**Philippine Journal of Science**
149 (4): 1209-1215, December 2020
ISSN 0031 - 7683
Date Received: 10 Jul 2020

# *RAD51* 135G>C Single Nucleotide Polymorphism and Risk of Breast Cancer in Selected Filipino Cases

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**The *RAD51* gene encodes the protein that plays a central role in the repair of DNA double-strand breaks (DSBs) through the homologous recombination pathway. Association of *RAD51* single nucleotide genetic polymorphism (SNP) with the development of cancer has been observed to be tumor site- and race-specific. Thus, this study aimed to determine the potential association between *RAD51* 135G>C SNP and breast cancer among selected Filipinos. Patients with histologically confirmed breast cancer ($n = 60$) seen at the University of Santo Tomas Hospital (USTH Manila) were age- and sex-matched with clinically healthy controls ($n = 60$). Genomic DNA was extracted from the blood of participants and analyzed for *RAD51* genotype by polymerase chain reaction – restriction enzyme fragment length polymorphism (PCR-RFLP). A significantly higher incidence of *RAD51* C/C genotype was seen among the cases than the controls ($p < 0.05$). The more common G/C genotype was not associated with breast cancer development, while the recessive less common C/C genotype was observed to potentially increase the risk. However, passive smokers carrying the *RAD51* G/C genotype had a significantly increased chance of developing breast cancer. *RAD51* G/C genotype – even when combined with other established risk factors like alcohol use, active smoking, and family history – were not associated with breast cancer.**

Keywords: *BRCA* genes, breast cancer, Filipinos, passive smoking, PCR-RFLP, *RAD51* 135G>C

## INTRODUCTION

In 2018, breast cancer was ranked as the second most common type of cancer and the fourth leading cause of cancer mortality worldwide (IARC 2018). It was also the most prevalent cancer among women in both developed and less developed countries. It was the leading site of cancer for both males and females in the Philippines and recorded the highest incidence, mortality, and five-year prevalence among Filipino women (IARC 2018).

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Breast cancer is a type of tissue cancer in which the cells of the breast divide uncontrollably. It mainly involves the inner layer of milk glands or lobules and ducts (Ataollahi *et al.* 2015). A combination of lifestyle, environmental, and genetic factors predispose one to breast cancer. Body size, exposure to endogenous estrogens, early menarche, early age at first childbirth, and family history of cancer have been shown to increase the risk of developing breast cancer. In addition, genes and their mutations have been established to be significant risk factors in the development of breast cancer (Feng *et al.* 2018). Naturally, the body has its own DNA repair mechanism that could overcome genetic

aberrations and mutations. In breast cancer cases, however, this DNA repair mechanism is deemed dysfunctional (Silva *et al.* 2010). Thus, DSBs in the DNA can easily be induced by several carcinogens such as ionizing radiation and oxidative free radicals. When left unrepaired or misrepaired, it may lead to cell death, chromosomal rearrangement, and genomic instability, all of which enhance breast cancer risk (Silva *et al.* 2010).

The *RAD51* gene, located on the human chromosome 15, plays an important role in DNA repair, specifically in homologous recombination during DNA double-strand break repair (DSBR) where it promotes the invasion of broken ends of the DSB into the intact sister chromatid. A functional polymorphism of *RAD51* gene (135G>C, rs1801320), changing guanine to cytosine at position 135 in its 5' untranslated region, has been associated with the development of breast cancer through alteration of gene transcription, specifically the recessive C/C genotype (Wang *et al.* 2010). This SNP has been found to increase breast cancer risk among Caucasians, Iranians, Serbians, and Pakistani populations (Hosseini *et al.* 2013; Krivokuca *et al.* 2013; Qureshi *et al.* 2014). SNP is the most common gene polymorphism wherein a single nucleotide is substituted by another nucleotide, which alters the original DNA sequence and may affect the function of the protein that is being encoded. SNPs of the *RAD51* gene may lead to various protein structures and may affect the overall DSBR efficiency that may lead to the development of cancer. To date, there has been no study investigating the association of the *RAD51* SNP with breast cancer development among Filipinos.

Thus, the identification of cancer-related *RAD51* SNP is a valuable approach in the development of cancer therapeutics and diagnostic tests aimed at early cancer detection. This study was done to provide information on the possible association of *RAD51* 135G>C (rs1801320) SNP with breast cancer among Filipinos. It evaluated case-control differences in the distribution of *RAD51* alleles and genotypes and further correlated the results of molecular analyses with other established risk factors for breast cancer development.

## MATERIALS AND METHODS

### Ethical Consideration

Ethical clearance (IRB-2016-12-201-IS) was obtained from the USTH Institutional Review Board and all participants gave their written informed consent. All procedures performed in the current study were in accordance with the 1964 Helsinki Declaration and its later amendments.

### Study Subjects

Cases were female patients, 18 years old and above, with histologically confirmed breast cancer, whether newly diagnosed or undergoing treatment and seen at the USTH Manila between January 2016 and December 2017. They were age- and sex-matched with physician-assessed clinically healthy individuals living in the same locality where the cases reside. A total of 120 participants (60 breast cancer cases matched with 60 healthy controls), with the majority residing in Metro Manila, were recruited in the study. All study participants were natural-born Filipinos and were not products of interracial marriage of parents or grandparents.

All participants were asked to accomplish a standardized questionnaire inquiring about their lifestyle, family history of cancer, and reproductive health. Clinical data of the cases were retrieved from clinical records and histopathologic reports.

### Genomic DNA Extraction

Five (5) mL of blood was collected from all participants and the cellular elements were immediately separated and stored at –80 °C. Genomic DNA was extracted from all blood samples using ReliaPrep™ Blood gDNA Miniprep System (Promega, USA) following the manufacturer's protocol, and then stored at –20 °C until analysis. DNA quality and quantity were determined with the Implen Nanophotometer (Munich, Germany).

### *RAD51* Genotyping

PCR was performed, as previously described (Sliwinski *et al.* 2005). The 5'-TGGGAACTGCAACTCATCTGG-3' (forward) and 5'-GCGCTCCTCTCTCCAGCAG-3' (reverse) primers were used to amplify the 157-bp target region within the *RAD51* gene containing the 135G>C polymorphic site. Each 20 µL of the PCR reaction contained 10 µL of PCR master mix (20 mM Tris-HCl pH 8.3, 50 mM KCl, 1.5 mM $MgCl_2$, 0.2 mM of each dNTPs, 2.5 mM U Taq DNA polymerase), 0.5 µL each of 0.25 µM forward and reverse primers, 7 µL nuclease-free water, and 2 µL DNA (89 ng/µL). Thermal cycling conditions were as follows: initial denaturation at 95 ˚C for 3 min, 35 cycles of denaturation at 94 ˚C for 30 s, annealing at 57.4˚ C for 30 s, extension at 72˚C for 30 s, and a final extension step at 72 ˚C for 5 min. The 157-bp PCR products were digested for 60 min with 1U *BstNI* restriction enzyme (New England Biolabs, USA) and the digested amplicons were subjected to 3% agarose gel electrophoresis. Expected fragment sizes were as follows: 157-bp band corresponded to the C/C genotype; 86- and 71-bp fragments to G/G genotype; and 157-, 86-, and 71-bp fragments to G/C genotype.

**Data Analysis**

To determine the prevalence of *RAD51* genotypes, allele and genotype frequencies were computed, including deviations, using the Hardy-Weinberg equilibrium. Pearson's chi-square test was used to evaluate the relationship, specifically the differences in genotype frequencies, between cases and controls. Fisher's exact test was used if the expected frequencies were less than 5.00. Meanwhile, the Wilcoxon rank-sum test was used to compare ordinal variables. *RAD51* genotypes were further correlated with the other well-established risk factors for breast cancer. Relative risks of independent and combined genotypes for the cancer cases were determined by computing for the crude OR (odds ratio) with a 95% confidence interval (CI) and a level of significance of 0.05. All statistical analyses were run with IBM® SPSS ® Statistics 20.

## RESULTS

The breast cancer cases were not significantly different from the controls in terms of risk factors except for passive smoking where there were more passive smokers among the cases than the controls ($p < 0.05$) (Table 1).

No significant difference was seen between cases and controls in terms of *RAD51* 135G>C allele frequencies ($p > 0.05$). However, a significantly higher incidence of *RAD51* C/C genotype was seen among the cases than the controls. None of the participants had the *RAD51* wild type G/G genotype, but 80.0% and 93.33% of the cases and controls were carrying the *RAD51* G/C genotype, respectively ($p < 0.05$) (Table 2).

The study also attempted to determine the combined effects of the *RAD51* genotypes with lifestyle risk factors

**Table 1.** Clinical profile of the participants ($n = 120$).

| Characteristics | Cases ($n = 60$) | Controls ($n = 60$) | *p*-value* |
|---|---|---|---|
| Age (yr) | 51 *(46–59.50)* | 52 *(45–60.50)* | 0.990 |
| Sex | | | 1.000 |
| Male | 1 *(1.67%)* | 1 *(1.67%)* | |
| Female | 59 *(98.33%)* | 59 *(98.33%)* | |
| Age at diagnosis (yr) | 50 *(44–56.50)* | – | – |
| Alcohol use | | | 0.061 |
| Yes (former, current) | 49 *(91.67%)* | 40 *(66.67%)* | |
| No | 11 *(18.33%)* | 20 *(33.33%)* | |
| Active tobacco use | | | 0.783 |
| Yes (former, current) | 8 *(13.33%)* | 7 *(11.67%)* | |
| No | 52 *(86.67%)* | 53 *(88.33%)* | |
| Passive smoking | | | **0.006*** |
| Yes | 39 *(65.00%)* | 24 *(40.00%)* | |
| No | 21 *(35.00%)* | 36 *(60.00%)* | |
| Family history of cancer (immediate family member) | | | 0.547 |
| Yes | 19 *(31.67%)* | 16 *(26.67%)* | |
| No | 41 *(68.33%)* | 44 *(73.33%)* | |
| Family history of cancer (extended family member) | | | 0.702 |
| Yes | 22 *(36.67%)* | 20 *(33.33%)* | |
| No | 38 *(63.33%)* | 40 *(66.67%)* | |
| Age at menarche (yr) | 13 *(12–14)* | 13 *(12–14)* | 0.908 |
| Age at menopause (yr) | 50 *(46–52)* | 50 *(45.450–51)* | 0.769 |
| Age at first pregnancy (yr) | 27 *(21–31)* | 25 *(21–28)* | 0.516 |
| Oral contraceptive use (N = 117) | | | 0.374 |
| Yes | 19 *(32.76%)* | 24 *(40.68%)* | |
| No | 39 *(67.24%)* | 35 *(59.32%)* | |

Chi-square test of homogeneity compared nominal variables. If expected frequencies were less than 5.00, Fisher's Exact was used. Ordinal variables are compared using the Wilcoxon Rank Sum test. *Significant at 0.05

**Table 2.** Comparison of *RAD51 135G>C* allele and genotype frequencies ($n$ = 120).

| Genotype | Cases ($n$=60) | | Controls ($n$=60) | | OR (95% CI) | p-value (two-tailed) |
|---|---|---|---|---|---|---|
| | Frequency | % | Frequency | % | | |
| ***C/C*** | **12** | **20** | **4** | **6.67** | **1.00** | **0.0324** |
| *G/C* | 48 | 80 | 56 | 93.33 | 0.29 (0.08, 0.97) | – |
| *G/G* | 0 | 0.0 | 0 | 0.0 | – | – |
| *G allele* | 0.40 | | 0.47 | | | |
| *C allele* | 0.60 | | 0.53 | | | |

**Table 3.** Combined effect of *RAD51* G/C genotype and other risk factors ($n$ = 104).

| Gene | Cases ($n$ = 48) | Controls ($n$ = 56) | OR (95% CI) | $p$-value (two-tailed) |
|---|---|---|---|---|
| | $f$ (%) or median (IQR) | $f$ (%) or median (IQR) | | |
| *RAD51* G/C and alcohol use | 9 | 16 | 0.58 (0.23, 1.46) | 0.245 |
| *RAD51* G/C and active tobacco use | 7 | 7 | 1.20 (0.39, 3.69) | 0.757 |
| ***RAD51* G/C and passive smoking** | **31** | **22** | **2.82 (1.27, 6.26)** | **0.011** |
| *RAD51* G/C and history of cancer in immediate family | 17 | 15 | 1.50 (0.65, 3.46) | 0.343 |
| *RAD51* G/C and history of cancer in extended family | 20 | 19 | 1.39 (0.63, 3.09) | 0.417 |
| *RAD51* G/C, alcohol use, and active tobacco use | 3 | 5 | 0.84 (0.21, 3.40) | 0.812 |
| *RAD51* G/C, alcohol use, and passive smoking | 8 | 4 | 2.75 (0.70, 10.74) | 0.145 |
| *RAD51* G/C, alcohol use, smoking exposure (both active and passive), and family history of cancer (both immediate and extended) | 6 | 3 | 2.00 (0.38, 10.58) | 0.415 |

such as alcohol consumption, tobacco use, and history of cancer in the family. Results showed that most risk factors did not increase the risk of breast cancer when combined with the G/C genotype except for passive smoking. The combination of *RAD51* G/C genotype and passive smoking was associated with a threefold increased risk of developing breast cancer ($p < 0.05$). There were no significant differences in the number of cases and controls carrying the *RAD51* C/C genotype who practiced a similar lifestyle and used contraceptive pills ($p > 0.05$) (Table 3).

## DISCUSSION

The *RAD51* gene is a homolog of recA protein in *Escherichia coli* and is located at chromosome 15q15.1. It is required for mitotic and meiotic recombination and plays a central role in the homologous recombination repair pathway of DSBs. RAD51 recombinase catalyzes strand invasion and polymerizes the DNA end where it mediates the transfer and annealing of the resulting nucleoprotein filament to the complementary homologous strand (Nogueira *et al.* 2012). It has been shown that polymorphisms in the *RAD51* gene can affect mRNA translational efficiency or stability, leading to altered polypeptide products and less efficient DNA repair mechanisms (Thacker 2005).

While multiple polymorphisms of the *RAD51* gene have been identified, the present study focused on 135G>C (rs1801320), which is one of the most studied polymorphisms in terms of its association with breast cancer (Parvin *et al.* 2017). This study showed that the *RAD51* C/C genotype, the recessive less common genotype, was associated with breast cancer development

among Filipinos. This is further supported by previous studies done among Caucasian and Iranian populations where the *RAD51* C/C genotype was shown to increase the risk of breast cancer. In contrast, *RAD51* C/C genotype was not associated with breast cancer development among the East Asians and populations with mixed ethnicities (Hosseini *et al.* 2013; Sekhar *et al.* 2015). Romanowicz-Makowska *et al.* (2011) speculated that the presence of the C allele could cause linkage disequilibrium with another, so far unknown, mutation located outside the coding region in the *RAD51* gene. This may then play a role in regulating the RAD51 recombinase concentrations, which can affect DNA repair mechanisms.

Meanwhile, the *RAD51* G/C genotype was more associated with breast cancer among Serbians (Krivokuca *et al.* 2013), Pakistani (Qureshi *et al.* 2014), and Iranian populations (Hosseini *et al.* 2013). No link has been established between *RAD51* G/C and the risk of breast cancer among Saudi Arabians (Tulbah *et al.* 2016), Ashkenazi Jews (Kadouri *et al.* 2004), and Australians (Webb *et al.* 2005).

Findings from previous studies also showed an association of *RAD51* G>C polymorphism with other tumor sites. *RAD51* G>C genotype has been linked to an increased risk of esophageal and oropharyngeal cancers among Chinese (Kayani *et al.* 2014; Sun *et al.* 2015). Further, acute myeloid leukemia has also been linked to the *RAD51* G/C genotype. However, it is interesting to note that this genotype could confer protection from head and neck cancers among heavy smokers (Seedhouse *et al.* 2004).

The effects of a polymorphic *RAD51* 135G>C gene when combined with lifestyle factors and history of cancer in the family were also analyzed. Based on the results, carrying a *RAD51* G/C genotype in combination with other established breast cancer risk factors – such as active smoking, alcohol use, and family history of cancer – may not increase the predisposition of Filipinos to breast cancer development. However, passive smoking was the only risk factor in the presence of the *RAD51* G/C genotype, which increased the risk of breast cancer predisposition. According to Betts (2007), the concentration of nitrosamines and other carcinogens are much higher in secondhand smoke compared to mainstream smoke. In addition, the vapor-phase components of passive smoke are more readily absorbed into the blood and lymph than the particulate-phase components found in mainstream smoke. Thus, the toxicants may easily access the mammary tissues, forming DNA adducts which if unrepaired may further mutate and eventually lead to breast cancer development. Similarly, passive smoking was shown to increase breast cancer risk among Filipinos carrying the *XRCC4* c.1394G>T, *GSTM1* null, and *GSTT1* positive genotypes (Garcia *et al.* 2019; Kalacas *et al.* 2019).

To the researchers' knowledge, this is the first report on the association of *RAD51* 135G>C with breast cancer susceptibility among Filipinos. Moreover, the results of the study contribute to existing evidence supporting the hypothesis that polymorphisms in the *RAD51* 135G>C gene may influence the functioning of the DNA repair pathway.

It is also worth noting that *BRCA1/2* could mediate the homologous recombination activity of *RAD51* and are, therefore, essential for the repair of DNA DSBs. In the study of Matsuda *et al.* (2002), the prevalence of *BRCA* mutations among unselected breast cancer cases in the Philippines was at 5.1%, while the prevalence for *BRCA2* mutation alone was 4.1%. Matsuda *et al.* (2002) also suggested that the penetrance of *BRCA* mutations is persistent in the Philippines, with germline mutations more common in *BRCA2* than the *BRCA1* gene among Filipino cases. In the present study, however, the *BRCA1/2* status of breast cancer patients was not determined. It is possible that there might be carriers of *BRCA1/2* mutations among the sampled cases. Although there is no experimental evidence to prove this, the researchers recommend future studies to conduct a thorough investigation of the possible association between *BRCA1/2* mutations and the *RAD51* SNP in Filipino women with breast cancer.

Interestingly, for Caucasians or Europeans, there were conflicting findings regarding the association of the *RAD51* 135G>C with breast cancer risk. The meta-analysis of Wang *et al.* (2010) concluded that the *RAD51* 135 G>C polymorphism was associated with breast cancer. Meanwhile, the meta-analysis of Yu *et al.* (2010) concluded that there was no association between the two. These conflicting results might be attributed to the differences in breast cancer cases included in their meta-analysis. The epidemiological studies used by Wang *et al.* (2010) focused solely on cases carrying the *RAD51* 135G>C SNP without taking into account their *BRCA* mutation status. In the contrary, Yu *et al.* (2010) included only those participants without the non-*BRCA1/2* mutation. Considering the role of *BRCA* on *RAD51*, it is possible that the difference in the *BRCA* mutation status of the cases included in their studies might have affected their analysis of epidemiological data.

In summary, the study showed that *RAD51* C/C genotype was an independent risk factor for breast cancer development among Filipinos. It was also observed that passive smokers carrying the *RAD51* G/C genotype had significantly increased the risk of breast cancer. *RAD51* G/C genotype – even when combined with other established risk factors like alcohol use, active smoking, and family history – may not increase the risk of breast cancer.

The results of this study agreed with what has been observed in other studies wherein the more common G/C

genotype is not associated with breast cancer development and even protective of other cancers, while the recessive less common C/C genotype potentially increases the risk of breast cancer. This observation may be attributed to the interplay of the allelic, genotypic, and possibly epistatic factors and interactions of this particular SNP. It must be noted that genetic factors only contribute 5–10% risk for developing cancer compared to environmental factors at 90–95% (Anand *et al.* 2008). For instance, the increased risk for breast cancers among passive smokers carrying the G/C genotype seen in this study exemplifies the interaction between mutations and the environment. Future studies should also determine the interaction of *RAD51* G/C genotype with steroid receptor expression, immune conditions, diet, obesity, radiation, and even infectious organisms. Epistatic gene-gene interactions are also critical for gene regulation, such as in the case of *BRCA2* regulating both the intracellular localization and DNA binding ability of RAD51. It has been proven that *BRCA2* inactivation leads to loss of RAD51 function, which can then lead to genomic instability and tumorigenesis (Davies *et al.* 2001). Hence, future studies on a Filipino population should also include the interaction between *BRCA* and *RAD51* mutations.

Despite being a prevalent type of cancer, this study was limited by a small sample size. Not all qualified participants agreed to enroll in the study. Those who refused were usually diagnosed with an advanced stage of the disease. Considering that this was a pilot study, funding was limited that is why there was no chance to expand the number of samples. Despite this limitation, the strict age- and sex-match design added to the reliability of the findings. However, future studies should screen for other polymorphisms of the *RAD51* gene and other DNA repair genes, and to determine their combined effects with known risk factors, such as *BRCA* mutations, obesity, and the steroid receptor expression status of the patient. Furthermore, participants from other parts of the country should be included to accurately represent the Filipino population.

## ACKNOWLEDGEMENT

Our thank you to the Research Center for the Natural and Applied Sciences of the University of Santo Tomas for partially funding this study. We also thank Ms. Mariel Capungcol and Mr. Kevin Rae Ngo for their technical support.

## STATEMENT OF CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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