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Does Educational Level Influence Postmenopausal Breast Cancer Mortality Among Asians in U.S.?

Sfurti Maheshwari
University of Nevada, Las Vegas

DOES EDUCATIONAL LEVEL INFLUENCE POSTMENOPAUSAL BREAST CANCER MORTALITY AMONG ASIANS IN U.S.?

By

Sfurti Maheshwari

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Sfurti Maheshwari

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Master of Public Health
Department of Environmental and Occupational Health

Paulo Pinheiro, Ph.D.
Examination Committee Chair

Brain Labus, Ph.D.
Examination Committee Member

Rachelle Rodriguez, Ph.D.
Examination Committee Member

Carrie Gillis, PT, DPT
Graduate College Faculty Representative

Kathryn Hausbeck Korgan, Ph.D.
Graduate College Interim Dean

Abstract

Studies on mortality from postmenopausal breast cancer (PMBC) by education level have not shown consistent results among US women. For US Asians, often seen as a "model" minority in terms of affluence and education this relationship has never been studied despite PMBC being the most common cancer in the country.

We analyzed 2008-2012 California Vital Statistics data and population data from the American Community Survey 2012 to compute age and education adjusted mortality ratios using negative binomial regression model for White (as a reference category) and Asian women. In total 3,277,106 (80%) White women and 852,376 (20%) Asian women died of breast cancer (ICD-10 code C50) during the study period. Educational attainment was positively associated with mortality from PMBC both in White and Asian women. However, for Whites those who attended college were 11% more likely to die of PMBC [1.1 (C.I- 1.037-1.188)], While Asians were 2.6 times more likely to die from PMBC [2.6 (C.I.-2.3-3.1)]. Asians showed considerable heterogeneity in the effect of education on PMBC mortality with Filipino women [2.8 (C.I. - 2.0- 4.0)] showing higher differential according to education level compared Chinese women [1.9 (C.I. 1.5-2.5)]. At all education levels, Whites had a higher risk of dying due to breast cancer than Asians.

Since survival has been shown to be higher among women with higher education across all races, our mortality findings can only be explained by a true increased risk of PMBC among highly educated women. Lower parity, old age at first birth, higher uptake of hormone replacement therapy and negative acculturation for Asians are possible causes. More studies are necessary to further clarify the etiology of this important cause of death with a focus on education level and socio-economic status.

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Getting through my thesis required more than academic support, which I received from my husband, Amit Rathi throughout this venture. He was always there motivating me up and supporting me when it was difficult to balance academics with other responsibilities. This success stands as a testament to his unconditional love and encouragement. I must express my very profound gratitude to my parents, Jawahar Jagani and Dr. Shashikala Maheshwari and my brother, Dr. Jaideep Jagani for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. I am incredibly blessed and eternally grateful to have you all in my life.

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Chapter 1

Background and Significance

Education

Importance of education and mortality risk

"Social determinants of health disparities," constitutes social, economic, and political elements and assets that influence health outcomes (Baker, Metzler, and Galea, 2005). According to Healthy People 2020, "inequalities in income and education underlie many health disparities in the United States." (U.S. Department of Health and Human Services). Education is fundamental social component of health, which can be accounted based on evidence of its association with health outcomes. Large numbers of reports of significant relationship between educational attainment and individual health risks such as mortality and incidence of diseases have been presented.

In general, research portrays an inverse relationship between mortality and education (Link, 2008; Link and Phelan, 2002; Phelan et al. 2004; Phelan et al. 2010). Individuals with relatively higher education are at lower risk of dying compared to those with less education (Masters et al. 2012). Individual level resources related to education such as wealth, dignity, social connections combined with knowledge of health awareness strongly influence person's ability to minimize the aftereffect of the disease (Link and Phelan 1996:472).

Education affects mortality risk through individual's behaviors related to health, economic assets, socially through psychological relationship (Lynch, 2006; Mirowsky and Ross, 2003). Education decreases risk of mortality through better knowledge and adequately use treatment technologies. The well-educated have advantage to have more awareness, frequent access to health

care settings, and indirectly to advanced treatment and technologies that decrease mortality risk (Glied and Lleras-Muney, 2008; Link 2008; Phelan et al. 2004). On the other side, low educated population will be continuously exposed to barriers like poor housing, hazardous workplaces, work stress, no insurance, limited access to health care, more unhealthy behaviors and limited knowledge of disease prevention (Masters et al. 2012). Thus, despite of breakthrough research in understanding disease, its effect on health, and treatment of disease, the strong relationship between education and mortality will persist due to widening socioeconomic stratification (Montez et al. 2011).

Education as proxy for SES

Population SES can be determined through various indicators such as combination of years of education, occupation, and family income (Warren et al. 2004). Unfortunately, most of the SES indicators are usually missing from common sources of primary health data such as medical records and death certificates. Most cancer data sets do not have complete socioeconomic measures. But Cancer data are linked ascertain vital records, includes educational level, and can be used for SES disparity assessment. In the study done by Kwok & Yankaskas (2001), education was considered as reliable method of determining individual's SES. However, they also reported that it works better for majority of population (Whites) rather than minority population. They also said that research using education as proxy to SES- must also consider limitation attached with it such as misclassification of education level (Kwok & Yankaskas, 2001).

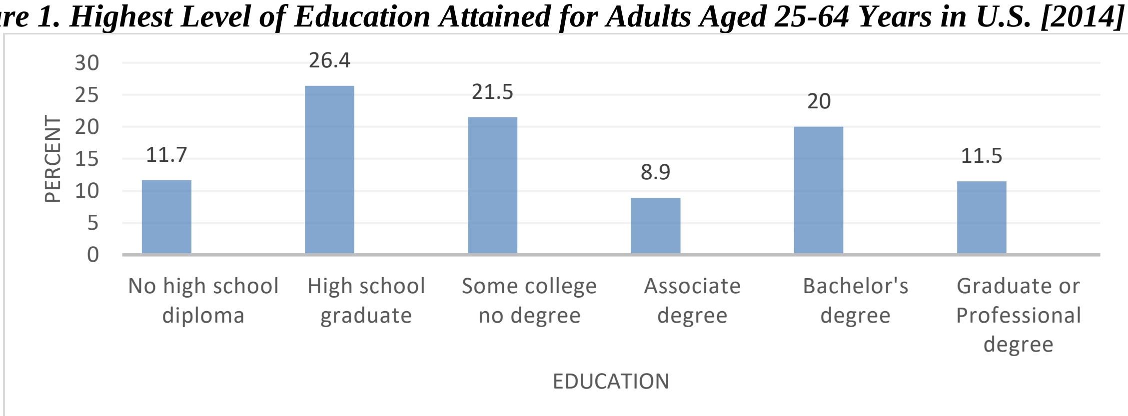
Education Trends

Education status in United Status varies with different race and ethnicity. According to U.S Census Bureau (2014), out of total population between ages 25-64 years, 26.4% received only high

school diploma degree while 11.7% population did not receive a high school diploma. About 60% of population opted for education above high school (U.S Census Bureau, 2014) (Figure 1).

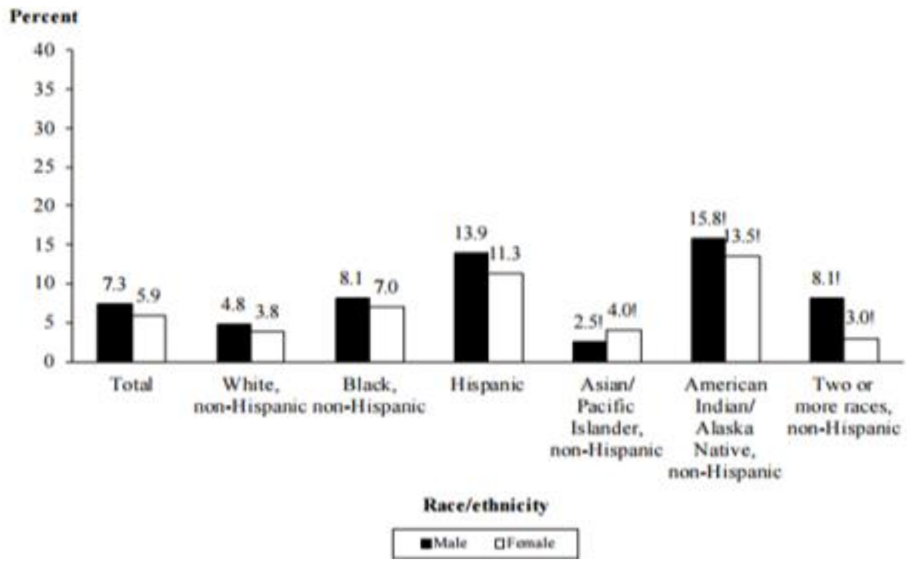
According to U.S. Department of Education (2016), the national averaged freshman graduation rate (AFGR) increased from 71% to 82% between 2000 through 2012. In school year 2012–13, 3.2 million high school students from public schools acquired regular high school diploma degree. Between 2011 and 2012, the AFGR was highest for Asians (93%) followed by whites (85%) and least among Blacks (68%). Since 1972, high school dropout rates have trended downward, from 6.1 percent in 1972 to 3.4 percent in 2012. The 2012 high school dropout rates were lower among Asian/Pacific Islander (3.3 percent) and Non-Hispanic Whites (4.3 percent) compared to Blacks (7.5 percent), Hispanics (12.7 percent), and American Indian/Alaska Native (14.6 percent) among 16- to 24-year-olds (Figure 2). Among students who began seeking a bachelor's degree at a 4-year institution in fall 2008, only 60% attained graduate degree by 2014. The rates were even lower for 5 and 6-year institutions. However, the graduation rate was highest for Asians (47.7%) followed by Whites (43%) and lowest among Blacks (21.4%) (U.S. Department of Education, 2016).

Figure 1. Highest Level of Education Attained for Adults Aged 25-64 Years in U.S. [2014]



Source: US Census Bureau, American Community Survey, 2014

Figure 2. Dropout Rates of 16-24 Years Old by Race/Ethnicity and Sex, 2012



Source: U.S. Department of Education, National Center for Education Statistics. (2016)

Education and Cancer outcomes

Widening socioeconomic inequalities are seen in cancer incidence, morbidity, mortality, and survival despite of better understanding the ways to reduce cancer risk factors and innovations in early detection and treatment for several cancers (Jemal et al. 2004). In some instances, such inequalities may even be widening. Cancer measures have shown an inverse gradient with education (Clegg et al. 2009). But mechanisms by which education impact cancer rates are not always clear.

In general, people with higher educational status have lower incidence, and better survival outcomes, than those with lower educational status (Clegg et al. 2009). Risk and behavioral risk factors like smoking, unhealthy diet, less physical activity, obesity, changing reproductive behaviors, and human papillomavirus (HPV) infection due to education level is also responsible for cancer incidence inequalities (Schoenborn et al. 2004, van Loon et al. 1995). Differences in

cancer survival reflect differences in SES, social networks and support (Greenwald et al. 1996), disparities in health care access and use of cancer screening (Hoffman-Goetz et al. 1997), contribute to late stage diagnosis and poor survival. Thus, the relationship between cancer and education can be accounted to socioeconomic factors related to education.

Breast Cancer

Cancer is second leading cause of death in the United States. According to Centre for Disease Control & Prevention [CDC] (2016), more than 1.5 million people are diagnosed with cancer, and more than 500,000 died due to it in 2012 (Centre for Disease Control & Prevention [CDC], 2016).

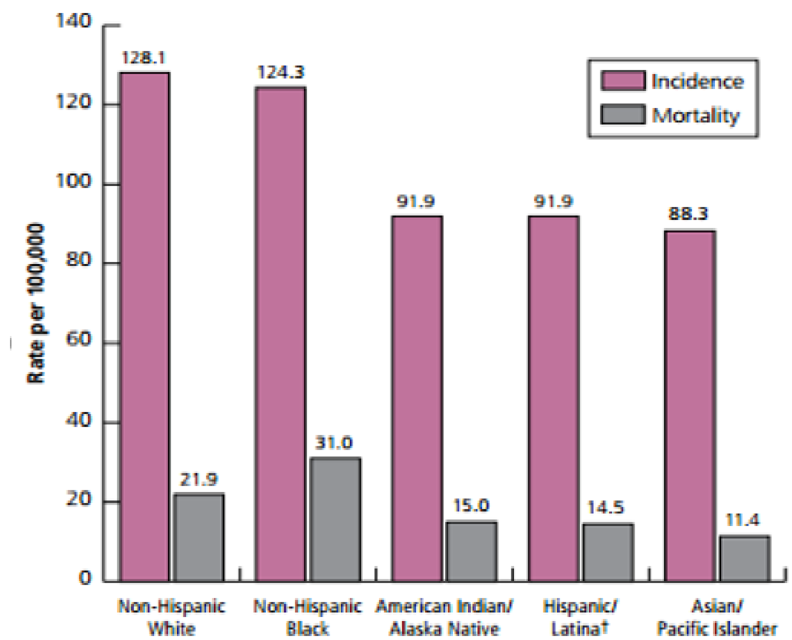
Breast cancer is one of the commonly diagnosed cancers among women in US after skin cancers accounting for about 29% of all newly diagnosed cancer (American Cancer Society, 2015). According to Centre for Disease Control & Prevention [CDC] (2016), breast cancer is also the second leading cause of death due to cancer among women of all race and ethnicities. Although the risk of death due to breast cancer has decreased overtime, the risk of acquiring breast cancer has not. In January 2014, more than 3.1 million women were present in United States. Every year about 220,000 breast cancer cases are diagnosed in women, out of which 40,000 women die in United States (Centers for Disease Control and Prevention [CDC], 2016).

Trends

Age and Race are the most key factors that affect the breast cancer rates. Age standardized incidence rate between 2008-2012 are highest among Whites but death rates are highest among Blacks (Figure 3). Asians have lowest incidence and death rates (Copeland et al. 2015). During 2008 through 2012, Blacks experienced 0.4% per year increase in breast cancer incidence rates,

while increase was only 1.5% per year among Asian women. No notable change was seen among other races (DeSantis et al. 2016). The highest increase in Asians might be due to rising rates of obesity and low physical activity in them (California Health Interview Survey [CHIS], 2009). Between 2007 and 2013, the average annual percent fall in mortality rates of breast cancer was 1.60. Highest decline in annual death rates due to breast cancer was seen among Whites (1.8%), while lowest was seen among Asians/Pacific Islanders (1%). Combination of several factors have played role in this type of trend like increase in health care access and improved technologies (Curtis et al. 2008 and Ooi et al. 2011).

Figure 3. Age-Adjusted Incidence and Mortality Rates of Breast Cancer by Race/Ethnicity in US, 2008-2012.

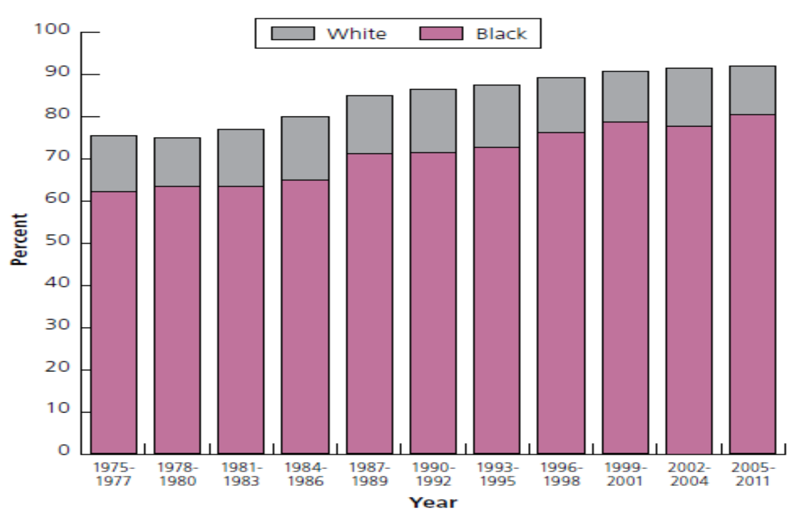


Source: Copeland et al. Mortality: US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention, American Cancer Society, Surveillance Research,2015

Remarkable progress has been made in improving survival rates of breast cancer in United States. The survival rate of women diagnosed between 1995 and 2005 was 90% compared to 75%

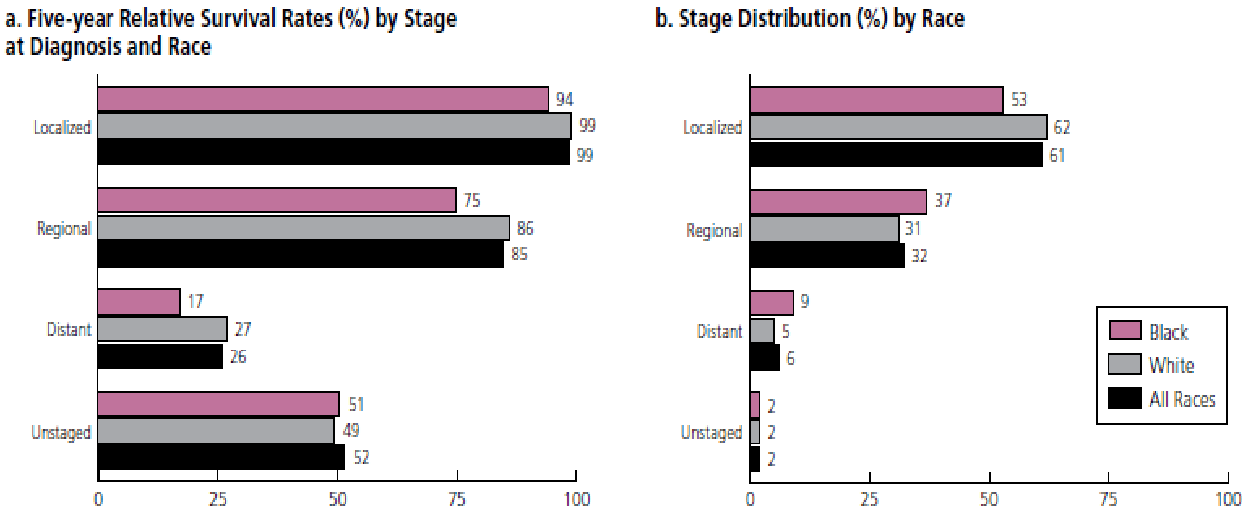
among those who were diagnosed between 1975 and 1977 (Figure 4) (American Cancer Society, 2015). This massive change was the outcome advancement in early detection through screening and in efficacy of breast cancer treatment (Sprague et al., 2011). However, not all age and racial/ethnic groups are benefited equally from this advancements and disparities in survival still exist. Differences in the stage and size of tumors at the time of mammography (Haggstrom et al. 2005 & McCarthy et al. 2000), invasive tumor biology, inadequate and inappropriate treatment (Haggstrom et al. 2005), and underlying patient comorbidities attributed to difference in SES are the possible reasons (Newman et al. 2006 and Polite & Olopade, 2005). Considering all races, 5-year relative survival (Figure 5) decreases depending on distant distribution (Howlander et al. 2015) and decreases as tumor size increases (Surveillance, Epidemiology, and End Results [SEER]). Table 1 represents five year breast cancer survival rates according to race and ethnicity for the year 2005-2011. Highest breast cancer survival rates were seen among Chinese and Japanese, while Black women experienced lowest survival rate (American Cancer Society, 2015).

Figure 4. Five Year Breast Cancer Relative Survival Trend (Female)* by Race, 1975-2011



*Survival based patients diagnosed between 2007 and 2011 and followed through 2012.
Source: American Cancer Society, Inc., Surveillance Research, 2015

Figure 5. Female Breast Cancer Survival Rates and Stage Distribution, US, 2005-2011*



*Survival based patients diagnosed between 2007 and 2011 and followed through 2012.
Source: American Cancer Society, Inc., Surveillance Research, 2015

Table 1. 5-year Cause-Specific Breast Cancer Survival Rate by Race/Ethnicity, 2005-2011*

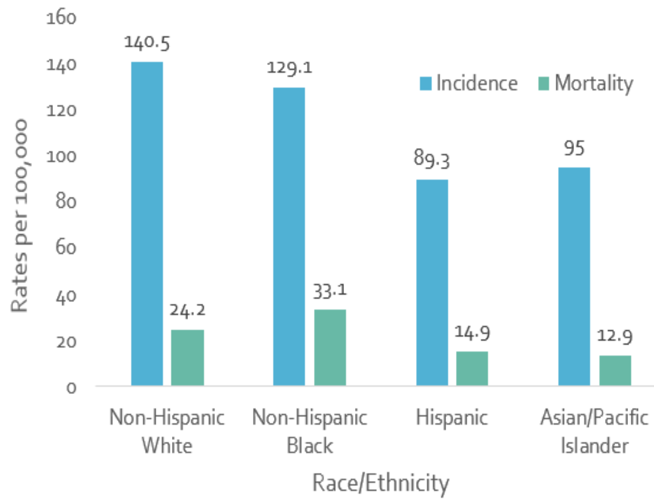
	Survival Rate (%)
Non-Hispanic White	*89*
Black	*80*
American Indian/Alaskan Native	*85*
Asian	*92*
Asian Indian/Pakistani	91
Chinese	93
Filipino	90
Japanese	93
Korean	92
Vietnamese	91
Other Asian	93
Pacific Islander	*87*
Hawaiian	90
Other Pacific Islander	82
Hispanic	*88*

*Survival based patients diagnosed between 2007 and 2011 and followed through 2012.
Source: American Cancer Society, Inc., Surveillance Research, 2015

California State

In California, non-Hispanic white women experienced the highest incidence rate (140.9 new cases per 100,000 women per year) and Asians experienced 95 new cases per 100,000 women per year between 2008 and 2012 (California Cancer Registry [CCR], 2016) (Figure 6). Between 2008 and 2012, female breast cancer incidence rate in California has declined by 1% among Asians/Pacific Islanders and 8% higher among non-Hispanic whites as compared to other states. There was a shift to earlier stage diagnoses (71%) in 2013 (California Cancer Registry [CCR], 2016) reflecting increasing the number of women receiving regular breast cancer screening (American Cancer Society [ACS], 2015).

Figure 6. Female Breast Cancer Incidence & Mortality Rates by Race/Ethnicity, California 2008–2012*

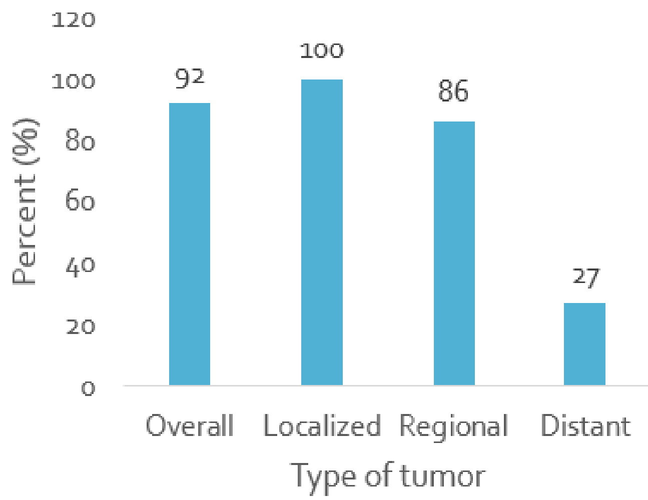


* Rates are age-adjusted to the 2000 U.S. Population.
Sources: Incidence: NAACCR, 2015. Mortality: US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention. American Cancer Society, Inc., Surveillance Research, 2015

The breast cancer mortality rate for women in California was 20 deaths per 100,000 women in the year 2013 (California Department of Public Health [CDPH], 2016). With respect to race/ethnicity (Figure 6), Asian/Pacific Islander experienced lowest mortality rate (12.9 deaths per 100,000 women) (California Cancer Registry [CCR], California Facts & Figures, 2016).

Overall, relative survival rate for 5 years (Figure 7) among breast cancer diagnosed women in California was 92% when followed from 2001-2010 (California Cancer Registry [CCR], California facts & Figures, 2016).

Figure 7. Breast cancer Five-Year Relative Survival Rates According to Type of Tumor, California, 2001–2010



Source: California Cancer Registry, California department of Public Health

Postmenopausal Breast Cancer (PMBC)

The lifetime of risk of being diagnosed with breast cancer of women in United States is 1 in 8 (12.3%) compared to 1 in 11 during 1970s (Howlander et al. 2015). Overall the median age of women with breast cancer diagnosis is 60 years. While, median age of death due to breast cancer is 68 years (Howlader et al. 2015). Recently in U.S, number of women above 50 years of age has increased (Alberg and Singh, 2001). Older and postmenopausal females above age of 50 years have greater incidence rates compared to younger females accounting for about more than one-third of all breast cancer deaths (Alberg and Singh, 2001, Jemal et al. 2010).

Risk Factors

Between 2006 and 2012, breast cancer incidence rate increased 1 to 1.2% per year) among above 60 year of age. Decline in death rate is higher among women ages 20 to 39 years (2.8% per year) compared to 1.5% per year in women of 70 years and above (DeSantis et al. 2016). Relative survival rates for women suffering from breast cancer also decreases with increasing age. There is a considerable decrease in survival from 89% to 78% between 5-15 years after initial diagnosis (American Cancer Society, 2015). However, the research among older postmenopausal women to determine factors which continue to drive this type of trend is limited (Shantakumar et al. 2007).

Age-specific risk factors

Increasing age is a crucial component of increasing risk for cancer overall and for breast cancer as well. Table 2 below shows the percentage of women who will get breast cancer over different period of life based on current age. It implies that 4 out of every 100 women aged 60 years today will suffer from breast cancer by 70 years of age (Howlander et al. 2015).

Table 2. Percent of U.S Women Who Develop Breast Cancer Over 10, 20 and 30 Years of Intervals According to Their Current Age, 2010-2012

Current Age	***10 years***	***20 years***	***30 years***
30	0.44	1.87	4.05
40	1.44	3.65	6.80
50	2.28	5.53	8.75
60	3.46	6.89	8.89
70	3.89	6.16	N/A

Source: Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=4&pageSEL=sect_04_table.17.html

Many breast cancer risk factors do indeed have complex age interactions (Colditz & Rosner, 2006). Previous studies have clearly reported that PMBC risk is significantly increased

for every year younger at menarche and every year older at menopause (Sweeney et al., 2004, Shantakumar et al., 2007, Vacek et al. 2011 and Britt, 2012). According to Collaborative study (2001), risk of PMBC is 20% higher among girls who start menstruating before age 11 compared to those after 11 years. Likewise, women who experience menopause after 55 years of age have about a 12% higher risk compared to those aged 50-54 (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). This is due to fact that early menarche leads to early rise in estrogen levels which induces early proliferation of breast cells (Clavel-Chapelon & Gerber, 2002). Moreover, it is being said that estradiol concentrations in postmenopausal women are greater if they were younger at age of menarche (Breast Cancer Collaborative group, 2011). Age at menarche and age at menopause determine reproductive period and number of ovulatory cycles in entire women's life (Bernstein, 2002). Therefore, the increased breast cancer risk associated with early age at menarche and late age at menopause among elderly women may be attributed to long term hormonal exposures during reproductive age.

Family History

Considerable number of studies have shown consistent results for positive relationship between family history and risk of breast cancer (Andrieu et al. 1995, Anderson et al. 1992 & Colditz et al. 1993). However, characteristics of family history like order of relative affected, age at which the relative developed breast cancer and number of relatives affected also affects the risk (Pharoah et al; 1997) Thus, women with a family history of breast cancer in first-degree relative are at increased risk compared to others. Risk is twice higher with one first-degree female relative, 3 times higher for women with two relatives, and 4 times higher for women with three or more relatives compared to no family history (Collaborative Group on Hormonal Factors in Breast Cancer, 2011). Risk of developing breast cancer also increases when the affected relative is

diagnosed at an early age (Pathak, 2002). Cases of ovarian cancer in family also increases breast cancer risk of PMBC (Figueiredo et al. 2007).

Genetic Predisposition

Better understanding of genetic susceptibility to breast cancer is witnessed with the help of multiple approaches. B*RCA1* and *BRCA2* are high-penetrance breast cancer predisposition genes. Inherited mutations in *BRCA1* and *BRCA2* account for 5%-10% of all female breast cancers and 15%-20% of all familial breast cancers (Schwartz et al. 2007). CHEK2, ATM, BRIP1, and PALB2 are other rare genes rare (less than 1%) responsible for breast cancer. Mutations in these genes confer an intermediate risk of breast cancer (Turnbull & Rahman, 2008). They are more frequently present in individuals with multiple relatives having history of breast or ovarian cancer or of Ashkenazi Jewish ancestry (2%) (Malone et al. 1998; Anglian Breast Cancer Study Group; 2000 & Gabai-Kapara et al. 2014). Loss-of-function mutations in *PALB2* is associated with hereditary breast cancer. The absolute breast-cancer risk for *PALB2* female mutation carriers by 70 years of age is 58% for those with two or more first-degree relatives with breast cancer at 50 years of age. (Antoniou et al; 2014). Li-Fraumeni and Cowden syndromes are some of the other rare chromosomal disorders affecting PMBC (Turnbull & Rahman, 2008).

Pregnancy

Decision of having or not having children and age at having first birth is also associated with having breast cancer (Kelsey et al. 1993). Nulliparous women are at 20-40% higher risk of postmenopausal breast cancer compared to parous women (Pathak, 2002). Several studies provide evidence that high number of births (> 5 births) is associated with decreased breast cancer risk in all age groups of postmenopausal women among parous women (Lubin et al. 1982; Kvale, Heuch & Eide, 1987; Bouchardy, Le and Hill, 1990 and Lund, 1991). One of the important findings from

study is that women who gave birth after age of 35 years are at even higher risk in comparison to nulliparous women (Colditz & Rosner, 2006).

Breastfeeding

Early initiation and longer duration of breast feeding reduces breast cancer risk among premenopausal women is widely been studied (Breast Cancer and Breastfeeding, 2002; Yang & Jacobsen, 2008; Ilic et al. 2015 and Islami, 2015). This protective effect is seen to be stronger for triple negative cancers (Faupel-Badger, 2013). Association between breastfeeding with risk of PMBC have also been studied but remains controversial (Enger et al, 1998 and Chang-Claude, 2000). Protective mechanism of behind is that breastfeeding by inhibiting menstrual cycles, reduces the lifetime exposure to steroid hormones or due to structural changes in breast tissues following lactation and weaning (Faupel-Badger, 2013).

Use of postmenopausal hormones

Although, the number of women taking HRT has dropped dramatically after evidence of elevated risk of breast cancer in 2000 (Toriole and Colditz , 2013). Still, many women continue to use HRT to ease menopausal symptoms. Studies have showed that current use of HRT is associated with an increased risk of breast cancer and the effect is substantially greater for estrogen-progesterone combinations than for other types of HRT (Million women study collaborators, 2003). The risk of breast cancer increases with longer use of HRT (Chlebowski et al. 2010). According to Women Health Initiative study, risk increases with starting HRT soon after the onset of menopause but decreases within 5 years of discontinuation (23% less) (Chlebowski & Anderson, 2012 and LaCroix et al. 1997).

Obesity & Physical Activity

Obesity is associated with many chronic diseases, including postmenopausal breast cancer (Stein and Colditz, 2004 and American Institute for Cancer Research, 2007). Risk of PMBC is two times more among obese women (La Vecchia, 2011). Many studies have reported that weight gain in early adulthood is associated with breast cancer at later age (Morimoto et al. 2002; Lahmann et al. 2003; Feigelson et al. 2004; Lahmann et al. 2005 and Eng et al. 2005). There is an increase in 11% risk for PMBC with each 5 kg of weight gained during young age (Nelson et al., 2012). Studies also report that weight loss in postmenopausal women decrease estrogen levels and indirectly lead to decreased breast cancer risk. Evidence among postmenopausal women shows that regular physical activity lowers the risk of PMBC by 10%-15% compared to physically inactive females (American Institute for Cancer Research, 2007; Eliassen e al., 2010; Hildebrand et al., 2013 and Wu; Zhang & Kang, 2013). The benefit may be due to change in body mass, hormones and energy balance (Neilson et al. 2009). Obesity leads to type II diabetes which indirectly increases risk for PMBC (Boyle et al. 2012 and De Bruijn et al. 2013).

Factors affecting Survival

Survival rate means number of people with the same type and stage of cancer that live for certain amount of time (usually 5 years) after they were diagnosed with disease. The overall 5-year relative survival rate for patients with female breast cancer has increased from 74.8% to 90.3% between 1975 and 2009 (Howlader et al. 2013). The 10-year relative survival is 83.1% and 15-year relative survival rate is 77.8% (Breast Cancer Statistics, 2015). Cancer survival is a measure of effectiveness of health-care systems. Increase in survival is largely due to improvements in chemotherapy, hormone therapy, and targeted drugs. Also, earlier diagnosis due to widespread use of mammography is crucial factor (Berry et al. 2005). Women with a screen-

detected breast cancer had a significantly higher 5-years overall survival than women who had their breast cancer diagnosed by examination or imaging, as well as a significantly lower prevalence of locoregional and distant recurrences (Carla et al., 2014). Advanced stage diagnosis is also associated with poor survival (Howlander et al., 2012). Breast cancer surgery along with radiation treatment has improved survival rates among older women and regarded as best treatment (Mara et al., 2010). Breast cancer survival is positively associated with low socioeconomic status, less income, less education and lack of health insurance (Halpern et al. 2007; Harper et al. 2009 and Shi et al. 2015).

Thus, survival is a complex measure. Advancement in treatment options and efficacy lead to longer survival among patients diagnosed earlier. However, other factors like type of diagnostic testing, cancer biology, comorbidities, and socioeconomic status, directly or indirectly affect survival (De Angelis et al. 2014).

Breast Cancer Screening

Breast cancer screening helps in detecting early-stage tumors with favorable tumor characteristics which is helpful in treating them early with breast conservative options like surgery, irradiation or hormonal therapy. Mammography has been incredibly beneficial for reduction in breast cancer mortality according to many RCTs and observational studies (Berry et al. 2005; Broeders et al. 2012 and Gøtzsche and Jørgensen , 2013).Results from these studies suggest that 20% decrease in mortality risk due to PMBC is seen due to increased usage of mammography (American Cancer Society, 2015). Between 1980 and 1987, proportion of postmenopausal women having mammography increased from 5% to 29% (Behavioral Risk Factor Surveillance System, 1987). The proportion of women screened among the 40–49 and 50–59 age groups were 58.5 and

62.5%, respectively, between 2008 and 2009, and 56.9 and 62.0%, respectively, between 2010 and 2011 (Qin et al. 2017)

The American Cancer Society recommends that women should start screening around age 40-45 years for at least once a year and at age 55 women should undergo screening twice a year or continue with annual screening. Women who have been diagnosed with it should also continue to get screened until their overall health is favorable having 10 years or higher life expectancy (Oeffinger et al. 2015). Under Obama Care Act, women get full insurance coverage for mammography screening (American Cancer Society, 2015).

However, mammography has some limitations. It is associated with overdiagnosis, rates ranging from <5% to as high as 50%. Moreover, it is not 100% effective in diagnosis and have led to false positive cases. Concerns have raised regarding radiation exposure with it (Marmot et al., 2013). Inspite of these drawbacks, mammography is the most efficient and affordable way to effective and quick detection of breast cancer and is highly recommended.

Asians in United States

The Office of Management and Budget (OMB) defines Asians as “person[s] having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent” (US Department of Commerce, 1978). It includes Chinese, Japanese, Filipinos, Koreans, Southeast Asians (e.g., Vietnamese and Hmong), and persons from the Indian subcontinent. Asian Americans are the most rapidly growing racial/ethnic group in the United States, recently surpassing Hispanics in rates of immigration (Asian American Center for Advancing Justice, 2013). In 2000 census, Asian Americans represented 5.1% (15.8 million) of total population of United States and are predicted to exceed by 40 million in 2050. Among all the states, California has largest and

most varied Asian population (16%) (Gomez et al. 2014). According to US Census Bureau (2014), between 2007 and 2009, 78% of Japanese residents were U.S. born compared to only 20% among Vietnamese. Large proportions (70%) of Asian Indians and Koreans are foreign born (US Census Bureau, 2014).

Asians also differ in their immigration patterns leading to varying degree of acculturation. Chinese population were the first to arrive in 19th century followed by Vietnamese, Filipinos and South Asians in 2000s, and this varied acculturation has led to highly heterogeneous population varying profoundly in socioeconomic status. The percentage of Asians with less than high school education ranged from 7% among Japanese to 56% to 68% among Southeast Asians (Gomez et al. 2014). The average annual income among Asians also showed big difference with lowest income ($24,337) among the Hmong population and highest ($68,935) among the Asian Indian population in California (Asian & Pacific Islander Demographic Profile. Los Angeles, 2005). The net result is extreme variation in characteristics in English language proficiency, insurance coverage, health beliefs, use of health services, diets, body size, and lifestyles (California Health Interview Survey [CHIS], 2007; Tseng et al. 2010). Despite this diversity, Asians are often seen as “model minority” in research masking important disparities in cancer incidence/risk and outcomes (Gomez et al. 2014). Lack of disintegrated data and thus of the limited awareness of the need and value of examining specific ethnic groups are responsible for this type of persistent practice. This failure to disaggregate groups is a disservice to public health by allowing potential disparities and vulnerable populations to go undetected (Gomez et al. 2010).

Many studies reported that their migration patterns revealed clear differences in cancer incidence between Asians living in their native countries and those living in the United States, as well as changes in rates associated with length of residence and number of generations in the

United States (Frisbie et al. 2001). For example, higher proportions of hormone estrogen receptor positive ($HER2^+$) breast cancers among Filipinas, Koreans, and Vietnamese (Telli et al. 2011), higher incidence of premenopausal breast cancer among U.S.-born Chinese and Filipino women relative to non-Hispanic whites (Gomez et al. 2012; Callahan et al. 2016) and higher grade prostate tumors among Chinese, Japanese, foreign-born Filipinos, foreign-born Koreans, and foreign-born Vietnamese (Lichtensztajn et al. 2014). Thus, the concept of "model minority" have resulted in lost opportunities to leverage the tremendous heterogeneity across these populations in the United States for the purpose of uncovering potential group-specific cancer risk and prognostic factors. Deeper inquiries into factors underlying potentially unique etiology and prognosis profiles in these groups is needed.

Chapter 2

Methodology

Aims and Hypothesis

While there is inconsistent evidence that PMBC mortality rates have the positive gradient with increasing education levels, this gradient is not being felt equally among women of all races at different educational levels of different races. As Asians vary profoundly in education attainment, it is important to study if the same relationship exists in Asian women. This study will attempt to clarify the association between education level and PMBC mortality by looking at differences among Whites and Asian population as whole as well as subgroups living in the United States. Specifically, the aim of this study is to:

1. To calculate and compare PMBC mortality rate ratio for White and Asian postmenopausal women according to their education level in USA, in aggregate and by subgroup.

   Corresponding hypothesis for Non-Hispanic Whites will be:

   H_o: There will be NO significant differences in postmenopausal breast cancer (PMBC) mortality rate among NHW women across different education levels.

   H_a: There will be significant differences in postmenopausal breast cancer (PMBC) mortality rate among NHW women across different education levels.

   Corresponding hypothesis for Asians will be:

   H_o: There will be NO significant differences in postmenopausal breast cancer (PMBC) mortality rate among Asian women across different education levels.

   H_a: There will be significant differences in postmenopausal breast cancer (PMBC) mortality rate among Asian women across different education levels

Corresponding hypothesis for Asian subgroups will be:

Chinese

H_o: There will be NO significant differences in postmenopausal breast cancer (PMBC) mortality rate among Chinese women across different education levels.

H_a: There will be significant differences in postmenopausal breast cancer (PMBC) mortality rate among Chinese women across different education levels.

Filipino

H_o: There will be NO significant differences in postmenopausal breast cancer (PMBC) mortality rate among Filipino women across different education levels.

H_a: There will be significant differences in postmenopausal breast cancer (PMBC) mortality rate among Filipino women across different education levels.

2. To examine and compare the effect of each educational level on PMBC mortality among total Asian population relative to White population.

Corresponding hypothesis for less than high school education will be:

H_o: There will be NO significant differences in postmenopausal breast cancer (PMBC) mortality rate between Asian and NHW women at less than high school education level.

H_a: There will be significant differences in postmenopausal breast cancer (PMBC) mortality rate between Asian and NHW women at less than high school education level.

Corresponding hypothesis for high school education will be:

H_o: There will be NO significant differences in postmenopausal breast cancer (PMBC) mortality rate between Asian and NHW women at high school education level.

H_a: There will be significant differences in postmenopausal breast cancer (PMBC) mortality rate between Asian and NHW women at high school education level.

Corresponding hypothesis for above high school education will be:

H_o: There will be NO significant differences in postmenopausal breast cancer (PMBC) mortality rate between Asian and NHW women at above high school education level.

H_a: There will be significant differences in postmenopausal breast cancer (PMBC) mortality rate between Asian and NHW women at above high school education level.

Study Design

This is a population-based, cross-sectional study designed to assess the association between breast cancer mortality and education level. Age-adjusted mortality rate ratios were calculated through death certificate data on age, race and level of education. Binomial negative regression modelling was used for the multivariate analysis.

Data Acquisition & Ethical Approvals

Mortality data

The death records from all causes for five years [2008-2012] were retrieved from California Vital Statistics (California Department of Public health [CDPH]). Permission to use vital statistics data was sanctioned by two entities of California Department of Public Health, Vital Statistics Advisory Committee and Center for Health Statistics and Informatics, after approval of protocol #15-08-2161 from Committee for the Protection of Human Subjects. As the data was in de-identified format, the consent from individual participants was not required. Institutional Review Board (IRB) at the University of Nevada, Las Vegas (UNLV) approved exempt research under Protocol # 979057-1.

Underlying causes of death classified according to the 10th Revision of the International Classification of Diseases was used. Only those deaths caused due to breast cancer (ICD-10 C50) were considered for the study. Total 10,086,287 number of deaths due to breast cancer were reported between 2008 and 2012 in California.

Population data

Population data specific for California state, race, sex, age, Asian subgroup and educational attainment was derived from the US Bureau of Census. Data represents 5 year estimates provided by American Community Survey (ACS), an ongoing yearly survey of nationally representative

samples of US households. The data were organized, cleaned and recoded before the mortality rate ratio were calculated.

Variables and Recoding

Age

The age represented the age at the time of death due to cancer. Age was further categorized into 18 age groups at interval of 5 years each except the final age group which includes 85 and older. However, we restricted our analysis to the age group above 10^{th} age category (beginning at age of 50 years) because 1) our objective of the study was to estimate PMBC rates which has distinct etiology from premenopausal breast cancer. According to the study done by Bromberger et al. 1997, the median age of menopause among women in the sample was 51.2 years. Therefore, we included women above 50 years in our analysis. Moreover, 2) education level is stable after 35 years of age and 3) information on individual's education is accurately documented on death certificates (Sorlie & Johnson, 1996) and better predicts SES (Shai & Rosenwaike, 1989 and Kogevinas et al.1997). Also, 4) majority of the cases were aged 50 years & older while age groups lower than these had smaller count which would affect the estimates. Total number of deaths among women above 50 years was 14,369.

Race

Race was categorized into 8 major groups: Non-Hispanic Whites (NHWs), Chinese, Japanese, Koreans, Vietnamese, Filipinos, South Asians, while the remainder of the Asian groups were categorized Other Asians. This category included Southeast Asians-Cambodians/Kampucheans, Laotians, Indonesians, Malaysians and Hmong. The cases were then aggregated according to age group, sex, education level, recoded race and site. Non-Hispanic Whites were taken as referent group, while deaths from all the other races/ethnicities were not

included. All Asians cases were included regardless of Hispanic ethnicity. We included Chinese (30%) and Filipinos (27.4%) sub population in our analysis as those populations comprised most Asian population in California, while Japanese, Koreans, Vietnamese, South Asians were very small in numbers.

Education level

Education level attainment in the data represented the total number of school years attended. This data was given by a relative of the decedent. Ninety-eight percent (98%) of cases had education information available. We categorized educational attainment into three categories based on number of school years completed. Women having less than a high school (<HS) education attending school for less than 11 years were regarded as first category, those who completed high school (=HS) and attended school for 12 years made up the second category. Those with schooling more than 12 years attaining education above high school (>HS) formed the third category. This type of categorization is appropriate because it included sufficient number of deaths in each age category (Masters, Hummer & Powers, 2012). Also, educational disparity in U.S. mortality risk can be better recognized by this type of categorization. (Montez, Hummer, and Hayward, 2012). First category (<HS) was taken as the referent category. Table 3 shows how the education level was recoded and distribution of postmenopausal women accordingly.

Table 3. Education Recode

Category Code	***Descriptor***	***Primary/Secondary Years Reported***	***Numbers of College Years Reported***	***(%)***
1	No high school completed	Less than 11	None	8
2	High school completed	12	None	38
3	More than high school	13 or more	Equal or more than 1	54

Missing data

Cross tabulations were conducted continuously to identify any incorrect coding or missing data. The number of those with missing education information were very less than 2%, therefore, we decided to not to use imputation as proportional imputation models will not make meaningful difference in the results.

Statistical Analyses

Hypothesis Testing

Since the sample size was very large we were confident that dataset had sufficient power to detect meaningful association between education levels in this study. Significance level (α) below 0.05 was selected as the threshold. If α is less than 0.05 then the null hypothesis was rejected. Two-sided p-values less than 0.05 and corresponding 95% confidence intervals were calculated.

Mortality Rate Ratio

Negative Binomial Regression modelling was used to calculate mortality rate ratios. Deviance statistics were used to evaluate overall goodness-of-fit of the model. Initially, numerator and denominator data were generated from death and population data for corresponding 5-year age category, race/ethnicity (non- Hispanic white and Asians), sex, education category. Next, age-adjusted mortality rate ratios were obtained for postmenopausal Whites (referent group) and Asian women.

A Negative Binomial model is a form of generalized linear model used specifically to model count data or rates. It is used when Poisson assumption of equality of mean and variance does not hold true met (Kim & Kreible, 2009). Moreover, it resolves the issues of overdispersion

in the model, which is often seen in mortality data (Coxe, West, and Aiken, 2009). It uses negative binomial exponential probability distribution in the model building. It adds an offset to numerator and adds natural log of the population denominators to the model (Kim & Kreible, 2009). A measure of the goodness-of-fit of this type of regression model is obtained by using the deviance statistic of a baseline model against a final model.

Interactions

An effect of interaction is said to exist when effect of an independent variable on a dependent variable differ depending on the presence of a third variable (Rothman et al. 2008) In this study, the association of education level and PMBC mortality is affected by race. Interactions between race and educational level were tested in the Negative Binomial model. Stratified analyses were carried out, stratified by Race and Education level, to better understand the independent impact of educational level on mortality, after interactions were found to be significant.

Sub analyses

To assess if an association exists between the breast cancer mortality and education level among Asian subgroup, stratified analyses were performed for each group. As the number of deaths among all other Asian subgroup was lower; we ran analysis among Chinese and Filipinos.

Software

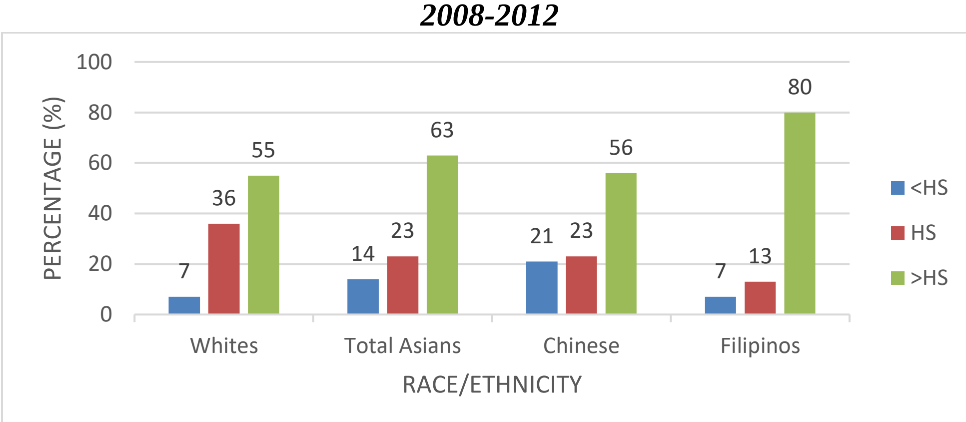
Statistical analysis software IBM SPSS 22 (Armonk, NY: IBM Corp) was used for data management & analysis.

Chapter 3

Results

In total, 14,369 deaths due to PMBC among women above 50 years were reported between 2008 and 2012 in California. Out of which 12,809 (80%) of deaths were reported among White women. While 1,587 (20%) deaths were reported among the Asian population. Among all the Asian subgroups, highest number of deaths by breast cancer was reported among Chinese 599 (30%) followed by Filipinos 430 (27.4%). The least number of deaths was reported among Japanese population (12%). Figure 8 provides the distribution of education level among included Race/Ethnicity.

Figure 8. Distribution (%) of Education Level Among Postmenopausal Women in California, 2008-2012



Note: HS= High School

Model Selection

Initially, three models were proposed. Age-adjusted mortality rate ratios were obtained for two population groups, Non-Hispanic Whites (reference group) and all Asian subgroups. Second model was run to obtain mortality rate ratio adjusted for age and education for NHWs (referent group) and all Asians combined. Finally, we assessed the existence of significant interaction with

the help of third model taking NHWs as reference group between population and education level; since association between education and mortality could be affected differently by both the race.

The mean and variance were noticeably different in each of the three model (Table 4), suggesting that required assumption of equality between mean and variance was breached. Thus, it is more justified to use negative binomial regression model. Ideally, the model goodness-of-fit deviance value should be close to 1. It was less than 3 for all the models. The overall high significance of the models (p-value <0.001) justified keeping all the models. Also, the mortality rate ratios obtained by these models are much more robust than crude rate ratios.

Table 4. Characteristics of Negative Binomial Regression Models

					Model Goodness of Fit	**Overall Model Significance**
Models	***Maximum Value***	***Minimum Value***	***Mean***	***Variance***	***Deviance (Value/df)***	***P-value***
Model 1	134	2669	899.75	631,748	2.716	0.000
Model 2	13	1179	299.92	124,203	1.361	0.000
Model 3	13	1179	299.92	124,203	1.606	0.000

Note: Model 1- Age adjusted model
Model 2- Adjusted for Age and Education level
Model 3- Adjusted for Age and Education level along with interaction between race and education

Mortality Rate Ratios

Tables 5 and 6 below represent the mortality rate ratios computed from the negative binomial regression models (1 & 2). Postmenopausal Asian women (including all subgroups) in California were 48% less likely to die from PMBC than NHWs. The age-adjusted mortality rate ratio was 0.52 (95% C.I. [0.457-0.595], p-value=0.000) for combined postmenopausal Asian females compared to that of Non-Hispanic Whites. After adjusting for education level as well, postmenopausal Asian females were about 53% less likely to die from breast cancer than NHWs. The breast cancer mortality rate ratio was 0.47 (95% C.I. [0.421-0.539], p-value=0.000) for combined postmenopausal Asian females compared to that of Non-Hispanic Whites after adjusting for age and education level.

We assessed effect modification by creating multiplicative interaction terms between race/ethnicity and education level. P-values less than 0.05 were interpreted as a significant interaction between the two terms. The overall model as well as the interactions were significant (Table 7). The association between education level and PMBC mortality was significantly modified by race in our analysis. As the interaction term was significant, it suggests that the slope for regression coefficient is different for Whites and combined Asians. Therefore, we conducted a stratified analysis according to race and education levels and ran separate models for both the races and then by education levels.

Table 5. Age adjusted Mortality Rate Ratio for PMBC for Asian and Non-Hispanic Whites Women in California [2008-2012]

Race	*Rate*	*95% CI*	*P-Value*
Non-Hispanic Whites	Referent	-	-
Total Asians	0.521	0.457-0.595	0.000

*Mortality Rate ratios were adjusted for age.
† Non-significant at p<0.05, CI: Confidence Interval

Table 6. Age adjusted Mortality Rate Ratio for PMBC for Asian and Non-Hispanic Whites Women in California [2008-2012] after Adjusting for Education Level

Race	*Rate*	*95% CI*	*p-value*
Non-Hispanic Whites	Referent	-	-
Total Asians	0.476	0.421-0.539	0.000

*Mortality Rate ratios were adjusted for age and education level [1,2 & 3]
† Non-significant at p<0.05, CI: Confidence Interval

Table 7. Age adjusted Mortality Rate Ratio for PMBC for Asian and Non-Hispanic Whites Women in California [2008-2012] after Adjusting for Education Level

Race	*Rate*	*95% CI*	*p-value*
Non-Hispanic Whites	Referent	-	-
Total Asians	0.282	0.242-0.328	0.000
Total Asians*Education level 3	2.616	2.211-3.096	0.000
Total Asians*Education level 2	1.604	1.330-1.935	0.000

*Mortality Rate ratios were adjusted for age.
† Non-significant at p<0.05, CI: Confidence Interval

Stratification

Stratified by Race

The results for mortality rate ratios computed from the stratified analysis for each race are presented in Tables 8 and 9. We observed a reversed association between PMBC mortality and education level among both races after running stratified analysis according to race. For instance, White postmenopausal women who had higher education (above high school) were at 11% higher risk of dying due to PMBC compared to those who were less educated (less than high school). But the association between PMBC mortality and education was not significant among White women who completed their education through high school in comparison to the lowest level of education. After running a separate model, Asian postmenopausal women of higher education have a significant death disadvantage. Similar, but of much greater magnitude, risk was observed among Asian women compared to White females. Asian postmenopausal women who had higher education above high school were at 2.6 times higher risk of death due to breast cancer compared

to those who were less educated (less than high school). Those women who completed high school had 63% higher risk of dying due to breast cancer compared to those who did not complete the high school. This association was statistically significant (95% C.I. [1.381-1.934], p-value=0.000).

Table 8. Mortality Rate Ratio after Adjusting for Age and Education Level for PMBC Among Postmenopausal White Women in California [2008-2012]

	Non-Hispanic Whites		
	Rate	***95% CI***	***p-value***
<high school	Referent	-	-
=high school	1.060	0.990-1.136	0.094
>high school	1.110	1.037-1.188	0.003

*Mortality Rate ratios were adjusted for age and education level.
† Non-significant at p<0.05, CI: Confidence Interval

Table 9. Mortality Rate Ratio after Adjusting for Age and Education Level for PMBC Among All Postmenopausal Asian Women in California [2008-2012]

	Total Asians		
	Rate	***95% CI***	***p-value***
<high school	Referent	-	-
=high school	1.634	1.381-1.934	0.000
>high school	2.621	2.253-3.050	0.000

*Mortality Rate ratios were adjusted for age and education level.
† Non-significant at p<0.05, CI: Confidence Interval

To assess if the same pattern was observed among specific Asian subgroups, stratified analyses were evaluated for the two largest groups. As the number of deaths among all other Asian subgroups were quite small; we decided to run analyses among Chinese and Filipinos only. Among Chinese postmenopausal women, we observed a PMBC mortality rate ratio 1.9 (95% C.I. [1.511-2.509], p-value-0.000) after adjusting for age and education level (Table 10). This mortality rate

ratio indicates that Chinese postmenopausal women who had higher education above high school were about 2 times higher risk of dying due to breast cancer compared to those who were less educated (less than high school). While those Chinese postmenopausal women who completed their high school were at 37% increased risk of death due to breast cancer compared to those who did not complete high school. A similar pattern was also seen among Filipino women (Table 11). Filipino postmenopausal women who had higher education above high school were at 2.8 times higher risk of death due to breast cancer compared to those who were less educated (less than high school). The association between breast cancer mortality and education was not significant among those who just completed high school.

Table 10. Age Adjusted Mortality Rate Ratio for PMBC by Education & Racial Subgroup among Chinese & Filipino Postmenopausal Women in California [2008-2012]

	Chinese		
	Rate	***95% CI***	***P-value***
<high school	Referent	-	-
=high school	1.369	1.027-1.824	0.032
>high school	1.947	1.511-2.509	0.000
		Filipino	
<high school	Referent	-	-
=high school	1.386	0.941-2.041	0.099
>high school	2.834	2.019-3.979	0.000

*Mortality Rate ratios were adjusted for age and education level.
† Non-significant at p<0.05, CI: Confidence Interval

Stratified by Education level

The results for mortality rate ratios computed from the stratified analysis for each race are presented in Table 9. After stratifying according to education level, the risk of death due to breast cancer among Asian postmenopausal women is reduced as compared to White women (Table 12). Postmenopausal Asian women with an education level less than high school, completed high school and above high school are at lower risk of death due to breast cancer compared to Whites. For instance, among all the Asian postmenopausal women who completed education above high school, breast cancer mortality risk is 20% lower as compared to Non-Hispanic Whites women with the same education level (Rate- 0.794, C.I [0.701-0.801]). However, among all the Asian women who have completed only high school, the risk of dying due to breast cancer is 55% lower compared to NHW women with the same education level. While those Asian women who have completed an education of higher than high school are at 30% lower risk compared to higher educated NHW women.

Table 11. Age Adjusted Mortality Rate Ratio for Breast Cancer Stratified by Education Among All Asian Postmenopausal Women in California [2008-2012]

	Education Level I	*Education Level II*	*Education Level III*
All Asians	0.276	0.450	0.794
C.I.	0.238-0.320	0.405-0.501	0.701-0.801
p-value	0.000	0.000	0.000

*Mortality Rate ratios stratified by each education level
† Non-significant at p<0.05, CI: Confidence Interval

Chapter 4

Discussion

To the best of author's knowledge, this is the first study to assess educational level disparity in PMBC combined for White and Asian postmenopausal women. It demonstrates the positive relationship between breast cancer mortality and education level among postmenopausal women. Both, Whites & Asian postmenopausal women with education above high school were at higher risk of dying due to breast cancer compared to those who did not complete the high school. Although the risk of dying due to breast cancer among Whites is higher at highest level of education and increases moderately across increasing level of education. However, the risk among Asian women increases substantially, more than twice with increase across education level from lowest to the highest level. Results of this study also suggest that different level of acculturation among different Asian subgroup has negative health impacts on Asian immigrants.

Comparing with past research

Studies have been conducted to observe the influence of education level on lung cancer, breast cancer, colon cancer and prostate cancer among Whites and Blacks (Albano et al. 2007; Kinsey et al. 2008; Steen land, Henley & Thun, 2002; Catharine, Elizabeth & John, 2005), but none of them concentrated on the Asian population living in United States. Albano et al. (2007) conducted study among White females and showed that among women who died in 2001, the risk was lower among higher educated than among less educated women. (Albano et al. 2007). The results conducted by Kinsey et al. (2008) and Steenland, Henley, and Thun (2002) were also consistent with this study (Steenland, Henley, and Thun, 2002 and Kinsey et al. 2008). Overall, these studies documented negative association between education level and breast cancer mortality. These studies suggested that this type of outcome is due to diminishing differences in

reproductive patterns by education level. Frequent use of screening and advanced treatment options among higher educated women may partly be responsible this type of observation. However, the present study reveals different pattern of association between education and PMBC mortality.

Our study shows that White postmenopausal women who had higher education above high school were at 11% higher risk of dying due to breast cancer compared to those who were less educated (less than high school). The results are similar to the previous research in other countries showing highly educated women have higher PMBC mortality rates than those with lower educational levels after controlling for education and other individual-level risk factors like age, mammography use, family history, parity, age at first birth, alcohol, body mass index, hormone replacement use, oral contraceptive use, and menopausal status. (Robert et al. 2004; Strand et al. 2007 and Gadeyne et al. 2012). These studies tend to support the theory that change in individual's reproductive behaviors play an important part in the observed socioeconomic gradient. The study carried out by Catharine, Elizabeth & John (2005) found that white women with greater education had greater breast mortality after adjustment of age, marital status and rural/urban status. The reason for such outcome might be because less educated women might have more favorable risk profile like greater parity, younger age at birth of first child and lesser use of hormone replacement therapy (Catharine, Elizabeth, and John, 2005).

Thus, higher risk of acquiring or death from breast cancer among higher educated women is likely to be affected by several risk factors related to education. But whether the observed pattern in mortality differences has been primarily driven by changes in incidence inequalities or by changes in survival inequalities is an important question.

Role of education

Education is a central social factor because it affects all of life's choices, including dying or living (Lawrence et al. 2016). Materialistic progress in one's life attained by educational degrees determines adult's SES in society, determines self-image; direction during childhood and adolescence; and better understanding of future orientation (Baker et al. 2011). Education determines healthy behaviors and its outcomes through several pathways. Higher education leads to higher income and in turn access to better health care, more exposure to health related information, self-efficacy and involvement in social networking (Rogers et al. 2010). It is an important attribute guiding the selection of many important aspects of individual's life including health related behavior, residential and lifestyle factors, seeking and affordability of healthy food, participation in health promotional and screening programs and access to and use of healthcare services (Hemminki, & Li, 2003). Additionally, people can be placed on different health routes based on education during early life that otherwise indirectly affects morbidity and mortality in old age. (Montez et al. 2012).

Each of these mechanisms has been used by past research to explain the education effect on health (Baker et al. 2011). Although education is vital component but still it is only a single dimension of socioeconomic status. Additional measures such as occupation, household income, wealth and assets, and human capital may more accurately characterize a woman's individual-level SES (Yao and Robert, 2011) For example, education may not accurately capture individual-level SES of a married woman, who with low education level is married to an educated and rich man, which changes her SES status. However, after postmenopausal age; income and other social circumstances change rapidly. Therefore, education may represent socioeconomic status more accurately because it is a more constant measure of lifelong social status than other variables.

Moreover, response rate to education level is high independently of age or working circumstances (Galobardes, Lynch, and Smith, 2007).

Role of factors affecting Survival

The positive association between education and breast cancer survival is very well documented in literature (Bouchardy et al. 2006; Pokhrel et al. 2010; Sprague et al. 2010 and Sprague et al. 2011). Survival rates in breast cancer mortality increased considerably during the 1990s due to modern technologies, screening programs and novel and efficient treatment options. And these tend to be more available to highly educated women (Louwman et al. 2007).

Overall, survival of any cancer is influenced by three important characteristics: tumor biological, patient, and treatment (Woods, Rachet, and Coleman, 2006). Stage at which breast cancer was diagnosed is the strongest predictor of survival which has been linked to screening through mammography (Onitilo et al. 2013). Socioeconomic inequalities lead to low rates for breast cancer screening which directly lead to worse stage diagnosis and lower survival for women with low education. This fact is consistently documented in many studies examining Socioeconomic (SES) disparities in breast cancer survival in the United States (Bradley et al. 2002; Byers et al. 2008 and Callahan et al. 2016) and in other parts of the world (Aarts et al. 2011, Dalton et al. 2006 and Rutqvist & Bern, 2006). The contribution of timeliness and type of cancer treatment to the differential in breast cancer survival is also important. Possible explanations for women with low education and living in low SES area for receiving inadequate care more often include lack of health insurance (Bickell & Cohen, 2008), comorbidities (Hershman et al. 2006), patient's refusal or not adherence to therapies (Bickell et al. 2006), and provider bias (Bickell et al. 2007). Griggs et al., (2007) suggested that lower quality of chemotherapy doses during treatment of breast cancer

among lower SES women is responsible for disparities in breast cancer survival outcomes (Griggs et al. 2007).

Role of hormone replacement therapy (HRT) is complicated. The risk increases soon after postmenopausal but decreases after 5 years of stopping the treatment (American Cancer Society, 2015). Studies report that HRT use is associated with better grade tumors, smaller size, lower growth rates which are more favorable prognostic features leading to better survival (Fletcher et al.2005, Sacchini et al. 2002). Estrogen receptor is also an important biological factor. Estrogen receptor positive tumors are slower growing, less aggressive, and receptive to drugs like tamoxifen, aromatase inhibitors, luteinizing hormone-releasing hormones, and fulvestrant (American Cancer Society, 2015). Gordon et al. (1995) reported that disparity in estrogen receptor is seen with different education level. According to this study, women with higher education tend to have more estrogen receptor positive tumors and is responsible for better prognosis compared to low educated women with estrogen receptor negative tumors (Gordon et al. 1995). Low education is also related to inadequate knowledge of cancer, attitudes, health consciousness, cultural differences, language problems and low psychosocial support (Stein et al. 2007; Wardle & Steptoe, 2003 and Lehto et al. 2006) and could contribute to the socioeconomic gradient in survival disparities.

Role of risk factors

Of all cancers, Breast cancer in women is one of the rare cancer that exhibit a positive incidence gradient with attained education (Hemminki & Li, 2003; Hussain et al. 2008; Lund & Jacobsen, 1991). An argument here arises that whether this link between education and the incidence of breast cancer is due to change in lifestyle factors associated with prolonged education,

or can be attributed to individual characteristics correlated with both educational attainments and risk of getting breast cancer.

Socioeconomic differences in incidence have typically been attributed to behavioral change in personal risk factors such as increasing age, age at menarche, age at menopause, age at first birth, parity and genetic predisposition. Since the mid-1960s, fertility has declined and shifted towards later ages in all industrialized countries, mostly due to the expansion of education. According to the Norwegian study, 26% of the social disparity in breast cancer was explained by parity (Braaten et al. 2005). The study done by Gadeyne et al. (2012) clearly documents that less number of children and older age at first birth are largely responsible for higher PMBC mortality. The risk of PMBC increases by two times higher risk among postmenopausal parous women who had their first child at age 30 or older than those who had their first child at age 20 or before (Strand et al. 2005). It is said that parity leads to short term increase in estrogen levels which reduces breast tumor promoting events by inhibiting cell signaling pathways involved in cell survival, cell migration and cell death (Arumugam et al. 2014). Change in behavioral factors like age at first pregnancy, breast feeding or use of hormone replacement therapy have been attributed as important means in decreasing breast cancer mortality among postmenopausal women. (Heck & Pamuk, 1997).

Research has devoted quite some attention on burden of hormone replacement therapy (HRT) on PMBC risk. Educational differences in HRT-use have declined during the 1990s among younger age groups, but still is significant among women aged 55 and older (Cauley et al.1991). It has been documented in the past research that higher educated postmenopausal women are more likely to use hormone replacement therapy compared to other women who are less educated. (Cauley et al., 1991 and Pesch et al., 2005). According to Brett & Chong (2001), HRT use is

strongly related to education level. “HRT use was 35% higher among postmenopausal women with above high school education and 44% higher among menopausal women with less than 12 years of education compared to those with 12 years’ education (Brett & Chong, 2001 p.17). Increased use of oral contraceptives and hormone replacement can clearly be attributed to decreased parity and old age at first birth and indirectly to increased breast cancer mortality (Beral et al.1997).

Obesity is a modifiable risk factors in the development of PMBC, which is also related to education. Studies have documented high prevalence of obesity and being overweight in postmenopausal women (Begum et al. 2009 and van den Brandt et al. 1997). This higher risk is due to increased amount of estrogen among fat women due to excess fat cells which makes hormone-receptor-positive breast cancers develop and grow (Heng et al. 2016). Previous studies have shown substantial disparities in both breastfeeding initiation and duration rates in the United States by several sociodemographic factors and socioeconomic status (*Grummer-Strawn et al. 2006 and Heck et al. 2006).*

Apart from this, postmenopausal women with less education and those who are unemployed, reside in a poor area, or are uninsured or underinsured and are therefore higher disadvantage than higher educated women (MacKinnon et al. 2007; Saatino et al. 2008 and Ward et al. 2008). Literature related to stress due to education level and breast cancer mortality has not been much studied so far. However, those with high education face problems like higher living costs, high work stress due to additional working hours and therefore have different levels of stress and coping mechanisms compared to low education level. This type of stress may result in worse health through relative deprivation of enough time to invest behind healthy behaviors (Winkleby et al. 2006).

PMBC among Asians

Our second novel finding suggest that Asian postmenopausal women who had higher education above high school were at 2.6 times higher risk of dying due to breast cancer compared to those who were less educated (less than high school). The risk of PMBC among higher educated Asian women was quite high compared to less educated Asian women unlike results for White women. PMBC disparities due to education attainment for non-Hispanic whites has been explained largely in literature in United States and other countries. However, for Asian Americans, the evidence is limited on this type of association. Asian Americans are the most rapidly growing racial/ethnic group in the United States, recently surpassing Hispanics in rates of population growth, representing 1 in 20 persons in the United States (United States Census Bureau, 2014). Despite of this fact, the PMBC mortality pattern among Asians cannot be attributed to factors responsible for incidence and survival in non-Hispanic Whites. Asian population in United States includes people from more than 30 different countries, and from extremely different social and economic backgrounds (Gomez et al. 2014). Diversity in pattern of immigration, native culture and lifestyle among them have led to varying degree of acculturation among each subgroup. The net result is that Asian population is highly heterogeneous, varying profoundly in characteristics such as English language proficiency, socioeconomic status, insurance coverage, health beliefs, use of health services, diets, body size, and lifestyles (Gomez et al. 2004). All these factors affect cancer risk and associated outcomes, and thus have important implications for health. Despite of such diversity, Asians in aggregate are regarded as "model minority" and thus, masking need and value of examining subgroups separately (Gomez et al. 2014).

Acculturation is ‘‘a process of cultural adaptation that occurs when groups of individuals from different cultures come into contact, leading to changes in the cultural patterns of either or both groups’’ (Harmon, Castro, & Coe, 1996). New cultures are adapted while dominant cultures are retained and internalized. This has been the focus of considerable research and highly influence immigrants’ health behaviors and outcomes (Trimble, 2003). It affects both, incidence and survival rates of breast cancer among Asians (Gomez et al. 2004).

Many studies have accounted Acculturation playing central role in increasing breast cancer incidence among immigrants by affecting personal and environmental factors. It is due to this societal shift that has resulted in changes in the population distribution of breast cancer risk factors such as higher SES, higher stress higher body mass index, lower parity, later age at first birth, increased use of OCP, etc., (Gomez et al. 2010 and Marfani, Rimal & Juon, 2013). According to California health Interview Survey [CHIS], between 2001 and 2015, the obesity increased from 6.2% to 11.1% among postmenopausal Asian women in California. Based on 2009 data, about 14% white postmenopausal women take HRT compared to 2.5% among Asian women in California. Asian postmenopausal women who were nulliparous (12.8%) were low compared to Whites (17%). However, women those who gave birth after age of 30 in Asian women (30%) was high compared to Whites (15%) (California health Interview Survey [CHIS], 2015).

Along with the above factors, previous work has also demonstrated interplay between acculturation and cancer survival through its link to language proficiency, health beliefs, socioeconomic status, social network or access to care (Shen & Takeuchi, 2001). Influence of strong association between socioeconomic status and indicators of acculturation have been reported previously (Minkler, Fuller-Thomson and Guralnik, 2006). Time spend in U.S by Asian Americans is also related to rate of cancer screening. Longer time in the United States was

associated with increased use of cancer screening. Thus, highly acculturated women were more likely to obtain a mammogram than others (Kagawa-Singer et al. 2007 & Gomez et al. 2010) which might have led to early detection and better survival among women. Shariff-Marco and his colleagues reported that lower SES was associated with worse all-cause survival among Asian-Americans, with a 3-fold worse survival among lower SES compared to highest (Shariff-Marco et al. 2014).

Another novel finding from this study is that highly educated Filipino women are at higher risk of dying due to PMBC when compared to Chinese postmenopausal women. This pattern can be reflection of the higher level of acculturation among Filipino women compared to other Asian women as reported by study focusing on Filipino American registered nurses (Ea et al. 2008). About 65% of Filipinos who migrated to U.S. are aged above 50 years of age (De Souza & Fuller-Thomson, 2013). Moreover, compared to the general U.S. population, Filipinos are better educated, have more professional job, and earn higher salary (Ryu, Crespi & Maxwell et al. 2013 and Migration Policy Institute, 2015). On the other hand, Filipinas are most obese Asian subgroup compared to any other Asian subpopulation (Ryu, Crespi & Maxwell et al., 2013). In a study on relation between BMI and body-dissatisfaction among multiple ethnic subgroups found that Filipinos had one of the highest BMIs whereas Chinese had lowest BMIs in comparison to all other Asian subgroups (Nguyen et al., 2015). Studies done on incidence and mortality among Asian women in California found that Filipina women had the worst breast cancer outcomes among Asian subgroups (McCracken et al., 2007 and Callahan et al., 2016). In contrast, Chinese is the oldest and largest Asian subgroup in U.S, but the rate of acculturation among them is low (McCracken et al. 2007). Chinese older adults overwhelmingly use Chinese as their primary language which indirectly acts as a barrier to breast cancer screening. Moreover, Chinese have

higher number of offspring compared to other subgroups which can act as protective factor for breast cancer (Dong et al. 2015). This might be due to lower use of OCP among less acculturated women. Chinese have reported better dietary choices, more likely to stick to their native diet and physically more active compared to other Asians (Wong et al. 2010). Overall, Chinese older adults have better overall health status and quality of life.

A study comparing older Asian-Americans with U.S.-born non-Hispanic Whites showed that in later life, immigration leads to disability in later life (Mutchler, Pracash and Burr, 2010), mainly due to variations attributable to nativity, age and SES status (Cho and Hummer, 2001). Immigration related directly to stress specifically due to personal or political turmoil due to separation from friends and family, major lifestyle changes, and acceptance of lower-status occupations (Mui & Kang, 2006).

Thus, the 'healthy migrant effect' due to migration to U.S. in search of more wealth and better health (Landale et al. 1999 and Parker, 2008) has diminished over time with acculturation resulting in deterioration of healthy behaviors (Singh and Miller, 2004) and adoption of American lifestyle and practices.

Limitations and Strengths

There are several caveats worth noting in this study. First, death certificate data provided us with limited amount of information, only regarding race/ethnicity, age, sex, and education. Information on individual specific risk factors for breast cancer like type of breast cancer, stage of breast cancer, parity, age at first birth, etc. could be obtained from death certificates. Thus, our discussion is based on previous researches in order to identify risk and protective factors. Moreover, it is not clear as which factors are responsible for observed difference among White and Asian postmenopausal women and deeper research is needed to understand the mechanism.

Education information on the death certificates brings along biases in this study which accounts for another limitation. Sorlie and Johnson (1996) showed that, people who did not complete high school were more likely of being misclassified as high school graduates (Sorlie and Johnson, 1996). This would have resulted in underestimation of deaths among women who did not graduate out of high school and overestimation of deaths for high school graduates.

Third, the accuracy and utility of cause of death data from death certificates are uncertain and often questionable. According to Mieno et al. 2015, cause of death for cancer is highly misclassified compared to any other disease. They also reported that cause of death is highly uncertain for elderly people due to presence of comorbidities among them (Mieno et al. 2015) and this would have been the cause for low PMBC death rates.

Asian populations in this study only represented Asians from California. However, almost 50% of all US Asian live in California alone (United States Census Bureau, 2010), which means we covered half of the Asian population. However, due to comparatively low death counts among other subgroups, we were not able to compute mortality rate ratios for each of them.

Our population based study design was the most important strength of this study. Therefore, every single death has been that occurred between 2008-1012 in California has been included in the study. Over 98% of education information and more than 99% of information on race is present on the death data, exhibiting another important strength of our study. Very small percentage of information (less than 2%) regarding education level was missing. This allowed for reliable classification of education level. Moreover, complete information on demographics of the death cases was available from the data. Most importantly, most of the studies in United States have been done on White and Black population. This is the author’s first attempt to see association between education and breast cancer mortality in Asian subpopulation.

Chapter 5

Conclusions and Implications

Our study takes the first step toward providing the evidence base for a better understanding the breast cancer mortality and level of education among postmenopausal women. Our analyses revealed positive gradient in educational patterns of breast cancer mortality among Whites and Asian women. It helped us to confirm that the higher breast cancer mortality seen among well-educated women can be attributed to changes in modifiable risk factors leading to increased rather than due to increased survival.

Combination of educational differences in reproductive behavior and other risk factors and screening practices gives rise to observed pattern. These risk factors are not easily modifiable or difficult to control at the population level. Therefore, future research can be done by obtaining data by level of education on fertility patterns. Thus, there are many unexplored facets that requires further research. For example, a research question arises that does competitiveness of work in highly educated women affect the PMBC rates? or does the psychological stress in highly educated women affect the PMBC rates?

The process of immigration and acculturation among American-Asian women, as well as intrinsic cultural differences between groups have important and lasting effects on the health of these populations. The heterogeneity in socio-demographic, immigration pattern and level of acculturation, and health among Asian subgroups emphasizes the need of efforts to improve the quality of nationwide cancer incidence, mortality, and behavioral risk factor data for each of the Asian American ethnic populations. Efforts should be made to better address the cancer burden among them to help prevent its future occurrence and development of culturally appropriate health interventions.

Appendix I

UNLV

UNLV Biomedical IRB - Administrative Review
Notice of Excluded Activity

DATE: November 7, 2016

TO: Paulo Pinheiro, PHD
FROM: UNLV Biomedical IRB

PROTOCOL TITLE: [979057-1] Education Level and Cancer Mortality among US Asian Populations, 2008-2012
SUBMISSION TYPE: New Project

ACTION: EXCLUDED - NOT HUMAN SUBJECTS RESEARCH
REVIEW DATE: November 7, 2016
REVIEW TYPE: Administrative Review

Thank you for your submission of New Project materials for this protocol. This memorandum is notification that the protocol referenced above has been reviewed as indicated in Federal regulatory statutes 45CFR46.

The UNLV Biomedical IRB has determined this protocol does not meet the definition of human subjects research under the purview of the IRB according to federal regulations. It is not in need of further review or approval by the IRB.

We will retain a copy of this correspondence with our records.

Any changes to the excluded activity may cause this protocol to require a different level of IRB review. Should any changes need to be made, please submit a Modification Form.

If you have questions, please contact the Office of Research Integrity - Human Subjects at IRB@unlv.edu or call 702-895-2794. Please include your protocol title and IRBNet ID in all correspondence.

Office of Research Integrity - Human Subjects
4505 Maryland Parkway . Box 451047 . Las Vegas, Nevada 89154-1047
(702) 895-2794 . FAX: (702) 895-0805 . IRB@unlv.edu

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Curriculum Vitae

SFURTI MAHESHWARI

2121 E. Warm Springs Rd, #2073, Las Vegas, NV - 89119

sfurtimaheshwari@gmail.com, (702)481-8653

OBJECTIVE

Seeking to position myself in the healthcare industry where my commitment to people welfare, using analytical and investigative skills and sound understanding of the preventive healthcare, would be put to good use.

EDUCATION

University of Nevada, Las Vegas **Las Vegas, Nevada**

Master's in Public Health (GPA: 3.94) ***May 2017 (anticipated)***

Concentration – Epidemiology & Biostatistics

Core Areas – Biostatistical Methods for Health Sciences, Linear Statistical Models, Non-Parametric Statistics, Basic Epidemiology, Advanced Epidemiology, Chronic Disease Epidemiology, Infectious Disease Epidemiology, Mixed Methods, Fundamentals of Public Health, Fundamentals of Environmental Health, US Health Care Systems, Program Planning.

Thesis Title – *Does the Education Level Influence Post-Menopausal Breast Cancer Mortality among Asian Women in US?* ***Jan 2016 – April 2017***

The aim of this project was to calculate and compare PMBC mortality rate ratios for Non-Hispanic Whites and Asians by educational level and investigate the influence of education on mortality experience. This study is first of its kind ever done in US among Asians. It further gives the insight to research important PMBC related risk factors associated with increase in education level.

Sumandeep Vidyapeeth University **Baroda, India**

Bachelor of Medicine & Bachelor of Surgery (M.B.B.S) ***February 2013***

Core Areas – Internal Medicine, Family Medicine, Surgery, Pediatrics, Gynecology, Anesthesia, Emergency Medicine and Psychiatry.

PROFESSIONAL EXPERIENCE

Positively Kids Neopediatrics Clinic **Las Vegas, Nevada**

Public Health Internship ***January 2016***

- Describe the roles that epidemiology and biostatistics serve in the discipline of public health and describe a public health problem in terms of magnitude, people, time, and place.
- Understand and apply proper terminology and definitions used in epidemiology and biostatistics.
- Identify key sources of data for epidemiologic and Bio statistical studies.
- Interpret, articulate, and critique results of statistical and epidemiological analyses found in public health studies.
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Sahayadri Ram Krishna Mission Hospital **Gandhidham, India**

Medical Officer ***April 2013-July 2014***

- Administered and responded to Medical Emergencies in a timely fashion.
- Examine medical history and test results and prescribe medications to patients.
- Helped determine proper medical procedure and plans based on above examinations.
- Specialized in diagnosis treatment and interpret the required submissions/tests.
- Overseen and monitored the Pediatrics and Neonatal department and provided the necessary post Natal card and vaccination.
- Worked with Senior Doctors and assisted in surgical operations in Pediatrics dept.
- Worked long shifts and graveyard shifts to help assist team schedule.

B.J. Medical College & Civil Hospital **Ahmedabad, India**

Medical Intern ***March 2012-Feb 2013***

- Undertook 2 months of extensive training each in areas of Specialty Medicine, Surgery, Pediatrics, Obstetrics & Gynecology, Ophthalmology, Emergency Medicine, Anesthesia, Dermatology, Orthopedics and Psychiatrics.
- Shadowing of major procedures under specialized surgeons.
- Collect and review the patient charts, perform tests and discuss them with doctors.

- Raise questions and curiosity during procedures to better understand them and answer questions and concerns when assisting surgeons.
- Understand hospital administration and work flow and patient charge/discharge process.

Volunteer Work **Gandhidham, India**

Observership & Assistant ***March 2013 – January 2014***

- Worked with Dr. Dinesh *(M.S. O.R.L)* in patient management which included treatments, operations, maintaining patient records, guiding and counseling patients.
- Participated in voluntary work for Smruti Trust in preventive cancer and comprehensive cancer care programs.

Community Health Program Participation ***January 2012***

- 6 weeks of school health elective program in Dept. of Preventive and Social Medicine.
- Examined 30K+ students in 6 weeks' time with my team in outpatient setting under Community Health Centers that provided diagnosing the diseases, providing necessary treatment and counseling.

National Service Scheme for NGO ***January 2010- December 2012***

- Closely worked with NGO for 3 years conducting awareness programs.
- Helped several NGO teams with Blood Donation Camps, Health Checkup Camps, Women Empowerment Scheme, Consumer Protection lectures and Benefits of Plantation.

Poster Presentation ***August 2016***

Presented poster at Nevada Institute of Personalized Medicine (NIPM) and Nevada Public Health Association Conference (NPHA) on The Risk of Incident Asthma among Overweight and Obese Children: A Meta-Analysis of Prospective Studies.

OTHER SKILLS

- Experienced with data analysis programs: SPSS, R and SAS
- Educated in the critical evaluation and interpretation of epidemiological literature
- Collect, manage and organize data
- Statistical skills possessed to calculate and interpret epidemiologic measures
- Well-informed on strengths and limitations of different study designs
- Knowledgeable about chronic and infectious disease surveillance
- Knowledge about data analysis using Regression Models
- Handling, evaluating, diagnosing and educating patients using basic critical care aptitude.
- Extensive knowledge of diagnostic methods and equipment
- Proficient in Word, Excel, Power point
- Several poster and paper presentations on various topics of healthcare industry.