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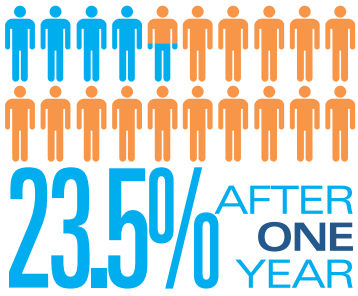

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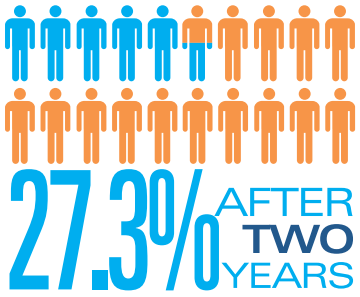

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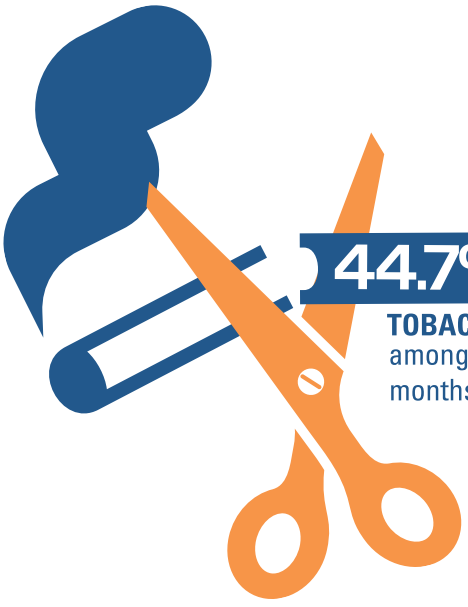

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Hereditary Diffuse Gastric Cancer Associated with E-cadherin Germline Mutation: A Case Report

Michael D. Black MD; Raynette Kaneshiro PA; Jennifer I. Lai; and David M. Shimizu MD

Abstract

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominate cancer syndrome that leads to an increased risk of developing invasive diffuse type (signet ring cell) gastric carcinoma. Approximately 30% of HDGC cases are caused by a germline mutation involving the E-cadherin (CDH1) gene. Those with the CDH1 mutation have an 80% and 60% cumulative lifetime risk of developing diffuse type gastric carcinoma and lobular breast carcinoma respectively. Due to the focal nature of early diffuse type gastric carcinoma, identifying early lesions with surveillance endoscopy is limited. As a result, elective risk-reducing total gastrectomy is currently recommended. In this report, the clinical, intraoperative, and pathologic work-up is reviewed regarding a patient with known CDH1 germline mutation.

Introduction

Gastric cancer is the second leading cause of cancer death world-wide with nearly one million new diagnoses per year. More than three-fourths of those individuals die from their disease.[1] In Hawai'i, gastric cancer is the fifth leading cause of cancer-related death as reported by the Hawai'i Tumor Registry. The majority of gastric cancers are intestinal type adenocarcinomas that have been linked to *Helicobacter pylori* colonization and diet.[2] However, 1%-3% of all gastric cancers are attributed to hereditary diffuse gastric cancer (HDGC).[3] HDGC is an uncommon autosomal dominant form of diffuse type gastric carcinoma that generally presents at an early age with advanced stage and poor prognosis.[4]

The first indication of a genetic link to certain diffuse-type gastric cancers was reported in 1998 when Guilford and colleagues discovered 3 germline truncating mutations in the E-cadherin (CDH-1) gene within a large New Zealand family of Maori ethnicity.[4] Following this discovery, other germline CDH1 mutations have been identified in patients with HDGC from a wide range of ethnic backgrounds, including but not limited to Filipino, African American, Korean, Japanese, and European.[5-8] Mutations in the CDH1 gene result in its loss of expression that leads to defective intercellular adhesion (Figure 1). The Gastric Cancer Linkage Consortium currently specifies two criteria for the diagnosis of HDGC (Table 1).[9,10,16] Of those individuals meeting either of these two criteria, approximately 25%-30% will demonstrate the CDH1 germline mutation.[11] The mechanism of disease in the remaining HDGC cases is largely unknown.

Once an individual meets the criteria for HDGC, it is recommended that the patient and at-risk family members be tested for the CDH1 germline mutation. Those with the mutation will carry an 80% risk of developing diffuse type gastric carcinoma by 80 years of age.[11] In addition, female patients carry an additional 60% lifetime risk of developing lobular breast carcinoma by 80 years of age.[12] Many of these individuals undergo annual endoscopic evaluation. However, the sensitivity of endoscopic biopsies has been called into question owing to the focal nature of early invasive/in-situ gastric carcinoma.[3] In addition, there is conflicting data as to the predominant site of involvement, proximal versus distal, which may further limit the sensitivity of screening endoscopic biopsies.[13]

Pathologic handling of the total gastrectomy specimen consists of submitting the entire specimen for routine histologic examination. Traditionally only hematoxylin and eosin staining has been used. However, periodic acid-schiff (PAS) staining has demonstrated improved detection of invasive and in situ gastric carcinoma.[11,12] Few studies have demonstrated the complete mapping of the total gastrectomy specimen using PAS staining. Therefore, this institution's experience using this technique is described.

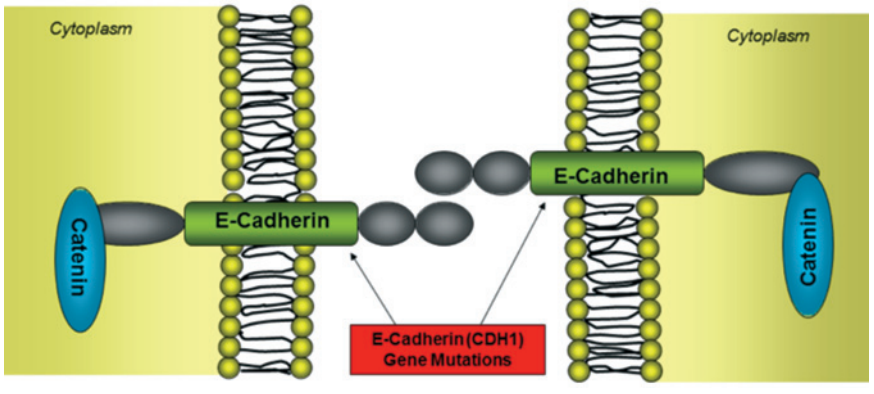

Figure 1. Germline mutations within the epithelial cadherin (CDH1) gene results in loss of expression and ultimately defective intercellular adhesions between cells.

Table 1. The Gastric Linkage Consortium Criteria for Hereditary Diffuse Gastric Cancer requires Criteria 1 or Criteria 2 to be met before the diagnosis of HDGC.

Gastric Cancer Linkage Consortium Criteria for Hereditary Diffuse Gastric Cancer [9,10,16]	
Criteria 1	Two or more documented cases of diffuse gastric cancer in first or second degree relatives, with at least one diagnosed before the age of 50
Criteria 2	Three or more cases of documented diffuse gastric cancer in first/second degree relatives, independent of age of onset

Case Report

A 22-year-old woman presented for genetic work-up due to strong family history of early onset diffuse gastric carcinoma. The patient's mother was diagnosed with stage IV diffuse type gastric cancer at the age of 41 despite having negative endoscopic gastric biopsies the year prior (Figure 2). In addition, the patient's aunt died of gastric cancer in her early 40's and maternal grandfather died of gastric cancer in his 50's (Figure 2). As a result of her strong family history, the patient underwent CDH1 germline testing that demonstrated a deleterious trp20stop CDH1 germline mutation. She subsequently underwent three screening endoscopic gastric biopsy evaluations that were negative for malignancy or dysplasia. It was the patient's decision then to undergo a prophylactic total gastrectomy.

Pathology

Intraoperative consult was obtained to ensure that margins were free of gastric mucosa. This was done by taking sections of the entire proximal and distal margins and embedding en face. Once negative margins for gastric mucosa were obtained, the specimen was opened along the greater curvature, pinned to a cork board, and allowed to fix in formalin overnight. No lesions were identified grossly (Figure 3). The entire specimen was mapped using a photograph with superimposed graph (Figure 4) and submitted for histologic examination in 225 cassettes. Each section was stained with PAS as recommended by current guidelines.[11,12]

Histologic examination revealed 109 foci of invasive diffuse type (signet ring cell) gastric carcinoma and 6 foci of in situ (including pagetoid spread) diffuse type gastric carcinoma. The size of invasive foci ranged from single cells to 1.5 mm in greatest dimension (Figure 5). They were predominantly seen within the proximal two-thirds of the stomach with a single focus in the distal one-third (Figure 4). The invasive component was limited to the superficial lamina propria and no perineural or lymph-vascular invasion was identified. Fifteen regional lymph nodes were also examined that were negative for metastasis.

Discussion

The world-wide incidence of sporadic gastric cancers has been decreasing over recent years.[1] One hypothesis for the decrease in sporadic carcinoma is increased recognition and treatment of *Helicobacter pylori* infection. While the incidence of sporadic gastric carcinoma appears to be decreasing there has been increased awareness of non-sporadic gastric carcinomas such as hereditary diffuse gastric carcinoma.

This institution received the risk-reducing total gastrectomy specimen from a patient known to harbor the CDH1 germline mutation. As has been reported by Rogers and colleagues, when dealing with prophylactic total gastrectomy specimens there is

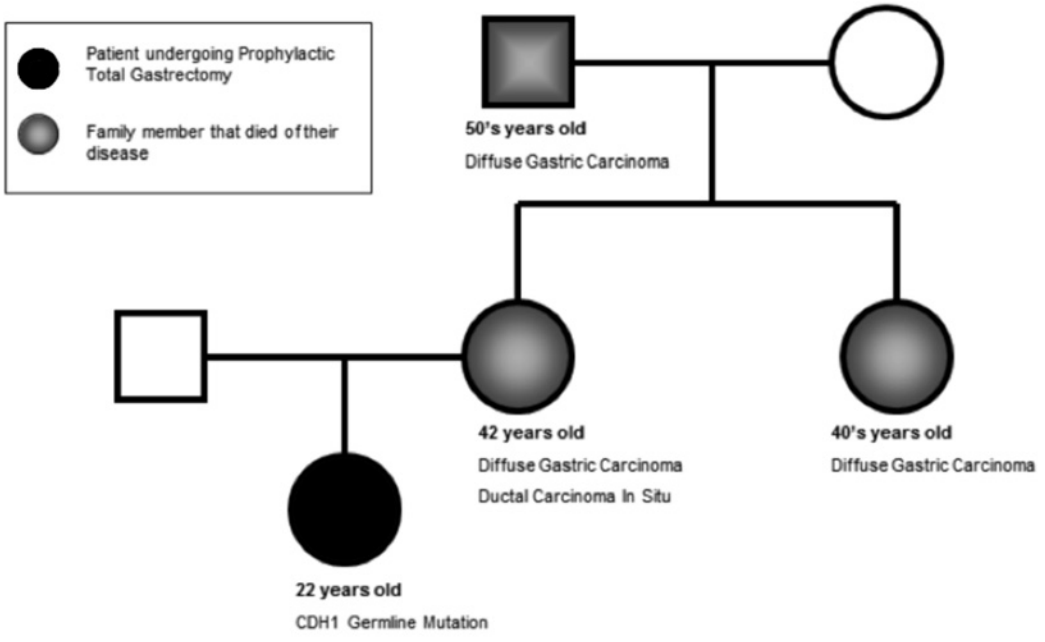

Figure 2. Patient's pedigree showing strong family history of diffuse gastric carcinoma.

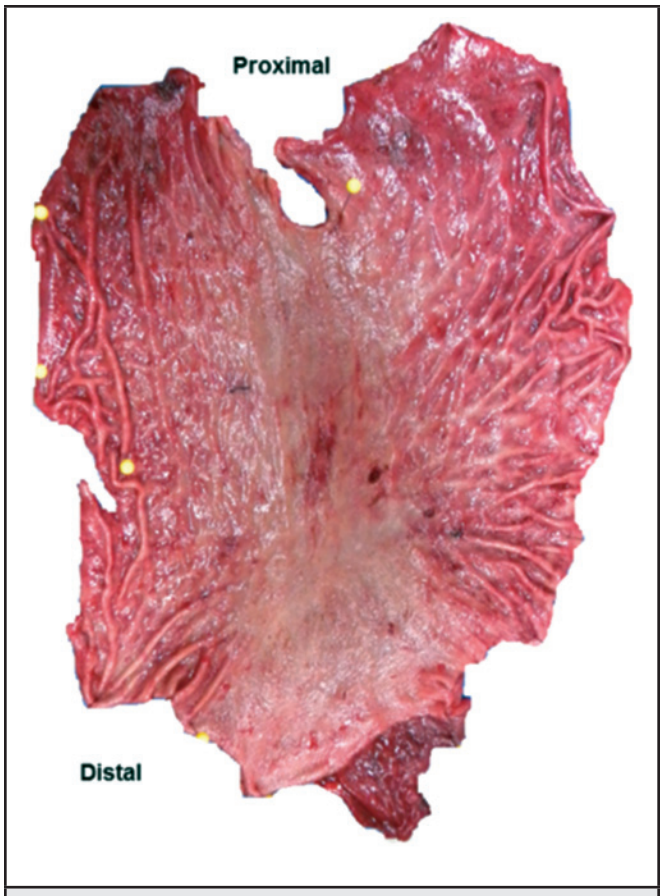

Figure 3. Gross total gastrectomy specimen opened along the greater curvature with no identifiable lesions.

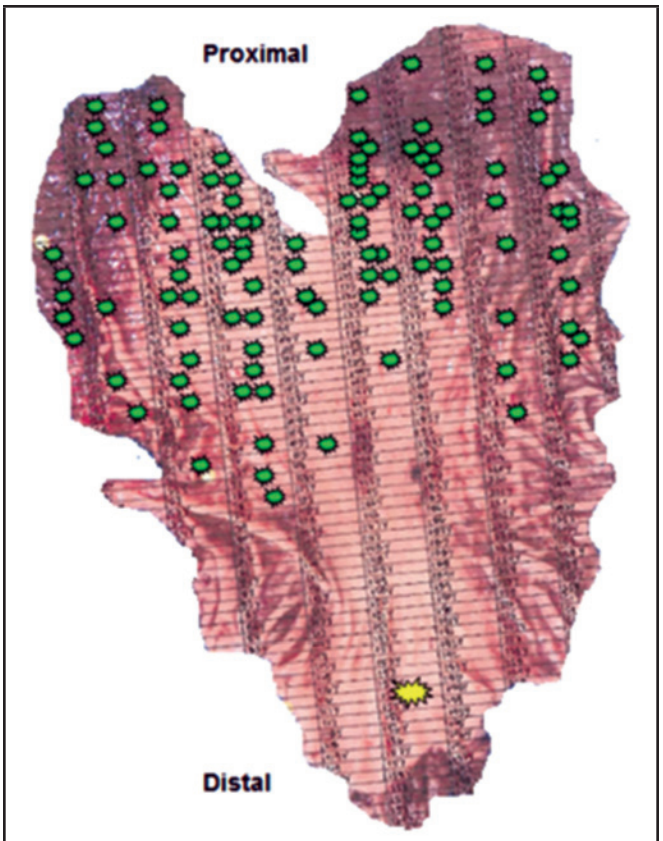

Figure 4. Total gastrectomy specimen with grid used for mapping. Green indicates foci of invasive or in-situ diffuse-type gastric carcinoma. Yellow indicates a single focus of invasive diffuse-type gastric carcinoma in the distal half of the stomach.

commonly no gross evidence of disease.[13] It is therefore necessary to sample the entire specimen in order to detect microscopic foci of invasive and/or *in situ* tumor.

It was found that carefully graphing a photograph of the pinned out gastrectomy was the most efficient means of correlating the gross with microscopic findings. Two hundred and twenty-five slides were examined that revealed 109 and 6 foci of invasive and in situ diffuse-type gastric (signet ring cell) carcinoma, respectively. The 6 small foci of in-situ diffuse-type carcinoma (Figure 5) are characteristic of HDGC as described by Oliveira and colleagues.[14] Moreover, it is this institution's experience that the use of PAS staining was helpful in identifying these small tumor foci. This technique as outlined by Lee and colleagues allows for the detection of invasive and in situ components with increased sensitivity as compared to routine hematoxylin and eosin sections.[12] The average number of foci identified in gastrectomy specimens as seen in prior reports was 10.9 using H&E alone, compared to the 115 foci found in this case using PAS.[13]

In addition, this case showed tumor burden was concentrated within the proximal stomach. A review of the literature shows this is in concordance with Rogers and colleagues.[13] However, Charlton and colleagues reported two out of six cases with a distal stomach predominance.[15] This suggests variability may exist in regards to the predominant location of early CDH1 diffuse gastric carcinoma. In addition to this variability, multiple foci of tumor may be identified throughout the entire specimen as highlighted in this case by a single focus of invasive diffuse gastric carcinoma within the distal stomach (Figure 4). Such variability reiterates the importance of submitting the entire gastrectomy specimen for histologic examination.

Conclusion

Recognition of a strong family history of diffuse type gastric carcinoma and/or lobular breast carcinoma is critical for identifying those patients at risk for HDGC. Individuals at risk can be tested for the germline mutation of the epithelial cadherin (CDH1) gene and those with a positive test should be offered prophylactic/risk-reducing total gastrectomy.[11] Lastly, it is this institution's experience that surveillance endoscopy has limited sensitivity in identifying occult diffuse gastric carcinoma in patients with CDH1 germline mutations.

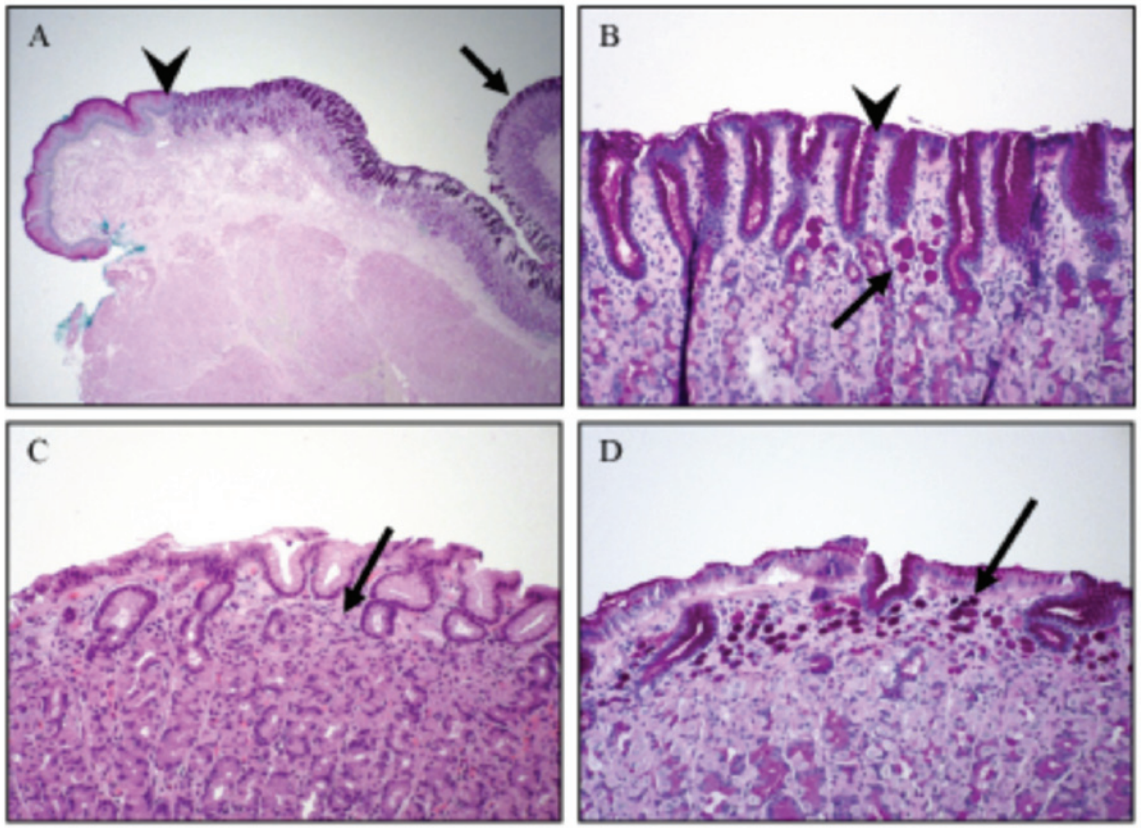

Figure 5.

Disclaimer

The findings and conclusions of this study do not necessarily represent the views of the Queen's Medical Center.

Conflict of Interest

None of the authors identify a conflict of interest.

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Neuropsychological Test Performance of Hawai'i High School Athletes: Updated Hawai'i Immediate Post-Concussion Assessment and Cognitive Testing Data

William T. Tsushima PhD and Andrea M. Siu MPH

Abstract

The present study reviewed the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) baseline test scores of 247 high school athletes ages 13 to 18 from a private school in Hawai'i. The aim of the research was to update a prior exploratory investigation conducted in 2008 that compared the test scores of Hawai'i public high school athletes with the normative data provided by the ImPACT publishers. The results of this study provide assurance that the present ImPACT scores of the Hawai'i high school athletes are similar to the general ImPACT norms. The present study is a rare effort to compare the ImPACT scores of high school athletes from an ethnically diverse region with the ImPACT norms. The findings offer further support for the use of the ImPACT norms when evaluating high school athletes from Hawai'i. Future research in various regions of the United States and with other sociocultural backgrounds is encouraged.

Keywords

neuropsychological test, concussion, ImPACT, high school athletes

Introduction

Recently medical research and media coverage have increasingly focused on sports-related concussion, or mild traumatic brain injury. While concussions in professional sports and college have captured public attention, epidemiologic studies indicate that most concussions in organized sports occur in high school, probably because of the sheer quantity of athletes participating at this level.[1] A study of emergency services found that 3 in 1000 children ages 14 to 19 had an emergency department visit for concussion sustained in organized team sports, demonstrating an increase of more than 200% between 1997 and 2007.[2]

Neurodiagnostic methods for head injuries, such as X-ray, CT scan and MRI, remain the standard for accurate diagnoses and management of sport concussion. In addition, the use of neuropsychological testing plays a significant role in the evaluation of the concussed athlete.[3] Traditional paper-and-pencil neuropsychological tests have been applied for head injury assessments, but more recently computer-based neuropsychological test batteries, such as the Immediate Post-Concussion Assessment and Cognitive Testing(ImPACT) and Cog Sport, have gained widespread acceptance.[4,5] Currently, ImPACT is used in over 400 high schools and is one of the most utilized neuropsychological test instrument, according to its website, *http://impacttest.com*.

To assess the head-injured athlete, ImPACT score interpretation compares the athlete's post-injury test performance with preseason baseline levels. The ImPACT creators suggest baseline testing every two years. When baseline test scores have not been obtained, however, the post-injury scores can be compared to normative data provided by the publishers of this test battery.[4] Normative data are provided for 4 of the 6 composite scores generated by the ImPACT test and are based on a sample of 75,000 athletes.[4] Potential diagnostic problems could occur when assessing test scores of ethnic minority athletes based on the norms of the mainstream population, as longstanding research has established that minority individuals, eg, African Americans and Hispanic Americans, tend to obtain relatively lower scores on standard psychological tests.[6] In view of the possible influence of sociocultural factors on psychometric tests, there are concerns that ImPACT norms developed in the continental United States may not be an appropriate reference base for the unique multi-ethnic population residing in Hawai'i.[7,8]

There is, to date, practically no study that examines the influence of sociocultural or regional factors on the test scores of ImPACT, which is widely employed across the United States. In 2008, ImPACT research on 751 Hawai'i high school athletes was reported in the Hawai'i Medical Journal.[9] The ImPACT test scores of the Hawai'i student athletes were similar to the continental United States norms, but with a trend toward slightly lower scores among the Hawai'i athletes. This difference suggests that the normative percentiles in Hawai'i may be different from the larger population of ImPACT exam takers. The Hawai'i study, however, did not account for those whose primary language was not English, and did not provide details about the different ethnic groups in the research. In addition, the investigation did not exclude invalid ImPACT profiles, ie, those with Impulse Control scores > 30, suggestive of suboptimal test effort.[10]

The purpose of the present study was two-fold: (1) to update the ImPACT normative data with baseline testing and improved inclusion/exclusion criteria on a large population of male athletes at a Hawai'i private high school, and (2) compare the findings with the available normative data from ImPACT to the 2008 ImPACT study in Hawai'i. The hypothesis was: current Hawai'i high school ImPACT data is similar to that obtained in high schools on the continental United States.

Methods

The study was reviewed by the Hawai'i Pacific Health Research Institute and was determined to be exempt from Institutional Review Board review.

Test Instrument

The ImPACT test is a 20-30 minute computerized neuropsychological test battery administered by certified athletic trainers trained in the standardized administration of the examination.

ImPACT consists of 6 individual test modules that measure different neurocognitive abilities. ImPACT yields five composite scores, including Verbal Memory, Visual Memory, Processing Speed (Visual Motor), Reaction Time, and Impulse Control. The test also provides a Total Symptom Score. A partial list of biopsychosocial data collected with ImPACT includes age, gender, years of education, primary spoken language, ethnicity, sport played, position played, years of experience, prior concussion, history of seizures, psychiatric illness, learning disability, attention deficit disorder, and headache treatment by a physician. The ImPACT test provides standard racial/ethnic categories in a drop down list for participants to choose from. Participants were allowed to choose more than one race/ethnic group.

Participants

The participants were 247 male athletes, ages 13 to 18 years old, in a private high school in Hawai'i during the 2011-2012 and 2012-2013 school years. All athletes underwent baseline testing individually with the computerized ImPACT battery prior to their sport seasons. For the fewer than 10 students in the sample who had multiple baseline scores, repeat baseline scores were removed and only the first baseline score was used in the analysis.

Participants were included if they were male, 13-18 years old, and spoke English as their primary language. Five student-athletes whose first language was not English were excluded from the study. The excluded students spoke Japanese (2), Korean (1), Hakka-Taiwanese (1) and Tongan (1). No athlete was excluded because of invalid profiles, ie, Impulse Control score >30, because there were no invalid Impulse Control scores.

Consistent with the ImPACT normative categories, participants were divided into two age categories, 13 to 15 year olds and 16 to 18 year olds.

All statistical analysis was done using STATA/IC 11.2 for Windows (StataCorp LB, College Station, TX). Descriptive statistics were calculated for all variables. Percentile tables were created for the 4 ImPACT scores with corresponding normative values for the two age groups.

Results

The mean age of the student-athletes was 15.2 years (SD = 1.3). Participants included 144 in the 13 to 15 year-old age range and 103 in the 16 to 18 year-old age range. The self-identified racial/ethnic backgrounds of the participants were categorized into the following groups: Native Hawaiians or other Pacific Islanders (34.0%), Asians (11.7%), Caucasians (5.0%), Hispanics (2.1%), African Americans (1.3%), Native Americans or Alaskan Natives (0.4%), and mixed racial backgrounds (43.3%). Participants who listed more than one race were placed in the mixed race category only. Participants were allowed to choose more than one racial/ethnic category from a drop down list of standard categories. Nine students did not list a race/ethnicity.

Seven students (2.8%) reported a history of learning disability, which was lower than reported in a previous study of high school athletes(8%) and in the general population, perhaps because of the academic selectivity of the private school the participants attended.[11,12]

The number of athletes participating in each sport varied. Students selected only their primary sport. The sports chosen were football (74.1%), basketball (7.7%), baseball (6.9%), wrestling (4.5%), soccer (6.1%), cheerleading (0.4%), and paddling (0.4%). Fifty-one (20.6%) athletes reported having a previous concussion; 37 (15.0%) had one concussion, 11 (4.5%) had 2 concussions, and 3 (1.2%) had 3, 4, and 5 concussions respectively.

The means and standard deviations (in parentheses) for each of the five ImPACT composite scores and the Total Symptom Score of the 247 high school athletes are presented in Table 1 as a whole and by age group. Two sample t-tests were performed to test for statistically significant differences in scores between the two age groups (13-15 years and 16-18 years). Significantly different scores between age groups were found for Visual Motor Score (P-value < 0.001) and Impulse Control Score (P-value = < 0.001). The classification ranges of the composite scores (not including Impulse Score and Total Symptom Score) of the two age groups of this study are shown in Table 2. ImPACT provides normative data for the 4 listed composite scores. The Hawai'i scores were similar to the classification ranges in the ImPACT normative sample for the 13 to 15 and 16 to 18 year-old age ranges.

Table 1. Means, standard deviations, and standard errors of measurement of the participants by age group

	All (n=247)			Age 13-15 (n=144)			Age 16-18 (n=103)		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Verbal Memory	82.85	10.11	0.64	82.46	10.15	0.85	83.39	10.08	0.99
Visual Memory	74.01	12.60	0.80	73.84	12.56	1.05	74.24	12.71	1.25
Visual Motor Score	36.40	6.60	0.42	34.88	6.19	0.55	38.53	6.60	0.65
Reaction Time	0.60	0.08	0.01	0.61	0.07	0.01	0.60	0.09	0.01
Impulse Control	7.40	5.48	0.35	8.42	5.87	0.49	5.98	4.53	0.45
Total Symptom Score	7.84	11.70	0.74	8.74	12.85	1.07	6.57	9.80	0.97

Table 2. Classification Ranges for Composite Scores								
	Verbal Memory		Visual Memory		Visual Motor Speed		Reaction Time	
	Hawai'i	ImPACT	Hawai'i	ImPACT	Hawai'i	ImPACT	Hawai'i	ImPACT
Males, Ages 13-15								
Impaired (<2%ile)	<55	<59	<44	<47	<21.81	<24.28	>0.77	>0.84
Borderline (2-9%ile)	56-67	60-69	45-56	48-56	21.82-27.61	24.28-27.97	0.76-0.71	0.84-0.73
Low Average (10-24%ile)	68-78	70-75	57-65	57-65	27.62-30.96	27.98-31.84	0.70-0.67	0.72-0.67
Average (25-75%ile)	79-90	76-89	66-82	66-83	30.97-38.42	31.85-40.29	0.66-0.56	0.66-0.55
High Average (76-90%ile)	91-95	90-94	83-91	84-89	38.43-43.48	40.30-44.46	0.55-0.51	0.54-0.51
Superior (91-97%ile)	96-97	95-97	92-93	90-94	43.49-47.60	44.47-47.92	0.50-0.48	0.50-0.47
Very Superior (>98%ile)	>98	>98	>94	>95	>47.61	>47.93	<0.47	<0.46
Males, Ages 16-18								
Impaired (<2%ile)	<63	<60	<45	<47	<24.86	<26.30	>0.86	>0.86
Borderline (2-9%ile)	63-68	61-70	46-53	48-58	24.87-29.30	26.30-30.74	0.85-0.72	0.86-0.71
Low Average (10-24%ile)	69-76	71-77	54-66	59-66	29.31-33.08	30.75-34.37	0.71-0.65	0.70-0.64
Average (25-75%ile)	77-90	78-91	67-83	67-83	33.08-43.45	34.38-45.12	0.64-0.54	0.63-0.53
High Average(76-90%ile)	91-97	92-96	84-91	84-89	43.46-47.99	45.13-49.14	0.53-0.50	0.52-0.49
Superior (91-97%ile)	98-99	97-99	92-97	90-94	48.00-50.74	49.15-51.71	0.49-0.48	0.48-0.46
Very Superior (>98%ile)	100	100	>98	>95	>50.75	>51.72	<0.47	<0.45

Discussion

The current study presents mean ImPACT composite scores and Total Symptom Score of the Hawai'i high school athletes, as shown in Table 1. The study also provides the classification ranges of the present ImPACT composite scores according to age groups, along with the classification ranges from the general ImPACT norms. As can be seen, the present research revealed data that are similar to the ImPACT normative data obtained on the continental United States. The present data support the continued use of percentile ranks based on norms obtained in the continental United States with Hawai'i high school athletes. The current results were consistent with those obtained in a previous normative study in Hawai'i five years ago when ImPACT scores were found to be similar but slightly lower compared to the mainland norms.[9]

Although the present results reveal similarities with the general norms for ImPACT, the recognition of normative data for a culturally unique population like Hawai'i is a step in the right direction, with increased awareness that diversity is a feature of our population that needs to be appreciated in the use of neuropsychological tests. A future study could examine ImPACT scores for the different subgroups of minorities in Hawai'i, such as Native Hawaiians, varied Polynesian and Asian groups, African Americans, Hispanics, and Caucasians.

The significant role of age in the test findings was expected. In prior studies employing ImPACT and other neuropsychological test batteries, older student-athletes have performed better than younger student-athletes.[13]

In this research, none of the athletes obtained invalid profiles due to Impulse Control score >30. This finding suggests that the student-athletes in this study did not display suboptimal effort on the ImPACT test and provided valid data for research. This compares favorably with the 13% of high school football players who scored >30 on the ImPACT Impulse Control score in the literature.[14]

The limitations of the current research are worthy of note. Only male athletes were included in this study, mostly football players. ImPACT normative data are listed by gender and age group. Male scores by age group were used for this study. Nonetheless,the present results of only male athletes were similar to those obtained from the combined male and female study in Hawai'i in 2008.[9] Another limitation of this study was the exclusion of athletes who attend public high schools that are a significant segment (83%) of the high school population in Hawai'i; as a result, the findings may not apply to Hawai'i public school athletes. However, as mentioned above, the present data of private school athletes were similar to those obtained in the previous study of public high school athletes in Hawai'i.[12] Lastly, the research design excluded those whose first language was not English and, thus, may not be applicable when interpreting the scores of those whose primary language is not English.

The present study provides support for the use of ImPACT norms in regions of the country, like Hawai'i, where ethnic minority populations may be substantial. The present investigation is a rare effort to compare the ImPACT scores of high school athletes in an ethnically unique geographic region with the general ImPACT norms. Further research on the use of ImPACT with other ethnic and racial minority high school athletes is recommended.

Conclusion

The current study provided important findings for those who utilize the ImPACT test battery for the evaluation of athletes who sustain a concussion. The results revealed that ImPACT test scores of multi-racial high school athletes in Hawai'i are similar to the scores provided by the ImPACT normative sample and thus support the hypothesis. As such, the use of separate baseline ImPACT norms for Hawai'i high school athletes in neurocognitive concussion assessment is not warranted. The present comparison of local ImPACT test scores with the national ImPACT sample is a unique effort that can serve as a model for other users in the U.S. and other countries that employ this widely used neuropsychological test battery.

Conflict of Interest

The authors have no financial interest in or relationship with ImPACT Applications, Inc.

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Willingness to Favor Aggressive Care and Live with Disability Following Severe Traumatic Brain Injury: A Survey of Healthy Young Adults in Hawai'i

Kazuma Nakagawa MD and Kyle K. Obana

Abstract

Traumatic brain injury (TBI) is a major public health problem that significantly impacts young adults. Since severe TBI patients lack decision-making capacity, the providers and patient surrogates are often faced with the challenging task of deciding whether to continue with aggressive life-prolonging care or to transition to comfort-focused care with an expected outcome of natural death. The assumption is often made that aggressive care is appropriate for young patients who suffer severe TBI despite the high likelihood of a poor outcome. However, the young community's attitude towards goals of care after severe TBI has not been studied. A questionnaire-based survey study on young healthy adults was conducted to assess their attitude towards aggressive care after a hypothetical case of severe TBI. Logistic regression analysis was performed to determine the factors associated with the decision to favor aggressive care. Among a total of 120 community-dwelling young adults (mean age: 19±1 years) who were surveyed, 79 (66%) were willing to live with severe motor disability, 78 (65%) were willing to live with expressive aphasia, and 53 (44%) were willing to live with receptive aphasia. Despite being presented with a high likelihood of long-term moderately severe-to-severe disability, 65 of the 115 respondents (57%) favored aggressive care. A willingness to live with receptive aphasia was the only independent factor that predicted aggressive care (OR 2.50, 95% CI: 1.15 to 5.46). Even among the young adults, preference of care was divided between aggressive and conservative approaches when presented with a hypothetical case of severe TBI.

Keywords

Quality of life; traumatic brain injury; ethics; end-of-life care

Introduction

Traumatic brain injury (TBI) is a major public health problem that significantly impacts young adults, with an estimated incidence of 1.5 million total cases per year in the United States.[1] Compared to mild or moderate TBI, severe TBI is associated with worse outcomes.[2] In Hawai'i, approximately 36 cases of severe TBI are admitted to the state-designated trauma center annually.[3] Although the majority of patients with severe TBI may survive after aggressive neurosurgical and neurocritical care management, only about 25 percent of them achieve long-term functional independence.[2,4,5] Furthermore, 5 to 15 percent of patients with severe TBI are discharged in a vegetative state;[4,5] only about half of these persons eventually regain consciousness but with chronic severe disability.[6]

In a neurocritical care setting where patients are unable to make important end-of-life decisions due to their neurological injuries, the families and/or surrogate decision-makers are often faced with the challenging task of making a major decision in the patient's goals of care: whether to continue with aggressive life-prolonging care in the intensive care unit or to transition to comfort-focused care with an expected outcome of natural death. The process of coming to the final decision in this ethically challenging situation often involves utilizing the "substituted judgment" standard and is based on the family and/or surrogate's understanding of the patient's previously stated wishes and known values.

When deciding to proceed with a life-saving treatment in a young patient despite the low likelihood of a favorable outcome, families and providers often presume that aggressive care is justified.[7] Frequently, the assumption is made that every young person would want to survive even with severe cognitive and/or physical disability. In most circumstances, young adults have not had an opportunity to express their wishes in the fairly unlikely circumstance of a severe brain injury resulting in a loss of decision-making capacity at a young age, thus leaving no information for the surrogate decision-makers to base their substituted decision-making. Parents, who often serve as the surrogate decision-maker, often view their young adult child as a vulnerable 'minor' who needs protection. As a result, they often make a paternalistic decision rather than acting upon the values of the patient (principle of autonomy).[8] Although the patient's values and wishes must be individualized, improving our general understanding of the young community's perception and attitude towards goals of care after severe TBI may assist the providers and families with the complex decision-making process in these challenging situations.

Methods

An approval from the University of Hawai'i Institutional Review Board was obtained to conduct a cross-sectional, questionnaire-based survey study by having young healthy adults (age ≥ 18) in the Honolulu County take an anonymous paper survey. The primary objective of this study was to assess the proportion of respondents who favored aggressive care after severe TBI. The secondary objective was to assess the perception of TBI disability and to identify the factors that would predict the young adults' decision to favor aggressive care after a hypothetical case of severe TBI. To simulate a realistic clinical decision-making dilemma, the respondent's willingness to receive aggressive care despite a high likelihood of moderately severe-to-severe long-term neurological disability after the treatment was specifically assessed. The highest degree of neurological disability they would be "willing to live with" based upon the descriptions from the modified Rankin Scale (mRS) (Table 1) was also assessed. The recruitment and data collection took place at public spaces, but the surveyor targeted areas with a high concentration of young adults such as high school athletic gyms, football fields, a local shopping mall, and private social

Table 1. Primary Outcome Questions
1) What is the most severe disability level you would be willing to live with? **0:** No symptoms at all. **1:** No significant disability despite symptoms; able to carry out all usual duties/activities. **2:** Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance. **3:** Moderate disability; requiring some help, but able to walk without assistance. **4:** Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance. **5:** Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
2) If you have a severe traumatic brain injury that will most likely result in moderately severe or severe permanent disability (see above definitions) or death no matter what type of treatment you get, would you choose treatment that is: **Aggressive:** involving temporary removal of your skull to relieve high pressure from brain swelling, removing a blood clot within the skull that may be causing damage to your brain, and/or prolonged care in the intensive care unit in the hospital. This will increase your chance of survival, but you would have moderately severe or severe disability. **Conservative and noninvasive:** This will likely decrease your chance of survival. If you survive, you would have moderately severe or severe disability. You will likely pass away comfortably in a natural way.

events. The participants were screened to be "young adults" based on the surveyor's subjective assessment of their physical appearance. Participants were included in the survey after confirming that they met the minimum age requirement (age ≥18). Besides the surveyor's subjective assessment of their "young adult" appearance, there was no upper age limit for enrollment. No incentive was provided for survey completion. Convenience sampling methodology was used in this study. Due to the exploratory nature of the study, power analysis was not performed. Waiver of consent was obtained from the Institutional Review Board to conduct this survey study since agreeing to take an anonymous paper survey was considered to be adequate consent.

Data Collection and Measures

The study personnel directly collected the self-administered paper surveys that were completed at the time of recruitment. Collected data included personal and demographic characteristics including the respondent's age, sex, race, education level, annual income, occupation, marital status, family status, insurance status, whether they had previously discussed with anyone the severity of disability they are willing to live with, and whether they knew someone who previously had a TBI, stroke, or other brain injury. Race was categorized as white, Asian, Native Hawaiian and other Pacific Islander (NHOPI), or "other" race. Since mixed racial background is relatively common in Hawai'i, race was defined as the racial background that the respondent most closely associates with and was based on self-identification. The primary outcome measure was to determine the young community's willingness to receive aggressive care. Respondents were presented with a hypothetical case of severe TBI with clinical features that would lead most healthcare providers to portray a poor neurological outcome if this were a "real life" setting (Table 1). Aggressive care was described to portray decompressive hemicraniectomy and prolonged intensive care treatment. Conservative care was defined as "noninvasive treatment." The secondary outcome measures included the young community's attitude towards the highest acceptable neurological disability that they would be "willing to live with," according to the mRS description. In addition to using the mRS, respondents were asked about specific language and motor disabilities that they would be "willing to live with." Expressive aphasia was described as "difficulty speaking", and receptive aphasia was described as "difficulty comprehending."

Statistical Analysis

Data analysis was conducted through commercially available statistical software (SPSS 22.0, IBM Chicago, IL). Descriptive summary statistics were calculated for all variables. After dichotomous grouping based upon whether or not aggressive care was favored, t-test and chi-square testing were performed, based on the variable types, to compare variables between the two groups. Multivariable logistic regression models were performed with forward stepwise inclusion of all variables with $P < .10$ in the univariate analysis (female sex, willingness to live with expressive aphasia, and willingness to live with receptive aphasia), to determine the factors associated with favoring aggressive care after severe TBI. Odds ratio (OR) and 95% confidence interval (CI) were calculated from the beta coefficients and their standard errors. Data are presented as means ± SD, and levels of $P < .05$ are considered statistically significant.

Results

A total of 120 young adults in the community (mean age: 19 ± 1 years, female 37%) were approached, recruited and surveyed. The response rate was 100%. The demographic and survey results of all respondents are shown in Tables 2 and 3. The racial, ethnic distribution consisted of a large proportion of Asian (37%) and NHOPI (37%) respondents compared to whites (20%). Overall, 79 (66%) respondents were willing to live with a severe motor disability, 78 (65%) respondents were willing to live with expressive aphasia, and 53 (44%) respondents were willing to live with receptive aphasia. The highest acceptable

Table 2. Demographics of all survey respondents (N = 120)	
	n ± SD [n (%)]
Age, years	19 ± 1
Female	44 (37)
Race/Ethnicity*	
White	24 (20)
Asian	44 (37)
Native Hawaiian and Other Pacific Islanders	44 (37)
Other	7 (6)
Education level	
High School	42 (35)
College	77 (64)
Graduate School	0 (0)
Other	1 (1)
Annual income	
< $15,000	115 (96)
$15-40,000	1 (1)
$40-80,000	2 (2)
> $80,000	2 (2)
Full time student	108 (90)
Married	1 (1)
Have children	2 (2)
Have health insurance	111 (93)
Know someone who had traumatic brain injury (TBI)	42 (35)
Have a family member who had a TBI, stroke or other brain injury	54 (45)
Previously discussed the level of disability that is worth living with parents, guardian, spouse or children	21 (18)

*One respondent did not report race.

Table 3. Survey results of all respondents (N = 120)		
	n (%)	**95% CI**
Willing to live with a severe motor disability	79 (66)	57 – 74%
Willing to live with expressive aphasia	78 (65)	56 – 74%
Willing to live with receptive aphasia	53 (44)	35 – 54%
Favoring aggressive care after severe traumatic brain injury*	65 (57)	47 – 66%
Most severe mRS score willing to live with:		
0	12 (10)	5 – 15%
1	15 (13)	6 – 19%
2	17 (14)	8 – 20%
3	44 (37)	28 – 45%
4	23 (19)	12 – 26%
5	9 (7)	3 – 12%

*Only 115 respondents answered this question.

modified on the Rankin Scale (0–5) participants "willing to live with" chose: 0 (10%), 1 (13%), 2 (14%), 3 (37%), 4 (19%), 5 (7%). Only 21 (18%) respondents reported having had a discussion with their families about the level of disability they were willing to live with.

Among the 120 respondents, five did not answer the question about the intensity of care they hypothetically desired (aggressive vs. conservative) during the survey. Among the 115 respondents who answered this question, 65 (57%) favored aggressive care despite the high chance of long-term moderately severe-to-severe disability. Univariate analyses showed that those who favored aggressive care were more likely to be willing to live with receptive aphasia than those who favored conservative care (55% vs 33%, $P = .02$). There were no significant differences in the demographics or the highest acceptable disability between the two groups (Table 4). In the multivariable analyses using a stepwise logistic regression model, a willingness to live with receptive aphasia was the only independent factor associated the decision to favor aggressive care (OR 2.50, 95% CI: 1.15 to 5.46, $P = .02$).

Discussion

More than half of the young adults in the community in this study responded in favor of wanting aggressive neurosurgical and neurocritical care after hypothetically experiencing severe TBI, even when given the high probability of a profoundly disabling outcome. Similar to a prior study that surveyed young adults with a hypothetical case of malignant middle cerebral artery (MCA) stroke syndrome,[9] most young adults (73-92%) in this study stated they would not want to live with a moderately severe-to-severe disability (mRS 4-5). Despite this unwillingness to live with a moderately severe-to-severe disability, when presented with a clinical scenario with high likelihood of undesirable outcome, many respondents still favored aggressive care. This may reflect the positive outlook, with hopes of "beating the odds," that many individuals naturally exhibit when suffering from a devastating illness.[10] In fact, the highest acceptable neurological disability that they would be "willing to live with," based on the mRS description, did not correlate with the decision to favor aggressive care, which was consistent with a prior study.[9] The only independent factor that predicted the response in favor of aggressive care was a

Table 4. Comparison of respondents' characteristics			
	Aggressive n ± SD n (%)	**Conservative n ± SD n (%)**	***P***
No. of patients	65	50	
Age, years	19 ± 1	19 ± 1	0.72
Female	28 (43)	14 (28)	0.10
Race/Ethnicity*			0.34
White	14 (21)	9 (18)	
Asian	27 (42)	14 (29)	
Native Hawaiian and Other Pacific Islanders	20 (31)	23 (47)	
Other	4 (6)	3 (6)	
Education level			0.19
High School	27 (41)	14 (28)	
College	38 (59)	35 (70)	
Graduate School	0 (0)	0 (0)	
Other	0 (0)	1 (2)	
Annual income			0.41
<$15,000	62 (95)	48 (96)	
$15-40,000	0 (0)	1 (2)	
$40-80,000	2 (3)	0 (0)	
>$80,000	1 (2)	1 (2)	
Full time student	59 (91)	46 (92)	0.68
Married	0 (0)	1 (2)	0.25
Have children	1 (2)	1 (2)	0.85
Have health insurance	60 (92)	46 (92)	0.72
Know someone who had TBI	22 (34)	17 (34)	0.97
Have a family member who had a TBI, stroke or other brain injury	30 (46)	22 (44)	0.76
Previously discussed the level of disability that is worth living with parents, guardian, spouse or children	12 (18)	6 (12)	0.34
Willing to live with a severe motor disability	46 (71)	30 (60)	0.23
Willing to live with expressive aphasia	47 (72)	28 (56)	0.07
Willing to live with receptive aphasia	**36 (55)**	**16 (33)**	**0.02**
Most severe mRS score willing to live with:			
0	7 (11)	5 (10)	
1	7 (11)	7 (14)	
2	6 (9)	10 (20)	0.51
3	24 (37)	17 (34)	
4	16 (25)	7 (14)	
5	5 (7)	4 (8)	

NHOPI, Native Hawaiians and other Pacific Islanders; TBI, traumatic brain injury; mRS, modified Rankin Scale. Data are n (%) or mean ± SD. Percents may not total to 100% due to rounding. *One respondent did not report race.

willingness to live with receptive aphasia. Perhaps, these results are suggestive of an aversion to poor cognitive outcomes, but a relative willingness to live with acceptable physical disability among young adults.

This study suggests that surrogate decision-makers may not be able to extrapolate a young adult's willingness to pursue aggressive treatment based on the patient's perception of physical disability. Perhaps the discussion involved in attempting to determine the intensity of care should focus on the most likely cognitive outcome after severe TBI such as the possibility of receptive aphasia or minimally conscious state. However, explicit discussion of the individual's unique values and previously stated wishes is still recommended to make the most accurate substituted decisions, since every individual will likely have a unique perspective on this topic. This study shows that only 18% of the respondents have previously discussed with their families the level of disability that they were "willing to live with," which highlights the importance of practitioner-initiated early discussions about the desired quality of life and goals of care in a hypothetical emergent medical condition even among the young adult population.

This study has several limitations. Although everyone who was approached by the study personnel agreed to participate in the survey, it was difficult to assess the true non-response rates in the public survey setting since some people may have avoided being approached by the study personnel altogether. Thus the impact of potential participation bias remains uncertain. The survey responses to a hypothetical situation may differ based on prior experience with a real disabling illness.[11] The level of understanding of these participants, and their abilities to make an informed decision remains uncertain since the survey did not give them the opportunity to ask specific medical questions. Therefore, the results of this study may not reflect the "real life" decision-making process, as it occurs within the complex context of acute-onset life-threatening illness, since the real life setting would involve extensive medical discussion with the expert physicians and support staff. Pre-specified power calculations were not made, and thus the negative results do not prove a lack of association. The small sample size limits the conclusions drawn from this study to preliminary observations. Finally, this study was conducted in a predominantly Asian and NHOPI community in the Honolulu County area with high proportion of educated, unmarried young students (age range: 18-22) with health insurance; thus the results of this study may not be generalizable to other populations with different age strata and socioeconomic backgrounds.

Conclusion

This study shows that even among young adults, preference of care was divided between aggressive and conservative approach when presented with a hypothetical case of severe TBI. The respondents' decisions to favor aggressive care were related to their willingness to live with receptive aphasia but were not associated with their level of expected physical disability. Further studies in larger populations and in healthcare settings are needed to gain a better understanding of the "real life" factors impacting young adults' decisions regarding aggressive care after severe TBI.

Disclosure

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Conflict of interest

None of the authors report a conflict of interest.

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Toxic Multinodular Goiter in a Patient with End-stage Renal Disease and Hemodialysis

Edison So MD and Richard Arakaki MD

Abstract

The management of symptomatic hyperthyroidism in patients with end stage renal disease (ESRD) is challenging because of altered clearance of medications and iodine with dialysis; moreover, many patients meeting these criteria are medically fragile. A 77-year-old man with type 2 diabetes and ESRD requiring hemodialysis, with dilated cardiomyopathy and paroxysmal atrial fibrillation, was found to have subclinical hyperthyroidism. Over a 2-year period he became clinically hyperthyroid with serum TSH level of <0.05 mIU/L and free T4 level of 4.3 ng/dL, attributed to toxic multinodular goiter. Despite antithyroid medication, he developed rapid ventricular rate from his atrial fibrillation that resulted in decompensated heart failure and multiple hospitalizations. His hyperthyroidism was successfully controlled with high dose methimazole and potassium iodide treatment, which were eventually discontinued after prolonged use. Nearly 6 months off medications, his hyperthyroidism recurred but was readily resolved when methimazole was restarted. Hyperthyroidism in the medically fragile ESRD patient may precipitate emergent conditions. Antithyroid medications are effective and should be considered as primary therapy for the treatment of hyperthyroidism in patients with hemodialysis. Moreover, clinical guidelines for the characterization and management of individuals with ESRD and subclinical hyperthyroidism should be developed.

Introduction

Thyroid hormone abnormalities in chronic renal failure (CRF) are usually characterized by low levels of serum levothyroxine (T4) and liothyronine (T3) attributed to decreased concentration of and impaired binding to thyroxine binding globulin (TBG), and decreased conversion of T4 to T3.[1] Hypothyroidism and goiter with nodularity appears prevalent in CRF.[2,3] The prevalence of subclinical hypothyroidism ranged from 7% in individuals with Chronic Kidney Disease (CKD) Stage 2 (≥90 ml/min) to 17.9% for CKD Stage 3 or worse (<60 ml/min), and 2-fold excess of nodular goiter was observed in uremic patients (54.8%) than non-renal failure patients (21.5%).[4,5] However, thyrotropin or thyroid stimulating hormone (TSH) and FreeT4 levels are usually normal in these patients despite symptoms consistent with hypothyroidism such as fatigue, swelling, lethargy, constipation, dry skin, and hair loss.[1]

The prevalence of hyperthyroidism in end-stage renal disease (ESRD) is similar to the non-CRF population.[1-3] However, symptomatic hyperthyroidism in CRF patients is uncommon with a few studies reporting the evaluation and treatment of thyrotoxicosis.[6-10] The management of hyperthyroidism in patients with ESRD is difficult and challenging because of hemodialysis (HD) or peritoneal dialysis, altered renal clearance of medications and iodine, and the medical fragility of these patients that may impact evaluation and treatment. This is a report of a case of symptomatic hyperthyroidism attributed to toxic multinodular goiter in a patient with diabetes mellitus and ESRD requiring hemodialysis and a discussion of the clinical course and treatment.

Case Presentation

A 77-year-old Japanese man with ESRD secondary to diabetes mellitus type 2, developed paroxysmal atrial fibrillation and was found to have subclinical hyperthyroidism with serum TSH level of <0.05 mIU/L (NL range 0.27 - 4.2 mIU/L) and free T4 level of 1.17 ng/dL (NL range 0.9 - 2.1 ng/dL) for the previous 2 years. His past medical history was significant for dilated cardiomyopathy with paroxysmal atrial fibrillation along with his diabetes mellitus that appeared well controlled on oral anti-hyperglycemic medications. He also had a history of idiopathic hypogonadotropic hypogonadism.

During an initial visit at an outpatient clinic, he was found to be overtly hyperthyroid with tremors, palpitations, and weight loss, and his free T4 level had increased to 4.3 ng/dL. His serum anti-thyroid peroxidase and anti-thyroglobulin antibody titers were < 10 IU/ml (Normal < 35) and < 20 IU/ml (Normal < 20), respectively. Physical exam revealed blood pressure of 110/50 mmHg and irregular heart rate of 80/minute. He was obese with a weight of 187 lbs and BMI of 34.2, which have been fairly stable since he was subclinically hyperthyroid. Pertinent findings included irregularly irregular rhythm without murmurs, a non-palpable thyroid, absence of proptosis, and dry skin. Despite treatment with beta-blocker and methimazole, the patient was hospitalized for decompensated heart failure and atrial fibrillation with a rapid ventricular response. His methimazole dose was increased gradually from 10mg daily to 60 mg daily prior to discharge after the 3-day hospitalization, however his symptoms persisted, as a result of which a second admission for congestive heart failure (CHF) was required.

During the second hospitalization, saturated solution of potassium iodide (SSKI) 1 gm/ml, 2 drops (approx. 600 mg) three times a day was added to his methimazole 60 mg daily treatment. His atrial fibrillation-induced rapid ventricular rate resolved and CHF markedly improved at discharge. On outpatient follow up 2 weeks after discharge, his free T4 level decreased to 2.5 ng/dL and he showed suppressed TSH level of <0.07 mIU/L. With continued methimazole and SSKI treatment, his TSH and free T4 levels normalized to 0.88 mIU/L and 0.8 ng/dL, respectively. An ultrasound of thyroid gland showed multiple nodules in both lobes consistent with multinodular goiter (multiple nodules of the thyroid gland; left lobe nodules measuring 3.3 x 2 x 2.2 cm and 2.1 x 2.6 x 2.7 cm; and right lobe with 8 nodules with largest measuring 1.7 x 1.2 x 1.2 cm; Figure 1).

His SSKI was discontinued (side effect of constipation was noted) as he remained euthyroid (TSH and Free T4 levels of 2.18 mIU/L and 0.8 ng/dL, respectively). His methimazole was later tapered and also discontinued after nearly 9 months of prolonged treatment. About 6 months off medication, subclinical

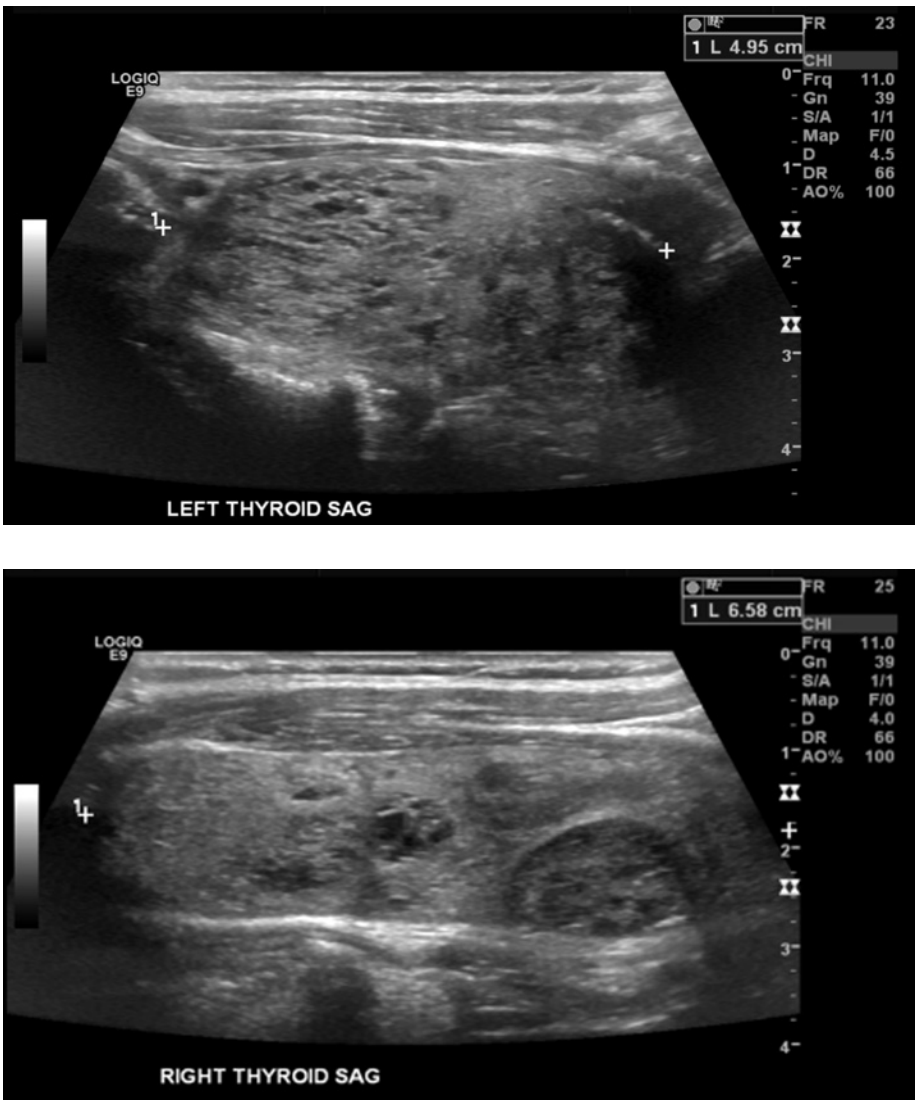

Figure 1. Ultrasound of thyroid gland. Neck was placed in hyperextended position and images obtained using a Philips HD 15 ultrasound machine. The right and left lobes of the thyroid gland were imaged in longitudinal and transverse planes. The location, size, number, and character of thyroid nodules were measured in three dimensions (Left lobe sagittal view-top; Right lobe sagittal view-bottom).

hyperthyroidism recurred as his TSH level was <0.01 mIU/L but his freeT4 level was 1.0 ng/dL. His radioactive iodine (RAI) uptake was 12% (10-30% normal uptake) at 6 hours with a heterogeneous distribution on thyroid scan (Figure2). He was restarted on methimazole 10 mg daily, which normalized his thyroid functions.

Discussion

Symptomatic and clinically significant hyperthyroidism in chronic renal failure patients is uncommon and challenging; treatment options include RAI, anti-thyroid medications or subtotal thyroidectomy. In this case of thyrotoxicosis in ESRD with cardiac manifestations resolution of hyperthyroidism was critical in restoring HD and improving the patient's overall condition.[11] Antithyroid medications are propylthiouracil (PTU), methimazole, and carbimazole (not available in the United States).[12] Methimazole is dialyzable and used after dialysis, whereas PTU is protein bound and used independent of dialysis.[13,14] Propylthiouracil is administered at standard doses in patients with thyrotoxicosis and renal failure; a case of hyperthyroidism due to Graves' disease in a patient on regular hemodialysis was successfully treated with propylthiouracil.[7,9]

RAI treatment provides permanent resolution of hyperthyroidism and appears safe with minimal exposure to staff and patients. A patient with Grave's disease on regular hemodialysis was successfully treated with I-131 after initial treatment with antithyroid drugs,[7] and a case of toxic multinodular goiter in a hemodialysis patient was also successfully treated with I-131

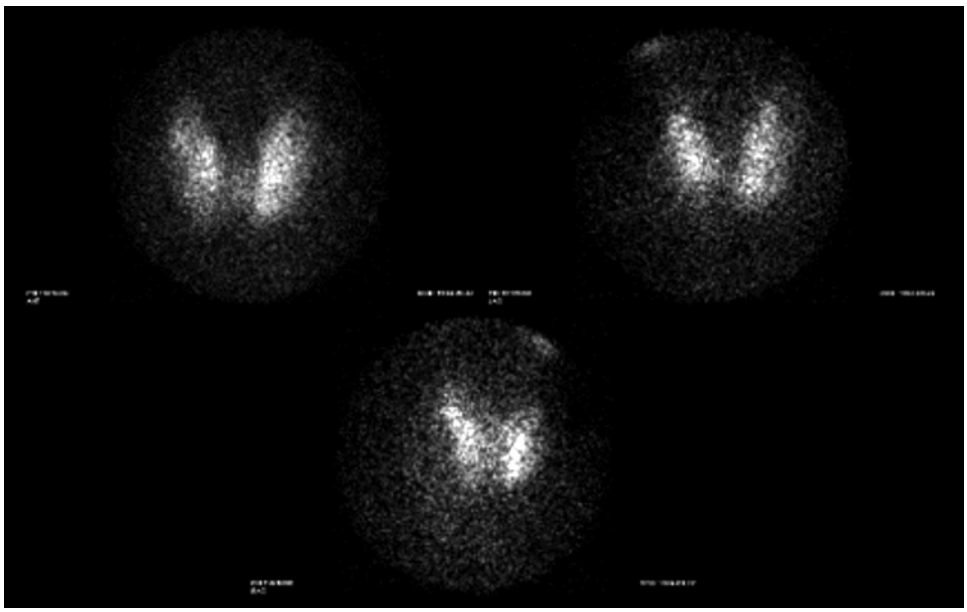

Figure 2. Thyroid scan. Five mCi of technetium(Tc)-99m pertechnetate was injected by vein after I-131 sodium iodide capsule was given orally. Fifteen minutes after intravenous injection of Tc-99m pertechnetate, pinhole views of thyroid gland were obtained in multiple projections.

ablation.[8] The care needed to collect and dispose excess RAI during hemodialysis is challenging, requiring cautious effort, but RAI treatment has been performed safely and effectively in ESRD.[1] Unfortunately, this patient had low to normal uptake (12%) of RAI even after 6 hours, which raised questions of the effectiveness of RAI treatment in our patient. Thyrogen (recombinant human Thyrotropin, rhTSH) could be used to increase radioactive iodide uptake in a low uptake condition such as this patient, but handling RAI excess remained a concern.[15,16] Moreover, the validity of RAI uptake in the setting of previous SSKI treatment in ESRD was uncertain. What is the expected uptake in patients with ESRD without thyroid disease; and what is the clearance of accumulated iodine with dialysis? Surgical intervention following normalization of thyroid functions with anti-thyroid medications was not an option in our patient with multiple medical problems. Other less common treatments such as cholestyramine were not considered but may have been an option for the treatment of this patient.[17]

This patient presented additional clinical dilemmas in the management and evaluation of hyperthyroidism in patients with ESRD. In retrospect, his subclinical hyperthyroidism should have been treated, especially with his pre-existing atrial arrhythmia. For nearly 2 years, the patient was observed as he was deemed clinically stable until he became overtly hyperthyroid which contributed to decompensated CHF and multiple hospitalizations. His recurrent subclinical hyperthyroidism was now addressed with low dose methimazole to normalize his thyroid status because of his past history.

Iodine excretion in ESRD is usually low and there is greater thyroid accumulation.[2,3] The use of SSKI during the patient's second hospitalization for the treatment of hyperthyroidism has not been previously reported. Indication and dosing of iodine in ESRD and hemodialysis is not clearly defined. The rapid reduction in thyroid levels with SSKI is noted in patients treated for thyroid crisis, but the effect in renal failure is unknown.[12] The patient responded to standard doses of SSKI added to high dose methimazole treatment.

The patient's hyperthyroidism recurred within 6 months after stopping prolonged methimazole treatment but was easily controlled with low dose therapy. The uncommon presentation of hyperthyroidism in ESRD and hemodialysis responded to antithyroid medications, which should be considered as primary and long-term therapy for these patients. Clinical guidelines for the characterization and management of individuals with ESRD and subclinical hyperthyroidism should be developed.

Conclusion

Hyperthyroidism in the medically fragile ESRD patient may precipitate emergent conditions. Antithyroid medications are effective and should be considered as primary therapy for the treatment of hyperthyroidism in patients with hemodialysis. Moreover, clinical guidelines for the characterization and management of individuals with ESRD and subclinical hyperthyroidism should be developed.

Conflict of Interest

None of the authors identify a conflict of interest.

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MEDICAL SCHOOL HOTLINE

Hold Fast to Your Dream — University of Hawai'i, John A. Burns School of Medicine, Convocation Address, May 18, 2014

Sidney A. McNairy Jr. PhD, DSc

The Medical School Hotline is a monthly column from the John A. Burns School of Medicine and is edited by Satoru Izutsu PhD; HJMPH Contributing Editor. Dr. Izutsu is the vice-dean of the University of Hawai'i John A. Burns School of Medicine and has been the Medical School Hotline editor since 1993.

Dean Hedges, Judge Burns, Mrs. Wong, as well as other distinguished guests, faculty, graduating medical students, family, and friends of the graduates, my wife of 48 years who is here today and I are deeply honored that I was selected to be the Robert T. Wong Endowed Lecturer and Keynote Speaker for the May 2014 John A. Burns School of Medicine (JABSOM) Convocation. Thank you very much. We will forever cherish this as one of the most significant honors of my professional career.

Little did I know when I started my interaction with the University of Hawai'i back in 1975—managing research programs funded through the National Institutes of Health in Bethesda, Maryland—did I envision that I would be standing before you on this auspicious occasion. Like Dr. Wong, I saw great value in this medical school in the middle of the pacific to assist the National Institutes of Health (NIH) in accomplishing its mission—to uncover new knowledge that will lead to better health for everyone. NIH conducts research in its own laboratories; supports the research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helps in the training of research investigators; and fosters communication of medical information.

Thanks to my dear friends and colleagues the late Dr. Fred Greenwood and his wife Dr. Bryant Gillian Greenwood, whom I met in 1975, we set about a course to facilitate the participation of the University of Hawai'i more fully in the NIH mission. They both were internationally renowned reproductive endocrinologist. Fred spent considerable time working with Senator Inouye and his able assistant Dr. Pat DeLeon as he developed the Pacific Biomedical Research Institute into an internationally recognized institution. He played a key role in developing the foundation for launching both the University of Hawai'i Medical School and Cancer Center. His efforts were key to making this such a special day for all of us.

Fred helped make me aware of the many needs of this community, especially evolving good health through biomedical research. Hawai'i's favorite son—President Obama has stated many times, a healthy nation is a strong and prosperous nation. Through the many hours that Fred and I talked about the University of Hawai'i, he convinced me that a special day like your commencement was a part of his vision and dream for you and the people of this great state. I was drawn to this university community because I sensed that there were many young minds, both faculty and students, that needed better infrastructure and other resources in order to develop their capabilities and launch careers in the biomedical sciences as you graduates are about to do.

Throughout my career at the National Institutes of Health I provided resources to the university through programs such as the Minority Biomedical Research Support (MBRS) Program, Research Centers in Minority Institutions (RCMI), Specialized Neuroscience Research Program (SNRP), Institutional Networks of Biomedical Research Excellence (INBRE), Centers of Biomedical Research Excellence (COBRE), Science Education Partnership Awards (SEPA), Clinical Research Education and Career Development (CRECD), RCMI Translational Research Network (RTRN), and the RCMI Infrastructure for Clinical and Translational Research (RCTR). These programs have played a crucial role in achieving the dream that Fred Greenwood and I dared to dream for the University of Hawai'i Medical School.

As I thought about my message to the graduates, and I will admit sometimes I dreamed about the words that I wanted to leave with you, I woke up one night and it came to me that I was compelled to tell you… "continue to hold fast to your dreams, as so many before you especially your parents, teachers, and fellow students have done for so long." Your becoming a physician is not simply a chance event but is holding fast to the dreams that your ancestors had for you. Without question your dedication, intellect, and persistence played a major role. However, I must tell you that your achievement after many days and nights of hard work, sometimes without time for sleep and perhaps proper nutrition, is directly related to the dreams that your parents and other ancestors have had for you for such a long time. I know this to be true since, like each of you, my career continues to honor my commitment with destiny. Like many of you, I did not start my life's journey with many creature comforts. I grew up in the government project with few if any books in the home and was the first in my family to attend college. However if there is one lesson that was instilled into my mind and my heart, it was that the greatest of all deeds is to be a servant of mankind. I came to this realization during my participation in

the 1963 Martin Luther King March on Washington. In a sense this was crystalized in the words that I uttered during the first day that I taught freshman chemistry. I stated these words, "in my quest for immortality I must transmit my knowledge and lessons learned to my young. Through service to mankind, my spirit will live on forever—I will be immortalized." The most significant words were "Service to Mankind." As 2014 medical school graduates you have a tremendous opportunity to make this statement ring true for you and your ancestors.

As you leave these hallowed halls, I urge you to remember three things as you move quicker than you can imagine to pursue your life's dream of becoming a medical practitioner. These are: use your mind, now loaded with more information than you know what to with, right now, use your hands, and listen to your heart as well as your patients' hearts in making all decisions regardless of where your career path will lead you. The didactic experiences here at JABSOM have prepared you well intellectually for whatever career path you choose; further study, community medicine, the practice of a medical specialty, a clinical investigator, administration, chancellor of a medical school, surgeon general, or whatever. With advances in molecular medicine—genomics, proteomics, glycomics, and all other "omics" you have some important new tools for the prevention, diagnosis, and treatment of human disease. New medical IT devices, such as robotic surgery or software that helps a physician specialist detect a patient's tumor, and medical devices that can relay information to a physician's smart phone, and more IT is emerging. That will enable you to provide much needed care for patients here in Hawai'i as well as many other parts of the world. With the very learned faculty and staff here at the JABSOM, I am confident that you are now expert in the molecular basis of human disease and you are fully aware of the fact that medicine of today is more and more becoming predictive, personalized, and preventive, the latter being especially true with the Affordable Care Act signed into law by President Obama. Your time now in medicine comes when scientific advances and technology play such an important role in medical practice of today. Not only has technology enabled the physician to keep electronic records of each patient, it has also provided medical devices such a robotic surgery, software that assists specialist to detect tumors, quantitative imaging used for diagnosing cancer, cardiovascular, and pulmonary diseases, as well as many other non-invasive diagnostic procedures. More and more technology is playing an increasingly important role.

With respect to listening to your heart as you deal with patients, you should listen to the heart felt expressions of your patients; you must become more familiar with some of the cultural traditions of many patients and be able to frame approaches for dealing with the health of diverse populations as you gain their confidence and develop a treatment paradigm. The AAMC has indicated that this lack of cultural competency contributes to health disparities or inequities in the United States. By listening to your heart and that of your patient it will open the doors to holistic treatment of each patient and will benefit the patient.

Let me end my message to you with a paraphrase of a quote from Dr. Elias Zerhouni, the 15th Director NIH 2002-2006: "Continue to hold fast to your dreams; they should be big dreams, full dreams, not half dreams. You know, it's very simple. You can't put a large dream in a small box. Well, you cannot put a full life in a small dream box. It was big dreaming inside and outside the box that led to the use of the body's own defenses to treat cancer, ie, cancer immunotherapy, taking advantage of the fact that cancer cells often have subtly different molecules on their surface that can be detected by the immune system. It took thinking big dreams outside of the big box to come up with this "cancer immunotherapy." I challenge each of you as you go forth in pursuit of your life's dream to wonder how might the discovery of the Higgs boson or Higgs particle on July 2012 impact the future practice of medicine.

I urge you to hold fast to your dreams using your minds, your trained hands, and compassionate hearts.

Congratulations and God speed.

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Public Health Perspectives on Colorectal Cancer Screening

Ranjani R. Starr MPH; Florlinda V. Taflinger MS, RD; and Christina M. Teel MBA

Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJMPH Associate Editors Jay Maddock PhD from the Office of Public Health Studies at John A Burns School of Medicine and Donald Hayes MD, MPH from the Hawai'i Department of Health in collaboration with HJMPH Manuscript Editors Tonya Lowery St. John MPH and Ranjani Starr MPH from the Hawai'i Department of Health.

Introduction

Colorectal cancer (CRC) is currently the third leading cause of cancer death in both men and women in the United States.[1] Reports estimate that 136,830 people will be diagnosed with, and 50,310 people will die from, CRC in 2014. Approximately 1 in 20 Americans will be diagnosed with CRC in their lifetimes.[2] Much of the improvement in CRC mortality rates has been attributed to improvements in treatment (12%), decreases in risk factors for CRC (35%) and improvements in screening rates (53%).[1] Early detection is key with studies showing approximately 90% 5-year survival rate among individuals whose CRC was found early and treated appropriately.[3]

This article will describe the national and state CRC burden; provide a brief overview of nationally-recommended screening options; inform the reader about national and local screening rates for CRC, emphasizing disparities in screening; and discuss the current national and local public health initiatives to reduce the burden of CRC.

CRC Incidence and Mortality Rates

CRC incidence in the United States increased from 1975 to the mid-1980s, but has declined since, with rates decreasing by 3.4% each year since 2001.[1] In 2011, the American Cancer Society (ACS) estimated approximately 141,210 new cases and 49,380 deaths due to CRC in the United States.[3] This translated to a national age-adjusted annual incidence rate of 43.7 cases per 100,000 and age-adjusted mortality rate of 16.4 per 100,000 population.[4] Nationally, incidence rates are 20% higher and mortality rates 45% higher among Blacks.[3] Also, incidence rates are approximately 30%-40% higher in men. National studies report the lowest incidence rates of CRC in Asian and Pacific Islander populations, potentially masking substantial disparities within this heterogeneous grouping.[1]

In Hawai'i, 669 deaths due to CRC occurred between 2010 and 2012, yielding an age-adjusted mortality rate of 13.4 deaths per 100,000, which was below the Healthy People 2020 (HP2020) target of 14.5 deaths per 100,000 persons.[5,6] This rate represented a decrease from 17.0 deaths per 100,000 in Hawai'i between 2001 and 2003. However, disparities in mortality rates exist within Hawai'i by geography, sex, and race-ethnicity. By county, the highest rate of CRC deaths occurred in Kaua'i whereas Honolulu had the lowest rate. Men in Hawai'i had higher death rates from CRC than women.[5] The most serious disparities in mortality due to CRC in Hawai'i are attributable to race-ethnicity; between 2010 and 2012, the CRC death rate in Native Hawaiian and Other Pacific Islanders was nearly four times the rate among Whites. In comparison, deaths among Asian and Blacks in Hawai'i were only slightly higher than in Whites (Table 1).[5]

Efficacy of Screening for CRC

Although it is among the most frequently detected and fatal cancers in the United States, colorectal cancers are also very preventable and treatable.[7] As a disease with a protracted course, early detection of pre-cancerous polyps or lesions is key to reducing rates of mortality. Screening is highly recommended, and full implementation of screening would save an estimated 18,800 lives in the United States per year.[8]

Table 1. Age-Adjusted[a] Colorectal Cancer Mortality Rates per 100,000 Residents in Hawai'i, 2010-2012

Category	Mortality Rate (deaths per 100,000)
Overall	13.4
County	
Honolulu	12.9
Maui	15.4
Kaua'i	17.5
Hawai'i	13.7
Sex	
Male	16.4
Female	11.1
Race-Ethnicity	
White	11.6
Native-Hawaiian and Other Pacific Islander	40.5
Asian	13.2
Black or African-American	17.1

Source: Hawai'i Health Data Warehouse: Hawai'i State Department of Health, Office of Health Status Monitoring Hawai'i Vital Statistics, 2010-2012.
[a]Rates are age-adjusted to the 2000 US standard population.

Recent data has shown that screening is the most important contributor to the decline in CRC incidence and mortality at the national level.[9] Randomized controlled trials have demonstrated that eliminating healthcare disparities in CRC screening and treatment can eliminate disparities in outcomes between race groups.[9] A recent study suggested that as much as 42% of the racial disparity in colorectal cancer incidence, and 19% of the disparity in colorectal cancer mortality between Whites and Blacks in the United States could be attributed to differences in screening between the two groups. Additional disparities in mortality were attributable to differences in treatment between race groups. Together, disparities in screening and treatment explained over 50% of the differences in CRC mortality between Whites and Blacks.[9]

Notably, the State of Delaware eliminated racial disparities in CRC mortality by offering universal screening and treatment for CRC.[1] Given the effectiveness of screening, increasing the proportion of adults receiving CRC screening based on the most recent US Preventive Services Task Force (USPSTF) guidelines is recognized as a Leading Health Indicator by the US Department of Health and Human Services.[10]

From a public health perspective, improving screening levels in the population is critically needed in order to eliminate disparities in CRC mortality, and reduce the overall disease burden on society.

Screening Recommendations for CRC

The national screening recommendations for CRC have undergone several revisions; in 2008, two slightly different guidelines strongly urging screening were issued by the USPSTF and by a joint task force comprised of the ACS, US Multi Society Task Force (MSTF) on CRC, and the American College of Radiology (ACR) (ACS-MSTF-ACR) (Table 2).[8,11] Of these, the USPSTF guidelines for CRC were adopted by the Centers for Disease Control and Prevention (CDC) and were included in the Affordable Care Act (ACA). The reader is referred to the ACS-MSTF-ACR guidelines for further information on screenings that are either not recommended or not addressed by USPSTF.[11]

The USPSTF guidelines recommend routine screening for average-risk adults aged 50-75, screening as needed for adults aged 76 to 85 years, and no screening in adults older than 85 years.[8] Recommended screening tests include stool based tests (high-sensitivity fecal occult blood tests [FOBT] and fecal immunochemical test [FIT]), and visual inspection of the colon using flexible sigmoidoscopy (FSIG) and colonoscopy. For screening recommendations for adults of all ages at increased risk for CRC based on family or personal history, the reader is directed to three excellent reviews.[12-14]

Stool-based tests have low up-front cost, do not require bowel preparation, and do not have safety concerns.[15] Both guaiac

Table 2. Colorectal Cancer (CRC) Screening Recommendations and Covered Preventive Services for Asymptomatic Adults Aged 50 to 75 in Hawai'i

	CRC Screening Recommendations		Covered Preventive Services in Hawai'i		
CRC Screening Option	US Preventive Services Task Force (USPSTF)	ACS-MSTF-ACR[a,b]	Medicare[c]	Hawaii Revised Statute (§ 431:10A-122)	Affordable Care Act
Colonoscopy	Every 10 years	Every 10 years	Covered every 10 years or 4 years after a sigmoidoscopy. No age restrictions.	Covered according to USPSTF recommendations	Covered according to USPSTF recommendations
Flexible Sigmoidoscopy	Every 5 years, combined with high sensitivity FOBT every 3 years	Every 5 years	Covered every 4 years or 10 years after a colonoscopy for routine screening with. Restricted to individuals 50 years or older.		
High Sensitivity Fecal Occult Blood Test	Every year	Every year	Covered every year. Restricted to individuals 50 years or older.		
Fecal Immunochemical Test	Every year	Every year	Covered every year. Restricted to individuals 50 years or older.		
Double Contrast Barium Enema	Not addressed	Every 5 years	Covered ever 4 years with co-pay. Restricted to once every 4 years for individuals 50 years or older.	Not covered	Not covered
Computed Tomographic Colonography	Not recommended	Every 5 years	Not covered	Not covered	Not covered
Stool DNA Test	Not recommended	Recommended, frequency not determined	Not covered	Not covered	Not covered

[a]Guidelines developed by the American Cancer Society, Multi-Society Task Force on CRC, and the American College of Radiology
[b]Applies to all adults 50 years and older
[c]Source: Colorectal cancer screenings. Medicare.gov

FOBT (gFOBT) and FIT can detect small quantities of blood in stool, but are limited in sensitivity for CRC detection because bleeding is often intermittent, and is a symptom only of larger polyps and cancerous tumors.[11] gFOBT tests require dietary restrictions prior to testing (such as avoidance of foods rich in vitamin C to minimize false-negatives), and the collection of multiple consecutive stool specimens. Reported sensitivities of gFOBT tests range from 37% to 79%; recently developed tests such as the Hemoccult SENSA have higher sensitivities, but at the cost of specificity.[11] Both USPSTF and ACS-MSTF-ACR guidelines note that stool testing is efficacious only if performed annually: fewer than 1 in 2 cases of cancer are successfully detected with one-time testing.[8,11] The ACS-MSTF-ACR further cautions the need to adhere to the recommended test protocol, given the loss in sensitivity that results from improper testing in patients undergoing fecal screening tests.[11] Both guidelines emphasize that positive tests must be followed up with colonoscopies.[8, 11] Stool DNA (sDNA) tests are recommended by ACS-MSTF-ACR guidelines, but not by USPSTF at this time due to insufficient evidence.[8,11]

Screening tests that are able to detect adenomatous polyps and CRC involve structural examination of the colon through direct visual inspection using sigmoidoscopy or colonoscopy, and indirect imaging using Double-Contrast Barium Enema (DCBE) and Computed Tomographic Colonography (CTC). These tests are generally more expensive and require bowel preparation; they have variable sensitivities largely attributed to differences in the quality of the examination performed.[3,11,15] DCBE and CTC are recommended by ACS-MSTF-ACR guidelines, but either not addressed (DCBE) or not recommended (CTC) by USPSTF at this time due to insufficient evidence.[8,11]

Flexible sigmoidoscopy (FSIG) visually examines the lower half of the colon; sedation is not required, allowing the procedure to be performed on an outpatient basis. However, the lack of sedation is associated with more discomfort and reluctance to re-test among patients. FSIGs have been associated with a 60-80% reduction in CRC mortality for the portions of the colon that are screened.[3,11] Nevertheless, up to 30% of cases with advanced neoplasia are not detected, since sigmoidoscopies do not inspect the proximal colon where up to 42% of all CRC tumors are located.[1,15] Disparities in detection may be more pronounced among women, certain race-ethnicity groups and persons of advanced age, in whom proximal colon neoplasia is more common.[11,15] Serious complications occur in 3.4 per 10,000 procedures. Positive tests require follow-up with colonoscopy.[8] A 5-year interval for FSIG is recommended by both the USPSTF and ACS-MSTF-ACR.[8, 11]

Colonoscopy enables full, direct, visual inspection of the entire colon, and is among the most commonly performed medical procedures in the United States.[3,11] Because sedation is offered, patients who undergo sedated colonoscopies are twice as willing as those who undergo unsedated FSIGs to return for follow-up screening. An important benefit is the potential for simultaneous polypectomies, eliminating the need for additional procedures.[11] Although considered the gold standard for CRC screening, colonoscopies miss between 6-12% of large adenomas, and 5% of cancer. A cohort study revealed a 72% decrease in 10-year incidence of CRC among patients receiving colonoscopies, with detection failures accounting for the majority of incident cases.[11, 15] The procedure is associated with a higher rate of serious complications such as perforations and hemorrhage, at approximately 25 per 10,000 procedures.[8] A 10-year screening interval is recommended by both the USPSTF and ACS-MSTF-ACR.[8, 11] The ACS-MSTF-ACR additionally recommends DCBE and CTC, but at this time, these tests are not recommended by the USPSTF; nevertheless, DCBE is covered by Medicare.[8,11,16]

Because of the availability of several comparably efficacious screening techniques, each with its own risks and benefits, the USPSTF recommends patient engagement in the selection of an acceptable form of screening for CRC.[8] This is an important consideration given that fear and concerns about the bowel preparation are the most cited reasons among patients for not getting screened for CRC.[17] Accordingly, the HP2020 indicator for CRC screening is defined as the number of persons aged 50 to 75 years who have had a blood stool test in the past year, a sigmoidoscopy in the past 5 years and blood stool test in the past 3 years, or a colonoscopy in the past 10 years.[18]

CRC Screening Rates

Nationally, 59.2% (National Health Interview Survey, 2010) of adults aged 50-75 years old received CRC screening based on the most recent USPSTF guidelines, a rate lower than the HP2020 target for this indicator, 70.5%.[19] Moreover, disparities in cancer screening by age, sex, race-ethnicity, educational level, household income, and health insurance status have been documented at the national level.[20]

In 2012, Hawai‘i's self-reported screening prevalence was 61.1% (Behavior Risk Factor Surveillance System, 2012) among those 50-75 years of age receiving CRC screening based on the most recent USPSTF guidelines, a rate comparable to the national average, but still substantially behind the HP2020 national target.[21] Disparities in screening exist in Hawai‘i, with lower rates among Native Hawaiians and Filipino populations, and among those with lower educational or higher poverty statuses (Table 3).[21]

National Public Health Efforts in CRC Prevention

Over the past two decades, the CDC has collaborated with state, tribal, and territorial health departments and various organizations to reduce morbidity, mortality, and health disparities associated with CRC. CDC's efforts to address the national cancer burden focus on conducting cancer surveillance, increasing access to screening, improving health outcomes for people living with cancer, and providing the evidence for and evaluation of policy and environmental approaches to reducing cancer.[22]

The CDC's early public health efforts in cancer prevention and control focused on tobacco, surveillance, and the prevention and early detection of breast and cervical cancers.[23] In

Table 3. Colorectal Cancer Screening Rates in Hawai'i Among Adults Aged 50-75 years, 2012

Category	Screening Rates[a] % (95% C.I.)
Overall	61.1 (58.6-63.7)
County	
Honolulu	63.3 (59.9-66.8)
Maui	56.5 (50.1-62.9)
Kaua'i	57.9 (51.2-64.7)
Hawai'i	57.6 (52.4-62.9)
Sex	
Male	60.8 (57.2-64.4)
Female	61.5 (57.8-65.1)
Race-Ethnicity	
Caucasian	64.2 (61.0-67.5)
Native Hawaiian	55.8 (48.7-62.9)
Filipino	53.6 (44.3-62.9)
Japanese	68.9 (64.1-73.6)
Highest Educational Level	
High school	55.4 (50.2-60.6)
Some college	64.2 (59.8-68.7)
College degree or more	68.7 (65.4-72.0)
Federal Poverty Level (FPL)	
0-130% FPL	50.4 (41.4-59.3)
131-185% FPL	59.4 (50.2-68.7)
186+% FPL	68.9 (65.6-72.3)

[a]Proportion of adults between 50-75 years old who reported receiving CRC screenings that met the USPSTF guidelines in 2012. (Source: Hawai'i Health Data Warehouse: Hawai'i Behavioral Risk Factor Survey, 2012)
Note: Risk status of adults is not assessed as part of the survey.

2009, the CDC initiated the Colorectal Cancer Control Program (CRCCP). Hawai'i was not among the 29 grantees (states and tribal organizations) who received CRCCP funding to screen uninsured and underinsured adults and promote CRC screening at the population level. The goal of the CRCCP is to increase population-level screening rates to 80%.[24]

In addition to the CDC-funded programs such as the CRCCP, other campaigns and efforts spearheaded by national public health and cancer agencies also strive to reduce CRC incidence and mortality.[25] Organizations such as the ACS support the National Colorectal Cancer Roundtable (Roundtable), a national coalition of public, private, and voluntary organizations whose mission is to advance CRC control efforts by improving communication, coordination, and collaboration among health agencies, medical professional organizations, and the public.[26] The ultimate goal of the Roundtable is to increase the use of proven CRC screening tests among the entire population for whom screening is appropriate and spearhead a national effort to ensure screening of 80% of at-risk individuals for CRC by 2018.[27]

State Public Health Efforts in Colorectal Cancer Prevention

In Hawai'i, many organizations have collaborated to improve colorectal cancer screening efforts. With support from the Department of Health's Hawai'i Comprehensive Cancer Control Program (HCCCP), a statewide group of over 200 dedicated health organizations, key stakeholders and individuals have worked as part of the Hawai'i Comprehensive Cancer Control Coalition (coalition) to develop a coordinated and comprehensive approach to cancer control in Hawai'i.[28]

As a result of the coalition's efforts, the Hawai'i Cancer Plan (2010-2015) recognizes the early detection of colorectal cancer as a priority.[29] In addition, coalition member organizations have implemented multiple awareness and education initiatives; used multi-media campaigns and educational materials to promote colorectal cancer screening to the public, community health centers, policy makers, and physicians; developed and implemented the Hawai'i Colorectal Cancer Screening Education and Outreach Resource Guide; and supported and advocated for CRC legislation.[30-32] A goal of the coalition has been to advocate for legislative efforts that support the development and implementation of a Colorectal Cancer Screening Awareness Pilot Program.

A 2012 survey conducted by the National Colorectal Cancer Research Alliance found that 31 states and the District of Columbia have laws requiring health insurance coverage for CRC screening.[33] Through the efforts of the coalition, Hawai'i joined these states in 2010 by passing legislation requiring health insurers to provide screening coverage for colorectal cancer.[34] Subsequently, Hawai'i received an "A" in the CRC Report Card for its exceptional CRC legislation requiring insurance providers to cover preventive CRC screenings for all policyholders over the age of 50, as well as those under 50 at high risk for CRC.[33] Universal insurance coverage in Hawai'i for CRC screening now includes colonoscopy every 10 years; FSIG every 5 years; and annual FOBT. The legislation references the USPSTF recommendations, enabling revisions as needed to include coverage of future evidence-based advances in screening methods.[34]

ACA implementation further impacts screening for a variety of chronic conditions, including CRC. The law requires new private health plans to eliminate cost-sharing (co-payment, co-insurance, or deductibles) for evidence-based preventive measures.[35] The ACA is expected to be instrumental in ensuring access to evidence-based cancer screenings among disparate populations, although its impact remains unclear at this time.

Conclusion

Despite dramatic decreases in CRC incidence and mortality nationally and in Hawai'i over the past decade, disparities by geography, sex, race-ethnicity, educational, and socioeconomic status remain. Multiple CRC screening options are available each with their own benefits and limitations, enabling patient engagement in choosing an acceptable screening option and

schedule. Substantial changes in legislation, both at the state- and national-levels, have increased coverage for recommended screening options. Nevertheless, much work remains to reduce the burden of CRC in Hawai'i.

State public health efforts are focused on advocating for funding for CRC screening programs; increasing awareness of screening guidelines among health care providers; educating the public on the risks of CRC and benefits of screening; and implementing policy, systems and environmental approaches to achieving sustainable changes in CRC screening. Statewide efforts are also underway to implement health system changes that ensure timely and appropriate referrals for CRC screening, so that the public can access and optimally receive screenings for which they have insurance coverage. These activities will only be successful through the collaborative and coordinated effort of multiple partners including public health officials, physicians, health professionals, health plans, community health centers, non-profit agencies, and policy makers.

Ultimately, reductions in the burden of CRC in Hawai'i will require comprehensive implementation of evidence-based cancer control interventions, both in screening and treatment, with an emphasis on reaching out to underserved populations that historically have the lowest screening and highest CRC mortality rates.

For more information about the Hawai'i Comprehensive Cancer Control Coalition or to become a member, call (808) 692-7480.

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THE WEATHERVANE

RUSSELL T. STODD MD; CONTRIBUTING EDITOR

SHOULD PATENT LAW OVER RULE SURGICAL SAFETY?

A federal court barred Medtronic Inc from selling its new artificial heart valve to all but a few patients in the United States. The court admitted that the device is safer and has a lower risk of death than a competing device. The ruling gives Edwards Lifesciences Corp. a near monopoly on the sale of a new type of aortic heart valve that is implanted by a minimally invasive procedure. The injunction was made at the request of Lifesciences Corp. A jury found in 2010 that Medtronic CoreValue infringed a patent held by Edwards. The Medtronic devices have better outcomes and lower risk of death, but "At the same time the Court cannot downplay the strong public interest favoring enforcement of patent rights." Later, Medtronic and Lifesciences settled the patent dispute to allow Medtronic to sell Corevalve all around the world. Medtronic will pay Lifesciences $750 million up front and $40 to $60 million annually through 2022. Guess who ultimately pays the cardiac surgery bill?

HAVING BELLY PAINS? COME SIT DOWN IN A WARM TUB.

Hydrotherapy is sitting in a water tub during maternal labor to promote relaxation, improve blood flow and reduce swelling. Tubs, with or without massaging jets, are available at many birthing centers and some hospitals. The Cochrane Collaboration published a review of 11 trials encompassing 3,146 women, concluding that hydrotherapy during the first stage of labor reduced the need for epidural anesthesia. However, the safety of staying in a tub during the birthing stage has not been established. A joint opinion of the American College of Obstetrics and Gynecology and the American Academy of Pediatrics, said, "Due to reports of newborn drownings, near drownings and infection described in medical literature, the procedure should remain experimental."

YES, IT IS TOXIC AND POSSIBLY FATAL. AVOID A BOTULINUS APPETIZER.

J. Michael Pearson, CEO of Valeant Pharmaceuticals is leading an attempted hostile takeover of Allergan Inc. Pearson is not into R&D spending, but is growing the company through mergers and acquisitions. Last year Valeant purchased Bausch and Lomb for $8.7 billion, and is now targeting Allergan. The big valuation driver is Botox (botulism toxin). Allergan originally developed the poison for eye muscle imbalance and spastic eyelids. Botox quickly became popular for facial muscle relaxation for Hollywood people (Botox parties). Now 54% of sales are for chronic migraine and overactive bladder. Research is proceeding for premature ejaculation, juvenile cerebral palsy, urinary incontinence and depression. Sales grew by 17% in 2013. Valeant offered $46 billion last week and was formally refused. Pearson wants no part of research when he can exploit someone else's work. What a guy!

WHY HUFF AND PUFF? WE CAN PUSH A COIL UP YOUR NOSE.

Chronic obstructive pulmonary disease (COPD) is the number three cause of death in the United States, trailing only heart disease and cancer. The main cause of COPD is smoking, but air pollution, secondhand smoke and workplace dust and chemicals may be involved. More than 24 medical centers are testing a technique that places metal coils into the lung to compress diseased tissue. Surgery is not necessary as the coils can be inserted through the nose or mouth and manipulated into place. The coils allow the healthier parts of the lung to breathe more freely. In Europe, where the coils have been in use since 2008, studies indicate that the procedure is safe and results in significant improvement in lung function, exercise capacity and quality of life. The trials do not address cost, but the hope is that hospitalizations, readmissions, and complications will be reduced.

IF IT AIN'T BROKE, BREAK IT.

Planners and politicians can make decisions that result in the opposite of intentions. The Affordable Care Act (ACA) was passed with the assumption that patients would have greater access to a physician and thus reduce emergency room visits. Still, few family physicians are willing or able to take on additional patients. ACA provides access to care, so ERs are seeing more patients than expected. Almost half of ER doctors say they are seeing more patients since key provisions of the ACA took effect January l. The basic problem that congress must address is the worsening doctor shortage.

WHEN A MAN HAS JUST TOO MUCH MONEY.

Larry Ellison, CEO of Oracle Inc. the fifth richest man in the world (Forbes), loves basketball. He reportedly is interested in buying the Los Angeles Clippers from the disgraced and ostricized owner Donald Sterling, and it appears he can afford it. He has basketball courts setup on two of his yachts solely for his amusement. He enjoys shooting hoops and sometimes rim shots or backboard bounces ricochet balls into the water. No problem. Ellison has a ballboy in a powerboat following behind to retrieve loose balls.

AT LAST: HAWAIIAN CUISINE HITS THE BIG APPLE.

Manhattan's New York Sushi Ko is the latest sophisticated eatery to feature dishes made with Spam. Upscale foodies and hipsters are flocking in for Spam musubi (fried Spam with rice and seaweed), seared ahi and other fried Spam dishes with a touch of pineapple. Sushi Ko's chef cheerfully acknowledges that his Spam dishes are fresh just off the shelf at the nearby bodega.

ADDENDA

- Fewer people golf on Tuesday than any other day of the week.
- The cost of a parking ticket in San Francisco is $74, $9 more than anywhere else in the world.
- Citing pollution, two-thirds of China's wealthy citizens have left or plan to leave the country.
- Don't contribute to the centers for research into the heeby jeebies.
- Cats are smarter than dogs. You can't get eight cats to pull a sled through snow.
- Avoid any restaurant that has kaopectate on draft.

ALOHA AND KEEP THE FAITH rts

(Editorial comment is strictly that of the writer.)

Guidelines for Publication of HJM&PH Supplements

The following are general guidelines for publication of supplements:

1. Organizations, university divisions, and other research units considering publication of a sponsored supplement should consult with the editorial staff of HJMPH to make certain the educational objectives and value of the supplement are optimized during the planning process. It is important that the sponsoring editor is aware of all steps to its publication. Please contact Drs. Kalani Brady or Michael Meagher for further information.

2. Supplements must have educational value, be useful to HJMPH readership, and contain data not previously published to be considered for publication.

3. Supplements must have a sponsoring editor who will be involved in every step of the development, editing, and marketing of the publication since HJMPH staff will only be reviewing final proofs.

4. Supplements should treat broad topics in an impartial, unbiased manner. Please prefer specific classes of drugs, rather than products, unless there are compelling reasons or unique properties of the drug (product) that justifies its treatment.

5. The authors are solely responsible for the content of their manuscripts and the opinions expressed. They are also responsible for the replicability, precision, and integrity of the data and may be asked to sign a statement to that effect prior to publication. All authors are required to disclose any primary financial relationship with a company that has a direct fiscal or financial interest in the subject matter of products discussed in submitted manuscripts, or with a company that produces a competing product. The sponsoring editor must ensure that each article submitted incorporates a disclosure statement from the authors within the body of the text. For more information, please refer to the Disclosure Statement within "Instructions to Authors" on the journal website.

6. All supplement manuscripts should undergo editorial and peer review. It is the responsibility of the sponsoring editor to ensure the integrity of authorship and review process. In addition, sponsorship implies compliance with all federal, state and local laws, rules and regulations that may be applicable in connection with its publication.

7. Publication of a HJMPH supplement is a flat fee of $3,000 (electronic edition) plus the required State of Hawaii sales tax. The subscription manager will email an invoice to the designated editor for payment. Checks may be made out to UCERA. (There may be additional costs for hard copy prints. Please contact Drs. Brady or Meagher.)

8. The sponsoring editor may decide to include advertisements in the supplement in or der to defray costs. Please consult with the HJMPH advertising representative Michael Roth at 808-595-4124 or email rothcomm@lava.net for assistance.

9. Supplement issues are posted online for full-text (PDF) retrieval on the HJMPH website at www.hjmph.org. An announcement of its availability will be made through our normal email distribution list. Full-text will also be available on PubMed Central.

10. It is the responsibility of the supplement editor and contributing team members to manage all editorial, marketing, sales, and distribution functions. If you need assistance, please contact our production manager. We may be able to help for an additional fee.

11. Timing of a supplement issue publication will be formalized once all required materials have been submitted to the production manager and payment made.

Biostatistical Guideline for HJM&PH

The following guidelines are developed based on many common errors we see in manuscripts submitted to HJMPH. They are not meant to be all encompassing, or be restrictive to authors who feel that their data must be presented differently for legitimate reasons. We hope they are helpful to you; in turn, following these guidelines will reduce or eliminate the common errors we address with authors later in the publication process.

Percentages: Report percentages to one decimal place (eg, 26.7%) when sample size is >=200. For smaller samples (<200), do not use decimal places (eg, 26%, not 26.7%), to avoid the appearance of a level of precision that is not present.

Standard deviations (SD)/standard errors (SE): Please specify the measures used: using "mean (SD)" for data summary and description; to show sampling variability, consider reporting confidence intervals, rather than standard errors, when possible to avoid confusion.

Population parameters versus sample statistics: Using Greek letters to represent population parameters and Roman letters to represent estimates of those parameters in tables and text. For example, when reporting regression analysis results, Greek symbol (β), or Beta (b) should only be used in the text when describing the equations or parameters being estimated, never in reference to the results based on sample data. Instead, one can use "b" or β for unstandardized regression parameter estimates, and "B" or β for standardized regression parameter estimates.

***P* values:** Using *P* values to present statistical significance, the actual observed *P* value should be presented. For *P* values between .001 and .20, please report the value to the nearest thousandth (eg, *P* = .123). For *P* values greater than .20, please report the value to the nearest hundredth (eg, *P* = .34). If the observed *P* value is great than *.999*, it should be expressed as "*P* > *.99*". For a *P* value less than .001, report as "*P* < .001". Under no circumstance should the symbol "NS" or "ns" (for not significant) be used in place of actual *P* values.

"Trend": Use the word trend when describing a test for trend or dose-response. Avoid using it to refer to *P* values near but not below .05. In such instances, simply report a difference and the confidence interval of the difference (if appropriate), with or without the *P* value.

One-sided tests: There are very rare circumstances where a "one-sided" significance test is appropriate, eg, non-inferiority trials. Therefore, "two-sided" significance tests are the rule, not the exception. Do not report one-sided significance test unless it can be justified and presented in the experimental design section.

Statistical software: Specify in the statistical analysis section the statistical software used for analysis (version, manufacturer, and manufacturer's location), eg, SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Comparisons of interventions: Focus on between-group differences, with 95% confidence intervals of the differences, and not on within-group differences.

***Post-hoc* pairwise comparisons**: It is important to first test the overall hypothesis. One should conduct *post-hoc* analysis if and only if the overall hypothesis is rejected.

Clinically meaningful estimates: Report results using meaningful metrics rather than reporting raw results. For example, instead of the log odds ratio from a logistic regression, authors should transform coefficients into the appropriate measure of effect size, eg, odds ratio. Avoid using an estimate, such as an odds ratio or relative risk, for a one unit change in the factor of interest when a 1-unit change lacks clinical meaning (age, mm Hg of blood pressure, or any other continuous or interval measurement with small units). Instead, reporting effort for a clinically meaningful change (eg, for every 10 years of increase of age, for an increase of one standard deviation (or interquartile range) of blood pressure), along with 95% confidence intervals.

Risk ratios: Describe the risk ratio accurately. For instance, an odds ratio of 3.94 indicates that the outcome is almost 4 times as likely to occur, compared with the reference group, and indicates a nearly 3-fold increase in risk, not a nearly 4-fold increase in risk.

Longitudinal data: Consider appropriate longitudinal data analyses if the outcome variables were measured at multiple time points, such as mixed-effects models or generalized estimating equation approaches, which can address the within-subject variability.

Sample size, response rate, attrition rate: Please clearly indicate in the methods section: the total number of participants, the time period of the study, response rate (if any), and attrition rate (if any).

Tables (general): Avoid the presentation of raw parameter estimates, if such parameters have no clear interpretation. For instance, the results from Cox proportional hazard models should be presented as the exponentiated parameter estimates, (ie, the hazard ratios) and their corresponding 95% confidence intervals, rather than the raw estimates. The inclusion of *P*-values in tables is unnecessary in the presence of 95% confidence intervals.

Descriptive tables: In tables that simply describe characteristics of 2 or more groups (eg, Table 1 of a clinical trial), report averages with standard deviations, not standard errors, when data are normally distributed. Report median (minimum, maximum) or median (25th, 75th percentile [interquartile range, or IQR]) when data are not normally distributed.

Figures (general): Avoid using pie charts; avoid using simple bar plots or histograms without measures of variability; provide raw data (numerators and denominators) in the margins of meta-analysis forest plots; provide numbers of subjects at risk at different times in survival plots.

Missing values: Always report the frequency of missing variables and how missing data was handled in the analysis. Consider adding a column to tables or a footnote that makes clear the amount of missing data.

Removal of data points: Unless fully justifiable, all subjects included in the study should be analyzed. Any exclusion of values or subjects should be reported and justified. When influential observations exist, it is suggested that the data is analyzed both with and without such influential observations, and the difference in results discussed.

GET READY FOR ICD-10

STAY ON THE ROAD TO 10 STEPS TO HELP YOU TRANSITION

The ICD-10 transition will affect every part of your practice, from software upgrades, to patient registration and referrals, to clinical documentation and billing.

CMS can help you prepare. Visit the CMS website at www.cms.gov/ICD10 and find out how to:

- Make a Plan—Look at the codes you use, develop a budget, and prepare your staff
- Train Your Staff—Find options and resources to help your staff get ready for the transition
- Update Your Processes—Review your policies, procedures, forms, and templates
- Talk to Your Vendors and Payers—Talk to your software vendors, clearinghouses, and billing services
- Test Your Systems and Processes—Test within your practice and with your vendors and payers

Now is the time to get ready.

www.cms.gov/ICD10

CMS ICD-10

Official CMS Industry Resources for the ICD-10 Transition

www.cms.gov/ICD10

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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Claims Supervisor
Brian Taylorson

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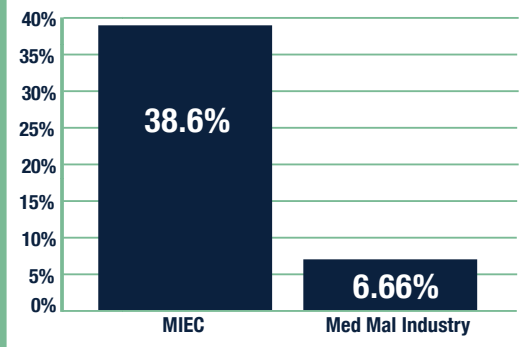

Added value:

- No profit motive and low overhead
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For more information or to apply:

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