself up after you fall, and you will be so glad, so happy when you are finally done four years from now, like I feel right now.*
>
> *These last four years here have been the best of my life by far. At times you will feel stressed and will struggle to find the light at the end of the tunnel…but in the end it is so worth it!*
>
> *You are lucky! If I could go back, I would do it all over again! Best of luck!*

Students surveys show that over 90% of senior students agreed that the opportunity to reflect during Senior Seminars deepened their awareness of how they got to where they are now and where they are headed in the future. It continues as an integral part of this educational experience with new reflection exercises already being developed for the future.

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Culture and Motivational Factors for Health Behaviors Among Young Adults

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Introduction

The transition from high school to college and from home to campus can be a critical period in the development of health habits in young adults. Although young adults are in a peak period for health, the lack of health promotion behaviors during this time can lead to serious health consequences later. In conjunction with this state of affairs, programs that were created for *adults in general* are not effective in inducing behavior changes among *young adults*. Thus, society would benefit from a better understanding of the unique motivational structure among the young adult population.

One potentially productive avenue of research that may enhance the ability to construct effective health communication interventions is to understand the social and cultural contexts that shape the behavior of individuals, families, and communities. As such, there is a great need for interface between health and intercultural communication research. However, beyond the application of intercultural communication theories to cultural sensitivity training in health care settings, there is not much cross-collaboration between health and intercultural communication scholars for population-based health communication interventions. This study, then, begins by investigating how cultural orientations of young adults influence their health perceptions and behaviors.

A prominent approach for examining cultural differences at the individual level is Markus and Kitayama's independent and interdependent self-construals.[1,2] As a link between culture and individual behavior, self-construals play a crucial role in influencing cognition, emotion, and motivation. The independent construal of the self, predominant in individualist Western cultures, places emphases on: (a) internal abilities, thoughts, and feelings; (b) realizing internal attributes and promoting one's own goals; and (c) being direct in communication. High independents construct themselves as individuals whose behavior is organized and is made meaningful primarily by reference to their own internal repertoire of thoughts, feelings, and actions.[1] Conversely, the interdependent construal of the self, predominant among individuals from collectivist non-Western cultures, is more 'other-oriented', emphasizing: (a) external, public features such as status and roles; (b) relationships; belonging and fitting in; and (c) occupying one's proper place and engaging in appropriate action. High interdependents adjust, restrain themselves, and maintain harmony with the social context across all behavioral domains, even those that can be designated as private or personal.[2] In this study, the authors investigated how these 2 different cultural orientations influence various types of health-related beliefs and motivations for health behaviors among a college student population.

Method

Data for the paper came from two studies conducted at the University of Hawai'i at Manoa (UHM) in 2003. The first study was a series of 5 focus groups of a total of 38 UHM students. The second study was a survey of 285 college students (range 18 to 26 years). The survey sample had a higher proportion of women (61%) than men (39%). Key measures investigated were: health perceptions, cultural orientation, health-related beliefs (i.e., locus of control and health locus of control), and motivations for health behaviors (i.e., motivator for health behavior change, motivator for health behavior maintenance, impetus for health behavior change, and sources of influence).

The descriptions of the key measures are as follows:

- ***Cultural orientation*** was measured by modified Leung & Kim's scale.[4]
- ***Locus of control*** was measured by 3 items developed by Newcomb and Harlow.[5]
- ***Health locus of control*** was measured by an 11-item scale, 6 of which measure external health locus of control and 5 measure internal health locus of control.
- ***Motivator for health behavior change*** was measured by a new scale developed based on the focus group findings: Three of the 5-item-index measure internal motivators (e.g. how I look, how healthy I am, how I perceive my self). Two items measure external motivators (e.g. how other people perceived me, how if affected those whom I care about).
- ***Motivator for health behavior maintenance*** was measured by a new scale developed based on the focus group findings: Six of the 9-item-index measure internal motivators, and 3 items measure external motivators.
- ***Impetus for health behavior change*** was measured by asking students to rate how important were 4 reasons in their attempt to change an important health behavior within the past 2 years on a 7-point scale (1=not at all important, 7=very important). Four reasons were: I just felt that I should change; a major event or incident made me feel that I need to change; someone else wanted me to change; it was an agreement between myself and someone else.
- ***Sources of influence*** was measured by asking students to rate how much influence do parents, family members other than parents, close friends, boyfriend/girlfriend, experts (doctors, researchers), and media/advertising have on their decisions about various health behaviors on a 7-point scale (1=not at all influential, 7=very influential).

Results

Overall Health Perceptions

In general, young adults do not think much about their health. A life of a typical college student consists of mostly attending school, working at a job, and socializing with friends and/or romantic partners. Their statements in the focus groups clearly reflected that health is a low priority:

"It is not my priority. It just is not."

"I can kind of postpone taking care of my health. I just feel like I shouldn't have to because I am young. Whenever I think about people having to worry about their health, they are usually older people."

"I'm young and I don't think about it…My dad has high blood pressure and high cholesterol. His brother died of heart attack. My grandfather also died of heart attack. High blood pressure runs in my family…But, it's not something that has affected me yet…I don't think about it on a day to day basis."

Survey data also supported this finding: Students thought significantly more frequently about money and romantic relationships than their physical and mental health. In fact, mental health was at the bottom of the list after money, romantic relationship, school, jobs, friendship, and relationship with family members. Furthermore, when students thought about health, their concerns focused primarily on physical fitness and looking attractive, rather than on being disease free or long-term health.

Cultural Orientation & Health-Related Beliefs

Students demonstrated moderately high internal locus of control, and moderate levels of internal and external health locus of control (Table 1). Students tended to agree consistently that internal motivators were more important for health behavior change and maintenance than external motivators. Three top influencers for their decisions regarding health behaviors were experts, parents, and romantic partners.

Overall, students reported a fairly high level of independent self-construal ($M = 5.90, SD = 0.76$), and a moderate level of interdependent self-construal ($M = 4.77, SD = 1.08$). Independent self-construal was *negatively* correlated with external locus of control, *negatively* correlated with external health locus of control, and *positively* correlated with internal health locus of control. Conversely, interdependent self-construal was *positively* associated with external locus of control, external health locus of control, and internal health locus of control.

Cultural Orientation & Motivations for Health Behaviors

Independent self-construal was associated with the presence of internal motivators for health behavior change, interdependent self-construal was associated with the presence of external motivators. This same pattern was true for motivators for maintaining health behaviors. Although there was no significant relationship between independent self-construal and impetus for health behavior change, (a) interdependent self-construal was associated with citing self, others, and others and self together as an impetus for their attempts to change health behaviors within the past 2 years and (b) interdependent self-construal was positively associated with being influenced by sources, such as parents, other family members, friends, experts, and media/advertising.

A key finding was that romantic relationships played a major role in young adults' lives. A majority of college students were currently (53%) or had been (38%) in a romantic relationship. Students reported

Table 1.— Cultural Orientation and Key Health Motivational Measures

Variables		Alpha	Mean#	SD	Correlation with Independent Self-Construal	Correlation with Interdependent Self-Construal
General Locus of Control (External)		.74	2.72	1.40	-.23**	.21**
Health Locus of Control	Internal	.71	4.83	1.01	.12*	.14*
	External	.74	3.58	1.07	-.14*	.21**
Motivator for health behavior change	Internal	.82	4.42	1.75	.17*	.03
	External	.75	3.32	1.76	.06	.18*
Motivator for health behavior maintenance	Internal	.84	5.64	1.19	.35**	.07
	External	.77	3.68	1.69	.17	.27*
Impetus for health behavior change	Self	n/a	5.68	1.34	.11	.18*
	Event/incident	n/a	3.64	1.97	.11	.09
	Others	n/a	2.89	2.13	-.09	.14*
	Others & Self together	n/a	2.45	2.03	-.03	.16**
Source of influence for health behavior	Parents	n/a	4.84	1.74	.01	.16**
	Other family members	n/a	4.07	1.95	.08	.13**
	Friends	n/a	4.51	1.69	-.03	.28**
	Romantic partner	n/a	4.79	1.90	.09	.07
	Experts	n/a	5.01	1.66	.10	.13*
	Media/Advertising	n/a	3.77	1.75	-.01	.14*

#Scores range between 1 and 7 (1=strongly disagree, 7=strongly agree), *p < .05, **p < .01

Table 2.— Cultural Orientation and Romantic Partner Influence and Tactics					
Variables		Mean#	SD	Correlation with Interdependent Self-Construal	Correlation with Independent Self-Construal
I think my romantic partner should try to change me if I am doing actions that are harmful to myself.		5.13	1.57	.04	.18**
I am more likely to change my behavior if it helps me to be seen as more attractive to my partner.		4.44	1.74	-.06	.22**
Tactics	Places a bet	3.40	1.93	-.12	.14*
	Offers reward if I change successfully	4.00	1.92	-.16*	.08
	Explains how it affects her/him too	5.31	1.51	.08	.16**
	Offers to do it with me	5.42	1.61	-.00	.13*
	Keeps reminding me the need to change	3.70	1.88	-.10	.20**
	Threatens to leave me	2.57	1.92	-.19**	.14*
	Threatens to do the same thing	2.84	1.93	-.12	.22**
	Casually brings it up	3.69	1.63	-.06	.19**
	Firmly demands the change	2.60	1.75	-.14*	.25**
	Incorporate the change into a daily routine	4.84	1.76	.09	.12

#Scores range between 1 and 7. For the first two items: 1=strongly disagree, 7=strongly agree. For the 10 tactic items: 1=not at all effective, 7=very effective. *p < .05, **p < .01

in the focus groups that it was easier to combine socializing and working out together with a romantic partner rather than separately. Moreover, they shared that partner encouragements were helpful in sustaining health promoting behaviors (e.g., adhering to an exercise routine). Some students even reported that making behavioral changes together resulted in improvements to relationship quality. In the survey data, students reported that they believed romantic partners should intervene to stop their partners from doing something harmful, and that romantic partners are influential in their decisions about various health behaviors (Table 2). Cultural orientation was significantly related to the extent and nature of romantic partner influence on health behaviors. Interdependent self-construal was positively related to believing that romantic partners should intervene to change a partner's harmful actions, and the willingness to change one's own behaviors to be perceived as more attractive to romantic partners. Interdependent self-construal was also positively related to perceptions that various persuasion tactics can be effectively used by romantic partners to influence their behavior. On the other hand, independent self-construal was either not related, or negatively related to the perception that various persuasion tactics can influence them.

Conclusion

Promoting healthy behaviors among the young adult population is a difficult challenge. This study demonstrated that cultural orientation is important in understanding motivational factors for health behaviors among young adults. Higher levels of interdependent self-construal were associated with higher levels of external locus of control in general, as well as more specifically for health. Given this, not surprisingly, the study found that increases in reports of interdependent self-construal were associated with increases in reports of being influenced by external motivators and affected by various sources other than oneself.

Additionally, those who reported higher levels of interdependent self-construal also more strongly believed that romantic partners should try to change them and would be more likely to change to be seen as more attractive to their romantic partners. Data also revealed that romantic relationships are important to students and may be a promising strategy for health interventions for this age group. These results are consistent with findings in the literature that social control plays an important role in health behaviors.[6] Social relationships can influence health behaviors both indirectly and directly.[7,8] However, how successful this strategy may work as well as what kinds of specific tactics can be employed by their romantic partners depends to a certain degree on the level of cultural orientation.

Thus, this investigation provides evidence that linking cultural orientation to health research can be quite informative. Taking into account self-construals, particularly interdependents, when designing health interventions and sources of influence that are relevant to young adults can help us (a) identify those who are more likely to be influenced for health behaviors; (b) tailor messages and tactics for those with different cultural orientation; and (c) tailor the message sources to maximize the impact.

For more information about the Cancer Research Center of Hawai'i, please visit its web site at www.crch.org.

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Issues in Medical Malpractice XIV

S.Y. Tan MD, JD, Professor of Medicine and Adjunct Professor of Law, University of Hawai'i

Question: Dr. E, an endocrinologist, diagnosed MEN Type I, a rare disorder that is inherited in an autosomal dominant fashion. Genetic measurements confirmed the diagnosis, but Dr. E did not inform or counsel the patient's 3 siblings and 2 children. Which of the following is (are) correct?

A. Dr. E's legal duty is only to his patient, and confidentiality prevents him from discussing the diagnosis with others.
B. He would escape liability because this is a rare and exotic disease.
C. He should be judged by the reasonable doctor's standard.
D. A reasonable endocrinologist would have provided family counseling after securing the patient's permission.
E. Unless injury results, there can be no malpractice action.

Answer: D and E are correct

The law requires that one acts reasonably, and for a doctor this means the standard expected of one who has the knowledge, skill and judgment ordinarily possessed by fellow members of the profession. The requisite standard of care is different for the specialist as compared to the generalist. In this case, an endocrinologist would be expected to offer counseling to a patient with this genetic condition, which includes informing immediate family members of the need for endocrine screening. This is an example of a physician's duty to "third parties". Whether this duty can be delegated to the patient, or whether the doctor should personally contact the family members is less clear. The latter appears preferable, and by obtaining prior patient permission, the doctor is no longer concerned with confidentiality issues.

Although it can be argued that a generalist or non-endocrinologist may not be expected to adhere to this standard, at the minimum, there is a separate duty to refer to the specialist. The test is not whether the disease is rare and exotic, but what a reasonably prudent doctor would do under the same or similar circumstances.

Thus D, but not A, B, or C, is correct.

E is also correct. For a malpractice suit to succeed, the plaintiff must prove, in addition to negligence, the elements of causation and damages. If no injury can be traced to the negligent act, then no cause of action will ensue. Failure to offer genetic counseling however may well lead to injuries that are potentially preventable.

Duty to Third Parties

Sometimes, a doctor is liable to someone other than his/her immediate patient. In such a circumstance, another person, often referred to as a "third party", may sue the doctor despite the absence of a doctor-patient relationship. An example is where an obstetrician fails to treat a pregnant woman known to have been exposed to German measles, who then delivers a child with birth defects. A Rhode Island court has ruled that a cause of action could be instituted by the child.[1] In another case, a missed diagnosis of meningitis in a mother led to her son contracting and dying from the disease. The son's estate sued. The lower court found no physician-patient relationship between the doctor and the son, but the appellate court reversed, holding that the physician-mother relationship resulted in a special situation for imposing a duty of care for her son.[2] Similarly, the Supreme Court of Tennessee held that a physician has a duty to warn persons in the patient's immediate family of the risk of a disease such as Rocky Mountain Spotted Fever although it itself was not contagious.[3]

A doctor may even be found to have a duty to a total stranger. The best known case is *Tarasoff*,[4] where a California court imposed a duty on a psychologist to warn an intended victim of harm even though that meant breaching confidentiality of a professional relationship.

An emerging area of malpractice litigation affects patients who drive. Consider the following example: Suppose a patient drives his car and hits a pedestrian. The patient is a diabetic and was recently placed on insulin. The accident was caused by the loss of control of his vehicle because of hypoglycemia. The pedestrian could bring a lawsuit against the driver, but could also sue the doctor for failing to adequately warn of the risk of hypoglycemia, its prevention, and its treatment. The doctor is now faced with potential liability to the injured pedestrian, a total stranger. Such an issue, with slightly different facts, was recently decided by the Hawai'i Supreme Court which held that:

> *"A physician owes a duty to non-patient third parties injured in an automobile accident caused by an adverse reaction to the medication … where the physician has negligently failed to warn the patient that the medication may impair driving ability and where the circumstances are such that the reasonable patient could not have been expected to be aware of the risk without the physician's warning."*[5]

The medication in that case was the anti-hypertensive drug, Minipress.

This article is meant to be educational and does not constitute medical, ethical, or legal advice. It is excerpted from the author's book, *"Medical Malpractice: Understanding the Law, Managing the Risk"* published in 2006 by World Scientific Publishing Co., and available at Amazon.com. You may contact the author, S.Y. Tan MD, JD, at email: siang@hawaii.edu or call (808) 526-9784 for more information.

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THE WEATHERVANE

RUSSELL T. STODD MD, CONTRIBUTING EDITOR

Russell T. Stodd MD

❖ **WHY GRANDMA! WHAT RED EYES YOU HAVE. ALL SOLUTIONS BREED NEW PROBLEMS.**

It used to be rare and it is ugly. The Centers for Disease Control and Prevention (CDC) is currently investigating 138 cases of corneal infection with Acanthamoeba. In some soft contact lens wearers this parasite has invaded the cornea with devastating result. It produces redness and severe pain, but little discharge. Specifically, the recent infections seem to be related to use of Advanced Medical Optics Inc., (AMO) contact lens solution *Complete Moisture Plus Multi-purpose Solution*. The company immediately invoked a voluntarily recall of the solution and instructed patients to discard any remaining solutions, affected contact lenses, and cases. Even when the diagnosis is made promptly, treatment is difficult and ongoing for months, frequently resulting in corneal transplant surgery, or even blindness. This ubiquitous amoeba can be found in tap water and is innocent normally, but can turn mean given the right corneal environment. There are always some bad bugs out there lurking and looming. The question is why have they suddenly reappeared.

❖ **WE ARE FROM THE GOVERNMENT AND WE ARE HERE TO PROTECT YOU.**

The subject of why Acanthamoeba is now turning up in AMO contact lens solutions and why fungus has crept into Bausch and Lomb solutions, may be related to an approach not previously suspected. The culprit may well be the *Environmental Protection Agency* (EPA), which in 2002 restricted the levels of byproducts of chlorine and other cleaning agents in drinking water in an effort to reduce chemical contamination. In the last five years microbial corneal infections have tripled, according to Reza Dana, M.D., director of the corneal service at Massachusetts Eye and Ear Infirmary. Both fungal and acanthamoeba infections were exceedingly rare until recent years. Now a Chicago team, Doctors Charlotte Joslin and Elmer Tu, has produced a soon-to-be published paper linking the EPA action with these nasty eye disorders. The EPA needs to remember that it is impossible to change just one thing.

❖ **IT IS IMPORTANT NOT TO RUN SHORT OF SCAPEGOATS.**

Michael Moore, the rotund "documentary" film maker who has become extremely rich by attacking the vulnerable, has turned his sights onto the American health care system. His latest effort called "Sicko" started appearing in theaters in the United States at the end of June, and features insurance and health care. Hey, any physician in active practice could write an exposé on the shabby methods and money-grubbing third parties who are milking big bucks out of the system. The issue is not whether health care in America is sick, but rather what to do about it. Congress generated most of our problems by initiating Medicare, irrespective of ability to pay, and then embarked on a deliberate plan to destroy the independent family physician by rewarding "health plans". Medical expenditures would decrease and doctors and patients would be much happier if third parties were limited to catastrophic coverage only, and first dollar coverage would be eliminated.

❖ **TURN LEFT, SWEETIE; I WANT A PROFILE VIEW.**

Seventy years after Superman showed us the way with X-ray vision, the imaging industry has developed high energy "backscatter" X-ray which allows examiners to visualize the human body through wearing apparel. We are told that the exposure is harmless and the *Transportation Security Administration* (TSA) has announced that it will conduct a trial run with the device in Sky Harbor Airport in Phoenix, Ariz. The machines are very expensive, and probably do represent an invasion of privacy. Will the traveling public put up with this additional demand? There could be a major groundswell of resistance to security officers arbitrarily selecting passengers for a radiographic strip search.

❖ **ALL I WANT FROM THIS LAWYER IS AWAY.**

It almost reads like a script from the archives of the "Keystone Kops" or a reprise for a W. C. Fields film. After an X-ray for a chest injury, Andrew Speaker, a 31-year-old personal injury lawyer, was found to have tuberculosis, not just a common mycobacterium, but one called XDR TB, a highly resistant bug. According to Julie Gerberding MD, director of Center for Disease Control and Prevention (CDC), Mr. Speaker was advised not to travel, but he had plans to honeymoon in Italy with his bride, so who worries about spreading a little harmful bacteria? When the CDC determined the virulence of his infection, officials attempted to contact the patient and found that he was in Europe contaminating Italy, not to mention his bride. He was advised to seek help promptly from Italian health authorities, which he did not do. Instead, Mr. Speaker flew to Canada and chose to return to the United States through the backdoor at Champlain, N.Y. The Homeland Security Administration (HSA) border guard screened his passport and found specific instructions to hold the man, but "the guy didn't look sick" so he just let him go! Apparently, if you don't hack, cough, sneeze, faint, or vomit, you're not sick. So, smile for the HSA people while removing your shoes, your jacket, your wrist watch, your newspaper, and whatever else. Somehow I don't feel safer.

❖ **HE IS GOING WHERE TO DO WHAT?**

At New York's Presbyterian/Columbia Medical Center a 66-year-old woman had her gall bladder removed with an "extremely experimental" approach through the vagina. According to her surgeon, Dr. Marc Bessler, the standard laparoscopic gall bladder removal, entering through the abdominal wall, results in muscle damage and post-operative pain. He claimed that entering through the body's natural orifices causes less tissue injury and less post-operative pain. "Going through a natural orifice, the mouth, rectum or vagina, to get into the abdomen and do an operation is being worked on by a lot of people." Well maybe, but when he can do a laparoscopic C-section through the ear canal, then I'll be a believer.

❖ **WHEN IGNORANCE GETS ROLLING THERE ARE NO LIMITS.**

Mike Lake, a member of Canadian Parliament, has agreed to introduce a petition to place Sasquatch (Bigfoot) on the Canadian version of the endangered species act. This is very reassuring because it affirms the fact that not all the nut cases are south of the 49th parallel. How can a species that has never been counted nor even seen be considered "endangered"?

❖ **FOR THE BOROUGH CHIEF NIMBY SUCCESS IS NOT ENOUGH.**

For decades until 2001, Staten Island was the dump for New York City, but now has the motto "greenest, cleanest and safest." A local ice cream company is marketing a delicious dessert concoction of fudge, chocolate crunchies, and other additives which it calls "Staten Island Landfill". Borough President James Molinaro is not amused and wants to boycott the treat claiming it is an ugly stereotype. Hey, loosen up, Dude! It's ice cream, not a housing project.

❖ **SHE MIGHT WANT TO CONSIDER A CAREER CHANGE.**

At the Marshalltown, Iowa, court house it was noted that toilet paper consumption was excessive. Careful employee oversight revealed that Suzanne Marie Butts (of course) was carrying rolls of two ply out of the court house under her skirt. Was she marketing these rolls for dough, or was this a thrill crime for excitement? In any case, the crapper napper paper caper has been wiped off the books.

ADDENDA

- ❖ At any given hour, the average number of people airborne over the United States is 61,000.
- ❖ Seventy-seven million baby boomers are expected to reach retirement age in the next 10 to 15 years and 75% of them will face unanticipated financial difficulties. Most will keep right on working.
- ❖ San Francisco cable cars are the only mobile national monuments.

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