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The association between educational level, DNA repair capacity and risk of breast cancer.

By
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APPROVAL PAGE

THE ASSOCIATION BETWEEN EDUCATIONAL LEVEL, DNA REPAIR CAPACITY AND RISK OF BREAST CANCER

BY

LUISA M MORALES

We, the members of the Doctoral Dissertation Committee of Luisa M Morales Torres, certify that the submitted investigation complies with the doctoral dissertations requirements established by the Ponce School of Medicine & Health Sciences Public Health Program, to get the DrPH with the specialty on Epidemiology and for the record we signed certifying the approval of it.

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Dedication

To my family, especially my husband Daniel Muñoz, who supported me throughout this process, my kids, Daniel, Miguel and Ana; they are my inspiration. To my mother Lourdes Torres and my uncle Jaime Morales for their love and support.

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First of all, thanks to God.

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List of abbreviations

BC	breast cancer
BMI	body mass index
CI	confidence interval
HRT	hormone replacement therapy
LEL	low educational level
HEL	high educational level
DRC	DNA repair capacity
OR	Odds ratio

Glossary of terms

1. **Association**: Statistical relationship between two or more events, characteristics or other variables.
2. **Case**: In epidemiology, a countable instance in the population or study group of a particular disease, health disorder, or condition under investigation. Sometimes, an individual with a particular disease.
3. **Case-control study**: A type of observational analytic study. Enrollment into the study is based on presence (``case'') or absence (``control'') of disease. Characteristics such as previous exposure are then compared between cases and controls.
4. **Confounding variable**- is an extraneous variable in a statistical model that correlates (positively or negatively) with both the dependent variable and the independent variable.
5. **Control**: In a case-control study, comparison group of persons without the disease.
6. **Covariate** is a variable that is possibly predictive of the outcome under study
7. **DNA repair**-refers to a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome
8. **Epidemiology**: The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of health problems.
9. **Host Cell Reactivation Assay**- is a technique used to measure the repair capacity of the cell of a particular DNA alteration

10. **Incidence rate**: A measure of the frequency with which an event, such as a new case of illness, occurs in a population over a period. The denominator is the population at risk; the numerator is the number of new cases occurring during a given period.
11. **Incident cases**- comprise cases newly diagnosed during a defined period. The use of incident cases is considered as preferential as the recall of past exposure(s) may be more accurate among newly diagnosed cases. In addition, the temporal sequence of exposure and disease is easier to assess among incident cases.
12. **Interaction**- is a term composed of the product of two characteristics. An effect of interaction occurs when a relation between (at least) two variables is modified by (at least one) other variable
13. **Logistic regression**- is a type of regression analysis used for predicting the outcome of a categorical dependent variable based on one or more predictor variables.
14. **Mortality rate**: A measure of the frequency of occurrence of death in a defined population during a specified interval of time.
15. **Multicollinearity**: a statistical phenomenon in which two or more predictor variables in multiple regression models are highly correlated.
16. **Mutation-** accidental changes in a genomic sequence of DNA.
17. **Nucleotide excision repair (NER)-** is a particularly important mechanism by which the cell can prevent unwanted mutations by removing the vast majority of UV-induced DNA damage (mostly in the form of thymine dimers and 6-4-photoproducts).
18. **Odds ratio**: A measure of association that quantifies the relationship between an exposure and health outcome from a comparative study; also known as the cross-product ratio.

19. **Phytohaemagglutinin**- is a mitogen to trigger T-lymphocytes cell division
20. **Progeria**- is a rare condition that is remarkable because its symptoms strongly resemble normal human aging, but occur in young children.
21. **Protective effect**- refers to anything that prevents or reduces vulnerability for the development of a disorder
22. **Tumor suppressor gene**- is a gene that protects the cell from one step on the path to cancer.
23. **Xeroderma pigmentosum (XP**) - is an autosomal recessive genetic disorder of DNA repair in which the ability to repair damage caused by ultraviolet (UV) light is deficient.

All definitions were obtained from:

http://www.cdc.gov/reproductivehealth/Data_Stats/Glossary.htm

Abstract

Breast cancer (BC) is the most prevalent cancer type among Puerto Rican women and is responsible for the majority of cancer-related deaths. Educational level is linked to BC for the influence in lifestyle changes like healthier behaviors and lower parity. Some studies have reported that after adjustment for parity and other reproductive risk factors, a higher educational level correlates with lower BC risk. A low DNA repair capacity (DRC) has been linked to increasing risk of BC. The primary objective of this doctoral dissertation is to evaluate the potential role of educational level as a modifier of the association between DRC and BC. The central **hypothesis in this study** is that high educational level improves women's DRC lowering BC risk. Additionally, it was investigated if there are any BC risk factors associated with educational level and DRC. The obtained results showed that a low DRC was strongly associated with BC. It was found that women with low DRC have up to 12 times more odds to have cancer. An important effect modification is observed even with no statistical significant interaction obtained. The association of low DRC and BC were stronger among women with high educational level (HEL) as compared to those with low educational level (LEL) before and after adjusting for all potential confounders. The results of this study could provide epidemiological evidence of why educational level is protective against BC in the population studied. DRC levels could be used to monitor the beneficial effects of education or any other DRC associated modifiable factors that could provide protection against BC.

I. Introduction

1.1 Purpose

The purpose of this study is to evaluate the role of educational level as a potential modifier of the association between DNA repair capacity (DRC) and the risk of breast cancer in Puerto Rican women. There are no published studies that have examined the association between educational level and DRC, as well as no studies have evaluated educational level as a modifier of the association between DRC and breast cancer.

1.2 Specific Aims

Cancer has recently exceeded heart disease as the leading cause of death among Hispanics in the USA (Siegel et al., 2012). Breast cancer (BC) is the most commonly diagnosed among Hispanic women (ACS, 2012a). BC is the type of cancer that affects more women worldwide than any other cancer type (Globocan, 2008). Currently is the second leading cause of cancer deaths in USA and Puerto Rico (Acs, 2010). BC has the highest incidence of all cancer types (in terms of organs) in Puerto Rican women (Torres-Cintron et al., 2010). BC accounted for 33.3% of all cancers diagnosed in women in the Puerto Rican population between 2004 and 2008; and was responsible for 18.8% of all female cancer deaths (Figueroa NR, 2008, Torres-Cintron et al., 2010, Nazario CM, 2000, Figueroa-Vallés et al., 2012).

Education as an indicator of socioeconomic status has been associated with cancer risk in several studies (Beiki et al., 2012, Cho et al., 2005, Fernandez and Borrell, 1999, Albano et al., 2007). Most studies suggest that an association exists between high educational level (HEL) and an increased in BC risk (Beiki et al., 2012, Vidarsdottir et al., 2008, Mouw

et al., 2008, Cho et al., 2005, Berwick and Vineis, 2005). However, Hajian-Tilaki *et al.*, concluded that this association could be masked because of the lack of adjustment for factors related to lifestyle and other factors that could bias this relationship. These may include parity, oophorectomy and other well-documented reproductive factors. Other studies report, that after adding reproductive factors to the analysis, a higher educational level is significantly associated with lower BC risk (Braaten et al., 2004, Hajian-Tilaki et al., 2012, Fernandez and Borrell, 1999). Overall, a positive association among education and health has been found in numerous studies (Grossman and Kaestner, 1997, Hammond, 2003, Stelmach et al., 2004, Koivusilta et al., 1998, Park and Kang, 2008). Improved education is associated with better health care and better lifestyle practices (i.e. more fruit and vegetables consumption, increased exercise, and less fatty diets (Collazo et al., 2010, Furnee et al., 2008, Garner et al., 1996). People with higher levels of education have more knowledge about health and healthy behavior (Grossman and Kaestner, 1997, Park and Kang, 2008).

DNA repair (DRC) is a key cellular mechanism for protecting the genome from environmental and cancer causing agents (Murray and Berg, 2004, Wei, 2007, Kelley, 2012). A number of epidemiological studies suggest that deficiencies in DRC are involved in human carcinogenesis (Kennedy et al., 2005, Irizarry et al., 2009, Ramos et al., 2004, Matta et al., 2003, Matta et al., 2012, Wang et al., 2007, Lin et al., 2005, Wei et al., 2003a, Wei et al., 1996, Grossman and Wei, 1994, Hall et al., 1994, Wei et al., 1993, Cheng et al., 1998) .A low DRC have been identified as an important risk factor for BC development (Ramos et al., 2004, Matta et al., 2012). Furthermore DRC can be a modifiable factor that may be affected by stress such as academic stress (Cohen et al., 2000), lifestyle principally

smoking (D'Errico et al., 1999) and diet, especially foods rich in magnesium like green vegetales, seeds and nuts (Mahabir et al., 2008, Mahabir et al., 2007, Gadhia et al., 2012, Wei et al., 2003b). Yeidyly et al. 2013, associates the use of calcium supplements with an increase in DRC (Vergne et al., 2013b).

The central **hypothesis in this study** is that an HEL is associated with a higher DRC, and lower odds of BC in Puerto Rican women. Additionally, this study investigates the factors associated with BC, with educational level and with DRC. No published studies exist linking educational level with DRC.

In order to conduct this study, the data set from a case-control study of Hispanic women in Puerto Rico was used. A sample of 502 BC cases and 685 controls were included, for a minimum total of 1,187 participants recruited during the last six years. The following specifics aims were proposed:

Specific aim #1: To study the association between educational level and BC, and educational level and DRC level.

Hypothesis: Educational level is associated with BC and DRC before and after adjusting for hormone related variables such as age of menarche, contraceptive use, menopause, pregnancy, hormone replacement therapy, and other confounders.

Specific aim #2: To study the possible impact of education in the association of DRC and BC. The relationship of DRC and BC is explored and compared among different educational levels before and after adjusting for hormone related variables such as age of menarche, contraceptive use, menopause, pregnancy and hormone replacement therapy; and other potential confounders.

Hypothesis: Education is a modifier of the association between DRC and BC before and after adjusting for hormone related variables such as age of menarche, contraceptive use, menopause, pregnancy, hormone replacement therapy, and other confounders.

1.3 Background and significance

1.3.1 Breast cancer

BC is caused by the development of malignant cell that starts from breast tissue, mostly from the milk ducts (ductal carcinoma) or the lobules (lobular carcinoma) (NCI, 2011). BC is a multifactorial disease caused by a combination of genetic, epigenetic and environmental factors (Martin et al., 2001, Vogel, 2006, Huang et al., 2011, Dumitrescu, 2012, Alvarez et al., 2012, Bosviel et al., 2012, Cho et al., 2012, Coyle, 2004, Bediaga et al., 2010, McPherson et al., 2000). The development of cancer is a complex process in which damage (mutations) occurs to genes that normally regulate cell proliferation (Dickson and Lippman, 2001, Hanahan and Weinberg, 2011). Mutations in tumor suppressor genes and proto-oncogenes are related to cancer development (Friedberg, 1995). These alterations can be inherited as germline mutation or acquired as somatic mutations (Russo et al., 2000). Although the primary cause of BC is due to alterations in DNA, lifestyle-related risk factors can increase the likelihood of BC development (Kushi et al., 2006).

In the USA, 15% of all BC can be attributed to familial and genetic influences. Sporadic BC is mainly influenced by factors related to lifestyle, environment, and other biological factors that also play a role in BC development (Figueroa-Vallés et al., 2012, Martin et al., 2001). Some of the modifiable risk factors studied include weight gain, especially after

menopause, physical activity, alcohol intake, breastfeeding for extended periods of time, use of hormone replacement treatment (Kushi et al., 2006, Chlebowski et al., 2009) and vitamin and calcium consumption (Vergne et al., 2013b).

1.3.2 Breast Cancer Risk Factors

Numerous studies have identified risk factors for BC, most of them agreed in the majority of the risk factors studied (Pollan, 2010, NCI, 2011, institute, 2011, Ma et al., 2010, Amadou et al., 2014). Some of the risk factors for BC are not modifiable (e.g., age, family history, age at full term pregnancy, early menopause, late menopause, breast density); however, other factors increasing the likelihood of BC can be modifiable (e.g., obesity, HRT, alcohol consumption, smoking and physical activity)(Kushi et al., 2006, Hayes et al., 2013, Thune, 1997). Torres-Cintrón *et al.* (2010), stated that BC among other cancer types is susceptible to primary prevention (reducing the risk factors) or even secondary prevention (early detection). The table below summarizes the major risk factors found in the literature divided among low and high risk groups.

Table 1. Established risk factors for BC in women.

Established risk factors for BC in women		
Factor	**High-risk group** *Relative risk >4.0*	**Low-risk group** *Relative risk <1.0*
Age	Old	Young
Country of birth	North America, Northern Europe	Asia, Africa
Mother and sister with a history of BC	Yes	No
Biopsy-confirmed atypical hyperplasia and a history of BC in the first-degree relative	Yes *Relative risk=2.1to 4.0*	No *Relative risk <1.0*
Nodular densities on the mammogram	Densities occupying >75% of breast volume	Parenchyma composed entirely of fat
History of cancer in one breast	Yes	No

Mother or sister with a history of BC	Yes	No
Biopsy-confirmed atypical hyperplasia without a family history of BC	Yes	No
Radiation to the chest	Yes	No
	Relative risk=1.1 to2.0	*Relative risk <1.0*
Socio-economic status	High	Low
Place of residence	Urban	Rural
Race/ethnicity		
BC at >45 years	White	Hispanic, Asian
BC at <45 years	Black	Hispanic, Asian
Religion	Jewish	Seventh-day Adventist, Mormon
Oophorectomy before age 40	No	Yes
Nulliparity, BC at >40 years of age	Yes	No
Age at first full-term pregnancy	>30 years	<20 years
Age at menarche	<11 years	>15 years
Age at menopause	>55 years	<45 years
History of primary cancer in the endometrium, ovary	Yes	No
Obesity		
BC at >50 years	Obese	Thin
BC at <50 years	Thin	Obese

Reproduced from Breast Cancer Facts and Figures 2013-2014 http://www.bci.org.au/about-breast-cancer/facts-about-breast-cancer/risk-factors-for-breast-cancer.htm

1.3.3 Epidemiology of BC

BC represents 27 % of all cancer cases among women in the USA(ACS, 2012b).

Figure 1: 2009 Estimated US Cancer Cases*

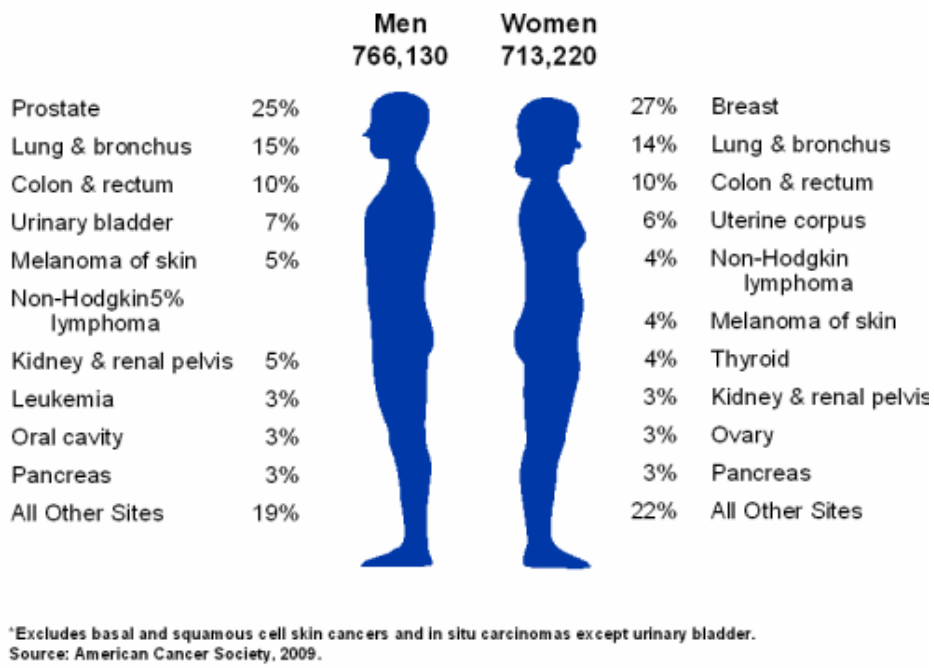
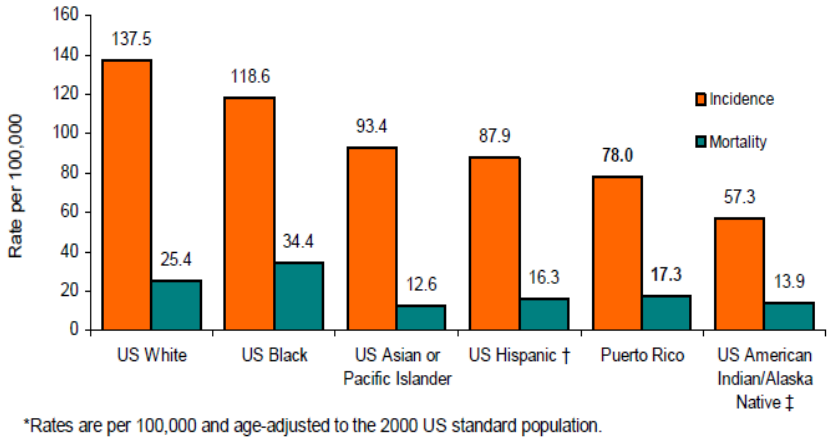


Figure 2: Female Breast Cancer Incidence and Death Rates by Race and Ethnicity, PR and US[2], 1999-2003



*Rates are per 100,000 and age-adjusted to the 2000 US standard population.

Source: Figueroa et al, 2007

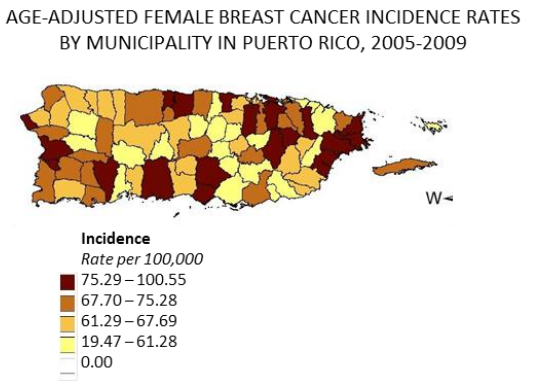
In terms of incidence and mortality, BC accounts for the 33.3 % of cancers among women in Puerto Rico being the most commonly diagnosed, and responsible for more deaths than any other cancer type (Departamento de Salud, 2011, Nazario CM, 2000). The lifetime risk for developing BC was 5.4% from the period of 1985-1989 , being less than US black females (8.8%) and US white females (13.0%) (Nazario et al., 2000). Studies among the Puerto Rican population indicates that incidence and mortality of cancer in Puerto Rico can vary by socioeconomic position (SEP) with the higher rates of BC in the areas with the highest SEP (Torres-Cintron et al., 2012). From 2005-2009, Puerto Rico had an age-adjusted incidence rate of 73.4 per 100,000 women per year (adjusted to the 2000 US Census).The incidence and mortality among Puerto Rican women compared with another ethnical group has been found to be lower except for US American Indian (Figueroa NR, 2008).

The following figures present the incidence and mortality by municipality in Puerto Rico (Cancer in Puerto Rico 2005 to 2009, (Figueroa-Vallés et al., 2012)). Darker colors represent municipalities with higher incidences and mortalities. These data was adjusted to the 2000 US standard population (Figueroa-Vallés et al., 2012). As shown on the maps below, incidence and mortality of BC is higher among the municipalities where major cities are located in PR, including San Juan, Bayamon, Ponce and Mayaguez. Other

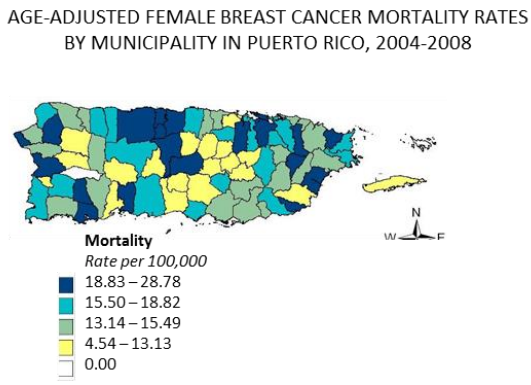
municipalities with high incidence included Rincon, Santa Isabel, Coamo, Arecibo, Barceloneta, Florida, Ciales, Orocovis, Sabana Grande, Guánica and Maunabo and with high mortality municipalities from the east coast including Fajardo, Ceiba, Naguabo and Humacao. This distribution can be partially explained by an increase in the use of mammography on these municipalities. Increases in incidence and decreases in mortality have been attributed to principally to the increase of the use of mammography in Puerto Rico for the last decades (Torres-Cintron et al., 2010).

Figure 3: Breast Cancer Incidence and Mortality Rates in Puerto Rico

a.



b.

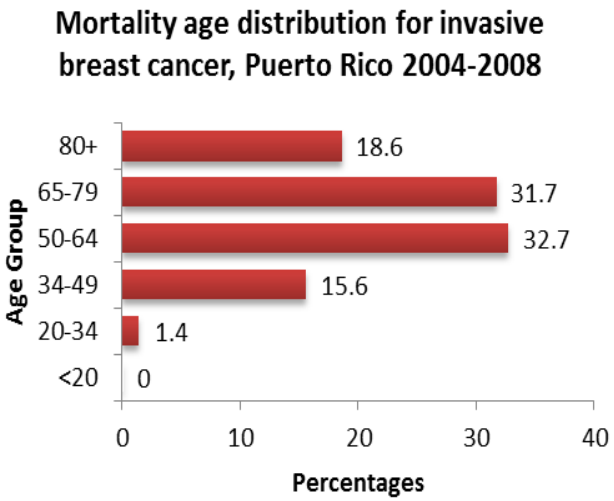


Source: Figueroa et al, 2012

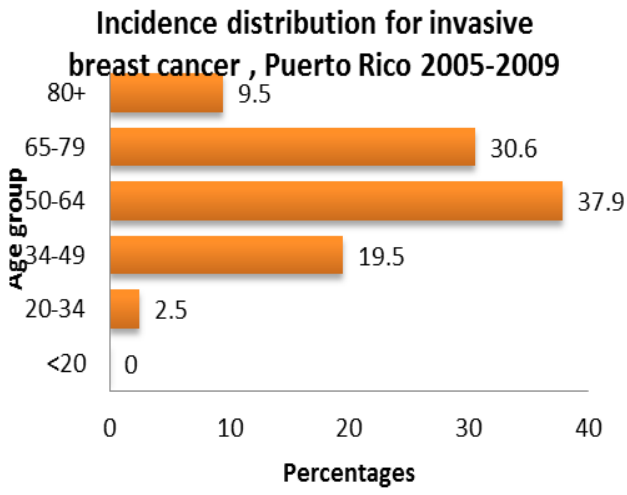
The median age of BC diagnosis among Puerto Rican women was 61 years for the years 2004-2009. The median age at death was 65 years (Figueroa-Vallés et al., 2012). The figure below summarizes the age incidence distribution and the mortality age distribution for invasive BC. The age range with the highest incidence and mortality are women of 50-64 years (Figueroa-Vallés et al., 2012).

Figure 4: Age Distribution of Breast Cancer Incidence and Mortality

a.



b.



Source: Figueroa et al, 2012

In some types of cancer, such as breast cancer, there is a good knowledge of risk factors. This information can lead to implement preventive measures leading to an early diagnosed. Most of the risk factors of breast cancer are related to the exposure to estrogens. Risk factors play a crucial role on the epidemiology of breast cancer development.

1.3.4 Education

Education has been linked to cancer risk and health by many epidemiological studies (Vidarsdottir et al., 2008, Hammond, 2003, Grossman and Kaestner, 1997). Higher level of education means lower mortality rates among cancer patients (Beiki et al., 2012, Sprague et al., 2011, Albano et al., 2007, Hussain et al., 2008). More education means more possibilities of early detection by screening (Reyes-Ortiz et al., 2007) leading to better survival (Beiki et al., 2012). Level of education is also a reliable indicator of socio-economic status and has been used as a proxy of social and economic resources (Beiki et al., 2012, Hajian-Tilaki et al., 2012). Torres-Cintrón et al., found that Puerto Rico have a

higher prevalence of smoking was associated with lower level of education and lower income status. Also, people with lower education had a lower consumption of fruits and vegetables (Torres-Cintron et al., 2012). Although educational level in Puerto Rico has been increasing, strong differences on socioeconomically status and education can be found among the population (Collazo et al., 2010). While studies shows high socioeconomic status related with high age at first birth, low parity, hormone replacement therapy and high BMI, others relate HEL with higher level of exercise, lower rates of obesity and overweight, high prevalence of exposure such as cigarette smoking and more likelihood of cancer screening utilization (Madsen et al., 2011, Hajian-Tilaki et al., 2012, Torres-Cintron et al., 2010, Robert et al., 2004). When relationship among three or more variables are being studied, interactions are used to describe the influence of two variables on a third one (Cox, 1984). If modifiable factors that are regulated by educational level and/or DRC such as vitamin and other supplements are found, they can be used to promote BC prevention or maybe identify factors that could help improve the DRC.

Table 2: Summary of the relationship between BC and educational level reported in the literature.

Authors, year	Study Design	No. of participants	Main Findings	Location	Comments
Mizoo *et al*, 2013	Case-Control	472 patients, 464 controls	Education were significantly associated with a decreased BC risk.	Japan	
Hajian-Tilaki *et al.*, 2012	case-control	100 BC cases, 200 age matched controls	Higher education level was significantly correlated with lower BC risk.	Iran	Adjustment for all traditional risk factors of breast cancers such as menarche age, age at first pregnancy, parity, total duration of breastfeeding, use of oral contraceptive and residence area.
Beiki *et al.*, 2012	population based cohort study	4,749,611 women from the Swedish population register	Highest educational level had significantly higher incidence of BC.	Sweden	Highest attained level of education was used as a surrogate indicator for socio-economic position. The cohort included women born after 1930 and lives in Sweden from 1961 to 2007 which develop BC.
Heck & Pamuk, 1997	retrospective cohort	8,596 women who took part of the NHANES I Epidemiologic follow-up study.	Positive relation between educational level and risk of BC	USA	Education was used to represent socioeconomic status. Adjustment for BC risk factors, including age, education, income, race, family history of BC, nulliparous/age at first birth, age at menarche, age at menopause, oral contraceptive use, HRT, alcohol use, BMI and height. Female participants in the study were followed from 1971-1974 to 1992-1993, participants were track and surveyed.
Naieni *et al.*, 2007	matched case-control study	250 biopsy-proven cases, 500 neighbor controls	Higher education is a risk factor for BC	Iran	Face to face interviews
Torres-Cintrón *et al.*, 2012	ecological study	Puerto Rico Central Cancer Registry	Incidence and mortality of cancer in PR varied by SEP. Rates for BC	Puerto Rico	Socioeconomic data was obtained from the US Census 2000. Education was used as one of the indicators for socioeconomic position.

		statistics from 1995 to 2004	were higher in areas with the highest SEP.		
Reyes-Ortiz *et al.*, 2007	cross-sectional study	4,183 men and 6,708 women.	High education is associated with higher odds of having a mammogram or a Pap smear. Illiterate and lower educated men and women have the lowest rates of cancer screening.	Buenos Aires, Bridgetown, Sao Paulo, Santiago, Havana, Mexico City, and Montevideo	Only Urban Areas selected. Data was from the Health, Well-Being and Aging in Latin America and the Caribbean Study. Interviews were used to assess the use of mammography and Pap smear among women and prostate examination among men.
Sprague *et al.*, 2011	prospective cohort	5,820 women	Compared to college graduates, women who had no education were 1.3 times more likely to die from BC.	Wisconsin	Women were identified from the mandatory statewide cancer registry. Telephone interviews. Study participants were followed for 7.2 years from the date of the BC diagnosis. Women were interviewed on SES (including education), reproductive and hormonal history, height, weight, use of hormones, personal and family medical history
Robert *et al.*, 2004	population-based, BC case-control study	14,667 women, 7,249 cases diagnosed with first invasive BC and 7,557 controls with no personal history of BC	Women living in the highest SES communities had greater odds of having BC than women living in the lowest SES communities.	Wisconsin	Telephone interviews. Information regarding age, education, family history of BC, parity, age at first birth, oral contraceptive use, HRT, alcohol use, BMI and height, menopause and urbanity. Women with BC were identified through the statewide mandatory cancer registry and controls were randomly selected from lists of licensed drivers
Hussain *et al.*, 2007	Prospective cohort Women were followed from the study start date until BC first occurrence.	1,571,511 women from the Swedish Family-Cancer Database	Compared to women completing less than nine years of education, university graduates were associated with the highest survival	Sweden	Women included in this study were a subset of those captured by the Family-Cancer Database, who were cancer-free, alive and residing in Sweden at the study start. The Swedish cause of death register was used tom assess deaths by BC.

			following a BC diagnosis		
Fernandez & Borre, 1999	ecological study	18, 153 subjects death from malignancies among the 64,721 deaths in subjects aged ≥25.	BC mortality was positively associated with education and may be related to delayed childbearing or another differential pattern	Barcelona	Educational level was used as an indicator of socioeconomic status. Analysis was performed by means of a record linkage between Municipal Death Registry and the Census. The data were derived from the record linkage between the Barcelona Mortality Registry and the 1991 Barcelona Municipal Census
Albano *et al.*, 2007	ecological study	137,708 cancer deaths among 119,376,196 individuals aged 25-64 years.	BC mortality rates were higher among women with less education	USA	Education information was obtained from the death certificates. Educational attainment was used as an indicator of individual socioeconomic status. US mortality data from 2001 was obtained from the National Center for Health Statistics (NCHS) and the population from the US Bureau Census.
Madsen *et al.*, 2011	register-based study	16,310 twins, 6,268 monozygotic and 10,042 dizygotic same-sex twins with no previous BC diagnosis and full information on education.	Increased risk associated with secondary/tertiary compared with the primary educational status. Education has an effect on BC risk beyond shared familial factors.	Denmark	Information on education came from Statistics Denmark. Age at first birth and parity were included in the model. Women twins born between 1921-1974 were identified at the Danish Twin Registry
Mouw *et al.*, 2008	prospective cohort	498,455 participants (302,721 men, 195,674 women). Persons with prevalent cancers	Women with the least education had a lower risk of invasive BC.	USA	Information was obtained on education, age, race, smoking, diet, alcohol consumption, weight, height, marital status, and personal and family history of cancer. Additional questions regarding age at first child, number of children, menopause hormone use, and history of oophorectomy and hysterectomy. Cohort was selected from the NIH-AARP Diet and Health Study in 1995/96 where a 16-page paper questionnaire was mailed to 3.5M

1.3.5 DNA Repair

DNA Repair is the mechanism responsible of maintaining genomic stability, principally defending the DNA from environmental damage (Murray and Berg, 2004, Li et al., 2010). The role of DNA repair involved in processed that minimize cell killing, mutations, replication errors and persistence of DNA damage(Kelley, 2012, Li et al., 2009, Han et al., 2009). DRC measurement is being studied as a potential biomarker in cancer prediction in human population studies (Saadat et al., 2012, Matta et al., 2012, Alexander et al., 2009). DNA Repair consists of various pathways that act to protect the DNA including nucleotide excision repair (NER) homologous recombination (HR); mismatch repair (MR); DNA strand crosslink repair and nonhomologous end-joining. Approximately 200 genes are involved in DNA repair process (2013).

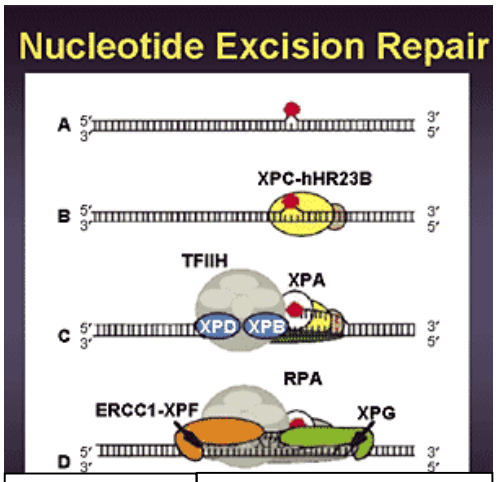


Figure 5 http://www.medscape.org

One of the mechanisms by which DNA repair occur is Nucleotide Excision Repair (NER), this pathway is responsible for the repair of lesions arising from ultraviolet light (UV) and many carcinogens that cause bulky lesions (Irizarry et al., 2009, Athas et al., 1991, Helzlsouer et al., 1996, Jyothish et al., 1998). Genetic variation or mutation to NER genes can impact cancer risk by affecting repair efficacy (Li, 2007, Shen et al., 2006).

It has been studied how DRC may have a substantial influence on individual susceptibility to sporadic BC, characterized by environmental interactions (Saadat et al., 2012, Mechanic et al., 2006). Latimer *et al.*, 2010, also found that NER plays an important role in the etiology of sporadic BC. They measured the NER capacity in breast tumors (n=19) and

compared them to normal primary cultures, they found that breast tumor only has a 44% of normal activity when compared to primary cell lines ($P < 0.001$). Research from the laboratory of Dr. Jaime Matta (PSMHS), published for the first time an important association among low DRC and high breast cancer risk (Ramos et al., 2004). The study has continued, and a considerable increment in sample size (1,188 participants) has been included to be more representative of the population studied. More recent results have reported that women with BC showed an average decrease of 60% in DRC levels as compared to controls after adjusting by age and other confounders (Matta et al., 2012).

In breast cancer patients, low levels of NER repair have been detected in lymphocytes and tumor samples. (Matta et al., 2012, Marta et al., 2003, Helzlsouer et al., 1996). DNA lesions arising from ionizing radiation and carcinogens causing bulky lesions are repaired by NER. Deficiencies in the NER pathway, such as the ones contributing to carcinogenesis are presented in breast cancer patients (Grossman and Wei, 1994, Athas et al., 1991, Helzlsouer et al., 1996, Jyothish et al., 1998, Ramos et al., 2004, Matta et al., 2003, Latimer et al., 2010, Matta et al., 2012).

DNA repair defects can lead to an accelerated aging disease or to an increased risk of cancer. Diseases like progeria and Wegner syndrome that had defects on DNA repair are more related to accelerating aging (Hoeijmakers, 2009), while other diseases increased the risk of cancer like Thompson syndrome or Xeroderma Pigmentosum (XP)(Bootsma et al., 1995). Also individuals with inherited malfunction of DNA repair has increased cancer risk, mutations on DNA Repair genes can alter the ability to recognized damage, accumulating errors that will lead to cancer development (Bernstein et al., 2002, Tomescu et al., 2001).

Table 3: Summary of the studies about DNA repair measured by the Host cell reactivation assay related to cancer.

Authors, year	Study Design	No. of participants	Main Findings	Location	Comments
Matta *et al.*, 2012	Case-control	539 controls 285 cases	The association of DRC as a measure of BC risk showed a sensitivity of 83.2% and specificity of 77.6%, supporting the usefulness of DRC level as a measure of BC risk.	Puerto Rico	DRC and BC. Associations were adjusted by DRC, age, body mass index, family history of breast cancer, number of children, marital status, and/or smoking
Wang *et al.*, 2007	Case-control	45 controls 48 patients	Lower DRC for alkylating damage is associated with an increased risk of lung cancer	Texas	Lung cancer. No correlation between DRC measured with DMS-HCR assay and that from the parallel BPDE-HCR.
Lin *et al.*, 2005	Case-control	89 cases 89 controls	Deficient DNA repair capacity for 4-ABP induced DNA damage and increases bladder cancer risk	Texas	Bladder cancer and DRC. Cases and controls were matched by age, gender, and ethnicity.
Ramos *et al.*, 2004	Case-control	33 cases 47 controls	Low DRC is a susceptibility factor for BC. A 1% decrease in DRC corresponded to a 22% increase in BC risk.	Puerto Rico	DRC and BC.
Matta *et al.*, 2003	Case-control	177 control 280 NMSC	A low DRC is a susceptibility factor for NMSC.	Puerto Rico	Nonmelanoma skin cancer (NMSC)
Wei *et a*l., 2003	Case-control	324 controls 312 cases	Reduced DRC is an independent risk factor for cutaneous malignant melanoma.	Texas	Melanoma. Adjusted for sex, age.
Wei *et al.*, 1996	Case-control	51 cases 56 controls	Individuals with reduced DRC are at an increased risk of developing lung cancer.	Texas	Lung cancer. Pilot, study.

Grossman *et al.*, 1995	Case-control	88 BCC 135 controls	Reduced repair of ultraviolet radiation DNA damage contributed to the risk of BCC.	Texas	Basal Cell Carcinoma
Hall *et al.*, 1994	Case-control	86 cases 87 controls	No evidence that the subject with non-melanocytic skin cancer had lower DNA repair capacity than controls.	Australia	Nonmelanocytic skin cancer
Wei *et al.*, 1993	Case-control	88 cases 135 controls	Reduced DRC was an important risk factor for young individuals with BCC and those for those with family history of skin cancer.	Maryland	Basal cell carcinoma.

There are other factors that can affect DNA repair of individuals with no genetic predisposition. Factors like stress and lifestyle can influence DNA repair (Cohen et al., 2000) (D'Errico et al., 1999). Studies have shown an effect on DNA repair by consumption of certain supplements in the diet, increasing the possibility of using nutrition as a possible adjuvant to traditional cancer therapy (Wei et al., 2003b, Mahabir et al., 2008, Gadhia et al., 2012, Mahabir et al., 2007, Raffoul et al., 2012).

2.0 Significance

It is unknown why education could be protective against BC unless it is a proxy for socioeconomic status, which in turn is associated with better living standards, less stress, a lesser amount of exposure to risk factors such as environmental carcinogens and smoking. Increase exposure to health information will contribute to better health practices, including vitamin and calcium supplements use, and use of preventive services such as a breast physical examinations and periodic mammography. The results of this study will provide possible explanations of why education can be a protective factor as the data analysis included variables that are potentially associated with education such as age, employment, gynecological and obstetrical history, diet supplements, and lifestyle.

3.0 Public health relevance

The results of this study may provide a possible explanation as to why women with a higher educational level and DNA repair capacity have a lower risk of breast cancer.

Education is a modifiable protective factor that seems to interact in a synergistic manner with DRC altering BC risk. As a part of this study, predictors for a high DRC will be

identified. Therefore, any factors identified in this study can be used to increase DRC and thus lower the risk for BC.

4.0 Methods

4.1.1 Study design

This study utilizes data from an incident-case, clinic-based case-control study as described by Matta et al. 2012. A total of 502 cases recently diagnosed (prior to initiation of any form of therapies such as chemotherapy and radiotherapy) histopathologically confirmed BC cases from participating clinics in Puerto Rico were included as cases (Wolff et al., 2014). Controls are women without BC and with a normal breast examination and a normal mammography in the previous six months. A total of 685 controls recruited in gynecological or medical offices concurrently with cases and in a consecutive manner. From this sample, educational level was obtained from 432 cases, and 653 controls for a total of 1085 participants included in the study.

Only cases with primary and metastatic BC tumors, rather than secondary to another type of cancer, have been included. Each participant has answered an epidemiological questionnaire soliciting anthropometrical, educational, family history of cancer and breast cancer, gynecological and obstetrical information, vitamins and calcium intake, lifestyle variables and other variables related to breast cancer risk found in previous research. The following table presents the classification of education that used during the proposed study.

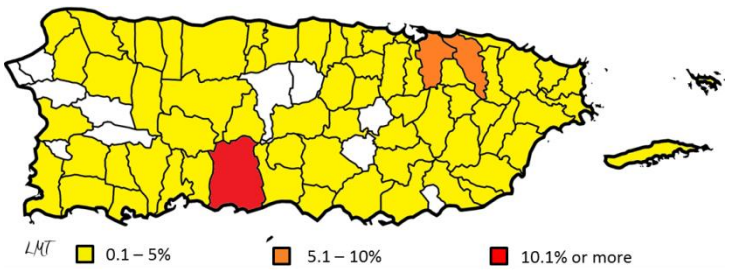
Table 4: Classification of educational levels

Educational Level	
1-8	Individuals with elementary and intermediate education (up to 8th grade)
High School	Individuals with 9th grade or higher up to incomplete associate degree or equivalent
Associate Degree	Individuals that completed associate degree or equivalent up to incomplete bachelor's degree
Bachelor or higher degree	Individuals with completed bachelor's degree, or who have education at a higher university level

This classification for education utilized due to the levels of education used in the educational system in Puerto Rico (Ladd and Rivera-Batiz, 2006). Also, this classification was asses due to other studies related to education (Vidarsdottir et al., 2008, Hajian-Tilaki et al., 2012). Compulsory school attendance in Puerto Rico is until the age of twenty-one or high school compliance although this not guarantee the completion of high school (Ladd and Rivera-Batiz, 2006).

4.1.2 Participants Recruitment

Figure 6: Recruitment map of Puerto Rico



Recruitment took place primarily in the Ponce School of Medicine and Health Sciences Outpatient Clinic, Auxilio Mutuo Hospital (San Juan), Damas Hospital (Ponce), and St. Luke's Hospital (Ponce), as well as from the area of Yauco. Figure 6 represents the distribution of the participants obtained in the study throughout

Puerto Rico, with samples collected in 65 (83.3%) of the 78 municipalities (counties) on the island (Matta et al., 2012). Control subjects were recruited consecutively from a population of individuals who were visiting the same gynecological and primary care medical offices as patients but for routine mammography and other types of screening. These selection procedures minimized selection bias due to differences in the mode and site of recruiting patients and controls that would occur if controls were recruited from the general population (for example, through random digit dialing)(Rothman and Greenland, 2008).

4.1.3 Participant population

As described in Matta *et al.* 2012, participants (patients and control subjects) were all women 21 years or older of Hispanic origin, which is the majority of the population of Puerto Rico. However, as shown from 100 ancestry markers for breast cancer (Avena et al., 2012, Via et al., 2011), this population is composed of an admixture of European, African, and Amerindian ethnic groups (Radimer et al., 2004). Consequently, the Puerto Rican population is genetically diverse.

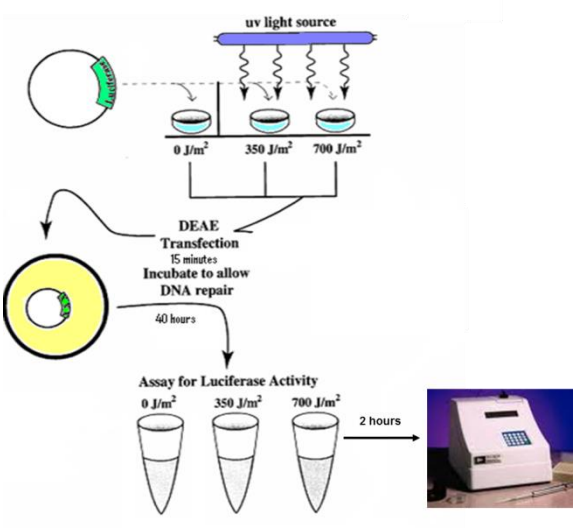
The two main inclusion criteria for selecting control subjects were having within the last six months 1) examination by the primary physician (normal clinical breast examination) and 2) having a normal mammogram as described in Matta et al, 2012. These inclusion criteria reduced the likelihood of the existence of BC among controls. Pathology reports confirming diagnosis were collected. Information like grading status, used by pathologists to classify the morphology of breast cancer cells at the time of biopsy and/or surgical removal of tumors, lymph nodes, tumor size, surgical margins and type of BC were obtained from the pathologies (ASCO, 2014). An epidemiological questionnaire was used

to assess information and variables that were related to BC risk were provided to each participant (patients and controls).

4.1.4 Host cell reactivation assay as a direct measurement of DNA repair capacity (DRC)

eactivation assay

Peripheral blood lymphocytes from patients and controls were assayed in batches as described by Ramos et al. 2004. The plasmid containing the luciferase gene (LUC) was irradiated at 0, 350, and 700 J/m2 using a 254-nm UVC lamp (Ramos et al., 2004, Matta et al., 2012). UV exposure was used to damage the plasmid in a controlled manner (dose-response curve). The level of plasmid expression can be correlated with the repair capacity of the host mammalian cell. Lymphocytes with >95% viability were incubated for 96 hours with phytohemagglutinin after incubation cells were transfected with undamaged or damaged plasmid DNA using DEAE-Dextran method. Cells isolated from xeroderma pigmentosum patients and corresponding to complementary groups C and D (XPC, XPD) were used as a positive control. Also, a cell line with known DRC was used as a control (Coriell Institute for Medical Research cell lines GM 02246D, GM 02253F and GM 08925, respectively).



4.1.5 Statistical Analysis

Specific aim #1: To study the association between educational level and BC, and educational level and DRC level. Hypotheses: (1.1) Women with higher educational level (associate degree or higher degree) have lower risk for BC as those with lower level of education (less than an associate degree), *(1.2) Women with higher educational level (associate degree or higher degree) have higher DRC level as those with lower level of education (less than an associate degree).* In order to reach this aim, we evaluated the association between educational level and BC, and the association between educational level and DRC; both association where conducted while assessing potential effect modifiers and adjusting for potential confounders.

The logistic regression adjusted odds ratio was used as a measure of association between BC and level of education adjusting for DRC and each of the rest of the covariates simultaneously (Rothman and Greenland, 2008, Breslow and Day, 1980). The same analysis, shown below, was used to assess the relationship between level of education and DRC level after dichotomizing the DRC level in low and high, using the median of the whole study sample as a cut-off point. Therefore, the statistical analyses were performed twice in the same manner to investigate the association of education al level with two different outcomes (i.e., DRC, and BC). First, for the association of educational level and BC, and then for the level of education and DRC level (low/high) were analyzed as follows. The exact 95% confidence intervals for the odds ratio were used to assess the precision of the estimate (Rosner, 2005), and the Wald test for the partial logistic regression coefficients were used to assess the statistical significance of the adjusted odds ratios because the adjusted odds ratio is the natural logarithm of the partial logistic regression coefficient (Szklo and Nieto, 2007, Mantel and Haenszel, 1959). Multiple logistic regression was used

to further identify/confirm and assess interaction and confounding of the association between breast cancer and each individual covariate with each of the rest covariates previously identified in the stratified analysis (Rosner, 2005, Szklo and Nieto, 2007, Kleinbaum and Klein, 2010). Interaction is assessed if the interaction term added in the logistic model, including two or more variables, is statistically significant. Confounding was identified if there is at least 15% difference between the crude and the adjusted odds ratio

Several logistic regression models were tested, and the best was used for adjustment after confounding and interaction have been identified. The variables included in each model were selected using several criteria including (1) a forward "conditional" selection, and/or (2) the confounders of any other variable included in the model, and/or (3) the variable(s) are biologically/epidemiologically significant according to current literature. Multicollinearity was explored by looking at the strength of the association (correlation) between variables. Multicollinearity occurs when two or more variables in multiple regression models are highly correlated affecting calculations regarding individual "predictors" (Farrar and Glauber, 1967). Strongly correlated variables were not used in the same logistic model. Variables involved in multicollinearity were combined into a single variable like weight, and height are combined into body mass index. When variables with multicollinearity cannot be combined, one of them was dropped from the model and then later analyzed in a model that do not contain the other highly collineate variable (Hosmer and Lemeshow, 2000).

To explore the relationship among educational level (low and high) and the different types of cancer a multiple logistic regression adjusted odds ratio was performed using infiltrating

ductal carcinoma as a referent. Also, multiple logistic regressions were used for the analysis of educational level (low and high) and the various tumoral grades, using grade one as a referent. For the analysis of tumor size, educational levels were divided into primary education, high school, and associate or more. Analysis of variance was performed using the Kruskal Wallis test. Mann Whitney test was used to assess the difference among the medians of tumors size between the different educational levels.

Specific aim #2: To study the possible impact of education in the association of DRC and BC. The relationship of DRC and BC will be explored at different educational levels before and after adjusting for hormone related variables such as age of menarche, contraceptive use, menopause, pregnancy and hormone replacement therapy; and other potential confounders. Hypothesis: Education is a modifier of the association between DRC and BC before and after adjusting for hormone related variables such as age of menarche, contraceptive use, menopause, pregnancy and hormone replacement therapy. The potential impact of education in the association of DRC and BC was first explored using Mantel-Haenszel stratified analysis in which the potential interaction was explored by studying the association of DRC dichotomous and BC, among the different educational levels before and after adjusting for each hormone associated variable and other potential confounders. After this part of the analysis, multiple logistic regressions were conducted to confirm whether or not, the protective effect of a high DRC level with BC is modified by the level of education. An effect modification was detected if the estimate (OR) is different among the different educational levels. If these differences are statistically significant, the effect modification can be considered a statistical interaction.

Selected variables were introduced one by one into the logistic regression model to ruled out if the interaction above mentioned is the product of confounding.

DRC was analyzed as a continuous variable first, and then dichotomized into "high" and "low" by using the median of DRC from the sample studied. Also DRC values were divided into high, medium and low DRC using tertiles, to study the effect of different levels of education among different levels of DRC and study if there is an important change in the trend of the association between DRC and BC that education may modify. In addition, this provided an opportunity to explore if a dose-response relationship exists.

4.1.6 Power Analysis

The sample size available for the study including 1,188 participants; 502 BC cases and 685 controls was enough to detect as statistically significant odds ratios as low as 1.8 when the frequency of exposure is 9% or larger (Power = 87%). If the frequency of exposure among controls is 10%, the odds ratio as low as 1.7 can be detected as statistically significant (Power = 80%). When exposures are as frequent as 15% in controls, odds ratios as low as 1.6 was detected as statistically significant (Power = 84%). For exposures as frequent as 20% or higher among controls, odds ratios as low as 1.5 can be detected as statistically significant (power = 80%) (CDC, Epi Info 7.0, 2012). Therefore, the sample size was large enough for this study in which the frequency of exposures under study among controls is 9.0% or higher (see Power Analysis Table below).

Table 5: Power Analysis for the Study with 453 BC Cases and 649 Controls

Percent Exposed Among Controls*	Odds Ratio	Percent Power Reached
9	1.7 1.8 2.0	79.0 87.0 96.0

10	1.7 2.0	80.0 97.0
15	1.5 1.6 2.0	72.0 84.0 99.5
20	1.5 1.6 2.0	80.0 90.0 99.8

* Percent exposed among controls is the relative frequency of the attribute or category among controls (e.g., 9.0% of controls smoke)

4.1.7 Ethical Issues

The Institutional Review Board (IRB) of Ponce School of Medicine and Health Sciences (PSMHS) has already approved the original project "DNA repair and expression associated with susceptibility to breast carcinoma" (P.I. Dr. Jaime Matta, protocol #: 090401-JM) and approved the current protocol "The association between educational level, DNA repair capacity and risk of breast cancer" (P.I. Dr. Manuel Bayona, protocol # 130206-MB). In addition, all members of the research team that conducted the case-control study from which data was used in the present study were trained and have passed the IRB training required by NIH. The breast cancer study started on 2006 and were still ongoing. It has been funded by the NCI Diversity Training Branch of the Center to Reduce Cancer Health Disparities (CRCHD) through the MBRS SCORE Program (Grant SO6 GM008239-23 and 1SC1CA157250-01)**.**

5.0 Results

5.1 Distribution of the educational level by case/control status, age group, and DRC level (low/high)

The distribution of the participants in the study divided by educational level by (1) case/control status, (2) age group, and (3) DRC level are presented in Table 6. A total of 432 cases and 653 controls (n=1,085) were included in the study. Of these, 166 were 21-40, 590 were 41-60, and 329 were 60+ years of age. In terms of educational level, cases to have lowest educational levels when compared to controls, especially among elementary school (1-8) educational level in which 8.1% of cases (n=35) and 1.5% controls (n=10)were in this category. Of the cases, 39.1% (n= 169) and 55.8% of the controls (n= 364) had a bachelor degree or higher education (BS+). In terms of age group, women over 60 years tend to have the lowest levels of education when compared to women between 21-40 years of age (Table 6). In the group of women between 21-40 years of age, 73.5% had BS+ while, in age groups 41-60 and 60+, this was 55.1 and 26.1% respectively. The most frequent educational level in women older than 60 years (51.7%) was high school (9 – 12 years of education). Larger proportion of women (53.5%) with high DRC level (DRC >3.8%) had higher levels of education as compared to those with low DRC level (DRC ≤ 3.8%). In summary, a higher level of education was found in controls, younger women, and in those with higher DRC levels. These three group findings showed a statistically significant linear trend (Chi Square for linear trend ≤ 0.001).

5.2 Demographic characteristics

Demographic characteristics of the variables under study divided into high educational level (HEL) or low educational level (LEL) presented in Table 7 for descriptive purposes. Among women with breast cancer (BC) and LEL, 56.5% (n=108) had low DRC (< 2.49%),

while 31.9% (n=61) had medium DRC (2.49-5.25%), and 11.5% (n=22) had high DRC levels (>5.25). Women with BC classified as having a HEL and a low DRC represented 66.2% of the study group (n=157), while 23.6% (n=56) had medium DRC levels and 10.1% (n=24) had high DRC level. These distributions were similar.

5.3 Reproductive variables

In terms of history of full-term pregnancy, 88.5% of the cases (n=169) and 89.3% of the controls (n=167) with a LEL reported at least one full term pregnancy, 83.0% of the cases (n=200) and 62.3% of the controls (n=375) with HEL reported at least one full term pregnancy. Women with LEL had a higher number of pregnancies compared to controls while the opposite trend was evident in women with HEL slightly. In terms of breastfeeding in women belonging to both LEL and HEL groups, most never reported having breastfed. In the LEL group 60.7% of the cases (n=116) and 64.2% of the controls (n=120) reported never having breastfed, while in the HEL group 53.9% of the cases (n=130) and 50.9% of the controls (n=237) reported never having breastfed their children. Eight point nine (8.9%) of the cases (n=17) and 7.0% of the controls (n=13) among the LEL group reported breastfeeding for more than 6 months, while in the HEL group 13.7% of the cases (n=33)and 10.3% of the controls (n=48) reported breastfeeding more than 6 months. No significant differences between these two distributions were found. In terms of parity status, the majority of the LEL group reported having 3-4 children (42.9% (n=82) in cases and 44.4% (n=83) in controls); while in the HEL group the majority reported having 1-2 children (50.6% (n=122) in cases, 51.7% (n=241) in controls). Most women in both groups had their first child at ages 20-29 years (LEL cases 57.6%, LEL controls 63.5%, HEL cases 67.9%, HEL controls 70.5%). In the LEL level group, 52.4 % (n=99) of the

women with breast cancer had their menarche at ≥13 years of age and 48.9% (n=91) of the controls. In the HEL group, 59.2% of cases (n=142) and 60.1% (n=280) of controls had their menarche ≤12 years of age.

In terms of endometriosis, only 2.1% of the cases (n=4) in the LEL group and 8.1% of the controls (n=8.1) had endometriosis. In the HEL group, 10.0% of the cases (n=24) and 11% of the controls (n=51) reported having had endometriosis. The age of oophorectomy was distributed similarly in the LEL group and the HEL group among the different categories of age (age ≤40 LEL cases 39.5%, controls 40.4%, HEL cases 37.5%, controls 39.8%). In terms of menopausal status, women belonging to the LEL group, 74.3% of the cases (n=142) were menopausal, and 63.1% of the controls (n=118) were in that category. In contrast, in the HEL group, 73.4% of women with BC (n=177) and 34.5% of the controls (n=161) were menopausal.

5.4 Hormone replacement therapy and other hormonal factors

Use of hormonal treatment (MHT) during menopause among women in the LEL group was 31.4% for the cases (n=60) and 44.9% for the controls (n=84). In the HEL group 31.1% of the cases (n=75) and 34.5% of the controls (n=161) were treated with MHT. Age of hysterectomy in the LEL group was more common in the <40 years of age group (cases 45.3% (n=29), controls 43.9% (n=25)). However in the HEL group it was more common in the 41-49 years group (cases 38.3% (n=18), controls 45.6% (n=47)). Forty three percent (42.6%) of the cases (n=81) and 52.2% of the controls (n=96) in the LEL group took oral contraceptives, while in the HEL group 54.0% of the cases (n=129) and 56.8% of the controls (n=260). In both groups, most women reported having taking oral contraceptives

after 21 years of age (LEL cases (n=59) 78.7% and 64.8% of the controls (n=59), HEL cases (n=103) 83.7%, 77.3% of the controls (n=198)). In terms of age, most of the LEL women were in the 61 years of age category (cases (n=103), 57.5%, controls (n=87), 47.0%) and in the HEL group most of the women were in the 41-60 years of age category (cases 61.2% (n=134), controls 62.3% (n=278)). In both groups most of the women reported a BMI >25 (cases of the LEL 75.9% (n=142), and 72.0% (n=131) of the controls; cases of the HEL 64.6% (n=155), and 61.7% (n=283) of the controls. In terms of smoking status, cases with LEL reported only 9.9% (n=19) of having being smoking, and in the controls was 9.2% (n=17). HEL cases reported 12.9% (n=31) of having being smoked and 8.7% (n=40) of controls. Six percent (6.3%) (n=12) of the LEL cases reported alcohol consumption and 13.6% of the controls (n=25), and HEL cases reported 12.9% (n=31) and controls 8.7% (n=40). These distribution differences are important. Forty four percent (44.6%, n=83)) of the cases in the LEL group reported being currently taking vitamins while the 60.8% (n=110) of the controls reported the same. In the HEL group, the 53.8% (n=127) of the cases reported current vitamins intake and 65.2% of the controls (n=300). Reporting taking vitamins in the last 5 years were cases with LEL (49.2%, n=92) and 65.6% in the controls (n=120); while HEL cases reported 56.4% (n=133) and controls 67.5% (n=311). In terms of multivitamin and calcium intake, the LEL group cases reported 25.3% (n=47) of multivitamin consumption and 18.3% (n=34) of calcium intake. In controls, multivitamin consumption was 33.9% (n=62) and 32.4% (n=59) of calcium intake. The HEL group cases reporting multivitamin intake were 30.5% (n=72) and calcium intake 19.5% (n=46), while controls reporting multivitamin intake were 40.0% (n=184) and calcium intake 25.7% (n=118). Regarding marital status in both groups most

women reported being married (LEL cases 45.3% (n=86), and controls 68.8% (n=128)), HEL cases: 58.9% (n=142) and controls: 65.6% (n=303)). The 66.5% (n=127) of the LEL cases reported having a family history of cancer (not BC) and 27.7% (n=53) of the cases reported having history of BC, while in the HEL group 65.1% (n=157) of the cases reported the family history of cancer (not BC) and 26.6% (n=64) of the cases reported having BC history in any member of the family.

5.5.1 Association of educational level and high and low DRC levels

Table 8 presents the association of DRC and educational level. Women who received primary school (1-8) education only had the higher odds for low DRC levels (OR: 1.8, 95%CI 0.3, 1.4), followed by high school educational level (9-12) (OR: 1.4, 95%CI 1.1-1.9). This finding was statistically significant after multiple adjustment procedures (p=0.027).

5.5.2 Association of educational level with breast cancer

Table 9 presents the association of breast cancer with educational level. After multiple adjustment procedures as described in Table 9, women with the lowest educational level (1-8 years of education) as compared to those with a higher educational level (BS+) had had 4.6 times the odds of developing BC. This group had5.9 times the odds of developing BC when adjusted for DRC by adding it to the linear regression model ($p = 0.006$ and $p<0.001$, respectively). While women with high school education had 1.6 times the odds of BC and 1.4 times the odds when DRC was also adjusted for (p=0.005, p=0.039, respectively).

5.5.3 Association of low and high DRC levels and breast cancer stratified by low and high educational level

In table 10, the results the association of DRC with BC is shown stratified in two educational levels. After multiple adjustment procedures, associations of DRC (low and high) stratified by educational level (low and high) showed that among women with LEL, those with a low DRC level have 8.9 times the odds of BC ($p<0.001$) as compared to those with high DRC level. Among women with HEL, those with low DRC had 11.7 times more odds of developing BC as compared to those with high DRC ($p<0.001$). Breslow-Day test for interaction was calculated, no statistical interaction was found $p=0.483$.

5.5.4 Association of low and high educational levels and breast cancer stratified by low and high DRC levels

Table 11 presents the association of educational level (low and high), and BC stratified by DRC levels (low and high). After multiple adjustment procedures, among those with high DRC, women with LEL had almost two times more possibilities to have BC than those with LOL (OR: 1.9, 95% CI 1.1- 3.3). In contrast, among those with low DRC women with LOL had 1.3 times the odds to have BC than those with high educational level. However, this last association was not statistically significant ($p = 0.175$). The Breslow-Day test for interaction was not statistical significance $p=0.483$.

5.5.5 Association of DRC levels and breast cancer stratified by four different educational levels

A further stratification of educational levels is presented in table 12. It can be seen that the highest level of education (bachelor or higher degree) increases the odds of BC among

women with low DRC (OR: 12.4, 95%CI 7.7- 20.2). However, an odds ratio as large as 26.0 was found with the lowest level of education probably because the sample size of this category was small and the results were imprecise as can be seen in the huge confidence interval. Breslow-Day for homogeneity of odds ratio was not statistical significant (OR: 2.7 p value 0.434).

5.5.6 Association of breast cancer with gynecological variables stratified by low and high educational level

The association of BC with gynecological variables stratified by educational level is presented in table 13. Variables that showed a statistically significant decrease in BC odds (protective effect) among women with low educational level (LEL) were: endometriosis (OR: 0.2, 95%CI: 0.1, 0.8), use of menopause hormone treatment (MHT) (OR: 0.6, 95%CI: 0.4, 0.9) and use of oral contraceptives after age 21 (OR: 0.4, 95%CI: 0.2- 0.9). In contrast, menopause appeared to increase BC odds in women that were in the LEL category (OR: 1.6, 95%CI: 0.9-2.5). None of these variables were found to have substantial differences in the strength of association with BC between the two educational groups. Pregnancy, breastfeeding, parity status, age of first live birth, menarche, age oophorectomy, and age of hysterectomy, did not showed statistically significant associations with BC among women in the two educational groups ($p>0.05$). Among women with LEL, who had an oophorectomy, the odds for BC decreased by 10% in women from 41-49 years of age and 30% in women with >50 years of age. While in women with HEL the odds increased by 1.7 for both age groups ($p>0.05$).

Among women with a high level of education (HEL), those that had a hysterectomy prior to 40 years (OR: 0.3, 95%CI: 0.1-0.8) had a decreased risk of BC that was statistically significant. Breastfeeding did not show a statistically significant association with BC after stratification by educational level ($p>0.05$). Use of oral contraceptive after 21 years of age showed a decrease odds of BC among women with HEL (OR: 0.6, 95%CI: 0.3, 1.1). Endometriosis was found to have an interaction ($p = 0.035$) with educational level in its association with BC: Women with LEL had 80% less odds to have BC ($p = 0.023$) while those with HEL only had 10% less odds for BC.

5.5.7 Association of breast cancer with DRC, family history of cancer and breast cancer, obesity, lifestyle, marital status by low or high level of education

Table 14 presents the association of BC with DRC, family history of cancer and breast cancer, obesity, lifestyle and marital status by level of education. Among women with a LEL and a low DRC (<2.49%), the odds of developing BC were elevated; 22.0 (95% CI 10.0, 45.0) and 3.8 for women with medium DRC level (95%CI 2.0, 7.2) as compared to those with high DRC. For the high DRC group, the associations were similar being the odds ratio as high as 25.4. That is; women with high educational level and low DRC had 25.4 times more odds of having BC as compared to those with high educational level and high DRC level. Women with HEL and medium DRC level had 3.2 times more odds of having BC than those with high educational level and high DRC level. In terms of age, LEL women 61 years of age or older have the greatest odds (OR: 2.8 95%CI: 1.1, 6.9) of developing BC than those of the youngest age group (21-40) that is used as a referent. LEL women 41- 60 years of age had 1.9 times more possibilities to have BC than the referent group. HEL Women 61 years of age or older had 2.0 times more odds to have BC than the

referent. HEL women 41 to 60 years of age had 1.4 times more odds to have BC than the referent. LEL women that consumed alcohol had 60% fewer odds to have BC than LEL women not consuming alcohol (OR: 0.4, 95%CI 0.2, 0.9). In contrast, HEL women that consumed alcohol had 10% fewer odds of having BC as compared to HEL women that did not consume alcohol (OR 0.9, 95%CI 0.6, 1.5). This difference between LEL and HEL was statistically significant (p = 0.047) constituting a statistical interaction between education and alcohol consumption as related to BC. HEL women had 2.1 times more odds of consuming alcohol than LEL women (OR 2.1, 95%CI 1.4, 3.1). This result is not shown in tables.

Associations with BC in HEL and LEL groups were similar for current vitamin consumption (LEL: OR 0.5, 95%CI 0.3, 0.7, HEL: OR: 0.6, 95%CI 0.4, 0.8). Those that were currently consuming vitamins had about 40% to 50% less odds to have BC than those that did not. Similar results were found with the consumption of vitamins in the last 5 years (LEL OR: 0.5, 95%CI: 0.3, 0.7 HEL OR: 0.6, 95%CI: 0.4, 0.8), and multivitamins consumption (LEL OR: 0.6, 95%CI: 0.4, 1.0, HEL OR: 0.6, 95%CI: 0.4, 0.9).

LEL women who consumed calcium supplements had 70% less odds to have BC than those that did not, while HEL women taking calcium supplements had 40% less odds as compared to those not taking it (LEL OR: 0.3, 95%CI 0.2, 0.6 HEL OR: 0.6, 95%CI 0.4, 0.9). This effect modification while important was not statistically significant (p = 0.157).

Important effect modifications were found between LEL and HEL women regarding marital status. LEL Women that were single, divorced and widows had 2.6, 1.5 and 3.6 times the odds of having BC when compared to married women (OR: 2.6 95%CI 1.4, 4.8,

OR: 1.5 95%CI: 0.7, 3.0, OR: 3.6 95%CI 1.6, 8.2, respectively). HEL Women that were single, divorced and women and widows respectively had 80% 39% and 79% less odds to have BC when compared to married women ((OR: 1.3 95%CI0., 2.0, OR: 1.1 95%CI: 0.7, 1., OR: 1.8 95%CI 0.7, 4.7, respectively). These results showed important effect modifications between LEL and HEL. However, they were not statically significant.

Similar results were found between LEL and HEL women in regards to family history of cancer (not BC). LEL Women that had family history of cancer (not BC) had 40% more possibilities of having BC as compared to those that did not have such family history (OR: 1.4, 95%CI: 0.9, 2.2). HEL Women that had family history of cancer (not BC) had 50% more possibilities of having BC as compared to those that did not have such family history (OR: 1.5, 95%CI: 1.1, 2.1).

Different results were found between LEL and HEL women in regards to family history of BC. LEL Women that had family history of BC had 2.0 times more odds of having BC as compared to those that did not have such family history (OR: 2.0, 95%CI: 1.2, 3.5). HEL Women that had family history of BC had 40% more possibilities of having BC as compared to those that did not have such family history (OR: 1.4, 95%CI: 1.0, 2.1). However, this effect modification between LEL and Hel women was not statistically significant ($p = 0.353$).

When a comparison was made of the high and low educational level by BMI, age, number of children, it was found that women in the LEL group had a higher BMI when compared to women with HEL (LEL BMI= $28.3 \pm .1$, HEL BMI=26.9 ± 5.1, $p<0.$ S001). In terms of age, women in the LEL group were older 59.8 ± 11.9 when compared with HEL women

50.2 ± 11.5 ($p<0.001$). LEL women had more parity 2.9 ± 1.6 and lowest age at first pregnancy 22.2 ± 4.7 when compared to HEL women (parity 2.2 ± 1.1, age first pregnancy 25.7, $p <0.001$ for both associations) (These results are not shown in the tables).

Potential Interactions of educational level (low/high) with multiple confounders were examined and presented in tables 13 and 14. The following associations between variables and BC were found to have statistically significant interactions with educational level.

5.6 Pathological categories of breast cancer and educational level

Figure 8 shows the distribution of BC cases when analyzed in terms of various pathological BC subtypes and divided into LEL and HEL. In women with LEL, the infiltrating ductal carcinoma represented 77.9% n= 141) of the cases while in the HEL group was 56.4% (n=132). Among LEL, 6 were in situ ductal (3.3%), while 11 (4.7%) have HEL. Among LEL 17 were infiltrating lobular (9.4%) and among HEL group were 60 (25.6%). The in situ lobular represented only 3% (n=7) of the cases in the HEL group while no woman with in situ lobular had LEL. The mixed components BC subtype represented 9.4% (n=17) of the LEL group and 10.3% (n=24) of the HEL group. Women with all types of BC have fewer odds (crude OR) to have low education as compared to women with infiltrating ductal BC (Table 15). These differences were statistically significant when compared to those with infiltrating lobular BC and for those with in-situ BC. In other words, women with infiltrating ductal have higher odds to have low education than women with any other cancer type: ID had two times more odds to have LED than in situ ductal BC ($p = 0.219$), five times more odds than women with Infiltrating lobular BC ($p < 0.001$), 1.4 times more odds than those with mix components

BC (p = 0.322) and more odds (undetermined) than women with in situ BC before adjusted analysis. After adjusting for age, BMI, smoke and alcohol consumption women with infiltrating ductal had more odds to have LEL than those with infiltrated lobular BC and in-situ ductal.

Figure 9 shows the distribution of BC severity grades divided into HEL and LEL among the cases in the study sample. Among women with HEL 19.2% had grade 1 (n=32) while those in the LEL group represented 12.3% (n=19) of the cases in this category.. In terms of grade 2, the LEL group 01represented 57.8% of the cases (n=89), while those in the HEL group were 47.9% (n=80) of the cases.. For women with grade three breast cancer, those in the LEL group represented 29.9% (n=46) of the cases while HEL cases showed the 32.9% (n=55). A comparison among educational level and grade status showed that women with LEL had 1.8 more odds of being grade 2 when compared to grade 1(OR=1.8, 95%CI 0.9, 3.7), and 1.8 more times of being grade 3 when compared to grade 1 (OR=1.8 95%CI: 0.8,3.8) (Table16). The analysis was adjusted by age, BMI and smoking status.

The potential association of breast cancer tumor size (cm) and educational level was analyzed and shown in Figure 10. As educational level increases the tumor size decrease (Kruskal-Wallis test p=0.031) (Table 17).

In the figure, 11a DNA repair levels were compared among cases and controls in women with low educational level. Cases in the LEL had DRC levels around 3% while controls is around 4%..

Table 6. Distribution of the educational level by case/control status, age group, and DRC level (low/high)

Educational Level	Cases n (%)	Controls n (%)	Age group 21-40 n (%)	Age group 41-60 n (%)	Age group 60+ n (%)	Total[1] n (%)	Low DRC n (%)	High DRC n (%)
1 – 8	35 (8.1)	10 (1.5)	1 (0.6)	14 (2.4)	30 (9.1)	45 (4.2)	27 (5.0)	18 (3.4)
9 – 12	156 (36.1)	177 (27.1)	22 (13.3)	141 (23.9)	170 (51.7)	333 (30.7)	187 (34.3)	145 (27.1)
AD[3]	72 (16.7)	102 (15.6)	21 (12.6)	110 (18.6)	43 (13.1)	174 (16.0)	86 (15.8)	86 (16.0)
BC+[3]	169 (39.1)	364 (55.8)	122 (73.5)	325 (55.1)	86 (26.1)	533 (49.1)	244 (44.9)	286 (53.5)
Total	432 (100.0)	653 (100.0)	166 (100.0)	590(100.0)	329(100.0)	1,085 (100.0)	544 (100.0)[2]	535 (100.0)[2]

[1] These totals are 100% for each educational level. [2] These totals are 100% for each DRC level. [3]AD- associate degree, BC+- bachelor degree or higher degree. Chi-square for linear trend <0.001 for each category

Table 7: Demographic characteristics of the variables under study in cases and controls divided by educational level.

	Low Educational Level		High Educational level	
Variable	BC cases n(%)	Controls n(%)	BC cases n(%)	Controls n(%)
DRC[1]				
Low <2.49	108 (56.5)	28 (15.1)	157 (66.2)	66 (14.2)
Medium 2.49-5.25	61 (31.9)	78 (41.9)	56 (23.6)	172 (37.0)
High>5.25	22 (11.5)	80 (43.0)	24 (10.1)	227 (48.8)
Pregnancy				
Yes	169 (88.5)	167 (89.3)	200 (83. 0)	375 (62.3)
No	22 (11.5)	20 (10.7)	41 (17.0)	227 (37.7)
Breastfeeding total				
never	116 (60.7)	120 (64.2)	130 (53.9)	237 (50.9)
0-5 months	58 (30.4)	54 (28.9)	78 (32.4)	181 (38.8)
≥ 6 months	17 (8.9)	13 (7.0)	33 (13.7)	48 (10.3)
Parity status				
nulliparous	25 (13.1)	20 (10.7)	45 (18.7)	102 (21.9)
1-2 children	59 (30.9)	74 (39.6)	122 (50.6)	241 (51.7)
3-4 children	82 (42.9)	83 (44.4)	64 (26.6)	115 (24.7)
≥5 children	25 (13.1)	10 (5.3)	10 (4.1)	8 (1.7)
Age at first live birth				
≤19	56 (33.9)	51 (30.5)	18 (9.2)	33 (9.1)
20-29	95 (57.6)	106 (63.5)	133 (67.9)	256 (70.5)
≥30	14 (8.5)	10 (6.0)	45 (23.0)	74 (20.4)
Menarche				
≤ 12	90 (47.6)	95 (51.1)	142 (59.2)	280 (60.1)

≥ 13	99 (52.4)	91 (48.9)	98 (40.8)	186 (39.9)
Endometriosis				
Yes	4 (2.1)	15 (8.1)	24 (10.0)	51 (11.0)
No	185 (97.9)	170 (91.9)	217 (90.0)	414 (89.0)
Age oophorectomy				
≤40	17 (39.5)	21 (40.4)	15 (37.5)	33 (39.8)
41-49	17 (39.5)	19 (36.5)	16 (40.0)	36 (43.4)
≥50	9 (20.9)	12 (23.1)	9 (22.5)	14 (16.9)
Menopause				
Yes	142 (74.3)	118 (63.1)	177 (73.4)	161 (34.5)
No	49 (25.7)	69 (36.9)	64 (26.6)	305 (65.5)
MHT (estrogen-only)				
Yes	60 (31.4)	84 (44.9)	75 (31.1)	161 (34.5)
No	131 (68.6)	103 (55.1)	166 (68.9)	305 (65.5)
Age hysterectomy				
≤40	29 (45.3)	25 (43.9)	15 (31.9)	42 (40.8)
41-49	21 (32.8)	22 (38.6)	18 (38.3)	47 (45.6)
≥50	14 (21.9)	10 (17.5)	14 (29.8)	14 (13.6)
Oral Contraceptives				
Yes	81 (42.6)	96 (52.2)	129 (54.0)	260 (56.8)
No	109 (57.4)	88 (47.8)	110 (46.0)	198 (43.2)
Age oral contraceptives				
<20	16 (21.3)	32 (35.2)	20 (16.3)	58 (22.7)
≥21	59 (78.7)	59 (64.8)	103 (83.7)	198 (77.3)
Age				
21-40	8 (4.5)	16 (8.6)	38 (17.4)	99 (22.2)
41-60	68 (38.0)	82 (44.3)	134 (61.2)	278 (62.3)

61+	103 (57.5)	87 (47.0)	47 (21.5)	69 (15.5)
BMI				
up to 24.99	45 (24.1)	51 (28.0)	85 (35.4)	176 (38.3)
≥25	142 (75.9)	131 (72.0)	155 (64.6)	283 (61.7)
Smoke (more than 100 cigarettes in a lifetime)				
Yes	19 (9.9)	17 (9.2)	31 (12.9)	40 (8.7)
No	172 (90.1)	167 (90.8)	209 (87.1)	421 (91.3)
Alcohol				
Yes	12 (6.3)	25 (13.6)	47 (19.7)	86 (18.8)
No	179 (93.7)	159 (86.4)	192 (80.3)	372 (81.2)
Current vitamin consumption				
Yes	83 (44.6)	110 (60.8)	127 (53.8)	300 (65.2)
No	103 (55.4)	71 (39.2)	109 (42.2)	160 (34.8)
Vitamins last five years				
Yes	92 (49.2)	120 (65.6)	133 (56.4)	311 (67.5)
No	95 (50.8)	63 (34.4)	103 (43.6)	150 (32.5)
Multivitamins				
Yes	47 (25.3)	62 (33.9)	72 (30.5)	184 (40.0)
No	139 (74.7)	121 (66.1)	164 (69.5)	276 (60.0)
Calcium				
Yes	34 (18.3)	59 (32.4)	46 (19.5)	118 (25.7)
No	152 (81.7)	123 (67.6)	190 (80.5)	342 (74.3)
Marital Status				
Married	86 (45.3)	128 (68.8)	142 (58.9)	303 (65.6)
Divorced	44 (23.2)	25 (13.4)	57 (23.7)	90 (19.5)

Single	23 (12.1)	20 (10.8)	31 (12.9)	57 (12.3)
Widow	37 (19.5)	13 (7.0)	11 (4.6)	12 (2.6)
Family history of cancer (not BC)				
Yes	127 (66.5)	109 (58.3)	157 (65.1)	267 (57.4)
No	64 (33.5)	78 (41.7)	84 (34.9)	198 (42.6)
BC history in any family member				
Yes	53 (27.7)	29 (15.5)	64 (26.6)	96 (20.6)
No	138 (72.3)	158 (84.5)	177 (73.4)	370 (79.4)

[1] DRC low (up to 2.50%), medium (2.51% to 5.50%), and high (5.51% and higher)

Table 8: Association of educational level and high and low DRC levels

Variable	Low DRC	High DRC	Crude OR (p-value)	Adjusted OR[1] (p-value)
Education				
1-8	27	18	1.8 (0.9, 3.3)	1.8 (0.3, 1.4)
			0.075	0.107
9-12	187	145	1.5 (1.1, 2.0)	1.4 (1.1, 1.9)
			0.003	0.027
Associate degree	86	86	1.2 (0.8,1.7)	1.2 (08, 1.8)
			0.366	0.389
Bachelor or more	244	286	Referent	Referent

[1]Adjusted by age, BMI, family history of BC, vitamins use, smoking and alcohol use.

Borderline statistically significant ($0.05 \leq p \leq 0.10$)

Statistically significant ($p < 0.05$)

Table 9: Association of educational level with breast cancer

Variable	BC Cases	Controls	Crude OR (p-value)	Adjusted OR[1] (p-value)	Adjusted OR[2] (p-value)
Education					
1-8	35	10	7.5 (3.6, 15.5) <0.001	4.6 (2.1, 10.3) 0.006	5.9 (2.3, 14.9) <0.001
9-12	156	177	1.9 (1.4, 2.5) <0.001	1.6 (1.1, 2.1) 0.006	1.4 (1.1, 2.1) 0.049
Associate degree	72	102	1.5 (1.1, 2.2) 0.021	1.4 (0.9, 2.1) 0.064	1.4 (0.9, 2.2) 0.118
Bachelor's degree or more	169	364	Referent	Referent	Referent

[1] Adjusted by age, BMI, family history of BC, vitamins use, smoking, and alcohol use

[2] Adjusted by age, BMI, family history of BC, vitamins use, smoking, alcohol use, and DRC

Borderline statistically significant ($0.05 \leq p \leq 0.10$)

Statistically significant ($p < 0.05$)

Table 10: Association of low and high DRC levels and breast cancer stratified by low and high educational level

Variable	BC Cases	Controls	Crude OR p-value	Adjusted OR[3] p-value
Education Low[1]				
Low DRC (<3.8)	141	62	7.6 (4.7, 12.3)	8.9 (5.2, 15.2)
High DRC (≥3.8)	36	121	<0.001	<0.001
Education High[2]				
Low DRC (<3.8)	177	129	11.1 (7.4, 16.6)	11.7 (7.7, 17.7)
High DRC (≥3.8)	396	316	<0.001	<0.001

[1]Education low: up to high school

[2]Education high: college degree and graduate studies

[3] Adjusted by age, BMI, family history of BC, vitamins use, smoking and alcohol use

Borderline statistically significant ($0.05 \leq p \leq 0.10$)

Statistically significant ($p < 0.05$)

Multiple logistic regression test for interaction= 0.483

Table 11: Association of low and high educational levels and breast cancer stratified by low and high DRC levels

Variable	BC Cases	Controls	Crude OR p-value	Adjusted OR[3] p-value
High DRC				
Education Low[1]	36	121	1.7 (1.2, 2.4)	1.9 (1.1, 3.3)
Education High[2]	39	316	0.009	0.020
Low DRC				
Education Low[1]	141	62	2.4 (1.5, 3.9)	1.3 (0.9, 2.0)
Education High[2]	177	129	0.001	0.175

[1]Education low: up to high school

[2]Education high: college degree and graduate studies

[3] Adjusted by age, BMI, family history of BC, vitamins use, smoking and alcohol use

Borderline statistically significant ($0.05 \leq p \leq 0.10$)

Statistically significant ($p < 0.05$)

Multiple logistic regression test for interaction= 0.483

Table 12: Association of DRC levels and breast cancer stratified by four different educational levels

Variable	BC Cases	Controls	Crude OR (p-value)	Adjusted OR[1] p-value
Education (1-8 grades)[2]				
Low DRC (<3.8)	26	1	26.0 (2.9, 234.0)	-----
High DRC (≥3.8)	9	9	0.001	
Education (9-12 grades)				
Low DRC (<3.8)	124	63	7.0 (4.2, 11.4)	7.2 (4.3, 12.2)
High DRC (≥3.8)	32	113	<0.001	<0.001
Education (Associate degree)				
Low DRC (<3.8)	55	31	8.4 (4.7, 17.1)	7.6 (3.6, 16.0)
High DRC (≥3.8)	15	71	<0.001	<0.001
Education (Bachelor or higher degree)				
Low DRC (<4.0)	137	107	10.9 (6.9, 17.2)	12.4 (7.7, 20.2)

High DRC (≥4.0)	30	256	<0.001	<0.001

[1] Adjusted by age, BMI, family history of BC, vitamins use, smoking and alcohol use

[2] Given that only one control had low DRC, multiple regression adjustment procedures could not be performed

Statistically significant ($p < 0.05$)

Breslow-Day for homogeneity of odds ratio

Breslow-Day $Chi^2 = 2.7$ $p = 0.434$

Table 13: Association of Breast Cancer (BC) with gynecological variables stratified by low or high educational level

	Low Educational Level					High Educational level					
Variable	BC cases	Controls	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	*P* value	BC cases	Controls	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	*P value*	Interaction *P value*
Pregnancy											
Yes	169	167	0.9 (0.5, 1.7)	0.9 (0.5, 1.9)	0.824	200	375	1.1 (0.7,1.7)	1.2 (0.8, 1.9)	0.353	0.774
No	22	20				41	91				
Breastfeeding total[3]											
never	116	120	Referent	Referent		130	237	Referent	Referent		
0-5 months	58	54	1.1 (0.7, 1.8)	1.2 (0.7, 1.9)	0.513	78	181	0.8 (0.6, 1.1)	0.9 (0.6, 1.2)	0.417	0.390
≥ 6 months	17	13	1.6 (0.7, 3.7)	1.4 (0.6, 3.2))	0. 458	33	48	1.3 (0.8, 2.2)	1.5 (0.9, 2.5)	0.165	0.974
Parity status [3]											
nulliparous	21	20	Referent	Referent		45	102	Referent	Referent		
1-2 children	60	74	0.8 (0.4, 1.6)	0.8 0.4, 1.6)	0.524	122	241	1.4 (0.5, 3.3)	1.7 (0.6, 5.0)	0.634	0.749
≥3 children	96	90	1.0 0.5, 2.0)	0.9(0.5, 2.0)	0.969	10	8	1.3 (0.8, 2.1)	1.2 (0.7, 2.0)	0.494	0.682
Age at first live birth											
≤19	56	51	0.7(0.3, 2.0)	0.5 (0.2,1.4)	0.148	18	33	0.8 (0.4, 1.7)	0.8 (0.4, 1.7)	0.483	0.644
20-29	95	106	0.7 (0.3, 1.7)	0.5 (0.2, 1.3)	0.145	133	256	0.8 (0.6, 1.4)	0.8 (0.5, 1.3)	0.333	0.506
≥30	14	10	Referent	Referent		45	74	Referent	Referent		
Menarche											
≤ 12	90	95	0.9 (0.6,1.4)	0.8 (0.5,1.3)	0.263	143	280	0.9 (0.7, 0.4)	0.9 (0.7, 1.3)	0.824	0.777
≥13	99	91				97	186				
Endometriosis[2]											
Yes	4	15	0.2 (0.1,0.7)	0.2 (0.1,0.8)	0.023	24	51	0.9 (0.5, 1.5)	0.9 (0.6, 1.7)	0.976	0.035
No	185	170				217	414				
Age oophorectomy[3]											
≤40	17	21	0.9 (0.3, 3.5)	0.9 (0.3, 3.3)	0.900	15	33	1.4 (0.5, 3.3)	1.7 (0.6, 5.0)	0.337	0.749
41-49	17	19	1.2 (0.5, 3.5)	1.4 (0.4,4.6)	0.618	16	36	1.4 (0.5, 5.0)	1.7 (0.5, 5.0)	0.449	0.682
≥50	9	12	Referent	Referent		9	14	Referent	Referent		
Menopause											

Yes	49	69	1.7 (1.1,2.6)	1.6 (0.9,2.5)	0.056	289	177	1.7 (1.2, 2.4)	1.6 (1.1, 2.3)	0.007	0.962
No	142	118				177	64				
Menopause age											
>50	100	79	1.3 (0.8,2.0)	1.3 (0.8, 2.1)	0.284	92	126	1.4 (0.9, 2.1)	1.4 (0.9, 2.1)	0.161	0.973
≤49	64	65				88	174				
MHT (estrogen-only)											
Yes	60	84	0.6 (0.4, 0.8)	0.6 (0.4, 0.9)	0.013	75	161	0.8 (0.6, 1.3)	0.7 (0.5, 1.0)	0.086	0.259
No	131	103				166	305				
Age hysterectomy											
≤40	29	25	0.8 (0.2,2.2)	0.7 (0.2,2.0)	0.513	15	42	0.4 (0.1, 0.9)	0.3 (0.1, 0.8)	0.020	0.429
41-49	21	22	0.7 (0.2,1.9)	0.7 (0.2-2.3)	0.565	18	47	0.4 (0.2, 0.9)	0.4 (0.2, 1.2)	0.072	0.908
≥50	14	10	Referent	Referent		14	14	Referent	Referent		
Oral Contraceptives											
Yes	81	96	0.7 (0.5,1.0)	0.8 (0.5,1.2)	0.295	129	260	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.641	0.398
No	109	88				110	198				
Age oral contraceptives											
<20	16	32	0.5 (0.2,1.0)	0.4 (0.2, 0.9)	0.019	20	58	0.7 (0.4, 1.2)	0.6 (0.3, 1.1)	0.072	0.825
≥21	59	59				103	198				

[1] Adjusted by age, BMI, smoking and vitamin use.
[2] Multiple logistic regression tests for interaction.
[3] Effect modification (OR is more than 15% different between strata but was not statistically significant (p>0.05).
Abbreviations: BC, breast cancer**;** CI, confidence interval; OR, odds ratio; MHT, menopause hormone therapy.

Borderline statistically significant ($0.05 \leq p \leq 0.10$)
Statistically significant ($p < 0.05$)

Table 14: Association of Breast Cancer with DRC, family history of cancer and breast cancer, obesity, lifestyle, marital status by low or high level of education

	Low Educational Level					High Educational Level					
Variable	BC cases	Controls	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	*P* value	BC cases	Controls	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	*P* value	Interaction *P value*
DRC[1]											
Low <2.49	108	28	14.0(7.5,26.3)	22.0 (10.0,45.0)	<0.001	157	66	14.0 (7.5, 26.3)	25.4 (14.8, 43.6)	<0.001	0.667
Medium 2.49-5.25	61	78	2.8 (1.6,5.8)	3.8 (2.0-7.2)	<0.001	56	172	2.8 (1.6, 5.1)	3.2 (1.9, 5.5)	<0.001	0.992
High>5.25	22	80	Referent	Referent		24	227	Referent	Referent		
Age											
21-40	8	16	Referent	Referent		38	99	Referent	Referent		
41-60	68	82	1.7 (0.7, 4.1)	1.9 (0.7, 4.8)	0.182	134	278	1.2 (0.8, 1.9)	1.4 (0.9, 2.2)	0.157	0.537
61+	103	87	2.3 (0.9, 5.8)	2.8 (1.1, 6.9)	0.031	47	69	1.7 (1.0, 2.9)	2.0 (1.2, 3.5)	0.013	0.533
BMI											
up to 24.99	45	51	1.3 (0.8,2.0)	1.1 (0.7,2.0)	0.638	85	176	1.1 (0.8, 1.7)	1.1 (0.7, 1.4)	0.871	0.825
≥25	142	131				155	283				
Smoke (more than 100 cigarettes in a lifetime)											
Yes	19	17	1.1 (0.5,2.2)	1.0 (0.5, 2.2)	0.930	31	40	1.6 (0.9, 2.6)	1.7 (1.0, 2.9)	0.038	0.468
No	172	167				209	421				
Alcohol[3]											
Yes	12	25	0.4 (0.2,0.9)	0.4 (0.2, 0.9)	0.035	47	86	1.1 (0.7, 1.6)	0.9 (0.6, 1.5)	0.864	0.047
No	179	159				192	372				
Current vitamin consumption											
Yes	83	110	0.5 (0.3, 0.8)	0.5 (0.3,0.7)	0.001	127	300	0.6 (0.5, 0.9)	0.6 (0.4, 0.8)	0.001	0.347
No	103	71				109	160				
Vitamins last five years											

Yes	92	120	0.5 (0.3-0.8)	0.5 (0.3-0.7)	0.001	133	311	0.6 (0.5, 0.9)	0.6 (0.4, 0.8)	0.002	0.326
No	95	63				103	150				
Multivitamins											
Yes	47	62	0.7 (0.4, 1.0)	0.6 (0.4,1.0)	0.057	72	184	0.7 (0.5, 0.9)	0.6 (0.4, 0.9)	0.005	0.933
No	139	121				164	276				
Calcium[4]											
Yes	34	59	0.5 (0.3,0.8)	0.3 (0.2,0.6)	<0.001	46	118	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)	0.008	0.157
No	152	123				190	342				
Marital Status											
Married	86	128	Referent	Referent		142	303	Referent	Referent		
Single	44	25	2.5 (1.4, 4.5)	2.6 (1.4,4.8)	0.002	57	90	1.4 (0.9, 2.1)	1.3 (0.9, 2.0)	0.206	0.091
Divorced	23	20	1.8 (0.9, 3.5)	1.5 (0.7,3.0)	0.298	31	57	1.3 (0.8, 2.1)	1.1 (0.7, 1.9)	0.612	0.497
Widow	37	13	4.1 (2.0, 8.5)	3.6 (1.6, 8.2)	0.002	11	12	2.1 (0.8, 5.3)	1.8 (0.7, 4.7)	0.219	0.250
Family history of cancer (not BC)											
Yes	127	109	1.4 (0.9,2.2)	1.4 (0.9, 2.2)	0.165	157	267	1.4 (1.0, 1.9)	1.5 (1.1, 2.1)	0.021	>0.99
No	64	78				84	198				
BC history in any family member											
Yes	53	29	2.1 (1.3, 3.5)	2.0 (1.2, 3.5)	0.010	64	96	1.4 (0.9, 2.0)	1.4 (1.0, 2.1)	0.085	0.353
No	138	158				177	370				

1 Adjusted by age, BMI, smoking, and vitamin use.
2 DRC low (up to 2.50%), medium (2.51% to 5.50%), and high (5.51% and higher)
[3] Multiple logistic regression tests for interaction.
[4] Effect modification (OR is more than 15% different between strata but was not statistically significant (p>0.05).
Numbers may not add up to 100% due to missing values

Abbreviations: BC, breast cancer**;** CI, confidence interval; DRC, DNA repair capacity; BMI, body mass index

Borderline statistically significant ($0.05 \leq p \leq 0.10$), statistically significant ($p<0.05$)

Table 15: Comparison of breast cancer by low and high educational level

Breast Cancer	Low Educational Level	High Educational Level	Crude OR 95% CI	[1]Adjusted OR 95% CI
Mixed lobular/ductal	17	24	0.7 (0.4, 1.4) p =0.322	1.0 (0.5, 2.1) p = 0.993
In situ lobular	0	7	Undetermined p = 0.007	Undetermined
Infiltrating lobular	17	60	0.2 (0.1, 0.4) p < 0.001	0.3 (0.2, 0.6) p < 0.001
In-situ ductal	6	11	0.5 (0.2, 1.4) p = 0.219	0.4 (0.1, 1.3) p = 0.123
Infiltrating ductal	141	132	referent	referent

[1] **Adjusted by age, BMI, family history of BC and smoking**

Table 16: Association of tumor grade and educational level

	Low educational level	High Educational level	Crude OR P value	[1]Adjusted OR P value
Grade 1	19	32	Referent	Referent
Grade 2	89	80	1.9 (0.9, 3.6) 0.057	1.8 (0.9, 3.7) 0.096
Grade 3	46	55	1.4 (0.7, 2.8) 0.387	1.8 (0.8, 3.8) 0.135

[1]Adjusted by age, BMI and smoking

Table 17: Association of tumor size and educational level

Education	Median (25, 57 percentiles)	Median difference	[2]p-value
Primary	2.00 (1.10, 3.75)	Referent	Referent
High School	1.65 (0.88, 3.0)	0.35	0.127
Associate or more	1.3 (0.8, 2.4)	0.70	0.014

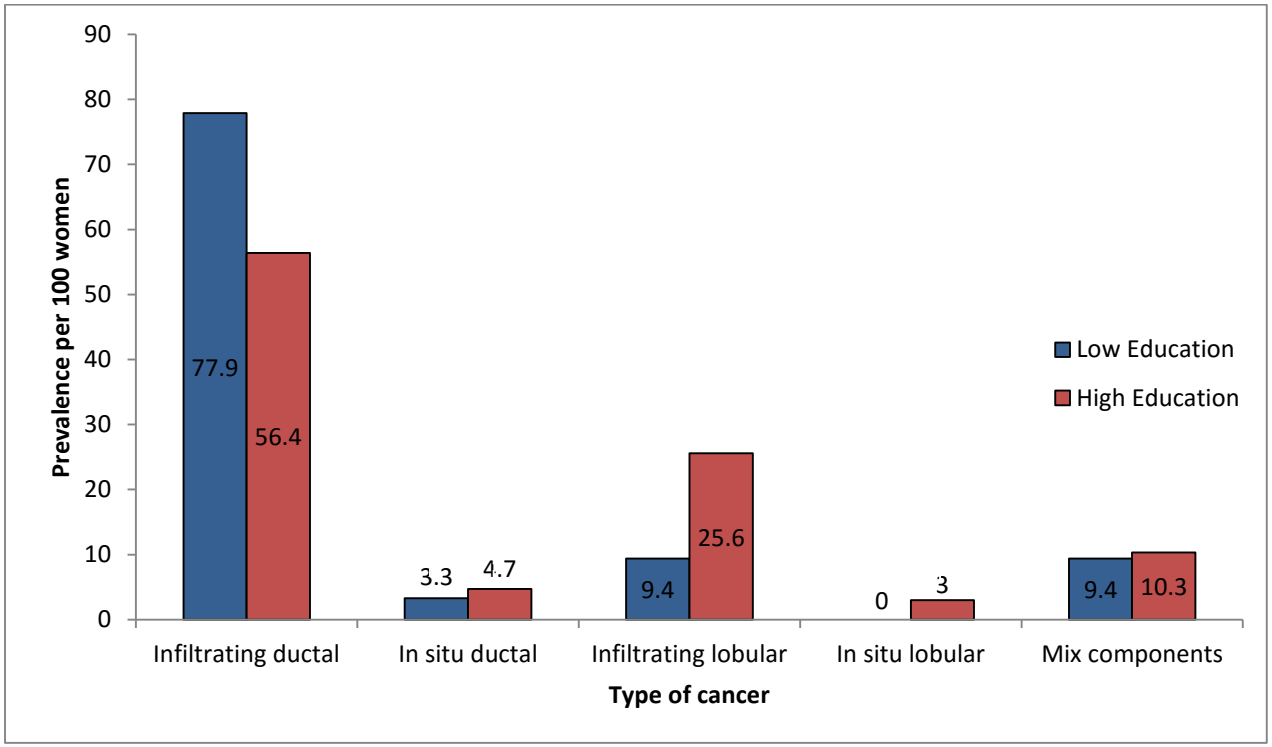
[1]Analysis of variance Kruskal-Wallis p=0.031. [2]Mann Whitney test.

Primary: Less than a high school diploma.

High School: High school diploma and more but less than an associate degree.

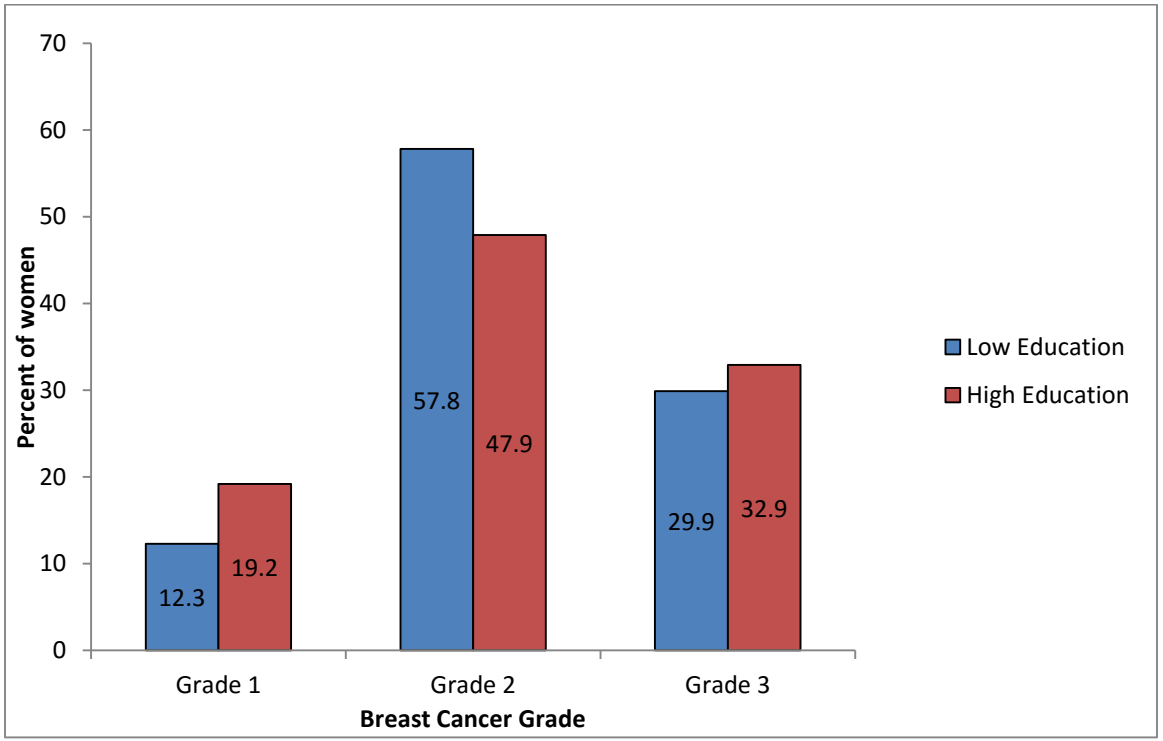
Associate or more: Associate degree diploma or more

Figure 8: Percent distribution of 432 breast cancer cases by cancer type divided in 177 low or 216 high educational level*



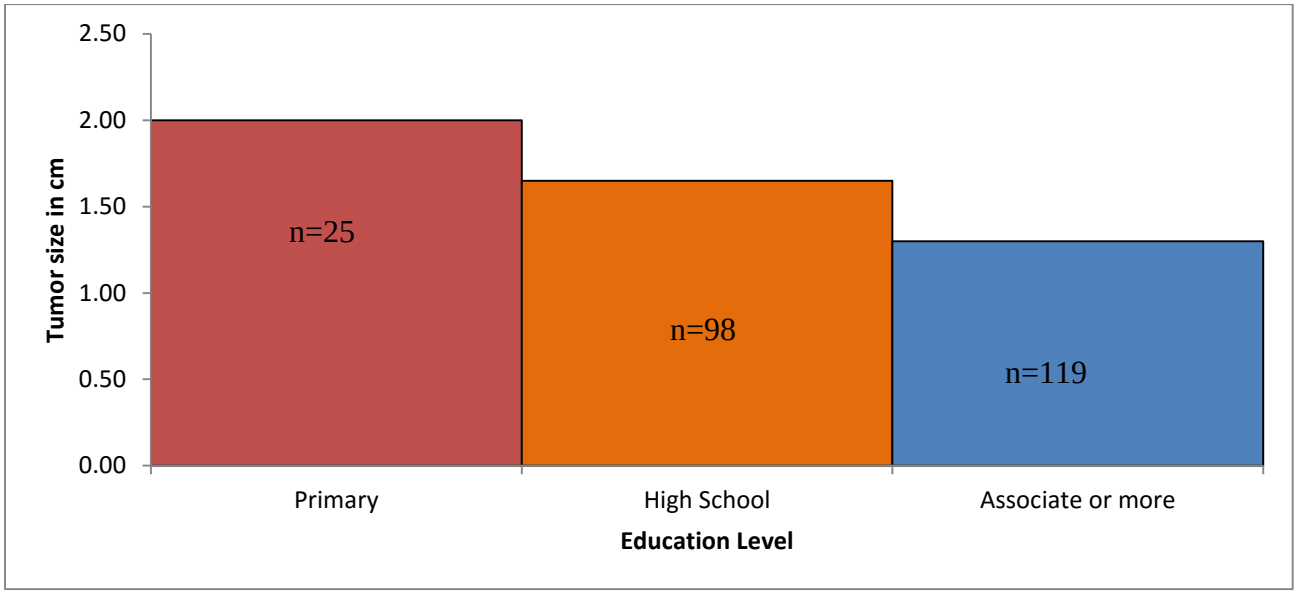
*Adjusted by age, BMI, smoke, alcohol and multivitamin.

Figure 9: Percent distribution of 432 breast cancer cases by cancer's Bloom Richardson grade system (I, II, and III) divided into 216 high and 177 low educational level among the cases in the study sample



*Adjusted by age, BMI, smoke, alcohol and multivitamin.

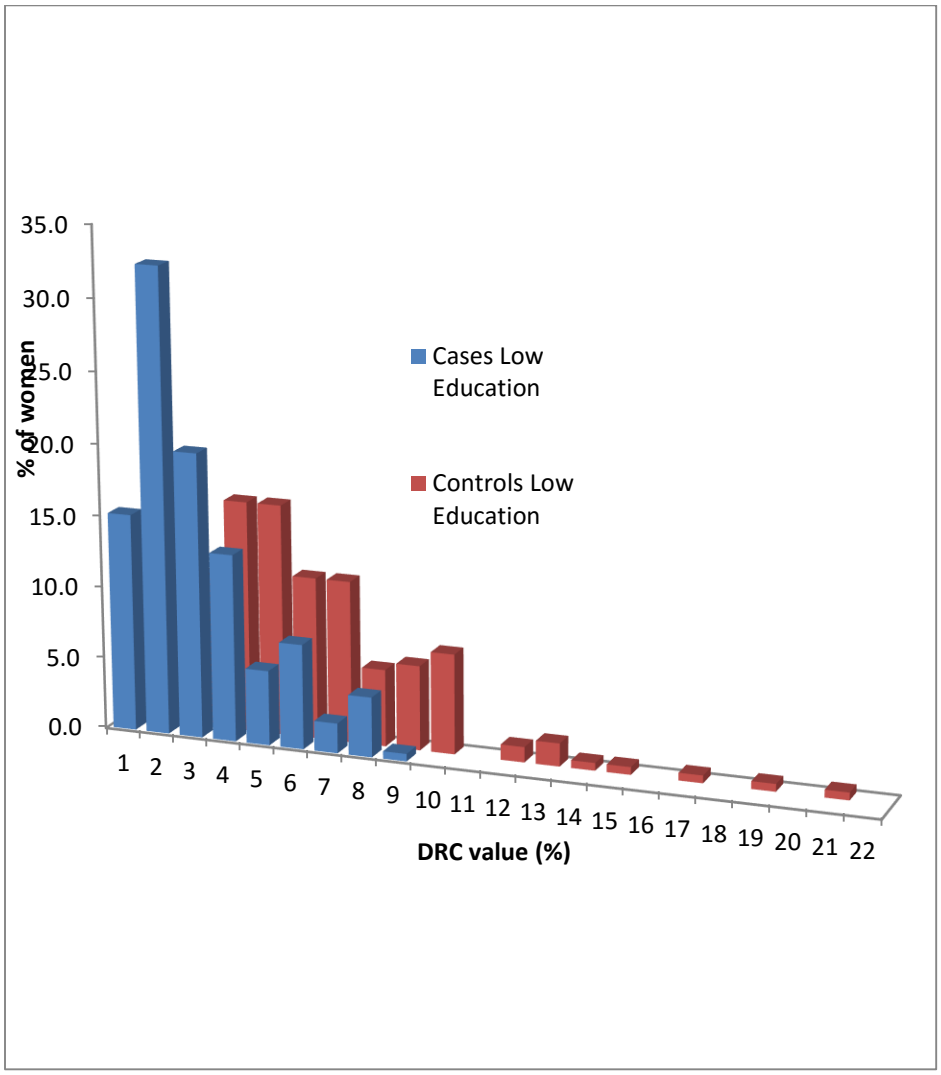
Figure 10: Median breast cancer tumor size by three educational levels among the 242 cases in the study sample



Primary: Less than a high school diploma.
High School: High school diploma and more but less than an associate degree.
Associate or more: Associate degree diploma or more.

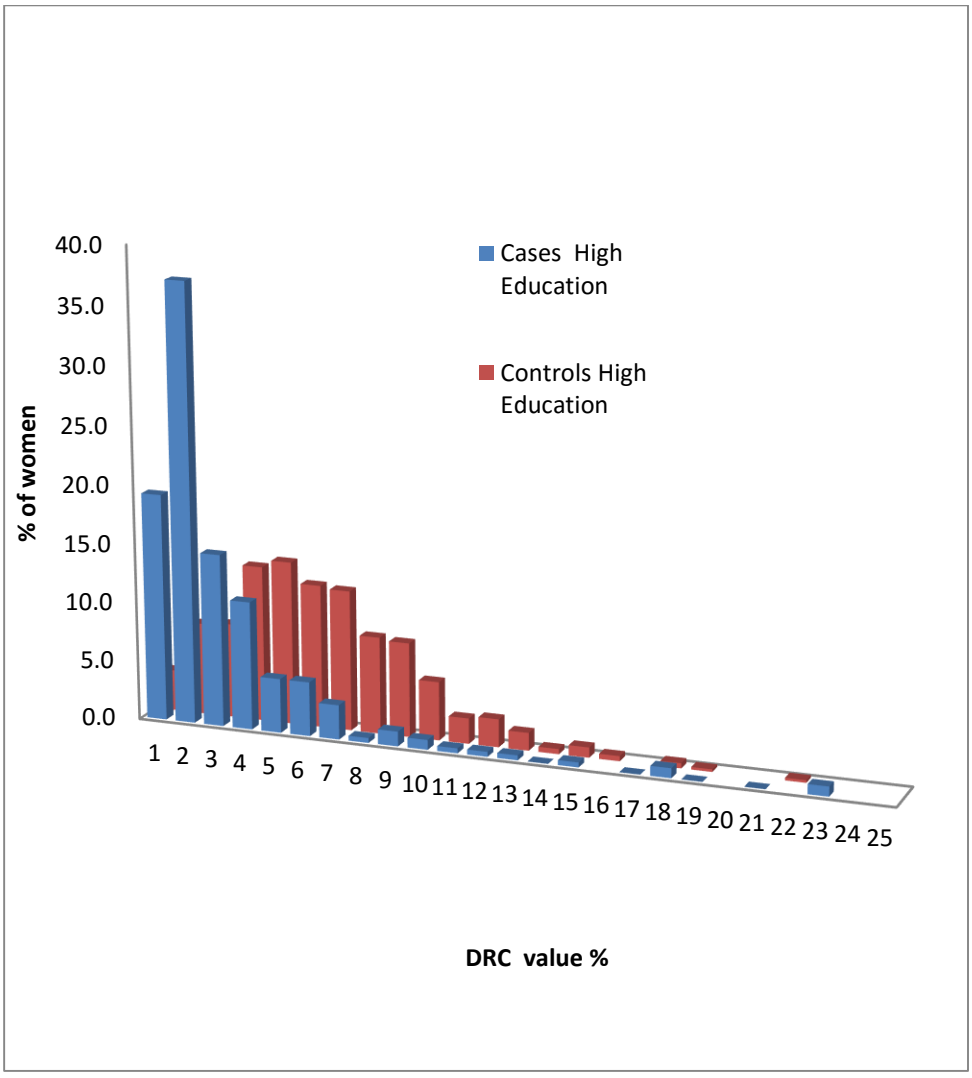
Comparison of tumor sizes by educational level among cases. As educational level increases the tumor size Wallis ANOVA p=0.031)

Figure 11a: DNA repair capacity distribution among low educational level from cases and controls



DRC was measured in lymphocytes by a host reactivation assay with a luciferase reporter gene.

Figure 11b DNA repair capacity distribution among high educational level from cases and controls



DRC was measured in lymphocytes by a host reactivation assay with a luciferase reporter gene.

6.0 Discussion

6.1 Demographics

Selected demographic, reproductive and other variables analyzed were associated with educational level in the group of Puerto Rican women studied. Women with low educational level (LEL) had a higher BMI and were older when compared to women in the high educational level (HEL) group. In addition, HEL women had lower parity and higher age at first pregnancy (data not shown). Other studies (Hajian-Tilaki et al., 2012, Beiki et al., 2012, Heck and Pamuk, 1997) have reported similar findings. When we examined the pathological subtype of breast cancer in terms of educational level (Figure 8), it was observed that most BC cases in the LEL group had infiltrating ductal carcinoma while in the HEL had *in situ* ductal carcinoma. This might be explained by less use of screening techniques leading to BC diagnosis at a later stage among women with a LEL lower. In the case of the infiltrating lobular, is less frequent than infiltrating ductal, and it is harder to detect due to his complexity (Arpino et al., 2004), making it difficult to detect by traditional screening methods such as breast self-examination, clinical breast examination, and mamography. Proper knowledge of BC screening methods for early detection of subclinical disease and a more thorough diagnosis are necessary for an early diagnosis of BC. Fletcher and Frisvold (2009) showed that a higher proportion of women with higher levels of education who also had private insurance were more likely to be diagnosed with BC at an early stage diagnosis (Fletcher and Frisvold, 2009). Consequently, it is reasonable to assume that Puerto Rican women diagnosed with infiltrating lobular BC who also had

private medical insurance are more likely to be diagnosed at an early stage. In situ lobular carcinoma is considered a pre-malignant breast lesion that is a precursor for BC (Olivotto and Levine, 2001). Only 3% of women with this type of cancer and all of them had HEL. Similarly, women with HEL women tend to utilize more BC preventive measures such as a healthier lifestyle like diet and physical activity. Therefore, *in situ* lobular carcinoma is normally e detected by frequent routine screening mammograms (Olivotto and Levine, 2001).

Another variable, a pathological characteristic that was studied among women with BC was the grading system. Grade 1 is the grade in which breast cancer generally has the the slowest (Bloom and Richardson, 1957), but where it is most difficult to detect or diagnose. In this study, grade 1 was more commonly found amongst women with HEL. Grade 2 which is the intermediate grade, more often and easier to detect was more commonly found in women with a LEL. Grade 3, which spread more aggressively and has more probabilities of metastasis, was slightly more often found in women with a HEL. Women in this group had more probabilities of being diagnosed with BC in the earlier stages. Diagnosis of lowest grades is correlated with early detection and more probabilities of treatment success (Dalton et al., 2000). Other BC studies with women from USA and Iran have shown that an early diagnosis is more frequent among those with a higher educational level (Sprague et al., 2011, Tazhibi and Feizi, 2014).

Tumor size is also a widely accepted clinical marker (Hammond et al., 2010, Wolff et al., 2007) of how advanced is breast cancer. Comparisons among tumor size by educational

level showed that breast cancer tumor size increased as the educational level decreased (Figure 10). Women with the highest levels of education had smaller tumors, consequently better chances for early treatment and better survival.

6.2 Effect modification of the association of DNA repair capacity and breast cancer by educational level

This study validates what our laboratory has previously published (Ramos et al., 2004, Matta et al., 2012, Morales et al., 2013) showing that a low DRC is strongly associated with the possibility of developing BC. In this study, women with low DRC can have up to 12 times more odds to have BC. Although no statistically significant interaction was observed, an important effect modification was found on the association between DRC and BC when assessed in terms of different educational levels. The association of low DRC and BC was stronger among women with High Educational Level (HEL) as compared to those with women with Low Educational Level (LEL) before and after adjusting for confounders. The odds of having BC for those with a low DRC was 8.9 times among those with LED and 11.7 times for those with HEL.

6.3 Association of educational level, DRC and breast cancer

Stratified analysis by educational level was used to observe if differences among risk or protective factors between two educational level groups (LEL (up to high school or incomplete AD) or HEL (complete AD or higher level).

Menopause-In both groups of women; LEL and HEL , menopause increases in a similar manner the odds for BC. Menopause status has been associated with risk of BC in numerous studies (Kerlikowske et al., 2003, Britt, 2012, 2012, Kelsey et al., 1993, Sprague et al., 2008). This association is explained primarily because of the relationship with age and prolonged exposure to hormones that exacerbate the risk of developing BC. However, it is noteworthy that in the women studied MHT (estrogen only) was associated with a decreased risk in both the LEL and the HEL groups. Morales et al. 2013 recently published this association between women treated with estrogen (MHT) and reduced odds of BC development. This finding is controversial because most studies relate hormonal therapies with increased BC risk (Chen et al., 2002, Rossouw et al., 2002). These are based mostly in the combined used of progestin and estrogen. Anderson *et al*. (2012) found that the use of estrogen only lowers the risk of BC, but this relationship is not true for all women. Women with certain risk factors like BC history, benign lesions in the breast can be at increased risk of BC with the use of hormones (Anderson et al., 2012). The use of estrogen only and why this effect is stronger in women in LEL group, needs to be further studied. The use of prescription drugs can be associated with frequent visits to the physician leading to an increase in the access and practice of use of more breast cancer prevention methods by these women such as mammograms, clinical breast exam and magnetic resonance imaging (MRI).

No significant association was found between the use of oral contraceptives and risk of BC risk in the population studied. However the use of oral contraceptives after 21 years of age, appears to decrease odds for BC, especially among LEL group. There is an increased

probability that women who started taking oral contraceptives at a younger age will have a higher lifetime exposure to oral contraceptives. The association of oral contraceptives containing high doses of estrogen (formulations containing 50 μg or more of ethinyl estradiol or 75 μg or more of mestranol) (Marchbanks et al., 2002) increases the risk for BC among women. . However, with oral contraceptives containing lower doses of estrogen (low-ogestrel, Necon, Mircette) this connection is not clear (1996, Beaber et al., 2014b, Thorbjarnardottir et al., 2014). The hormones contained in the oral contraceptives are mainly estrogen and progesterone produced artificially (Burkman et al., 2004). The development of BC is in part influenced by the long exposures to these hormones that stimulate the growth of the epithelial cells (including those that have been transformed to malignant cells) in the breast increasing the risk of BC (Beaber et al., 2014a). However, if women stop taking oral contraceptives regarless the dose and type of hormone for a period longer than 10 years, the association disappears and these women have the same risk as women who did not take oral contraceptives (Moorman et al., 2013, Thorbjarnardottir et al., 2014).

Endometriosis- For women in the LEL group, endometriosis decreased the odds for BC. An inverse association between endometriosis and BC has been recently reported in the same group of women studied, with endometriosis decreasing the odds for BC (Matta et al., 2014). When the stratification by educational level was performed in this study, this association was only statistically significantly in women with a LEL. A statistically

significant interaction among educational level and endometriosis was found, which prevailed even after multiple adjustment analysis. This suggests that endometriosis was associated with decreased odds for BC in the LEL group, but no evidence for such effect was observed in women with a HEL (Table 13). The mechanism by which endometriosis protects against risk of BC is currently unknown. However, one hypothesis is that pharmacological hormone treatments may provide protection for endometriosis (Matta et al., 2014, Bertelsen et al., 2007). Most treatments for endometriosis consist in suppressing the endogenous estrogen production especially among premenopausal women to suppress the symptoms of endometriosis; in other cases surgery is considered by means of a hysterectomy (Bertelsen et al., 2007), both alternatives modifies the amount of hormones present in that patient, affecting their BC risk. Suppression of this endogenous estrogen decreases the length of exposure of breasts to these hormones. Drugs such as Danazol and Gonadotropin-releasing hormone (GnRH), which suppress estrogen production to decrease the symptoms of endometriosis, may act as an indirect protector against BC.

In women with a HEL, we found that hysterectomy had a protective in terms of risk of BC. Women who had a hysterectomy at a younger age had a significant reduction in the likelihood of being diagnosed with BC. Hysterectomy alters the function of the remaining ovaries, decreasing the cumulative exposure to ovarian hormones, which are an important risk factor for BC (mZhao et al., 2013, Press et al., 2011). This alteration can affect the hormone levels before menopause or advancing age at menopause, decreasing BC risk. Studies have indicated a greater protection with hysterectomy is combined with

oophorectomy, even with partial conservation oophorectomy (Press et al., 2011, Irwin et al., 1988).

Consumption of alcohol-Alcohol consumption was more commonly reported among controls in both educational categories; LEL and HEL. Decreased odds for BC among women with a LEL who reported alcohol consumption were found. This is contrary to what has been reported in the literature. Alcohol consumption is related with increased BC risk, principally due to its effect in the increase of estrogen levels in blood (Coronado et al., 2011, Smith-Warner et al., 1998, Liu et al., 2015, Romieu et al., 2015). The breast cancer report from the American Institute for Cancer Research stated that per 10g of alcohol consumption there is an increase of 8% risk of breast cancer (World Cancer Research fund, 2010). The moderate consumption of alcohol, especially red wine has been shown to decrease the incidence of coronary heart disease (Moore and Pearson, 1986, Roswall and Weiderpass, 2015, Pearson and Terry, 1994) but even moderate consumption (up to one drink per day, Dietary Guidelines for Americans, 2010) has shown a slight increases in BC risk (Zhang et al., 2007, Nasca et al., 1994). The magnitude of the effect depends on the magnitude of alcohol consumption, while moderate alcohol consumption can decrease heart diseases, high blood pressure and death (Nelson, 2012, McLeish et al., 2013, Zakhari and Hoek, 2015). Careful consideration should be taken among women with other BC risk factors due to potential interaction of alcohol with other risk factors. The current guidelines recommend women no more than one drink per day (ACS, 2013). Folate, vitamin and antioxidant consumption seem to neutralize the effect of alcohol consumption because it neutralizes reactive oxygen species, a second-stage product of alcohol metabolism

(Coronado et al., 2011, de Batlle et al., 2015, Stolzenberg-Solomon et al., 2006, Maruti et al., 2009).

Smoking-Cigarette smoking increased the odds by 70% for BC in HEL women. This association was not found among LEL women. A possible explanation is that more women with a HEL were smokers compared to the LEL group. This could be due to increased power of acquisition; with an increase in prices of cigarettes it is possible that women in the HEL group will have increased accessibility to buy cigarettes due to economic reasons. Studies have shown that smoking increases the risk of developing BC (Milne et al., 2011, Xue et al., 2011, Bjerkaas et al., 2015, Khuder et al., 2001, Gaudet et al., 2013). Carcinogens found in tobacco smoke can be transported in the bloodstream to the breast increasing the risk of developing BC (Sanchez-Zamorano et al., 2011). Tobacco smoke carcinogens like benzoα pyrene, causes bulky DNA adducts which are repair by the NER pathway (Latimer et al., 2010, Bewick et al., 2011) . The NER pathway was used as an estimate of DRC in the women studied as part of this doctoral dissertation (see Matta et al. 2012)

Consumption of multivitamins and calcium-The use of vitamin supplements have been the intense focus of many studies (Ennever and Paskett, 1993, Ray and Husain, 2001, Lesperance et al., 2002, Bohlke et al., 1999, Zhang et al., 1999, Bright-Gbebry et al., 2011). These have generally failed to provide conclusive results have been obtaining due to difficult of ascertain a causal relationship among observational studies and issues associated with dosages and types of preparations (Gonzalez et al., 2005). While some

studies associated vitamin consumption with a decreased risk of BC (Nechuta et al., 2011, Larsson et al., 2010, Bassett et al., 2013), other studies found no association among vitamin intake and risk of BC (Ishitani et al., 2008, Dorjgochoo et al., 2008, Cho et al., 2012, Neuhouser et al., 2005). In our study, current vitamin consumption was a protective finding in LEL women (decreasing the odds for BC by 50%), while among HEL women no significant association was found. However, consumption of vitamins for a period of at least five years, multivitamin and calcium intake decreases the odds for BC in both educational groups with a more marked reduction among LEL women (50%) as compared to HEL woman (40%). In the same group of women enrolled in our study, it was recently reported that women with BC were 30% less likely to take multivitamins than controls, they suggested multivitamin and calciumsupplementation as a protective factor for BC (Vergne et al., 2013a). This suggests that independently of the level of education, women overall can reduce the risk of BC from vitamin and calcium supplementation, particularly when done over a period of at least 5 years.

Family history of cancer-Family history of cancer increased the odds of developing BC in both the HEL and LEL groups. However; this achieved statistical significance only in the HEL group. This finding has been previously published (Pharoah et al., 1997, Tazzite et al., 2013); there is an increased risk of breast cancer in women with a history of any cancer. Having family history of breast cancer also increased the odds for BC in both educational groups; however the odds for BC were slightly higher in LEL women as compared to HEL women.

DRC is an important risk factor for BC (Matta et al., 2012). The association of educational level and BC has been previously studied. However the significance and innovation of this study is that for the first time, the relationship between educational level, risk of breast cancer and DRC has been studied using a large sample size in a properly powered study. DRC is an important risk factor regardless the level of education, but this study demonstrates that a low DRC functions as a more pronounced modifier of breast cancer risk in women associated with a HEL while a medium DRC level had the biggest effect in LEL women (Table 14). DRC has been proposed as a biomarker to identify women at high of developing BC (Kennedy et al., 2005, Matta et al., 2012). High educational level has been implicated in changes in lifestyle factors like regular exercise, fruits and vegetable consumption that are well-established in the literature (Park and Kang, 2008, Kilander et al., 2001) as important modifiers of risk of several types of cancers including BC. By combining both variables; DRC and education, we can identify a target population and translate this knowledge into "actionable items or lifestyle factors" aimed at reducing BC risk. This knowledge fill a major gap in the literature relevant to BC risk, but more importantly it directly addresses specific key needs in the most fundamental national initiatives such as Cancer Care Quality (NICCQ) (Bailes, 2006), Florida Initiative for Quality Cancer Care (Laronga et al., 2014) Women's health initiative (Banegas et al., 2012) in the fight against breast cancer.

For example, knowledge gained in this study can now be used to identify and monitor women with low educational levels and low DRC and women with high educational levels

and a low DRC. These two groups have the highest risk for BC development in the study population, at least in terms of the variables we have studied.

6.4 Future recommendations

A follow-up study that includes a prospective component is currently being undertaken in the laboratory of Dr. Matta until 2017. These studies involves among many other objectives, recontacting breast cancer patients and controls and inquiring about their health status in terms of breast cancer recurrence in patients and development de novo of this disease in controls. The knowledge will be of great contribution to corroborate these results and explore new associations with BC risk. Some key questions that remain unanswered include the role of educational level and DRC in BC recurrence or in the development of this disease in women that were classified as controls in this study. Future studies should include variables such as physical activity, and additional nutritional variables (e.g., regular diet, dietary supplement composition and dosage) to confirm our findings and further investigate the association of such variables with both educational and DRC levels. There is a critical need for future studies aimed towards identifying modifiable behaviors that can serve to design more effective breast cancer preventive strategies for Puerto Rican women.

6.5 Limitations

In a case-control study design, like this one, the temporal cause-effect relationship is not always clear because at the time of the study the outcome has already occurred. The time of exposure is not always easy to ascertain especially when the study includes chronic cases

that have developed the disease sometime in the past and it is not clear if the disease (effect) occurred after the exposure (cause) (Hennekens, 1987, Szklo and Nieto, 2007). However, this can be minimized if only incident cases are recruited as it was done in the present study.

Recall bias is a limitation on this type of study that can be minimized if participants are queried about current exposures (current level of education, current use of supplements such as multivitamins and calcium), or current measurements (weight, height, DRC). Selection bias is a frequent limitation in these types of studies when the selection criteria for cases and controls differs producing differences in exposure status and/or reporting of exposure and disease outcome between cases and controls (Bailey et al., 2006, Szklo and Nieto, 2007). However, the participant selection procedures utilized in this study minimized this bias. Control subjects were recruited from the same clinics and hospitals from which the cases were recruited; this type of selection provides a similar reference population as long as the controls would go to these locations in case they develop BC that is the case in this study (Dumitrescu and Cotarla, 2005). If controls were recruited from the general population (i.e., neighborhood controls or random-digit dialing), selection bias may be larger given the socioeconomically (SES) diversity in many neighborhoods in Puerto Rico (Torres-Cintron et al., 2012, Bailey et al., 2006, Rothman and Greenland, 2008). Interviewer bias occurs when interviewers ask differently about exposure to cases and controls, to minimize that bias (Sackett, 1979). Only one nurse (Mrs. Wanda Vargas) performed all the recruitment and interviews (including questionnaire) of all the women that participated in this study. In addition, in order to identify potential variability in the

methods utilized by the nurse while performing the interviews of participants, Dr. Carolina Alvarez, was present during some of the interviews as part of an internal validation of the questionnaire. The questionnaire was revised as a product of this evaluation without changing the questions but by adding additional questions and additional explanations that were provided verbally to increase consistency and clarity to prevent as much as possible interviewer and interviewee biases.

Interviewee bias can occur when cases and/or controls do not understand, missinterpreted or do not feel comfortable answering certain questions during the interview. These potential biases were detected during the questionnaire evaluation and were found to be minimal for most of the questions in the questionnaire. Questions and variables that were found with these potential biases were excluded from the study. Other limitation could be random error in the ascertainment of exposures such as weight and height. These two variables were collected and were self-reported. Reverse causation could be present if (1) having BC lowers DRC level, rather than low DRC level increases BC risk, (2) having BC lowers educational level instead of low educational level (LEL) increasing BC risk, and/or (3) low DRC decreases educational level instead LEL decreases DRC level. Nevertheless, reverse causation is an unlikely explanation because biological evidence demonstrates that (1) a low DRC or deficiencies in DNA repair pathways and/or genes is a component involved in BC carcinogenesis (Jemal et al., 2010, Ramos et al., 2004, Matta et al., 2012, Matta et al., 2013, Sinha et al., 2008, Pooley et al., 2008, Kennedy et al., 2005) More importantly, several familial cancer phenotypes associated with mutations in DNA repair genes have been identified, eg. XP, Li-Fraumeni, Cockayne's syndrome and others. This

consititues evidence that our findings have consistency with other investigations in other diseases and conditions. Hill's causality criteria describes this type of evidence as the "causality criterion of analogy". Hill, AB (1965).

.(2) Around 75% of the study sample is over 40 years of age, and almost 100% of them had already terminated high school education. Therefore, educational level was attained before developing BC in most or all of the participants. (3) There is no plausible mechanism that could explain how a DRC level will influence the level of education unless there is an association between intellectual achievement and DRC. Unfortunately, this relationship cannot be explored with the variables available for analysis. Not all modifiable factors are included in the questionnaire provided to the participants. Information like physical activity and nutritional variables were not included in the present study.

6.6 Strengths

The current study uses incident cases, which makes more accurate the recall of past exposures because of recent diagnosis of breast cancer (dos Santos-Silva, 1999, Gregg, 2002). All diagnostic procedures used as the basis for selecting controls and breast cancer cases were conducted by physicians specialized in gynecology and/or oncologic surgery and confirmed by a pathological examination. Therefore, the potential error in ascertaining the outcome was very minimal (Gregg, 2002, Carlson et al., 2009). The primary exposure named DRC measurement was made by specialized technicians and modern laboratory technology that has been shown to have a high degree of validity and reliability and a low

variance (Qiao et al., 2002, Athas et al., 1991). Therefore, random error in determining the primary exposure was minimized. All the methods used in this study were recently validated through a recent peer-reviewed publication in BMC Cancer (Matta et al. 2012). The temporal sequence of disease and exposure that is difficult to elucidate in case-control studies is feasible to consider when using incident cases (Hennekens and Buring, 1987). In the proposed study we have a ratio of almost 2:1 of controls and cases from the same age range improving the statistical power of the analysis and potentially increasing the representativeness of the total population among controls (Rothman et al., 2008). The data collection was made using the same nurse, questionnaire, and phlebotomy procedures for cases and controls, minimizing interviewer/investigator bias. Case-control studies, commonly are less expensive than cohort studies, require less time to perform and give the possibility of exploring multiple exposures with a relatively smaller sample than the one needed for a cohort study (Youkeles, 1983), in this case DRC measurement is a costly process (approximately $466 per participant), but this data has already collected as part of the breast cancer study in the laboratory of Dr. Matta that was previously described.

7.0 Conclusions

In this study, we evaluated the potential association of educational level and level of DNA repair capacity (DRC) in women with and without breast cancer in Puerto Rico. DRC level was selected because it is well-established that it is an important risk factor for BC (Matta et al., 2012, Ramos et al., 2004, Morales et al., 2013). The host cell reactivation assay used to study DRC, measures the nucleotide excision repair pathway (NER) an important repair

mechanism that helps to maintain the genomic stability. Latimer et al. 2010 suggested that NER pathway plays a role in the etiology of sporadic breast cancers which are the majority of breast cancers reported (Latimer et al., 2010).

In general, women with breast cancer tend to have lower levels of education, broad age range and low DRC level. This sample consists of Puerto Rican women from 21 years of age and more with the majority of the sample in the 41-60 age range. The majority of the women surveyed were menopausal. In terms of educational level, it was observed that women with BC had the lowest levels of education, were older than controls and had lower DRC levels than controls (Table 6). Among BC cases, high educational level (HEL) tends to be associated with the higher DRC levels in most DRC categories. DRC among BC cases had the majority of DRC values around 2%, while in controls was around 5% (Figure 11a, 11b). In controls, HEL women were predominant at all DRC categories (Figure 11b). When the association of educational level and DRC was studied it was observed increased odds for low DRC in the lowest levels of education (Table 8). Again, because a low DRC is associated with increased risk of developing BC, a low level of education represents an increased risk of BC in the women studied. In terms of the association of BC and educational level alone, it was found increased odds for BC in women with the lowest levels of education; this relationship appears to increase when DRC was added to the model (Table 9).

In our study, an important relationship between high education and high DRC level was found, as well as, between high education and low BC risk. The association of low and

high educational level stratified by high and low DRC showed that a low DRC increased the odds for BC in both groups, but in women with high education this effect is stronger (Table 10). On the other hand, when the association was categorized by low and high DRC and compared by educational level, we found that women with low DRC and low educational level had slightly less odds for BC than those women with HEL and low DRC (Table 11). As educational level increases, the effect of a low DRC seems to be stronger, increasing the odds for BC (Table 12). Throughout the whole analysis, it was found a relationship between the level of DRC and level of education. Although no statistical interaction was obtained, an effect modification was found among DRC and educational level. DRC as a risk factor for BC has been published in several studies (Matta et al., 2012, Latimer et al., 2010, Ramos et al., 2004, Morales et al., 2013), but a possible modification of this effect by level of education has not been published. A possible explanation by this type of effect could be due to changes in lifestyle like more exercise, no smoking, less alcohol intake and fruit and vegetables consumption and preventive health behavior among HEL women that could lead to a reduction in BC risk (Mizoo et al., 2013, Sanchez-Zamorano et al., 2011, Hayes et al., 2013).

Although the level of literacy among Puerto Rican women is about 90.9% (Chlebowski, 2010), we still have a significant 40% percent of scholar desertion among students who did not finish high school education (Bauman and Graf, 2003). An important association of level of education and BC risk was found. The identification of more susceptible women in the Puerto Rican population is useful in targeting interventions and eliminating cancer disparities. In the current study different risk factors were related to higher or lower risk

according to the level of education. Among women with the lowest levels of educations, women with more than 60 years of age, who's in menopause and have a history of breast cancer on their families, have to be monitoring carefully, especially women with low DRC levels. In the case of women with highest levels of education, smokers, women in menopause, more than 60 years of age with family history of cancer and a low DRC level are the target population for interventions among this group.

A high level of education was found associated with high DRC and low odds for BC. Intimate mechanisms of these relationships are unknown. Evidence in this and other studies show that a low DRC level can predict BC. Further studies of how educational level could improve DRC level and how this relationship can be measured, will provide a modifiable factor for BC prevention. Additionally, these results provide valuable knowledge in terms of prevention and early detection of BC. Potentially modifiable risk factors like BMI, alcohol consumption, smoking, physical activity and hormone replacement therapy should be included in BC prevention programs.

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