

Identifying the Causes of Cancer Health Disparities: Biologic and Non Biologic Determinants

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Abstract

The causes of cancer health disparities amongst Pacific Islanders and other racial groups are complex and multifactorial. Both biologic and non biologic determinants have been identified as causal factors. Racial/ethnic classification can be used as a surrogate for non biologic determinants such as place of geographic origin, socioeconomic status, cultural practices, and diet. Given that non biologic and biologic determinants are not mutually exclusive, using racial/ethnic classification may be hypothesis generating and assist in the identification of biologic determinants such as infections, toxins, and/or environmental exposures that lead to carcinogenesis. This commentary provides several examples of cancer specific biologic determinants that may lead to cancer health disparities. It also discusses specific non biologic determinants of cancer health disparities that must be overcome in order to increase participation of underserved populations in clinical trial research. Taken together, these examples demonstrate the need to further our understanding of the determinants of cancer health disparities that can lead to the enactment of preventive measures and/or targeted therapies.

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Introduction

The causes of cancer health disparities in underserved populations such as Pacific Islanders are multifactorial and complex (Palafox, Buenconsejo-Lum et al. 2002; Tsark and Braun 2007; Tanjasiri and Tran 2008). Medical advancements that have been made in the early detection, diagnosis, and treatment of cancer have not been realized by all racial/ethnic groups in our society (Brawley and Berger 2008; Goss, Lopez et al. 2009). Although Pacific Islander-specific data is lacking, determinants of cancer health disparities as identified from other populations can be generally categorized into biologic and non biologic factors. The most identifiable and better understood causes of cancer health disparities are non biologic determinants including lack of access to quality health care, cultural barriers between health care providers and patients, and lack of education. The articles in this issue of the Journal document efforts within different Pacific Islander

communities in Southern California to further understand and resolve some of these disparities. These efforts predominately focus on overcoming non biologic determinants of cancer health disparities. This paper will describe recently identified potential biologic determinants that may lead to differences in cancer outcomes between racial groups, including Pacific Islanders. As biologic and non biologic determinants are not mutually exclusive, it will also discuss some of the important non biologic factors that need to be addressed in order to increase our understanding of, and identify solutions for, this complex problem.

Using Racial/Ethnic Classifications to Identify Potential Biologic Determinants

Recently, several articles have been published attempting to identify biologic determinants of racial disparities by analyzing data collected on participants in National Cancer Institute (NCI)-sponsored cooperative group clinical trials. The

advantage of analyzing clinical trial data includes standardized enrollment criteria, treatment, and follow-up. The largest study reported on over 19,000 adult cancer patients enrolled in Southwest Oncology Group (SWOG) randomized phase III clinical trials from October 1, 1974 through November 29, 2001 (Albain, Unger et al. 2009). Nearly 12% identified themselves as African Americans. After adjustment for prognostic, treatment, and socioeconomic factors, African American race was associated with increased mortality from early-stage premenopausal breast cancer, early-stage postmenopausal breast cancer, advanced-stage ovarian cancer, and advanced-stage prostate cancer but not from lung cancer, colon cancer, lymphoma, leukemia, or myeloma. The authors concluded that their findings “suggest that unrecognized interactions of tumor biological, hormonal, and/or inherited host factors must be contributing to differential survival outcomes by race (page 991).”

As Brawley aptly points out in his editorial (Brawley 2009), as well as in several correspondences sent to the editor, there are definite limitations to this study (Rosenberg, Maneshe, et al. 2010; Gravlee and Mulligan 2010). These commentaries discussed potential confounders in their study such as using zip code area income and education data as surrogates for socioeconomic status (SES) and not adjusting for racial differences in body mass index (BMI). Higher BMI has been linked to higher risk of ovarian and breast cancer (Huang, Hankinson et al. 1997; Renehan, Tyson et al. 2008; Leitzmann, Koebnick et al. 2009). Interestingly, a similar analysis done on 97 black women and 1392 white women with advanced ovarian cancer enrolled in Gynecologic Oncology Group (GOG) randomized clinical trials did not demonstrate significant differences in survival outcomes by race (Farley, Tian et al. 2009).

So what can we conclude from these recent reports? Can we say that African Americans and Caucasians enrolled on a clinical trial and given similar treatment will have similar outcomes? Or will one group have worse outcomes compared to the other despite similar treatments? My

answers are “yes”, and “yes.” As we are learning more about the biology of tumors we are finding that not all cancers are created equally. As we probe the genetic and molecular make up of these cancers we find that certain characteristics can portend to either higher or lower probabilities of response to therapy, risk of relapse, and overall survival. But what causes these genetic and biological differences? In almost all cases we do not know, but most genetic mutations found in cancers are somatic mutations and not germ-line mutations, meaning they are acquired mutations and not inherited (DeVita, Lawrence et al. 2008). It would not be surprising to find that certain racial groups, such as Pacific Islanders, have a higher proportion of mutations with either higher risk or lower risk mutations that may partially explain the differences in outcomes that are apparent amongst racial groups. Race, as Brawley points out (Brawley 2009), “is not a scientific categorization...it is more scientific to think of race as a surrogate for area of geographic origin, socioeconomic status (SES), and culture, all of which can have correlations with disease risk (page 970).” Race then is a surrogate for non biologic determinants of disease and is not a scientific descriptor (Brawley and Berger, 2008). However, as non biologic and biologic determinants are not mutually exclusive, using racial/ethnic classification may be hypothesis generating and assist in the identification of biologic determinants. An improved understanding of biologic determinants may enable us to identify causal factors. Factors such as infections, toxins, and/or environmental exposures that are associated with area of geographic origin, SES, cultural practices, diet or other factors associated with race/ethnicity that may provide opportunities for interventions to eliminate these carcinogens. The next section gives examples in which biologic determinants may contribute to cancer health disparities (Table 1).

Biologic Determinants of Cancer Health Disparities

Specific examples of biologic determinants in breast, gastric, oral pharyngeal, hepatocellular and lung cancers among Pacific Islanders and other ethnic groups demonstrate the value of

Table 1

Examples of biologic determinants that may contribute to cancer health disparities

Tumor Type	Biologic Determinant	Racial/Ethnic Differences in Biologic Determinants	Racial/Ethnic Cancer Disparity
Breast Cancer	Estrogen/progesterone receptor negative (ER-/PR-) breast cancer patients have a worse prognosis	<p>↑ incidence of ER-/PR- breast cancer in African American (AA) women</p> <p>↓ incidence of ER-/PR- breast cancer in Native Hawaiian (NH) women, other determinants must be contributing</p>	Worse breast cancer outcomes for AA and NH women
Gastric Cancer	H. pylori infection and diets high in nitrosamines are associated with gastric cancer	H. pylori infection and diets high in nitrosamines may contribute to gastric cancer in Asian/Pacific Islanders (API)	↑ incidence of gastric cancer in API
Oral Pharyngeal Cancer (OPC)	Improved outcome of human papillomavirus (HPV) positive OPC compared to HPV negative OPC	↑ incidence of HPV positive OPC in Caucasians compared to AA	Worse OPC outcomes in AA compared to Caucasians
Hepatocellular carcinoma (HCC)	Improved outcome of hepatitis C associated HCC treated with sorafenib compared to hepatitis B associated HCC	↑incidence of hepatitis B associated HCC in API	A new treatment that may lead to further cancer disparities
Non Small Cell Lung Cancer (NSCLC)	Improved outcome of EGFR mutated NSCLC treated with an EGFR tyrosine kinase inhibitor compared to EGFR wild type NSCLC	↑ incidence of EGFR mutations in East Asians	A new treatment that may lead to further cancer disparities

further epidemiologic, laboratory, and clinical research in underserved and underrepresented populations in order to advance our understanding of the complex interactions that are leading to carcinogenesis.

Breast Cancer

Native Hawaiian women have the highest breast cancer incidence and mortality rates compared to Hawaii’s other major racial/ethnic groups (Braun, Fong, et al. 2004). For years we have known that breast cancer is a heterogeneous disease with several different subtypes that have significant differences in prognosis and response to therapy (DeVita, Lawrence et al. 2008). Breast cancer patients whose tumors lack expression of estrogen receptors (ER-) and progesterone receptors (PR-) represent approximately 20-30% of breast cancer cases. ER-/PR- tumors do not respond to hormonal therapy and these patients have a worse

prognosis. A majority of these patients will also be negative for the human epidermal growth factor receptor 2 (Her2-). Tumors lacking Her2 expression do not respond to targeted Her2 therapies such as trastuzumab (Herceptin®) or lapatinib (Tykerb®). Recent molecular characterization of breast cancer tumors has identified ER-/PR-/Her2- tumors, also known as basal-like tumors, as being an aggressive subtype with the poorest prognosis (Sorlie, Perou, et al. 2001). Premenopausal African American women have been found to have the highest rates of basal-like tumors (39%) compared to premenopausal non African American women (16%) (Carey, Perou, et al. 2006). Of note however, a recent study of the SEER database found that even when taking into account tumor characteristics, such as hormone receptor status, racial disparities persist (Maneshe, Anderson, et al. 2009; Rosenberg, Maneshe, et al. 2010). Other non biologic

factors, such as access to quality cancer care and/or yet to be determined biologic factors likely contribute to this disparity.

The Multiethnic Cohort study has also analyzed breast cancer hormone receptor status in other racial groups including Japanese and Native Hawaiians living in California and Hawaii (Setiawan, Monroe, et al. 2009). ER-/PR-tumors were most common in African Americans (31%), followed by Latinas (25%), Whites (18%), Japanese (14%), and Native Hawaiians (14%). Despite the lower rate of ER-/PR- tumors, Native Hawaiian women have the worst breast cancer mortality rate compared to Hawaii's other major racial/ethnic groups (Braun, Fong, et al. 2004). Breast cancer health disparities persisted after controlling for age, stage, and ER/PR status (Braun, Fong, et al. 2004; Braun, Fong, et al. 2005). Comparatively, the biologic determinants of breast cancer disparities between African Americans and Native Hawaiians appear to be different. This exemplifies the complexity of cancer health disparities in that different racial/ethnic groups may or may not share biologic and/or non biologic determinants.

Gastric Cancer

Incidence rates of gastric cancer are higher amongst Pacific Islanders and Asian Americans compared to other racial groups (Brawley and Berger 2008; Miller, Chu et al. 2008). In the 1980's, a gram negative spiral bacteria called *Helicobacter pylori* (*H. pylori*) was initially described in patients with gastritis and peptic ulceration (Marshall and Warren 1984). Further epidemiologic studies would later identify an association between gastric cancer and *H. pylori* infection (IARC 1994; Nomura, Kolonel et al. 2005). However, only a minority of *H. pylori* infected cases have been found to develop gastric cancer (Correa and Houghton 2007). It has become evident that other environmental or host carcinogenic factors must be involved. Epidemiologic studies have identified an association between gastric cancer and the increased consumption of nitrosamine containing compounds found in pickled foods, smoked, and processed meats (Kolonel, Nomura et al. 1981; Jakszyn, Bingham et al. 2006). A

recent five-year prospective dietary study in rhesus monkeys found a synergistic carcinogenic effect in those monkeys infected with *H. pylori* and given a diet high in nitrosamines compared with either alone (Liu, Merrell et al. 2009). Interestingly, the increased incidence of gastric cancer in East Asian countries geographically correlates with an endemic *H. pylori* subtype (Yamaoka, Kato et al. 2008). This subtype of *H. pylori* has also been found to have a greater carcinogenic potential when compared to other subtypes in a mouse model (Miura, Ohnishi et al. 2009). These findings would suggest that the higher incidence of gastric cancer in Asian Americans and Pacific Islanders may be related to the carcinogenic effects of dietary nitrosamine intake and *H. pylori* infections that are endemic to areas of geographic origin. It also begins to identify populations at increased risk for gastric cancer for whom screening and preventive strategies, such as dietary modification and *H. pylori* eradication, may be effective in decreasing cancer health disparities.

Oral Pharyngeal Cancer (OPC)

OPC is a subset of head and neck cancer. Pacific Islanders and African Americans have a higher incidence and mortality rate of OPC compared to other ethnic groups (Brawley and Berger 2008; Haddock, 2005). Human papillomaviruses (HPV) are known causes of anal and cervical cancer (Devita, Lawrence et al. 2008). HPV is transmitted through unprotected vaginal, anal, or oral sex. Recently, HPV infection has been identified as a causative agent of OPC (D'Souza, Kreimer, et al. 2007; Mork, Lie, et al. 2001). Interestingly, patients with HPV positive OPC have an improved therapeutic response and survival compared to HPV negative OPC (Fakhry, Westra et al. 2008). In a retrospective study of a randomized phase III trial in patients with head and neck cancer the racial outcome disparity in overall survival between African Americans and Caucasians was entirely due to the disparity in the subset of patients with OPC (Settle, Posner et al. 2009). HPV-positive tumors were detected in 34% of Caucasian patients compared to only 4% in African American patients. Thus, it appears that the cancer health disparity between African Americans and Caucasians with OPC who

receive equal quality cancer care can be explained by a higher prevalence of treatment sensitive HPV positive tumors in Caucasians compared to African Americans.

So how do we account for the difference in HPV incidence in OPC between Caucasians and African Americans? A US national survey of adolescent males found that Caucasian males were 2.7 times more likely to engage in oral sex compared to African American males and were 1.4 times more likely to receive oral sex from a female (Brawley 2009; Gates and Sonenstein 2000). Another national survey found that Caucasian adolescent females were twice as likely as African American females to engage in oral sex (Brawley 2009). These surveys would suggest that the increased prevalence of HPV positive OPC in Caucasians may be attributable to higher rates of oral sex practices compared to African Americans. More importantly these findings support enactment of measures (HPV vaccination, education) to prevent HPV infection and subsequent OPC for all sexually active people. To my knowledge, the proportion of HPV positive OPC in Pacific Islanders has not been reported.

Hepatocellular Carcinoma (HCC)

Incidence and mortality rates of HCC amongst Pacific Islanders and Asian Americans are also significantly higher compared to other racial groups (Brawley and Berger 2008; Miller, Chu et al. 2008). HCC is a type of cancer that largely occurs in patients with liver cirrhosis secondary to viral hepatitis B and/or C, alcoholism, or other causes of chronic liver damage. Sorafenib (Nexavar[®]) is an oral multi-kinase inhibitor that was recently studied in a randomized placebo controlled phase III clinical trial of 602 patients with advanced HCC. Participating centers were mostly located in the United States (US) and Europe. The sorafenib treated group demonstrated an increase in median overall survival of 10.7 months compared to 7.9 months in the placebo group ($p < 0.001$) (Llovet, Ricci et al. 2008). A similar phase III clinical trial enrolling patients from Asia demonstrated improvement in median overall survival in the sorafenib treated group from 4.1 to 6.2 months (Cheng, Kang et al. 2008). Although the margin

of benefit was similar between trials, the patients in the Asian study did worse overall. The explanation given by the study investigators is that the patients in the Asian study had more advanced disease based on a higher number of tumor sites and lung metastases and poorer performance status compared to those on the US/European based study. Other factors may be contributing to this difference.

It is important to note that the proportion of patients with hepatitis B was higher in the Asian study. Conversely, the proportion of patients with hepatitis C was higher in the US/European based study. These patients appear to have an improved response to sorafenib compared to patients with hepatitis B or alcoholic cirrhosis based on a subgroup analysis which demonstrated a median overall survival of 14.0 months with sorafenib therapy versus 7.9 months with placebo (Bolondi, Casparly et al. 2008). Ongoing research may provide further insight as to the role that race and hepatitis virus subtypes may play in the sorafenib treatment outcomes of advanced HCC. If hepatitis B associated HCC patients have a decreased response to sorafenib compared to hepatitis C associated HCC patients, this may in fact increase cancer health disparities. However, it may also provide evidence that the development of hepatitis and carcinogenic pathways in HCC differs depending upon the causative mechanisms involved.

Lung Cancer.

Lung cancer is divided based on tumor tissue histology into two types, small cell lung cancer and non small cell lung cancer (NSCLC) (DeVita, Lawrence et al. 2008). NSCLC makes up a heterogeneous group of several different histological subtypes including adenocarcinoma and squamous cell carcinoma. Recently, it has been found that specific mutations of the epidermal growth factor receptor (EGFR) gene correlates with increased sensitivity and improved response to drugs that inhibit EGFR tyrosine kinase activity (Lynch, Bell et al. 2004). An analysis of lung tumor samples from the US, Japan, Taiwan, and Australia found that these mutations are significantly more common in patients of East Asian ethnicity versus other

ethnicities (30% versus 8%) (Shigematsu, Lin et al. 2005). These mutations were also more common in never smokers versus ever smokers (51% versus 10%), in adenocarcinomas versus cancer of other histologies (40% and 3%, respectively), and in females versus males (42% and 14%, respectively). African American lung cancer patients also appear to have a lower incidence of these mutations (Leidner, Fu, et al. 2009). To my knowledge, the proportion of Pacific Islanders with EGFR mutations has not been reported.

A recently reported phase III trial conducted in East Asia randomized never smokers or former light smokers with metastatic lung adenocarcinoma to standard cytotoxic chemotherapy versus gefitinib (Iressa®), an oral EGFR tyrosine kinase inhibitor (Mok, Wu et al. 2009). In this select population the EGFR mutation rate was over 50%. EGFR mutated patients treated with gefitinib had a significantly longer progression free survival compared to EGFR mutated patients treated with cytotoxic chemotherapy. Conversely, EGFR wild type patients treated with cytotoxic chemotherapy had a significantly longer progression free survival compared to EGFR wild type patients treated with gefitinib. The etiology of EGFR mutations has yet to be identified. Further defining the subset of patients with these mutations may provide insight into potential carcinogenic causes of this type of lung cancer. Interestingly, this new therapy may actually lead to more cancer health disparities.

A better understanding of the causes of acquired mutations and carcinogenesis will help us identify factors within our environment, i.e., diet, toxins, infections, or other exposures, that could lead to improved preventive measures and a likely decrease in cancer disparities. Currently, the lack of participation of underserved populations in clinical trials reduces opportunities to discover effects that may be particularly relevant to these communities and contribute to inequitable distribution of benefits and risks of trial participation. Pacific Islanders comprised only 0.25% of all NCI sponsored clinical trials (NCI 2008). Improving clinical trial participation will be a vital part in

extending advances in cancer care to all underserved populations. The non biologic determinants addressed henceforth contribute to the lack of participation of underserved populations in clinical trial research.

Non Biologic Determinants Contributing to Low Minority Participation in Cancer Clinical Trials

Unfortunately, in the United States today, there are several social, political, and economic issues facing underserved populations that must be resolved if we are going to reduce cancer health disparities. It is projected that over the next 20 years the burden of cancer in the United States is expected to increase by 45% between 2010 and 2030 (Smith, Smith et al. 2009). Most of this increase is attributable to an increased incidence in older adults and racial minorities. By 2030, more than an 100% increase in the incidence of most individual cancer sites is projected for Asian Americans and Pacific Islanders (Smith, Smith et al. 2009). These projections exemplify the need to further understand and address the multiple factors that contribute to cancer health disparities.

Quality Health Insurance.

Pacific Islanders in California have lower rates of health insurance coverage compared to Caucasians (Brown, Ponce et al. 2001). From 2000 to 2005 the percentage of US citizens without health insurance continued to increase from 14.2% to 15.9% (Goss, Lopez et al. 2009). Racial minorities have lower rates of health insurance which results in significant barriers to receiving health care (Ward, Halpern et al. 2008). Lack of health insurance is associated with lower rates of cancer screening, advanced stage at time of cancer diagnosis, and increased cancer mortality (Halpern, Ward et al. 2008; Ward, Halpern et al. 2008). Patients without insurance are also less likely to participate in cancer clinical trials (Colon-Otero, Smallridge et al. 2008) further limiting our understanding of the cancer experience in minorities. The passage of the Patient Protection and Affordable Health Care Act provides guaranteed health insurance for clinical trial participants and removes lifetime caps on insurance coverage (ASCO 2010). These changes should lead to increased

participation of minorities in cancer clinical trials but how large of an effect this will have is unclear.

Improving Patient-Provider Relations for Underserved Populations.

Although providing quality health insurance to all would be a huge step forward, not all cancer disparities would be resolved (Bach, Schrag et al. 2002). Pacific Islander and other minority cancer patients described increased problems with coordination of care, access to care, and dissemination and understanding of health and treatment related information (Ayanian, Zaslavsky et al. 2005; Tanjasiri, Kagawa Singer et al. 2002). These problems were significantly worse amongst non-English speaking cancer patients. Not surprisingly, provider-patient communication has been identified as an important factor in patient's decision making on participation in clinical trials (Albrecht, Eggly, et al. 2008). A patient's sense of trust and confidence in their treating physician was significantly associated with the patients' decision to participate in a clinical trial. Decreasing language and cultural barriers in provider-patient relationships would likely improve minority participation in cancer clinical trials.

Integration and education of the cancer care work force are two measures that may help to decrease cultural and language barriers. Unfortunately, only 13% of U.S. medical students are African American, Hispanics/Latinos, or Native Americans, even though these populations comprise 25% of the total U.S. population (AAMC 2005). At the University of California medical schools, only 17% of the 2005 new enrollments were African American, Hispanics/Latino, or Native Americans despite California having a much larger proportion of minorities compared to the overall U.S. population (Blumenthal 2007). Minority medical school graduates are also more likely to work in underserved areas (AAMC 2005). Increased enrollment of minorities in medical schools also gives Caucasian students the opportunity to interact with persons of different cultures and backgrounds, thus, better preparing them for the increasingly diverse

patient populations that they will serve (Saha, Guiton et al. 2008). In order to increase the proportion of qualified minority candidates for health professional schools, continued efforts, as described in this journal by Tran et al., must be made to cultivate future health care professionals.

Cultural competency education is another method that is being utilized to facilitate improved patient-provider interactions for Pacific Islanders (Palafox, Buenconsejo-Lum et al. 2001). Recently, the Liaison Committee on Medical Education (LCME) mandated that all medical schools in the United States and Canada include cultural competency among their central educational outcomes (LCME 2007). However, how to define, implement and quantify adequate cultural competency education is still unclear (Gregg and Saha 2006; Kumagai and Lybson 2009). As defined by Kumagai and Lybson, "cultural competency is not an abdominal exam. It is not a static requirement to be checked off some list but is something beyond the somewhat rigid categories of knowledge, skills, and attitudes: the continuous critical refinement and fostering of a type of thinking and knowing—a critical consciousness—of self, others, and the world...the outcome is therefore one of social justice—the open acknowledgment of the dignity and autonomy of, and delivery of high-quality medical care to, all members of society, regardless of gender, race, ethnicity, religion, sexual orientation, language, geographic origin, or socioeconomic background (page 782-3)." These are standards that all health care professionals should uphold. Therefore, the promotion and perpetuation of these values in health professional schools is an area that also needs continued discussion and research.

Although providing quality health insurance to all and increasing diversity and cultural competency of the cancer work force would reduce cancer disparities, other determinants of health such as socioeconomic status, education, and environmental factors still need to be addressed. Thus, many of the factors influencing health in underserved populations lie outside of the simple access and delivery of health care. Perhaps by enhancing our understanding of

determinants that lead to poor health and/or inadequate health care we may provide the ammunition needed by local communities to demand changes in laws and other policies at the local and national level.

Conclusion

Science will continue to unravel cancer biology. As we correlate these findings with race/ethnicity it may give us some insight into links between our diet, behaviors, environments and carcinogenesis. We must continue to work to increase participation of underserved populations in clinical trial research in order to

identify determinants of cancer health disparities. Only then will we be able to enact preventive measures or targeted therapies to reduce these disparities. However, as we become more of a global community with a continually increasing proportion of multiracial/multiethnic people, the use of racial/ethnic classification may become less informative as a surrogate for non biologic determinants. Conversely, a more multiethnic/multiracial society may be more equipped and better able to bridge the complex barriers leading to cancer health disparities for Pacific Islanders and other ethnic/racial groups that exist today.

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