



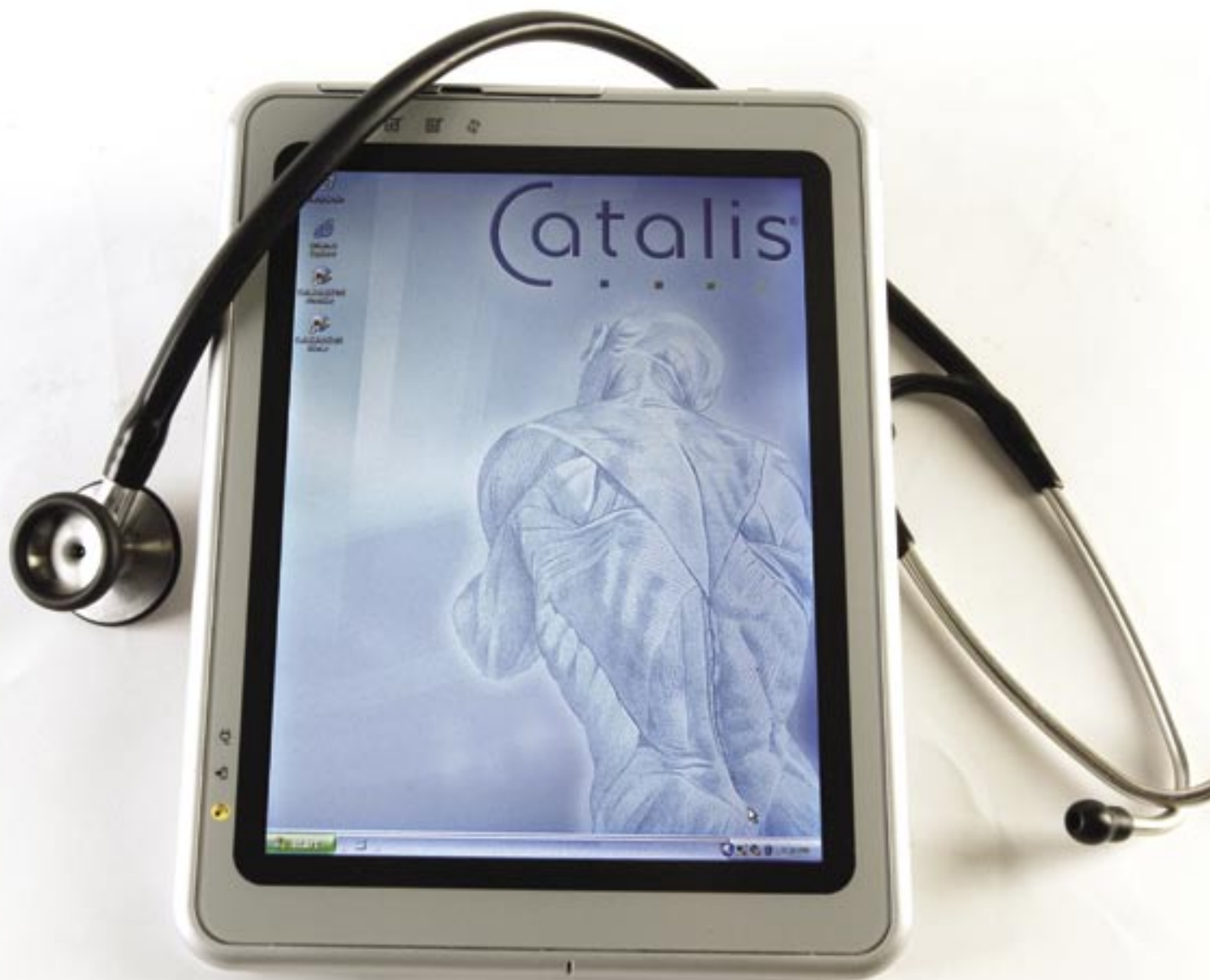
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Human Serum Albumin Levels and Cardiovascular Risk Factors in Elderly Japanese-American Men: The Honolulu Heart Program

Chung-Eun Ha PhD, Kamal H. Masaki MD, Helen Petrovitch MD, Randi Chen MS, Lenore Launer PhD, Nadhipuram V. Bhagavan PhD, Alan T. Remaley MD, PhD, and J. David Curb MD



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Abstract

The objective of this study is to investigate the relationship between low levels of human serum albumin (HSA) and the incidence of coronary heart disease (CHD) in a cohort of elderly Japanese-American men. Using data from the Honolulu Heart Program's fourth examination (1991-1993), HSA levels of 998 Japanese American men aged 71-93 years was compared with plasma levels of fibrinogen, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, diastolic BP, BMI, and fasting blood glucose. HSA was significantly negatively associated with age and fibrinogen, and significantly positively associated with total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, diastolic BP, BMI and fasting blood glucose. After adjusting for age, tertiles of HSA were significantly positively associated with total cholesterol, HDL cholesterol and triglycerides, and significantly negatively associated with fibrinogen. Using multivariate stepwise regression, significant correlations were seen between HSA and fibrinogen, cholesterol, age, HDL cholesterol and triglycerides, and a borderline correlation was seen with systolic blood pressure. However, the model R-square for all variables was only 0.10. In conclusion, HSA levels are significantly associated with several traditional cardiovascular risk factors, particularly serum lipid levels.

Introduction

Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide. The understanding of traditional risk factors, cigarette smoking, hypertension, obesity, diabetes mellitus, physical inactivity, and plasma levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides has made significant contribution in reducing the morbidity and mortality of CHD.¹ The major risk factors, nevertheless, are implicated in only as many as 75% of CHD cases.² Several epidemiological studies have supported the observation that a high concentration of HDL-C is cardio-protective. However, this inverse relationship between HDL-C and

CHD is not applicable to a significant number of CHD patients. For example, 27% of the men participating in the Framingham Heart Study cohort showed premature CHD but did not have HDL-C levels in the bottom 10th percentile.³ Thus, non-traditional risk factors may play a significant role in CHD risk. One of these is human serum albumin (HSA). Many observational epidemiological studies have demonstrated an association between low levels of HSA and increased incidence of CHD.⁴⁻¹² In particular, a population based study regarding the relationship between the levels of HSA and total cholesterol and mortality among the Japanese general population showed that a combination of low levels of HSA and above-average total cholesterol were associated with higher mortality.¹³ Furthermore, this study showed that the low serum albumin level group (≤ 43 g/L) was associated with higher cardiovascular mortality for men.

There is evidence that HSA levels may be dependent on, or influence other cardiovascular risk factors such as serum lipid levels. Before exploring the possible direct relationship of HSA levels to CHD incidence, it is important to determine the interactions that exist between HSA levels and proven CHD risk factors that might act as mediators. In this report, we examined the relationship between HSA and several other traditional cardiovascular risk factors in a cohort of elderly Japanese-American men.

Methods

Study Population

The Honolulu Heart Program (HHP) is a prospective epidemiologic observational study of cardiovascular disease that began in 1965. The identification of the study cohort was undertaken by using World War II Selective Service registration cards which were on file in Honolulu. This process led to the finding of registration

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cards for about 15,000 men with Japanese Surnames, born between 1900 and 1919 with Honolulu (O'ahu) addresses at the time of registration. It was decided that the study cohort should be limited to long-term resident men of Japanese ancestry, born between 1900 and 1919. Based upon these considerations 12,261 questionnaires were mailed and 8,006 men of age 45-68 years participated in the first examination between 1965 and 1968. The selection process for the cohort was published previously.¹⁴

This report is based on a sub-sample of the fourth examination of the cohort conducted in 1991-1993, when 3,741 men aged 71-93 years were examined (80% of survivors). Some data, augmented by telephone interviews, were obtained on 98% of survivors. We did a cross-sectional analysis on the association of serum HSA levels with CHD risk factors. The study was approved by the institutional review committee of Kuakini Medical Center, procedures followed were in accordance with institutional guidelines, and informed consent was obtained from all participants.

Data Collection

The fourth examination included demographic information, medical and psychological questionnaires, assessment of cognitive function, fasting blood tests and a two-hour glucose tolerance test, seated blood pressure, anthropometry, spirometry, and an electrocardiogram, collected in a standardized manner consistent with previous examinations of this cohort.^{15,16}

Serum albumin was measured in a random sub-sample of 998 participants, on a Hitachi 917 (Roche) by the bromocresol green (BCG) method, a colorimetric endpoint assay determined at 570 nm.¹⁷ Covariates included traditional and non-traditional cardiovascular risk factors. After a recommended overnight fast of at least 12 hours, blood specimens were collected, plasma was separated, and standard enzymatic measurements of lipids were performed using the same laboratory and methods used in the Cardiovascular Health Study (CHS).¹⁸ Measurements of total cholesterol, HDL cholesterol, and triglycerides were performed with an Olympus Demand System (Olympus Corp) and were standardized according to the Centers for Disease Control.¹⁹ LDL cholesterol was calculated for participants with triglyceride levels ≤ 400 mg/dL, based on the Friedewald method.²⁰ Plasma fibrinogen levels were measured at the Laboratory for Clinical Biochemistry Research, University of Vermont, Colchester, as the rate of clot formation by a semiautomated modification of the Clauss method²⁰ as determined on a BBL fibrometer (Becton Dickonson).²¹ Diabetes mellitus was defined by history (as told to the participant by a physician), or taking medications (insulin or oral hypoglycemics), or fasting glucose ≥ 126 mg/dl, or 2-hour post-load glucose ≥ 200 mg/dl (modified ADA criteria).²² Systolic and diastolic blood pressures were

measured with a standard mercury sphygmomanometer using a standardized protocol in the seated position after 5 minutes rest. Hypertension was defined as systolic BP ≥ 140 or diastolic BP ≥ 90 or taking antihypertensive medications. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Physical activity index was based upon one used in Framingham²³ and the Honolulu Heart Program,²⁴ which consists of multiplying the approximate oxygen consumption of 5 different levels of activity with the reported usual numbers of hours a day engaged in that activity.

Data Analysis

We computed Spearman Rank-Order correlation coefficients for serum albumin with other continuous variables due to the skewed distribution of some variables.²⁵ Subjects were divided into tertiles of serum albumin levels and age-adjusted means were calculated by tertiles.²⁶ We used stepwise multiple linear regression with $p < 0.1$ as model selection criteria to determine the variables that were independently correlated with serum albumin.²⁷ All statistical analyses were done using SAS software version 8.0 (SAS Institute Inc., Cary, North Carolina).

Results

Mean levels of serum albumin decreased significantly by 5-year age groups, $p < 0.0001$ (Figure 1). Spearman correlation coefficients are shown in Table 1. Serum albumin was significantly negatively associated with age ($p < 0.0001$) and fibrinogen ($p < 0.0001$). It was significantly positively associated with total cholesterol ($p < 0.0001$), HDL cholesterol ($p < 0.0001$), LDL cholesterol ($p = 0.005$), triglycerides ($p = 0.0007$), diastolic BP ($p = 0.01$), BMI ($p = 0.005$), and fasting blood glucose ($p = 0.004$). Borderline positive associations were seen with systolic BP ($p = 0.05$) and fasting insulin ($p = 0.06$). There were no significant associations seen with total/HDL cholesterol ratio, physical activity index, or pack years cigarette smoking.

We analyzed the mean levels of several traditional and non-traditional cardiovascular risk factors, by tertile of serum albumin levels (Table 2). After adjusting for age, total cholesterol, HDL cholesterol, and triglycerides remained significantly positively associated with albumin tertiles. Age-adjusted fibrinogen was significantly negatively associated with albumin tertiles. Prevalent hypertension was also significantly associated with albumin tertiles, without adjustment for age.

We studied the correlates of serum albumin as a continuous variable, using multivariate stepwise regression (Table 3). Significant correlations were seen with fibrinogen, cholesterol, age, HDL cholesterol and triglycerides, and a borderline correlation was seen with systolic blood pressure. However, the model R-square for all variables was only 0.10.

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Discussion

Many epidemiologic prospective studies have demonstrated an inverse relationship between serum HSA levels and evidence of CHD.^{4,8,10-12} However, the underlying mechanism is not known. In our investigation, we examined whether serum HSA levels are associated with CHD risk factors in the Honolulu Heart Program cohort of Japanese-American men aged 71-93 years.

Significant positive correlations were found between HSA level and total cholesterol, LDL-C, HDL-C, triglycerides, blood pressure, body mass index, and fasting blood glucose. Negative correlations were found with age and fibrinogen levels. The association of higher HSA levels with higher HDL-C and lower fibrinogen levels would tend to promote a protective effect of HSA against CHD. A previous study has shown that in both men and women aged 70 and older, a higher HSA and HDL-C level placed individuals in a low risk group for mortality.⁴ Several studies have demonstrated that increased fibrinogen level is a risk factor for CHD. A meta-analysis of several prospective studies has shown that higher levels of fibrinogen are associated with CHD.²⁸ Total cholesterol and LDL-C also tended to be higher in individuals with higher levels of HSA, but the total/HDL-C ratio was negatively correlated, with higher HSA favoring protection from CHD. In addition, a recent population based study of 7,894 Japanese men and women aged 30 to 59 showed that in the group with median and above total cholesterol level the concentration of HSA was inversely associated with all-cause and cardiovascular mortality for both men and women.¹³ However, several studies have shown that in elderly subjects (≥ 70 years of age), low cholesterol levels are associated with an increased risk of CHD and all-cause mortality.^{29,30}

Contrarily, HSA levels were also positively associated with diastolic blood pressure, body mass index, and fasting blood glucose levels, all of which have been shown to increase risk of CHD.^{16,19} It is important to note, however, that in a very elderly population such as the Honolulu Heart Program cohort, higher levels of blood pressure, body mass index, and fasting glucose may actually be indicators of better health, or relationships may be non-linear with the most protective values being around the means. In any case, the relationship of risk factors to CHD becomes complex in very old populations.

HSA is the most abundant plasma protein at a concentration of 3.5-5.0 g/dl and it is a multifunctional protein. Its well-established function includes its major role as a regulator of plasma oncotic pressure and its ability to bind and transport a number of endogenous ligands (e.g., bilirubin) and exogenous compounds (e.g., various drugs). It is synthesized in the liver and has a half-life of 19 days in the circulation. HSA levels in plasma are determined by a combination of gene expression and dietary factors.¹¹ Recent studies showed

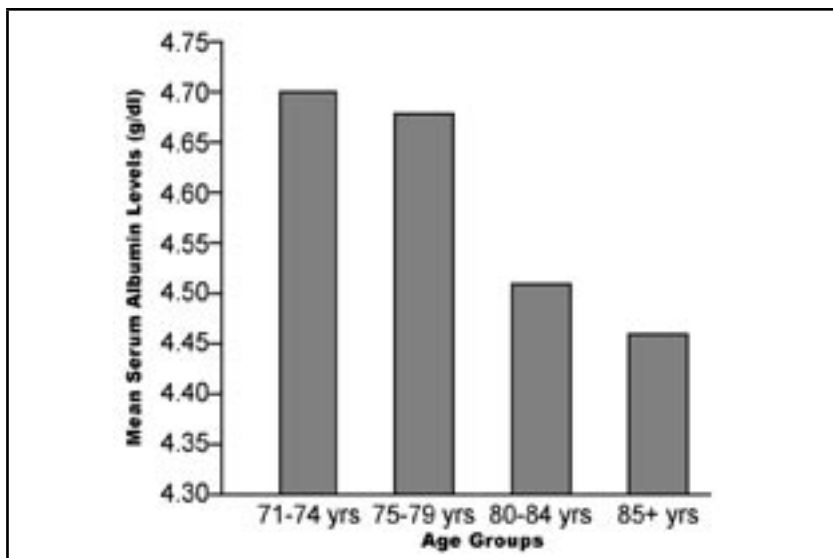


Figure 1.— Mean serum albumin levels and ranges by 5-year age groups (71-74, 75-79, 80-84, 85+) in the Honolulu Heart Program cohort. Test for trend $p < 0.0001$.

Table 1.— Correlation of serum albumin levels with cardiovascular risk factors (Spearman models).

	r value	p value
Age (years)	-0.17	<0.0001
Total cholesterol	0.17	<0.0001
HDL cholesterol	0.15	<0.0001
LDL cholesterol	0.09	0.005
Total/HDL cholesterol ratio	-0.02	0.54
Triglycerides	0.11	0.0007
Fibrinogen	-0.18	<0.0001
Systolic Blood Pressure	0.06	0.05
Diastolic Blood Pressure	0.08	0.01
Body Mass Index	0.09	0.005
Fasting Blood Glucose	0.09	0.004
Fasting Insulin	0.06	0.06
Physical Activity Index	0.05	0.11
Pack Years Smoking	0.05	0.16

that plasma levels of HSA can be elevated with increased level of leisure-time physical activity³¹ and statin therapy.³² It should be noted both exercise and statin therapy moderate CHD risk factors and indeed HSA may also participate in the risk reduction.

The mechanism by which HSA confers protection against CHD is not completely understood. However, several potential properties of HSA may contribute towards this benefit. The authors' previous studies in this regard include HSA's role in nitric oxide transport,³³ prostaglandin interconversions favoring an antiplatelet action,³⁴ and cholesterol efflux from peripheral tissue cells.¹² HSA's antioxidant property may also ameliorate CHD events.³⁵

Further investigations are required to elucidate the biologic relationship between HSA and its polymorphic forms with CHD.

Table 2.— Mean levels of cardiovascular risk factors by tertiles of serum albumin, and test for trend.

	T1	T2	T3	p value
Mean Albumin	4.08	4.53	5.17	
(range)	(3.1-4.3)	(4.4-4.7)	(4.8-6.9)	
Age (years)	79.6	77.5	77.3	<0.0001
Total cholesterol *	180.4	189.5	192.1	<0.0001
HDL cholesterol *	47.9	49.8	52.8	<0.0001
LDL cholesterol *	105.0	111.5	109.5	0.08
Total/HDL cholesterol ratio *	4.0	4.0	3.8	0.09
Triglycerides *	138.9	143.1	160.0	0.004
Fibrinogen *	324.5	310.5	292.6	<0.0001
Systolic Blood Pressure *	144.4	148.5	148.1	0.05
Diastolic Blood Pressure *	78.9	79.4	80.0	0.20
Body Mass Index *	23.2	23.5	23.5	0.26
Fasting Blood Glucose *	110.8	112.6	113.4	0.30
Fasting Insulin *	23.2	15.8	17.3	0.08
Physical Activity Index *	30.4	30.8	30.6	0.67
Pack Years Smoking *	22.0	25.8	27.7	0.06
Hypertension (%)	64%	75%	75%	0.002
Diabetes Mellitus (%)	24.6%	29.1%	30.5%	0.23

* Adjusted for age

Table 3.— Correlates of serum albumin using multivariate stepwise regression.

	Beta	Partial R-square	Model R-square	p value
Fibrinogen	-0.001	0.037	0.037	<0.0001
Cholesterol	0.001	0.023	0.060	<0.0001
Age	-0.015	0.012	0.072	0.0008
HDL cholesterol	0.006	0.007	0.079	0.01
Triglycerides	0.001	0.019	0.098	<0.0001
Systolic Blood Pressure	0.001	0.004	0.102	0.07

This study shows that HSA levels are significantly associated with several traditional cardiovascular risk factors. In the future, the authors plan to perform analyses to study the association of HSA levels with incident CHD in this cohort, with an emphasis on the interaction between HSA and lipids.

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Culturally Sensitive Strategies Designed to Target the Silent Epidemic of Hepatitis B in a Filipino Community

Michelle Marineau PhD, APRN, Alan D. Tice MD, David Taylor-Garcia, Kenneth T. Akinaka, Heather Lusk, and Fernando Ona MD



Michelle Marineau
PhD, APRN



Alan D. Tice MD



David Taylor-Garcia

Abstract

Hepatitis B is frequent in the Philippines. A high rate of immigration to the United States has brought many Filipinos with infections who are asymptomatic yet will go on to develop liver cancer and cirrhosis unless diagnose and evaluated. Interventions are necessary to educate this ethnic community, identify those infected, and offer therapy.

In an effort to reach this high risk population in Hawai'i an intervention program was designed to address the silent epidemic of hepatitis. Ethnic barriers were crossed through involvement of trusted, key stakeholders and individuals within the Filipino health care and church communities, along with groups that had joint missions to address viral hepatitis. After extensive planning and meetings with faith-based organizations and health care providers in the Filipino community, it was decided to hold a community health fair in the Filipino community to provide culturally appropriate health information and services. More than 500 individuals attended the health fair; 167 participated in a survey and were tested for hepatitis B. Significant knowledge gaps were found in relation to risk factors, prevention strategies, and transmission. Five individuals tested positive; all were immigrants and did not know of their disease. The objective to educate people and test them for hepatitis was successful through utilizing ethnic community leaders, religious organizations, health care professionals, and a collaborative health fair.

Introduction

The Asian American/Pacific Islander (AAPI) population is the fastest growing ethnic group in the United States (US).¹ By the year 2050 it is predicted that the AAPI's population will reach 41 million US residents (11% of the total US population). The AAPIs have increased from 1.5 million to 7 million between 1970 and 1990 with a total of 11.9 million at the last 2000 US Census figures.² These new immigrants come primarily from Taiwan, China, Korea, the Philippines, and Indochina. A majority of Hawai'i residents fall in the ethnic category of AAPIs.³ There are clear health disparities among them. The death rate of Native Hawaiians is 901 per 100,000, compared to 524 per 100,000 for the total US population.⁴ There are large gaps in the baseline information regarding AAPI health data making it dif-

icult to predict the current health care needs of this population. The ethnic diversity of Hawai'i provides an opportunity to explore the processes of health care seeking and care delivery barriers in a state without an ethnic majority.⁵

Of the AAPI population, the Filipino Americans are the fastest growing segment. Filipinos and part-Filipinos comprise nearly 23% of the population in the state of Hawai'i.⁶ Many of these individuals have been found to have active hepatitis B, which occurs approximately 10 times more often in the Philippines (11.4%) than the US mainland population (1%).⁷ Hawai'i is also thought to have a high rate because of a continued immigration from areas where chronic hepatitis B virus (HBV) infection is endemic. The high rate of hepatitis B among Filipinos is related to the lack of vaccinations programs for children compared to that of the United States. Most of the middle-aged and older immigrants have never been immunized or tested for hepatitis B. They may not even be aware they are infected until they present with liver cancer or complications such as cirrhosis with intestinal bleeding or encephalopathy. Among these immigrants, individuals testing positive for hepatitis B surface antigen (HBsAg) ranges from 5-15%. These infected people are a potential source of infections to others, and are at risk themselves for complications of chronic hepatitis B.^{8,9} Individuals with chronic hepatitis B have a 200 times greater risk of developing liver cancer than those not infected.¹⁰

Interventions to reach this population to implement serologic testing, vaccinations administration, and knowledge dissemination regarding hepatitis are essential. To be successful, interventions must be culturally sensitive and insightful. The population at highest risk for viral hepatitis is difficult to reach due to language, cultural, and economic barriers of health care.¹¹ Health disparities that exist in this community are due to more than just a lack of health care resources; it is also the result of a lack of engagement due to ethnic barriers. In general, many of the elderly Filipinos have minimal medical education, assume a passive role with a paternalistic interaction/decision making style¹³ with their health care provider, and have belief that "God will

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take care of things.” They have a *bahala na* (“whatever will be, will be”) value that means it is unnecessary to worry about events that are beyond their control.¹⁴ Their management style is crisis oriented, rather than concerned with preventing illnesses.¹⁵ The concept of chronic, yet asymptomatic, infection is beyond their usual understanding.

Intervention

In an effort to reach this high risk population in Hawai‘i a plan was instituted to address the silent epidemic of hepatitis among the Filipino population. The Filipino population seemed well suited for intervention because of their interests in health care professions and the active Filipino networks in Hawai‘i with many professional and faith-based organizations. Initially, a few members from the Filipino community were approached with the idea of an outreach plan and were asked to become part of the planning committee. The planning committee identified individuals within the Filipino health care community who were strategically selected in a two-step process. The first occurred in late 2005 when the need to address hepatitis B was broadcasted to the Filipino community via key medical and church community members. This resulted in the identification of key stakeholders within the Filipino community whose support would enhance the effectiveness of the event. The second phase of the project occurred in early 2006 when a sponsor was found to host a dinner party for these stakeholders resulting in approximately 50 participants attending an informational dinner meeting. These individuals assisted in targeting their community and passed on culturally sensitive information that would assist in marketing the event and disseminating important health care information directed at this ethnic group.

Several pre-planning meetings were scheduled with participation enhanced by involving the Filipino churches and providing food through donations at all of these meetings. A final important awareness rally was planned at a local restaurant inviting key Filipino members in the medical field, church community, the Consul General of the Philippines, state legislators, and various foundation members that have a mission to address hepatitis and related illnesses. It was decided to intervene with a health fair in the Filipino community and to promote it through the Filipino newspaper, Filipino radio station, and flyers placed at strategic locations.

May 6, 2006 was selected for the date of the community health fair to coincide with the centennial celebration of the arrival of the first people from the Philippines and Hepatitis Awareness Month. The event was hosted at the Filipino Community Center, a well-respected cultural hub in the largest community of Filipinos in Hawai‘i. The event occurred on a Saturday since Sunday is typically a day reserved for church by the Filipino community members. Entertainment was planned with performances by Filipino youth dancers and musicians.

There were health care booths which provided screening and one-on-one sessions with a physician. The interest generated by the intervention attracted many community-based organizations, which contributed booths with staff and educational materials about HIV, sexually transmitted diseases, smoking cessation, cancer awareness, tuberculosis, and Hansen’s Disease. A free, ethnic, Filipino style lunch was provided through donations from various individuals and institutions.

Free blood tests were offered for hepatitis B and C and a survey was developed to gather important data-related to risk factors. Risk factors specifically for the local resident population were included on the survey from a study conducted by the public health department.¹¹ The survey was collected while waiting in the blood draw line by local nurses who volunteered their time. Language barriers did exist requiring interpreters to be present in gathering the survey data, obtaining consent for the blood draws, and delivering pertinent health care information. In Hawai‘i there are 3 primary Filipino dialects, Ilocano, Tagalog, and Cebuano. Interpreters speaking the 3 dialects were recruited from the Filipino Nurses Organization, Hawai‘i Department of Public Health, and the Micronesian Community Network. These interpreters assisted in filling out the surveys. The majority of the individuals were elderly with English as their second language. This required the surveys and informed consent to be read to the participants with volunteers and/or interpreters reading the questions and assisting in filling out the survey data and informed consent. The Institutional Review Board of the University of Hawai‘i approved this project. Those surveyed identified a doctor to follow up with their care in the event that their test was positive. The survey and results were linked only by a number with no identifying patient data.

Results

Approximately 500 individuals attended the health fair; 167 participated in the survey and had their blood tested for hepatitis B and C. Of the 167 participants, 152 were Filipino and 140 identified themselves as immigrants. Five individuals tested positive for hepatitis B. All were born in the Philippines. None of the immigrants had hepatitis C. Of those born in the Philippines they had been living in the United States an average of 21 years and were predominately women (65%) with an average age of 64 years. Less than 10% knew they had ever been tested for hepatitis or HIV.

The greatest risk factor for hepatitis B was immigration status. All of the 5 individuals that tested positive were born in the Philippines. 2 of the 5, had a history of a blood transfusion in the distant past. There were no identified sexual exposures to hepatitis. Only 1 person consumed alcohol on a weekly basis; the remaining 4 declared abstinence to alcoholic substances. There was no injectable drug use. None were aware of their mother



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having hepatitis or liver disease. All positive and negative blood test results were sent to the health care providers they designated. None of the 5 people found to have hepatitis B were aware of it.

Discussion

The objective of an outreach plan was to reach a population of culturally distinct people to learn more about the incidence of hepatitis B and C and how to intervene with education, testing, and therapy as indicated. The challenges in these populations of immigrants are great given their language, cultural, and educational grounds. With viral hepatitis, there are the added challenges of advanced age and usually asymptomatic state before liver disease erupts. In follow-up care with the individuals that tested positive it was identified that there were significant knowledge gaps in this group related to perceived risk factors, prevention strategies, immunizations, and the need to test family members of the individuals who tested positive.

The care of individuals with chronic hepatitis B and C involves first identifying the people who are infected and then assessing the risk factors that may result in disease progression. The individual should be carefully evaluated and considerations made for antiviral therapy to enhance survival and decrease complications associated with this disease. These are difficult to achieve in the Filipino population. The health fair was successful in involving health care providers, educating the ethnic community, and identifying individuals who were infected.

Ethnic barriers were crossed through involvement of trusted key stakeholders and individuals within the Filipino health care and church communities along with groups that had joint missions to address viral hepatitis. Marketing the health fair through local newspaper/radio stations, using the Filipino Community Center to host the fair, and providing culturally appropriate food and entertainment provided additional bridges across these barriers. There was an impressive outpouring of individuals within the Filipino community willing to volunteer their time with significant monetary and in-kind donations to assist in sponsoring this important event.

The intervention of the health fair with food and entertainment was quite successful in reaching the immigrant elderly members of the Filipino community but there were some shortcomings. There were relatively few young and middle-aged Filipinos who attended. Individuals involved in the planning efforts did not strongly target this age group. New strategies should be developed to reach these important age groups. Their participation in planning for future health fairs is important since immunization of the population group below the age of 18 can significantly protect future generations. In a study with 806 members of 8 Asian communities in Montgomery county Maryland it was identified that 51.2% of the Filipino group were un-immunized for hepatitis B. Screening in this study found that ages 36-45 had the highest percentage of carriers (9.1%), making middle-age an important target population for disease prevention and management.¹⁶

There was a significant grass roots effort made by key religious groups, health care members, and organizations in the Filipino community to make the health fair event successful. By approaching this event through religious channels and planning the event in a culturally sensitive and insightful manner, more individuals were reached. Negative attitudes toward being identified as having hepatitis were avoided. There was recognition of the importance of educating

their community and developing a health promotion/disease prevention approach to health care in an ethnic community that does not naturally accept this way of thinking. They gave generously of their time and made a significant difference to the community members that this event touched.

Conclusions

The Filipino community health fair will be used as a model to guide future planning efforts to reach the diverse ethnic groups in the Hawaiian Islands. In planning health prevention/promotion interventions for individuals/communities it is important to examine their unique ethnic values and health care beliefs. This can be done by taking the time to involve key community stakeholders and individuals in the planning process within both the health care and religious community to enhance success. The assumption that one strategy will fit all ethnic groups will only result in failed efforts to reach very vulnerable groups who have immigrated to the US with risk factors of not just hepatitis, but numerous other infectious disease processes (HIV, TB, etc.).

There is a drastically different profile of the ethnicity make-up that exists in the United States today, which is forcing health care providers to communicate messages related to health promotion/prevention in non-traditional ways. This project demonstrates that health messages can be disseminated effectively in hard-to-reach communities when there is involvement with the targeted ethnic group in planning and implementing health prevention/promotion activities.

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A Rare Case of a Pancreatic Tumor in Association with the Syndrome of Inappropriate Antidiuretic Hormone Secretion

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Abstract

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a well-known complication in malignancy, especially small cell carcinoma of the lung. However, its association with pancreatic carcinoma is rare. To the best of our knowledge, only 9 cases have been reported in the literature. We present the case of a 90 year-old woman with pancreatic carcinoma who developed SIADH.

Introduction

Hyponatremia is a common electrolyte disturbance, and it may be defined by a serum sodium concentration of less than 135 mmol/l. Hyponatremia is classified clinically into 3 basic types depending on the extracellular volume status of the patient – hypovolemia, normovolemia, and hypervolemia. Normovolemic hyponatremia accounts for about 60% of all types of chronic hyponatremia, of which the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is by far the most common cause.¹

The cardinal criterion for SIADH is hyponatremia. SIADH is characterized by a sustained release of vasopressin in the absence of either osmotic or nonosmotic stimuli. When persistent secretion occurs in the absence of these stimuli, it leads to clinical manifestations grouped together under the name of SIADH. Possible causes of SIADH include an inappropriate excessive secretion of arginine vasopressin (AVP) from the hypothalamus or from extrahypothalamic tissues capable of such endocrine function. It has been recognized in association with various conditions including malignant diseases.¹

SIADH was first described in 2 patients with bronchogenic carcinoma in 1957 by Schwartz et al.² The patients had hypo-osmolality of the extracellular fluid and a urine persistently hypertonic to the plasma. AVP was not measured but postulated to be secreted at a sustained and inappropriate level. Bartter and Schwartz summarized the cardinal findings of SIADH in a paper published 10 years later in 1967 (Table 1).³

In the earliest papers it was hypothesized that the cause of the condition was the ectopic secretion of AVP as the condition could be mimicked in normal subjects by administering ADH.³ This was later confirmed by the finding of ectopic AVP in a patient with SIADH from small cell lung carcinoma.⁴ Currently, the syndrome has been reported in patients with esophageal cancer, gastric carcinoma, pancreatic carcinoma, and colon cancer.

SIADH is not commonly associated with pancreatic cancer and there appears to have been only 9 cases reported in the literature.⁵⁻¹² The first case was reported by Marks et al in 1968. In this case report, a patient with bronchogenic carcinoma (oat cell) demonstrated inappropriate antidiuresis. Resection of the primary lung tumor did not ameliorate the SIADH. At autopsy, a separate tumor (adenocarcinoma) was found in the pancreas that contained very high levels of AVP confirmed by both radioimmunoassay and biologic assay.⁷

We present the case of a woman who suffered from pancreatic carcinoma and developed hyponatremia due to SIADH.

Case Report

A 90-year-old woman with hypertension and osteoporosis with severe kyphoscoliosis presented to her primary care physician with an initial complaint of chest and abdominal pain of several months duration. She was noted to be disoriented and cachectic with a 26-pound weight loss. The patient was admitted to the hospital for failure to thrive and dehydration. Management consisted of rehydration with IV fluids and nasogastric tube feedings. Of note, the patient continued to receive her outpatient medications which included hydrochlorothiazide 25mg/losartan 100mg daily and escitalopram 5mg daily.

On hospital day 21, the patient was noted to have serum sodium of 128 mEq/L. There were no clinical or laboratory signs of cardiac or renal disease at this time. Urinalysis revealed a urine osmolality of 242

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mOsmol/kg and urine sodium of 149 mEq/L. Serum osmolality was 258 mOsmol/kg. Intravenous 3% sodium chloride was started on hospital day 34, but serum sodium continued to fall to a low of 119 mEq/L. The patient's hydrochlorothiazide/losartan and escitalopram were subsequently discontinued. Follow-up urinalysis revealed a urine osmolality of 572 mOsmol/kg and urine sodium of 195 mEq/L. Serum osmolality was 262 mOsmol/kg. Serum AVP and aldosterone were also measured at this time and were 3.8 pg/mL (1.0-13.3 pg/mL) and 3 ng/dL, respectively.

As this appeared to be a case of inappropriate secretion of antidiuretic hormone, renal, thyroid, and adrenal function were also assessed and found to be normal. A computed tomography (CT) scan of the chest with contrast did not reveal any intrathoracic masses or adenopathies. An abdominal CT scan with contrast revealed a large mass with ill-defined margins and a 5.57 x 3.16 cm hypodense area of central necrosis filling the lesser sac originating from the pancreatic body and tail with compression of the splenic and portal vein and effacement of the left adrenal gland (Fig 1). Subsequent screening for tumor markers revealed a markedly elevated CA 19-9 at 13,617 U/mL (<37 U/mL) and a mildly elevated carcinoembryonic antigen (CEA) at 3.5 ng/mL (0.0-3.0 ng/mL). Confirmatory diagnosis by biopsy was not attempted due to potential for morbidity and over all physical condition.

Following a nephrology consult, 4 grams of sodium was added to the patient's tube feed and 3% sodium chloride was discontinued on hospital day 45. Serum sodium was 132 mEq/L the next day. On hospital day 51, serum AVP was reassessed and found to be elevated at 19.0 pg/ml.

At the time of discharge, the patient's serum sodium had normalized to 141 mEq/L. In regard to the patient's pancreatic tumor, no further treatment was sought by family request. It was felt that palliation of the patient's symptoms would be the best course. The patient was subsequently discharged from acute care to a skilled nursing facility for comfort measures.

Discussion

Hyponatremia, generally defined as a plasma sodium level less than 135 mEq/L (135 mmol per L) is a common electrolyte disturbance.¹³ It is especially common among the elderly in the hospital and long-term care facility settings.¹⁴ SIADH is currently recognized as accounting for most cases of hyponatremia, more appropriately euvolemic hyponatremia.¹ This case is of interest because of the rare finding of a pancreatic tumor discovered in association with SIADH.

Aside from a small amendment by Skowsky & Kikuchi¹⁵ the clinical criteria for the diagnosis of SIADH has changed little since it was first defined by Bartter & Schwartz³ (Table 1). In this patient, SIADH was diagnosed on the basis of serum hypo-osmolal-

Table 1.— Criteria for definition of syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hyponatremia
Hypo-osmolality of plasma
Continued renal excretion of sodium although taking no diuretics
Absence of clinical evidence of fluid volume depletion
Urinary osmolality greater than appropriate considering the plasma osmolality
Normal renal function
Normal adrenal function
Normal thyroid function

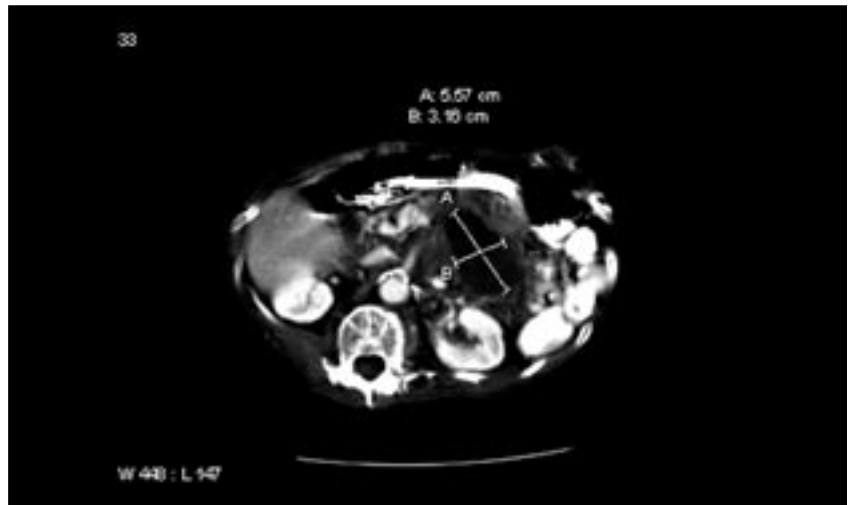


Figure 1.— abdominal CT scan with contrast showing a pancreatic mass with 5.57 x 3.16 cm area of central necrosis.

ity, inappropriate urine hyperosmolality, persistent hyponatremia, and elevated urine excretion of sodium in the presence of normal renal, adrenal, and thyroid function. Serum AVP was also notably elevated. Although this measurement is not currently required for the diagnosis of SIADH,¹⁶ the finding of elevated AVP despite adequate hydration in conjunction with a serendipitous pancreatic mass suggests this may be a case of an ADH-secreting pancreatic tumor.

Since Schwartz et al presented the first clinical case of 2 patients with bronchogenic carcinoma demonstrating inappropriate secretion of antidiuretic hormone,² the types of conditions associated with SIADH have expanded considerably. Among the current known etiologies of SIADH, we can only discern one other possible explanation for the occurrence of SIADH in this patient beside an ADH-secreting pancreatic tumor. The patient had been receiving scheduled doses of hydrochlorothiazide/losartan and escitalopram. Both of these drugs are known to produce SIADH. However, hyponatremia persisted despite discontinuation of these drugs. Therefore it is unlikely that this was a case of drug-induced SIADH.

In the absence of other etiological explanations, an ADH-secreting pancreatic tumor remains the most probable cause of SIADH in this patient. In the literature review, only 9 cases of SIADH associated with a pancreatic tumor were found since it was first reported by Marks et al in 1968.⁷ Corrin et al also presented a patient with oat-cell carcinoma of the pancreas associated with SIADH, but were unable to conclude that the tumor had been producing AVP.¹² The paucity of reports on ADH-secreting pancreatic tumors in the past 40 years speaks for the rarity of this case.

Unfortunately, due to potential morbidity in our patient, a biopsy of the pan-

creatic tumor was not obtained. As such, a definitive pathologic diagnosis could not be made. Despite this, we are confident that with a positive abdominal CT scan finding of a pancreatic mass, elevated serum tumor markers, and demonstration of elevated serum AVP; a diagnosis of ectopic ADH-producing pancreatic tumor may be made. Biopsy of the tumor, while helpful, is probably not essential for a diagnosis as long as other differentials can be excluded. As Kleibeuker & Doorenbos noted, evaluating a biopsy specimen for vasopressin containing cells may lack sufficient sensitivity to determine whether a particular tumor is responsible for ectopic ADH production considering that the site of vasopressin production within the tumor is variable.⁶ Although a biopsy specimen with a positive finding of elevated AVP would have strengthened the diagnosis, a negative biopsy would not have ruled it out. Therefore the authors are confident that there is sufficient evidence to conclude that this is likely a rare case of an ectopic ADH-producing pancreatic tumor.

Pulmonary neoplasm is the most common malignant cause of SI-ADH. Pancreatic tumors by contrast have been implicated in a small minority of cases.¹⁴ Despite the rarity of this case, it nonetheless argues for the need for thorough screening of patients presenting with the picture of inappropriate AVP secretion, especially when a malignant etiology is suspect.

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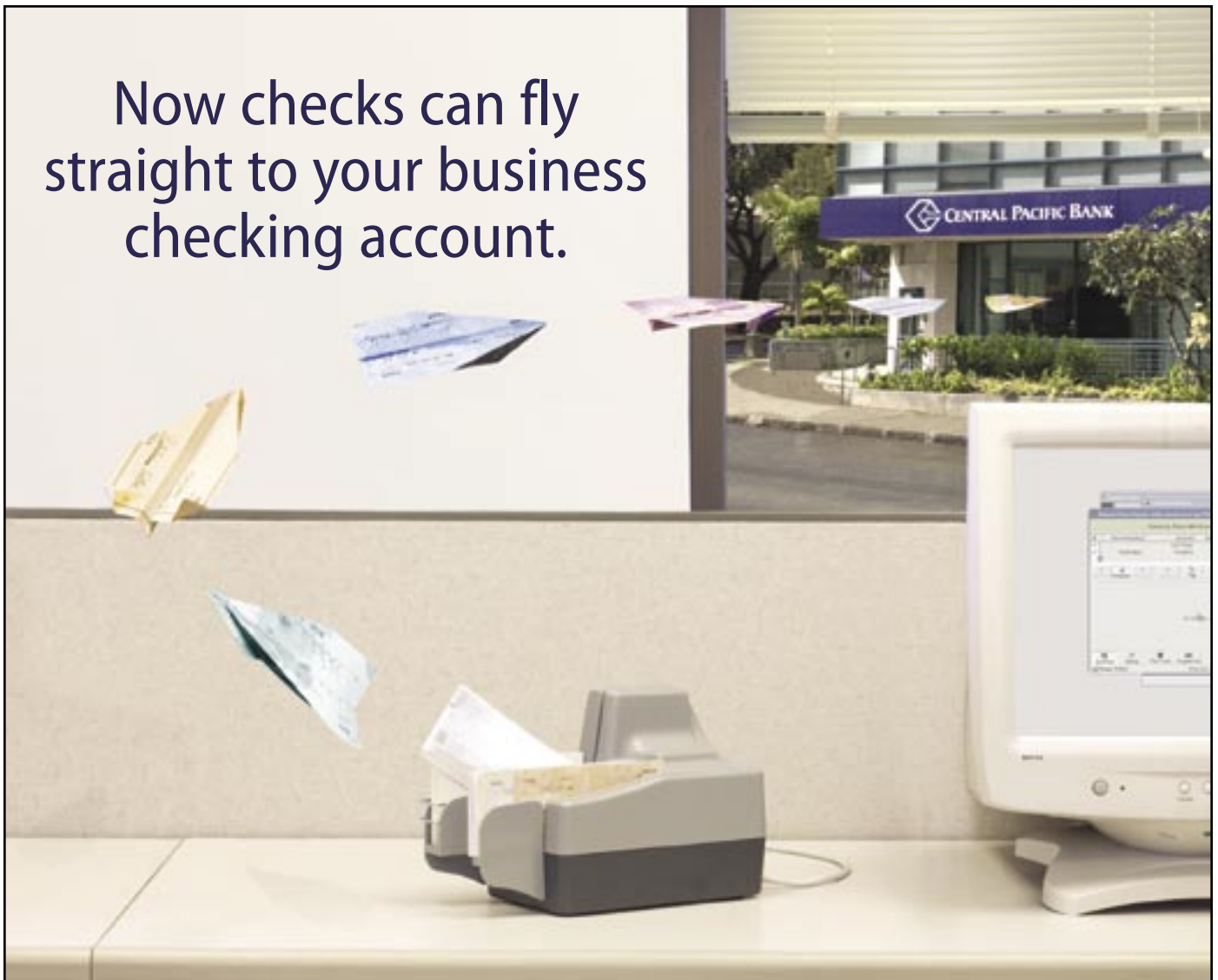
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Is Clinical Empathy Teachable? A Medical Humanities Initiative

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The practice of medicine delicately balances both humanism and science. The American Society for Bioethics and Humanities was established in 1998 to “promote the exchange of ideas and foster multidisciplinary, interdisciplinary, and inter professional scholarship, research, teaching, policy development, professional development, and collegiality among people engaged in all of the endeavors related to clinical and academic bioethics and the health-related humanities.”¹ Dr. Delese Wear states: “The possibilities of the humanities in the undergraduate medical curriculum remain unchanged: to deepen, enlarge, and sharpen one’s sensibilities as students move through an increasingly complex life in medicine, examining themselves, their patients, their profession, and the culture in which they serve.”²

In his history of medicine, “The Greatest Benefit to Mankind”, Roy Porter emphasizes the common ground in Greek thinking of the later separate disciplines of philosophy, medicine, and ethics. With evidence based medicine and the dominance of science, there is a need to re-establish balance.³

The study of medical humanities stimulates the development of communication, professionalism, patient care, and empathy, and the ability to maintain an interest in continued self improvement and education. Learned skills such as teamwork, partnership, and interdisciplinary collaboration contribute to the system based practice of medicine. Finally, patient perception of medical knowledge and expertise is often at least partially based on the quality of the physician’s empathy and ability to “connect” with the patient. Teaching and learning such ideals is challenging, requiring diverse techniques and self reflection.

The Accreditation Council for Graduate Medical Education (ACGME)⁴ have identified the following traits that contribute to development of the core competencies in strengthening the patient-physician relationship,

Table.— Core competencies for ACGME
1. Patient care
2. Medical knowledge
3. Practiced based learning and improvement
4. Interpersonal communication skills
5. Professionalism
6. Systems-based practice

In an era of ever increasing sub specialization in medicine, the role of medical education must be to guide physicians (and physicians in training) to see, interact, and treat the patient as a whole person, as an integral part of a family, a culture, and society. Physician and

patient together, in building this intimate relationship, must view difficult issues such as death and dying as a part of the continuum of birth, life, and living. Their decisions impact not only themselves, but also those in their extended family unit and community.

Currently, there are no elective or core courses offered in Medical Humanities at JABSOM. Threads of medical humanities are introduced in group discussions in the Problem Based Learning curriculum. By comparison, over three-fourths of U.S. medical schools now have medical humanities courses as part of their core curriculum.⁵

In Hawai‘i, multicultural patient, family, and physician encounters are the rule rather than the exception. The demands of practicing medicine in this increasingly complex discipline and cultural environment stimulates one to ask if a young medical student has sufficient life experiences to survive, even with good clinical knowledge. Understanding and incorporating humanities into daily practice perhaps defines the doctor who positively contributes to the well-being of his patient and confidently addresses the needs of diverse island communities.

Student response is positive to potential courses in the medical humanities and the “art of medicine”. Discussions with transitional residents in the University of Hawai‘i program in Honolulu and residents of the University of Hawai‘i Postgraduate Medical Education Program at the Okinawa Chubu Hospital revealed a keen interest and desire to learn more about medical humanities, specifically end of life ramifications. Discussions at James Cook University (Queensland, Australia), University of Papua New Guinea School of Medicine and Health Sciences⁶ and JABSOM, reflect a high level of student interest internationally. The University of California Irvine School of Medicine in particular has developed an integrative program of medical humanities in a third-year clerkship.⁷ There is interest in a collaborative course with JABSOM.

Clinical educators, in their daily practice, and by example, should teach passion and empathy.⁸ Encouragement and acceptance of premedical students with a background of “humanities” or ethics and philosophy rather than the narrower premedical degrees could foster this environment.⁹ Broadening the scope of a medical humanities course to include humanities students as well as medical students could increase diversity of the course interaction as well as the funding base. Lund University in Malmo Sweden has suggested this in further planning of their existing curriculum.¹⁰

A medical humanities pilot project for third year medical students is being suggested for an initial introduction of this discipline at JABSOM. Topics for small group discussions and participation include but are not limited to: history of medicine, philosophy,

Continued on p. 169

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Emerging Bone Health Issues in Women with Breast Cancer in Hawai'i

Jennifer Fu Carney MD, John A. Burns School of Medicine, Prevention and Control Program, Cancer Research Center of Hawai'i, University of Hawai'i, and James Davis, Hawai'i Medical Services Association

Abstract

Purpose: *Aromatase inhibitors have improved breast cancer outcomes for early stage, postmenopausal women who have hormone receptor positive disease. Aromatase inhibitors have replaced the prior gold standard treatment, tamoxifen, a selective estrogen receptor modulator. However, aromatase inhibitors markedly reduce estradiol and have the potential to increase the risk for osteoporosis and associated bone fractures. Guidelines for monitoring bone health in women with breast cancer exist but it is unclear whether these recommendations are the standard of care in Hawai'i. This study addresses adjuvant chemotherapy among women with early stage breast cancer and related issues of bone health in Hawai'i.*

Methods: *The patients were women age 50 and older with early stage breast cancer who were taking an aromatase inhibitor or tamoxifen and enrolled with the largest insurer in Hawai'i from 1999 to 2006. Their clinical histories were obtained from administrative data including their prior use of hormone replacement therapy and whether they had received radiation or adjuvant chemotherapy. Spine, hip, and wrist fractures, bisphosphonate therapy, and dual energy X-ray absorptiometry scans were the measured outcomes.*

Results: *In 2006, the percentage of women on tamoxifen was 29% compared to 71% for aromatase inhibitors. Women taking aromatase inhibitors were significantly more likely to have bone fractures than those on tamoxifen (rate ratio=2.42). More patients on aromatase inhibitors received bone density scans as well as medications to prevent bone loss (odds ratio=1.86).*

Conclusions: *In this Hawai'i population, the use of aromatase inhibitors has increased steadily since 2002 when the initial adjuvant trial for postmenopausal women with early breast cancer was reported. However, tamoxifen remained a commonly prescribed agent. Women taking aromatase inhibitors were at increased risk of developing fractures. In addition, preventative strategies, such as dual energy absorptiometry scans and bone health agents, were underutilized.*

Introduction

Breast cancer affects over 200,000 women annually and the majority of patients are candidates for adjuvant endocrine therapy. Until recently, tamoxifen, a selective estrogen receptor modulator, had been the standard drug of choice. Studies of postmenopausal women with early stage, hormone receptor positive breast cancer have shown improvement in disease free survival, time to recurrence, contralateral breast cancer development, and distant metastases with the third generation aromatase inhibitors compared to tamoxifen in the upfront setting.^{1,2} Studies examining sequential adjuvant endocrine therapy using tamoxifen followed by an aromatase inhibitor have demonstrated an improvement in overall survival in women with early breast cancer.^{3,4}

In postmenopausal women, tamoxifen acts as an estrogen agonist on bone and is associated with protection from osteoporosis. A major side effect of aromatase inhibitors, by contrast, is the effect on bone health likely due to the marked reduction in estradiol affecting bone physiology. Studies have reported a decrease in bone mineral

density, changes in biomarkers of bone turnover, and an increase in the number of bone fractures.⁵ Currently, the American Society of Clinical Oncology guidelines for bisphosphonate and bone health recommend a baseline dual energy X-ray absorptiometry (DEXA) scan before initiation of aromatase inhibitors, and annual DEXA scans thereafter.⁶ The guidelines also encourage lifestyle modifications such as exercise and calcium with vitamin D intake.

Osteoporosis is a skeletal disorder characterized by compromised bone strength resulting in a predisposition for an increased risk of fracture.⁸ The prevalence of osteoporosis is difficult to assess accurately but it is estimated that osteoporosis affects 30% of postmenopausal women and osteopenia affects 54%.⁹ The risk of osteoporosis is multi-factorial with non-modifiable risk factors including age, female gender, Caucasian or Asian race, and family history. Currently, the most common tool to measure bone mineral density is the dual energy X-ray absorptiometry (DEXA) scan. The World Health Organization has published diagnostic criteria for osteopenia and osteoporosis based upon DEXA scans.¹⁰

The current study examined whether the rising use of aromatase inhibitors impacted bone health among postmenopausal women diagnosed with breast cancer in Hawai'i. The study also determined whether community practice followed national guidelines for bone health among these women. The study compared aromatase inhibitors and tamoxifen by evaluating fracture rates, frequency of DEXA scans, and use of bone modeling agents.

Methods

Database

Data used were administrative data from the major third party payer for health insurance in Hawai'i, which insures approximately half of the state's population. Information on ethnicity was obtained from respondents to a satisfaction survey mailed to a random sample of members. Response rates averaged about 50% across the study years. Bone mineral density studies were identified using CPT-4 codes 76070, 76071, 76075, 76076, 76078, 76977, 78350, G0130, G0131, and G0132. Fractures were recorded using the ICD-9 codes for femur and hip (820, 821), vertebra (805, 806), and wrist fractures (814).

Study Population

Women were eligible for the study if they were age 50 or older, had a diagnosis of breast cancer (ICD-9 diagnosis code 174), and a prescription for an aromatase inhibitor or tamoxifen between the years 1999 and 2006. As the administrative database did not specifically identify post-menopausal status, the age minimum was set at 50 to limit the study primarily to postmenopausal women. Aromatase inhibitors included anastrozole, letrozole, and exemestane. Bisphosphonate use by the patients included oral regimens like ibandronate,

risedronate, and alendronate, but intravenous forms like pamidronate and zoledronic acid were excluded since these drugs are used in women with metastatic breast cancer to bone. Calcitonin use was also included as a bone health agent. For the analyses, patients were divided into those women ages 50 to 59 years, 60 to 69 years, and those greater than 70 years.

The protocol for this study was granted an exemption from institutional review board (IRB) review by the University of Hawai'i IRB.

Statistical Analysis

Descriptive variables of interest included use of chemotherapy and radiation therapy, age, and prior use of hormone replacement therapy. Dependent outcomes included fracture, DEXA scans, and bisphosphonate or calcitonin use. All analyses were performed using the SAS Enterprise Guide version 3.0. Regression analyses employed generalized estimating equations. Information for regression analyses were summarized by year and the analyses were corrected for the clustering of repeated years of measurements within patients. Use of a bisphosphonate or calcitonin was modeled as an outcome using logistic regression. The number of fractures was modeled using Poisson regression. The denominator was based on the patients' length of enrollment and not by calendar year. Therefore, the Poisson model included an 'offset,' a known constant giving the days of enrollment with the insurer during the year. The Poisson regression model included the Pearson adjustment of the standard errors to account for possible overdispersion.

Characteristics	Percent (Number)
Age group	
50-59	33.8% (353)
60-69	33.4% (348)
70 and older	32.8% (342)
Ethnicity	
Japanese	43.5% (316)
Caucasian	24.8% (180)
Hawaiian	12.8% (93)
Chinese	7.3% (53)
Filipino	5.6% (41)
Other	6.0% (44)
Past estrogen use	
Yes	44.5% (579)
No	55.5% (464)
Chemotherapy	
Yes	39.0% (639)
No	61.0% (407)
Radiation	
Yes	63.0% (657)
No	37.0% (386)

316 participants were missing ethnicity

Results

Table 1 shows the distribution of characteristics for the 1,043 patients included in the analyses. Patient age was evenly distributed between ages 50 to 59, 60 to 69, and greater than 70 years old. For this study, ethnicity was established through survey responses. Patients of Japanese ethnicity were the most common respondents followed by Caucasian and Hawaiian women. Forty-four percent of women had a history of estrogen use. Thirty-nine percent of women received chemotherapy for breast cancer and 63% received radiation therapy for breast conserving therapy.

As shown in Figure 1, tamoxifen was the principal agent used to treat early stage breast cancer patients in Hawai'i during 1999. A decline in tamoxifen use began during 2002; however, it remained a commonly prescribed agent. In 2006, 29% of women were treated with tamoxifen. While the use of tamoxifen decreased, aromatase inhibitor use steadily increased from 2002 to 2006. During 2006 aromatase inhibitors were prescribed 71% of the time.

Compared to women taking tamoxifen, women taking aromatase inhibitors in Hawai'i had an increased rate of fractures as shown in Figure 2. There were 19 hip fractures, 20 spine fractures, and 4 wrist fractures during the 8 year interval. After adjusting for age, the relative rate for fractures over the length of follow-up was 2.42.

Use of DEXA scans for postmenopausal women on tamoxifen has remained essentially stable with about a quarter of patients receiving bone imaging (Table 2). Although there was an initial rise in the use of dual energy absorptiometry scans for patients on aromatase inhibitors, there has been a slight decline in use since 2005. Usage peaked in 2004 when 38.1% of patients on aromatase inhibitors also received DEXA scans. Approximately one-third of patients on aromatase inhibitors received dual energy absorptiometry scans. The use of bone health agents to prevent osteoporosis was greater in women on aromatase inhibitors with an age-adjusted odds ratio of 1.86 (Figure 3).

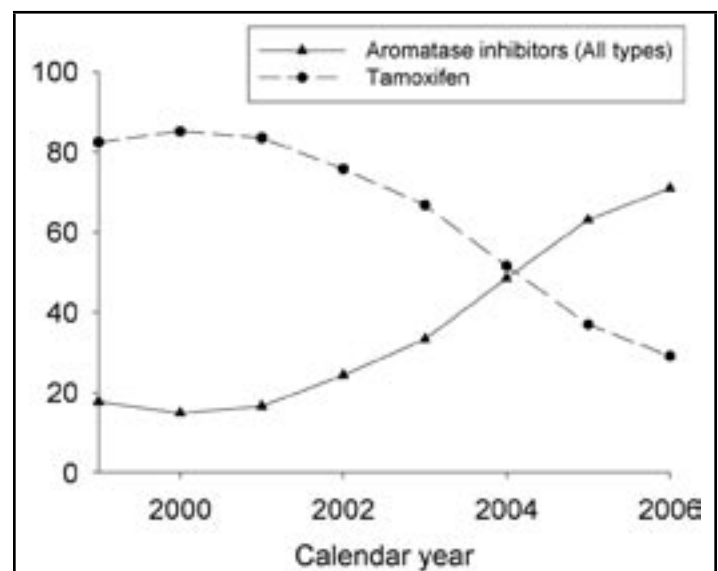


Figure 1.— Frequency of aromatase inhibitor and tamoxifen use from 1999 through 2006.

Discussion

We wanted to investigate trends in endocrine therapy use in Hawai'i. Since aromatase inhibitors may adversely affect bone health, we compared fracture rates among the treatment groups and frequency of DEXA scans and bone health modulators. While aromatase inhibitors may have better clinical efficacy, the effect on health care costs is not insubstantial.

Since 2002, use of aromatase inhibitors has increased dramatically when results of the anastrozole, tamoxifen, and combination (ATAC) trial were initially reported.¹ However, tamoxifen remains a commonly prescribed endocrine agent for the treatment of breast cancer in postmenopausal women despite its higher toxicity profile. The continued use of tamoxifen could be related to concerns over the skeletal effects of aromatase inhibitors. Despite the negative effects of aromatase inhibitors on bone health, there was less use of dual energy absorptiometry scans than recommended by national guidelines. The insurer allows bone mineral density testing every two years so the 30.8% use of DEXA scans during 2006, for example, is less than expected. The use of DEXA scans among patients taking tamoxifen remained relatively consistent across the study years. Bisphosphonates or calcitonin were used about twice as often by women taking aromatase inhibitors compared to women taking tamoxifen.

Our study limitations include a short length of follow-up, lack of cancer staging information, and potential problems regarding the accuracy of administrative data. In order to address some of these limitations, we attempted to capture early breast cancer patients by

type of chemotherapy, use of breast conserving therapy, and excluded some medications approved in the metastatic setting.

We found that women in Hawai'i with breast cancer on an aromatase inhibitor are 2.5 times more likely to have suffered a fracture compared to women on tamoxifen. The evidence also suggested that these women were not receiving DEXA scans as often as recommended which may contribute to an under diagnosis of osteoporosis and osteopenia. This in turn could affect bone health by limiting the use of bisphosphonates and other bone health agents. It is unclear from our study whether the lack of screening with DEXA scans is due to the practices of prescribing physicians or to lack of compliance by the patient population. More community-based education and awareness is essential to prevent the substantial morbidity and potential mortality from fractures among the population of breast cancer survivors in Hawai'i.

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

Acknowledgements

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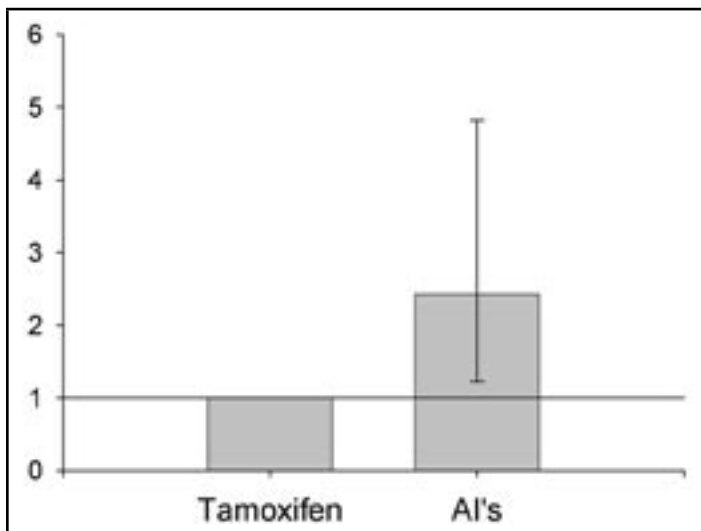


Figure 2.— Age-adjusted relative rate of fractures comparing endocrine therapies for breast cancer patients.

Table 2.— Percentage of dual energy X-ray absorptiometry scans by calendar year and drug treatment.

Year	Tamoxifen (%)	Aromatase Inhibitors (%)
2002	21.6	26.3
2003	25.1	33.7
2004	23.1	38.1
2005	34.8	37.7
2006	28.0	30.8

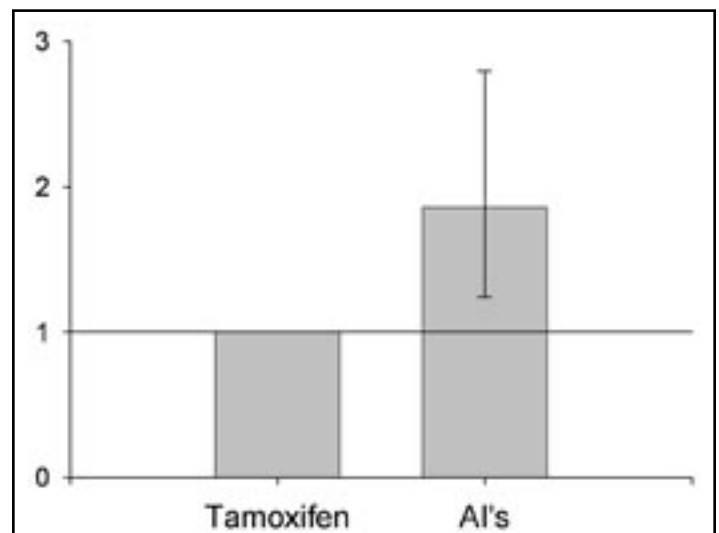


Figure 3.— Age-adjusted odds ratio of using bone health medications by women while on endocrine therapy.



Issues in Medical Malpractice XII

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

Question: In order to relieve intractable pain in a terminally-ill patient, Doctor D administered increasing amounts of morphine. This led to respiratory arrest and hastened the patient's death. Doctor D's action is:

- A. The legal cause of patient's death.
- B. Medical malpractice.
- C. The intentional tort of assault and battery.
- D. An example of 'double effect.'
- E. Homicide.

Answer: D. The 'double effect' phenomenon describes the situation where a foreseeable adverse outcome supervenes even though the intent is to provide a beneficial effect. The principle is clinically invoked to permit the aggressive use of comfort measures such as narcotics in terminally ill patients – even though they may hasten death. It is cognizable in both law and ethics as legitimate and acceptable practice.

The usual rationalization is to find the act did not cause death (the underlying terminal disease, not the narcotic, was the cause of death), or to find no duty to treat where the withholding or withdrawal of life-sustaining treatment led to early death. The very rare prosecution of physicians for homicide under these types of circumstances has never been successful.

Even if we accept there is causation, a civil suit would fail because there is no breach of the standard of care and therefore no negligence. This is also not an assault and battery, which is an intentional act that causes apprehension of or actual offensive touching without consent. Consent in this clinical setting has usually been explicitly given by the patient or the surrogate decision-maker, or is implied.

Failure to Adequately Treat Pain

Pain management and comfort care become primary treatment goals once cure is impossible. Dying patients fear pain will not be aggressively treated, and studies repeatedly show that physicians do not adequately treat pain. In addition to providing pain relief, physicians should communicate their plans regarding palliative care by using open-ended questions, screening for unaddressed spiritual concerns, and listening actively and with empathy.¹ Both the legal and ethical literature consistently attest to the principle that it is fully permissible to prescribe narcotics in sufficient dosage to effectively relieve pain, even if death is hastened because of respiratory depression or other systemic effect. This phenomenon is termed the 'double effect.'

In a recent California trial that received widespread media coverage, an Alameda County jury turned in a verdict against an internist charged with elder abuse and reckless negligence because he failed to give enough pain medication to a Hayward man dying of cancer.² Under California law, death of a plaintiff extinguishes a claim for

pain and suffering. The case was therefore brought under the elder-abuse law, although the burden of proof was higher, requiring a reckless rather than a simple negligence standard.

The case involved William Bergman, an 85-year-old retired railroad worker with lung cancer, who was admitted to Eden Medical Center in early 1998. The lawsuit alleged that the treating physician was reckless in not prescribing effective medication for Bergman who complained of severe back pain. Bergman stayed at the hospital for 6 days as nurses consistently charted his pain in the 7-10 range. On the day of discharge, his pain was at level 10. He died at home shortly thereafter.

After 4 days of deliberation, the jury, in a 9-3 vote, entered a guilty verdict, and awarded \$1.5 million in general damages. This amount was subsequently reduced to \$250,000 because of California's cap on non-economic damages. Eight jurors wanted to award punitive damages, as they believed that the doctor had acted with malice or had intentionally caused emotional distress. However, no punitive damages were assessed because 9 votes were needed. The hospital had settled privately with the family before trial. The guilty verdict came despite defense expert testimony that the treatment provided was reasonable and would be the same as that provided by 95% of all internists.

Bergman's family had earlier filed a complaint with the California Medical Board, which took no action despite a medical consultant's conclusion that the hospital's pain management was inadequate. The Board felt that it lacked clear and convincing evidence to find a violation of the Medical Practice Act. The verdict prompted a state legislator to author a bill that would require all California doctors to take a pain management course!

The *Bergman* case is notable for being the first of its kind, and squarely puts physicians on notice regarding their duty to adequately provide pain relief. The closest previous case of liability for failure to treat pain involved a nursing home's failure to administer pain medications that had been ordered by the doctor.³

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

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7/2-7/5	IMG	Methodist Healthcare	The Fairmont Orchid, Kona	Geriatrics for the Primary Care Physician	Tel: (901) 516-8933 Web: www.methodistmd.org
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7/29-8/03	R	University of California, San Francisco	Fairmont Orchid Hawai'i, Kamuela	Breast Imaging	Tel: (415) 476-5808 Web: www.cme.ucsf.edu
7/30-8/3	ORS	Department of Orthopaedic Surgery, Kaiser Permanente Hawai'i	Grand Wailea Resort & Spa, Maui	15th Annual Update in Orthopaedic Surgery, Hawai'i 2007	Tel: (877) 843-8500 Web: www.cmstravel.com
7/30-8/2	IM	University of California - Davis	Mauna Lani Bay Resort, Kohala Coast	New Advances in Internal Medicine	Tel: (866) 263-4338 Web: cme.ucdavis.edu
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8/1-8/4	N	Mayo Clinic College of Medicine	Hapuna Beach Prince Hotel, Kohala Coast	Mayo Clinic Practical 21st Century Clinical Neurology Review	Tel: (480) 301-8323 Web: www.mayo.edu/cme/
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8/5-8/11	IM, FM	Keck School of Medicine of USC	Ritz-Carlton Kapalua, Maui	50th Annual Refresher Course in Medicine	Tel: (800) 872-1119
8/9-8/10	Multi	Kaiser Permanente	Ihilani Resort & Spa, Honolulu	6th Annual Pai Symposium	Tel: (808) 432-7931
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8/15-8/18	EM	University of California - Davis	Waikoloa Beach Resort & Spa, Hawai'i	Emergency Medicine Update: Hot Topics 2007	Tel: (866) 263-4338 Web: cme.ucdavis.edu
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9/24-9/29	END	Mayo Clinic College of Continuing Medical Education	Hyatt Regency, Maui	20th Annual Techniques in Advanced Gynecologic, Endoscopic & Laparoscopic Surgery	Tel: (480) 301-4580 Web: www.mayo.edu/cme/
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10/6-10/12	PD	University Children's Medical Group	Hyatt Regency Maui Resort, Maui	"Aloha Update" Pediatrics 2007	Tel: (800) 354-3263 Web: www.ucmg.org/cme.html
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10/10-10/13	OMF	American Association of Oral and Maxillofacial Surgeons (AAOMS)	Hawai'i Convention Center, Honolulu	89th Annual Meeting & Scientific Sessions	Tel: (847) 678-6200 Web: www.aaoms.org
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10/18-10/20	GE	Stanford Hospital & Clinics	Mauna Lani Bay Resort, Kohala Coast	GI Cancers	Tel: (650) 724-7166 Web: www.cme.stanfordhospital.com
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November 2007					
11/10-11/13	Multi	American Medical Association	Hawai'i Convention Center, Honolulu	AMA Interim Meeting	Web: http://www.ama-assn.org/

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psychology, sociology, comparative religions, and the impact on patient-doctor decisions, art and music as disciplines for expression and for enhancing observational skills, writing from different perspectives (doctor, patient, and family), drama, and dance.

Collaboration between JABSOM and UH Manoa Department of Arts and Humanities is seen as an appropriate and complimentary use of expertise and resources.

Desired outcomes would extend this medical humanities curriculum to include other important members of the medical team, nurses, health and social workers. Future programs might include continuing medical education courses (CME) for physicians and a fellowship in medical humanities at JABSOM.

The practice of medicine delicately balances humanism and science. The goal is to foster a greater understanding of the human condition; how health, illness, and suffering are experienced by both patient and physician. As such, humanism can be modeled by teachers, but is also reflected in philosophy, ethics, theology, history, literature, art, music, language, and the social sciences. It is hoped that a balance of science and humanism will help to create physicians with an enhanced understanding of the holistic nature of good medicine, public and social issues in health care, and the need

for cooperation with patients, families, allied health professionals, and alternative care providers.¹¹

Life and medicine are not only about the collection and synthesis of facts, but the ability to explore. JABSOM is geographically, culturally, academically, and philosophically ripe for development of such a program.

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Russell T. Stodd MD

❖ TECHNOLOGY IS RAPIDLY FILLING OUR LIVES WITH DEVICES SMARTER THAN WE ARE.

While the concept of a “bionic eye” has been around for decades, a device to help a blind person actually see is approaching reality. At Stanford University, physicist Daniel Palanker, PhD, and associates have developed a three millimeter chip which can be implanted behind the failing retina to theoretically produce a ten degree field with visual acuity of 20/80. The patient would wear a pair of goggles mounted with a mini-video camera. The camera transmits a wireless message to a wallet-size computer which relays the message

back to an infra-red screen on the goggles, which is then transmitted to the retinal implant. Voila! The patient can read the headlines, enjoy Saturday Night Live, and live independently. Please don't step on the goggles.

❖ RESULTS OF THE TEXAS CHAIN SAW MASCARA.

Dry eye disease afflicts millions of Americans, especially women over age forty. It is estimated that 25% of eye-doctor visits are for dry eye complaints. Multiple factors can be a cause such as hormone imbalance, contact lens wear, after eyelid or lasik surgery, or environmental conditions such as air conditioning, wind, dust, and allergies. For some the problem can be serious and debilitating, but typically these patients receive perfunctory treatment. The doctor is likely to recommend increased blinking, or lacrimal punctum plugs, or over the counter moistening agents. These may yield transient relief, but are only temporarily effective. Allergan's prescription eye drop, Restasis, works for some, but fails for others. Moreover, many solutions are expensive. Pharmaceutical people now recognize that the market for a successful product can reach annual sales of \$1.5 billion. Now there are about 20 products in various stages of research, such as Alcon's low-dose steroid eye drop which should hit the FDA in 2009. AMO also has a dry-eye development program underway. Show me the money!! gets action every time.

❖ PLEASE NO MORE CHEESE! I JUST WANT OUT OF THE TRAP.

So what is next? Doctors with badges and issuing subpoenas? Six states, California, Delaware, Nevada, New Jersey, Oregon, and Pennsylvania, now require physicians to report people who may be unfit to drive, such as elderly patients with significant disease. Moreover, the feds even want doctors to document immigrants who come for help. Obviously it is necessary to report child abuse or elder abuse, but what about the pregnant sixteen-year-old girl who had consensual sex with an adult male? Failing to report is risky and may make the physician vulnerable to serious penalties, such as fines or even imprisonment. And is it wise to report female abuse when the police fail to lock up the abuser, and the woman has to return to the same home? Will patients seek help if they think the physician cannot be trusted to keep medical care confidential? It is the physician's role to always do what he/she feels is medically best for the patient within the parameters of ethics and logic. Please get the politicians and various government agencies out of the house of medicine.

❖ MAUI BUMPER STICKER - YOU WOULD DRIVE BETTER WITH THAT CELL PHONE UP YOUR A***.

A survey released by Nationwide Mutual Insurance showed that DWD, “driving while distracted,” is very prevalent. Of those who responded, 59% do not consider themselves distracted drivers, but 80% admit to multi-tasking on the road. As might be expected 73% confess to talking on cell phones, and 37% of young adults admit to text-messaging! Almost half of respondents (48%) said they eat a full meal while motoring. Less common DWD events were reading a book, putting on contact lenses, watching a movie, nursing a baby, and even changing seats with a passenger. OMG (oh my god) be careful out there!

❖ WOW! THIS LOOKS REALLY WEIRD. MOVE THE CAMERA OVER THIS WAY.

In Massachusetts, state representative Martin Walsh, a Democrat, has introduced a bill that would require licensed hospitals to make video and audio recordings of all surgeries. His expectation is that this would protect patients and possibly expose medical errors. Just what is needed in the OR; putting doctors and patients in adversarial positions! Both doctors and plaintiff attorneys do not like the bill and state that it would do more harm than good. The Massachusetts Medical Society is against the bill and President Kenneth Peelle, MD, stated that the measure implies that the surgeon is not to be trusted. Also, it is one more distraction to impair the surgeon's judgement.

❖ IF A WOMAN'S PLACE IS IN THE HOME, WHAT WAS SHE DOING IN THAT PICKUP?

In Arlington, Texas, a 38-year-old man arrived home earlier than expected. He found his wife having sex in the back of a pick-up parked in the driveway. When the woman saw her husband she screamed rape, so the man shot and killed the “rapist.” Subsequent investigation revealed that the sex was not rape, and that the woman had a relationship with the victim. The husband was not prosecuted and the police accepted that he was trying to defend his wife. The grand jury indicted the wife for “reckless behavior which caused the death” and she faces from two to thirty years in prison if convicted.

❖ THERE'S A SNAKE IN THE GARDEN OF WAL-MART!

In central Florida a man shopping in the garden section of a Wal-Mart store was bitten by a pygmy rattlesnake. The man tried to shake off the snake which was clinging to his finger, stepped backward into his shopping cart and fell, injuring his back. The snake's venom is poisonous and the man was hospitalized when his hand was paralyzed. Subsequent research revealed that at least seven other cases of snake bite have occurred at Wal-Mart garden centers. Of course, no need to worry at Hawai'i's Wal-Mart stores since snakes are banned in our state, but do the snakes know that?

❖ THE OTHER SENSES BELIEVE THEMSELVES. THE EARS BELIEVE OTHER PEOPLE.

In recent years media moguls Larry King, Paul Harvey, and others have been extolling the benefits of garlic with the claim that it lowers low density (bad) cholesterol (LDL). Oops! According to a study done at Stanford University and published in the Archives of Internal Medicine, it just ain't so. Researchers studied 192 adults with moderately high cholesterol for six months, and each was given either raw garlic or a garlic supplement while a control group received a placebo. The effect on LDLs was zero. It was noted that the placebo did not cause as many people to back away.

❖ EDUCATED INTELLIGENCE IS NO MATCH FOR NATURAL STUPIDITY.

A book on sale at the Grand Canyon National Park describes how this natural wonder was actually formed about five thousand years ago by Noah's biblical flood. Apparently, in order to avoid offending religious fundamentalists, the National Park Service was directed to suspend its belief in geology. Most geologists agree that the Grand Canyon was formed by the Colorado River about six or seven million years ago. The American Geological Institute and seven geo-science organizations sent letters to the Park Service asking that the book be removed. Because many park employees were enraged, the book was moved from the natural science section of the bookstore to the inspirational rack. The book completely sold out, presumably to non-scientific park visitors for something to read while waiting for the “rapture.”

ADDENDA

❖Memo to Al Gore: There's global warming on Mars. According to the US Geological Survey in Flagstaff, Arizona, Mars southern ice cap is shrinking and has lost billions of tons of carbon dioxide over the last four Martian years, and air temperatures may have increased as much as four deg. Celsius. Something should be done. More hybrid cars, perhaps?

ALOHA AND KEEP THE FAITH — rts■

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