Association of PIK3CA and PTEN Genetic Alterations with Cervical Cancer Mortality and Tumor Recurrence

By

Florence Femi Odekunle

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By

Florence Femi Odekunle

Dissertation Committee:

Dr. Frederick Coffman, Committee Chair

Dr. Shankar Srinivasan, Committee Member

Dr. Antonina Mitrofanova, Committee Member

Approved by the Dissertation Committee:

_____ Date _____

_____ Date _____

_____ Date _____

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ABSTRACT

Background: Despite the fact that cervical cancer is known to be a preventable cancer, it remains one of the major causes of cancer-related deaths in females. A number of studies have attributed differences in clinical outcomes of cervical cancer to several factors such as stage at presentation, treatment pattern, and socioeconomic status. However, the association of specific genetic alterations with differences in clinical outcomes remains largely unexplored.

Objectives: The initial research purpose was to identify the most common oncogene and tumor suppressor gene in cervical cancer with mutations and copy number alterations (CNAs)**.** The focused research purpose was to examine the association of the identified oncogene and tumor suppressor gene with clinical outcomes and racial differences.

Methodology: This study made use of the Cancer Genome Atlas (TCGA) database. The TCGA cervical cancer data were submitted between 2011 and 2014. The two genomic profiles used were mutation data and CNA data. The Fisher's exact and chi-square tests were used to test for associations between the categorical variables. Logistic regression analysis was used to quantify the strength of associations.

Results: There were 309 cervical cancer cases. Phosphatidylinositol3-Kinase Catalytic Subunit Alpha (PIK3CA) and Phosphatase and Tensin Homolog (PTEN) genes were identified as the most common oncogene and tumor suppressor gene respectively. 63 patients had mutations in PIK3CA or PTEN or both, and 70 patients had CNAs. The ORs (Exp(B)) of death and tumor recurrence for patients with mutations were 3.300(1.625–6.700) and 2.461(1.120–5.407) respectively. The ORs of death and tumor recurrence for patients with CNAs were 2.316(1.282–4.186) and 2.383(1.228–4.624) respectively. The ORs for CNA positive for the Black race compared to White race was 2.378(1.137–5.452).

Conclusions: Genetic alterations in PIK3CA or PTEN or both are associated with a higher risk of cervical cancer mortality and tumor recurrence. These genes can be explored as therapeutic targets to improve cervical cancer treatment. High prevalence of CNAs in African American women could be due to the fact that a larger percentage presented at a later stage as stages III and IV are significant predictors of the presence of CNAs in these genes.

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DEDICATION

I dedicate this dissertation to my father-in-law, late Special Apostle Emmanuel Ogundiya Odekunle and mother-in-law, late Mother-in-Israel Deborah Adedoyin Odekunle. They were the helpers of my destiny.

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immunodeficiency Syndrome
API	Asian/Pacific Islander
ASCII	American Standard Code for Information Interchange
ASC-US	Atypical Squamous Cells of Undetermined Significance
CDC	Centers for Disease Control and Prevention
CRT	Chemoradiotherapy
CIS	Carcinoma in-situ
CIN	Cervical Intraepithelial Neoplasia
CI	Confidence Interval
CNA	Copy Number Alteration
CNV	Copy Number Variations
DES	Diethylstilbestrol
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRT	Hormone Replacement Therapy
IARC	International agency for Research on Cancer
ICD	International Classification of Diseases
FIGO	International Federation of Gynecology and Obstetrics
IVP	Intravenous Pyelogram
LACC	Locally Advanced Cervical Cancer

NCI	National Cancer Institute
NHGRI	National Human Genome Research Institute
NHIS	National Health Interview Survey
NPCR	National Program of Cancer Registries
EXP (B)	Odds Ratio (OR)
OS	Overall Survival
Pap	Papanicolaou
PIK3CA	Phosphatidylinositol 3-kinase catalytic subunit alpha
PTEN	Phosphatase and tensin homolog
PFS	Progression-free survival
RCT	Randomized Controlled Trials
SES	Socioeconomic Status
SEER	Surveillance, Epidemiology, and End Results
SIL	Squamous Intraepithelial Lesion
TCGA	The Cancer Genome Atlas

CHAPTER I

INTRODUCTION

1.1 Operational Definition and Statement of the Problem

Cervical cancer is a type of cancer in which malignant cells form in the tissues of the cervix or cervix uteri. The cervix is the lower part of the uterus connecting the body of the uterus (corpus uteri) to the vagina. Cancer of the cervix, the third most commonly diagnosed cancer, is the fourth major cause of cancer related death in women globally. Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer related death in females globally with over 527,000 new cases (see figure 1) and perhaps the second most common malignancy among females in the third world countries[1-6] (see figure 2). It accounts for 9% of the total new cancer cases and 8% (more than 265,000) of the total cancer deaths among females (see figure 1).[1,2] More than 80% of these cases and deaths occur in developing countries.[1,2,4,7] The second most populous nation in the world, India, accounts for 27% (77,100) of the total cancer of the cervix deaths.[2] Globally, Western, Eastern, and Southern Africa, as well as South America and South-Central Asia have the highest incidence rates. While Western Asia, North America, and Australia/New Zealand have the lowest rates.[2]

Despite the fact that cancer of the cervix is known to be a preventable cancer, it remains one of the major causes of cancer related deaths in females under the age of 60.[1-4,7] For instances, in the United States, the percent of cervix uteri cancer deaths is highest

among females in the age of forty-five to fifty-four.[8,9] Over 12,000 women were diagnosed with cervical cancer in 2016[9] and more than four thousand deaths from cancer of the cervix.[9-11] The number of new cases of cervix uteri cancer is 7.4 per 100,000 women per year.[9] The prevalence of cervical cancer as of 2016 was estimated to 256,078 women.[9] Most of these women were younger than 55. Cervical cancer is rare in women under 20 years old.[9,12] Assuming that incidence and survival rates follow recent trends, it is estimated that $1.3 billion will be spent on cervical cancer care in the United States.[10]

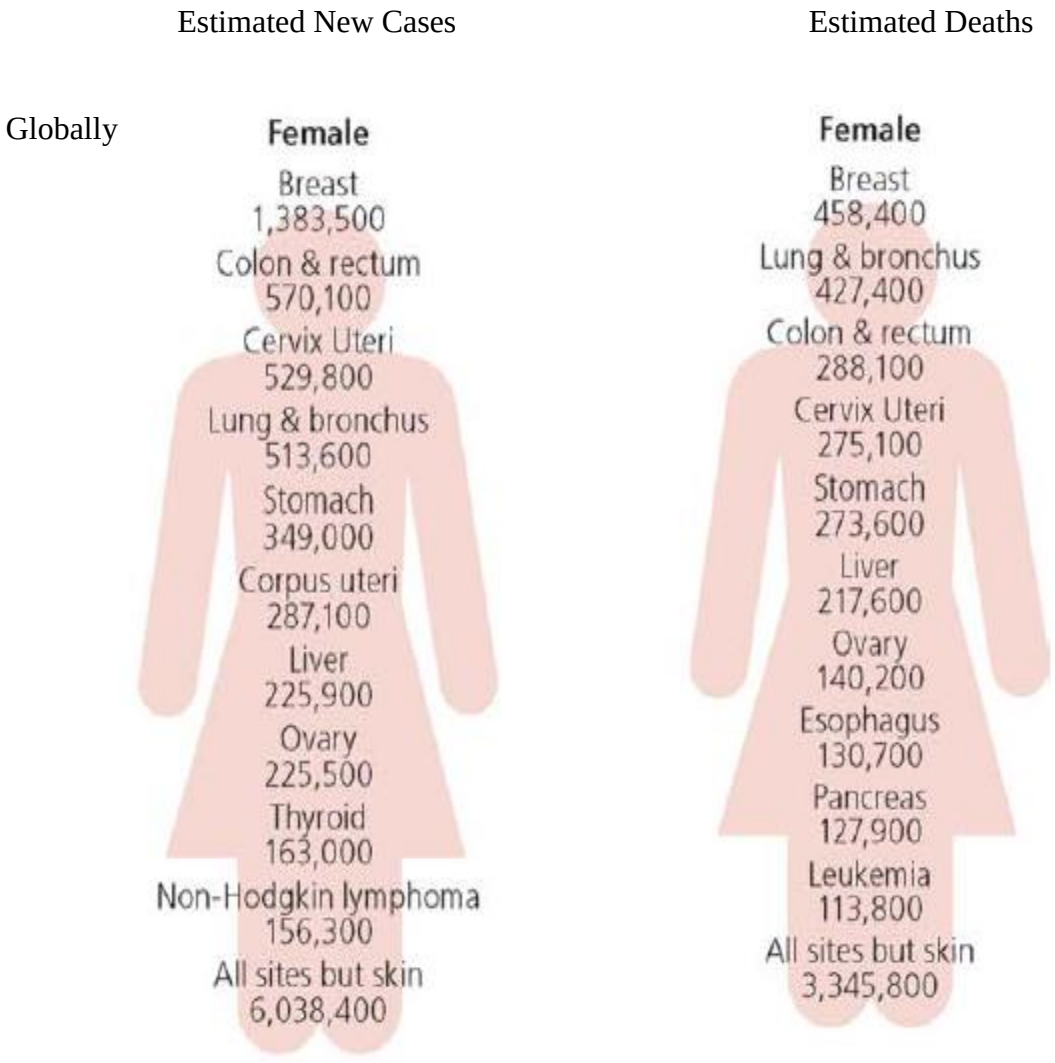


Figure 1: Adapted from Jemal A, Bray F, Center MM, et al. [2]

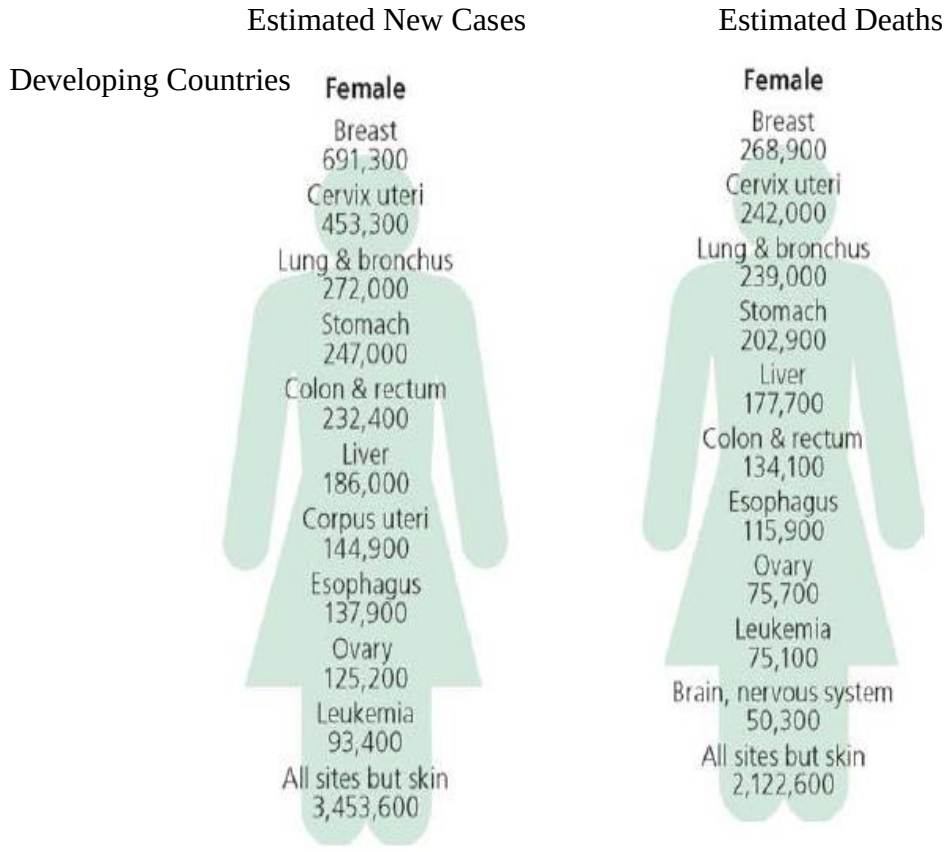


Figure 2: Adapted from Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman

A number of studies indicated differences in racial and cervical cancer outcomes and several factors are associated with it such as stage at presentation,[13-22] treatment differences,[13,14,17,19,,23] comorbid conditions,[23] racial group,[3, 13-20,] and socioeconomic status.[3,15,16,23,,25-31] For instance, African American women have been shown to have a higher mortality rate due to an advanced clinical stage at presentation, less aggressive treatment patterns, higher comorbidities, and lower socioeconomic status. However, the association of specific genetic alterations with cervical cancer clinical outcome and racial differences remains largely unexplored.

1.2 Research Goals/ Objectives

- The initial research purpose was to identify the most common oncogene and tumor suppressor gene in cervical cancer with both mutations and copy number alterations (CNAs) **Note (CNAs can be in the form of gene amplifications or gene deletions)**
  - An oncogene is a gene that has the potential to cause cancer. In tumor cells, they are often mutated and/or overexpressed/amplified.
  - A tumor suppressor gene/ antioncogene is a gene that protects a cell from one step on the path to cancer. In cancer cells, they are often mutated and/or deleted.
  - The decision to examine genes with both mutations and CNAs was based on the fact that often times a single genetic alteration may not result in significant biological and clinical effects.
- The focused research purpose was to examine the association of the identified oncogene and tumor suppressor gene with cervical cancer clinical outcomes and racial differences.

1.3 Significance of the Research

Despite the knowledge and innovative method to prevent and treat cervical cancer, significant numbers of women continue to be diagnosed with it and die as a result of this cancer. Therefore, this calls for more action, different approaches, and further research. Elucidation of the clinical outcomes of cervical cancer with specific genetic alterations is important in the execution of personalized medicine. Personalized

or precision medicine is a type of medicine that uses data and information about an individual's genes to prevent, diagnose, and treat a disease.[32] This study can influence the decision-making process regarding the use of specific inhibitors in patients with these genetic alterations. Uncovering the relationships between certain genetic alterations and cervical cancer mortality/tumor recurrence can guide medical professionals on creating targeted treatment plans that could aid in alleviating cervical cancer outcomes.[3, 33]

1.4 Focused Research Hypotheses

The hypotheses that are to be tested are as follows:

- Mutations involving the identified oncogene and tumor suppressor gene contribute to cervical cancer mortality.
- Mutations involving the identified genes affect tumor recurrence.
- CNAs involving the identified genes contribute to cervical cancer mortality.
- CNAs involving the identified genes affect the recurrence of cervical cancer.
- The prevalence of mutations involving the identified genes is different between African American and White women.
- The prevalence of CNAs involving the identified genes is different between African American and White women.

1.5 Novelty of the Research

To the best of my knowledge, this study is the first to examine the association of oncogene and tumor suppressor gene in cervical cancer with clinical outcomes and racial differences using the TCGA dataset.

1.6 Organization of Dissertation Paper

Chapter two discusses the relevant literature; chapter three covers the documentation of the methodology that was employed in the conduct of the study. Chapter four lays out the results and chapter five presents the discussion and conclusions.

CHAPTER II

LITERATURE REVIEW

2.1 Anatomy of the Female Reproductive System and Pathogenesis of Cervical Cancer

The organs in the reproductive system of a female are the vagina, uterus, fallopian tubes, and ovaries. The uterus has a muscular external layer termed the myometrium and an internal covering referred to as the endometrium[34-36]. The cervix is the lower part of the uterus connecting the upper part of the uterus to the vagina (see figure 3a).[37] It is a cylindrical structure, which lies below the internal OS [34-36]. The upper third of the cervix is made up of columnar/glandular cells (similar to. the rest of uterus). The lower two-thirds of the cervix is made up of squamous cells (similar to the vagina) (see figure 3b); [38] these 2 cell types meet at a point called the squamocolumnar junction (transformation zone or T-zone). The exact location of the transformation zone changes as you age and if you give birth. The normal squamocolumnar junction is located in the ectocervix and can be exposed to carcinogens, resulting in cervical intraepithelial neoplasia (CIN), an abnormal proliferation or overgrowth of the basal cell layer[34,35]. The T-zone is the most common site for cervical dysplasia which is a premalignant condition that results from an abnormal proliferation of cells characterized by changes in cell size, shape, and loss of cellular organization.[34,35]

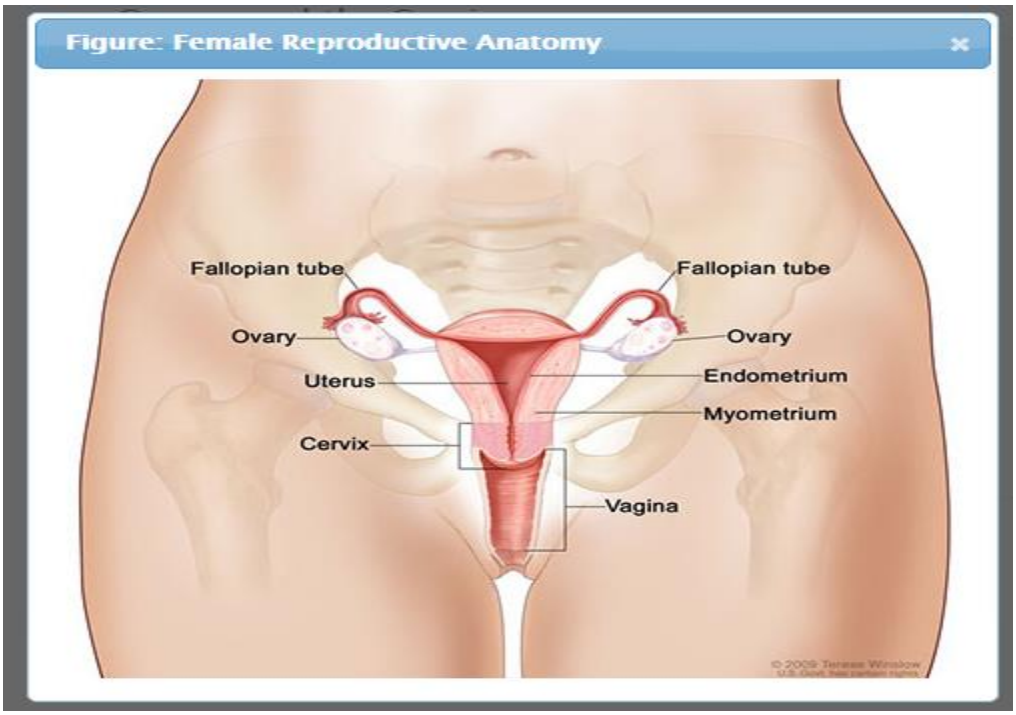


Figure 3a: Anatomy of female reproductive system, adapted from **SEER:** National Cancer Institute Surveillance, Epidemiology, and End Results Program[37]

http://seer.cancer.gov/statfacts/html/cervix.html

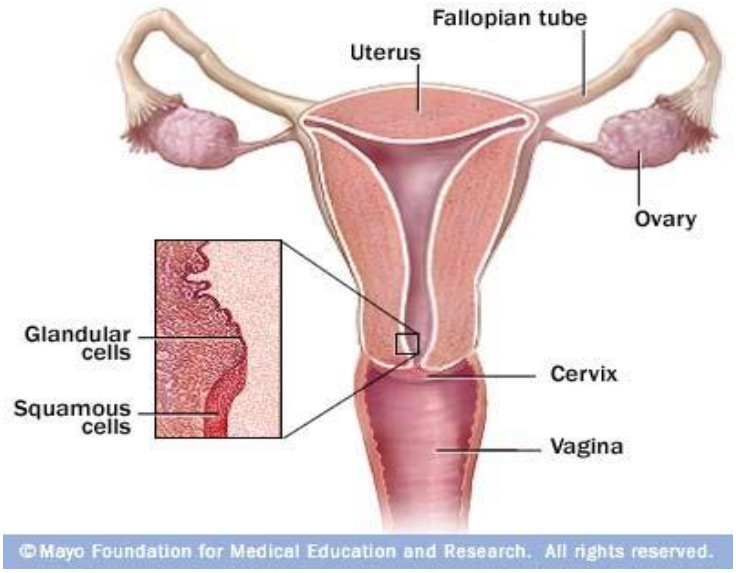


Figure 3b: Anatomy of female reproductive system, adapted from

http://www.bing.com/images/search?q=anatomy+of+cervix&id=4B21A47DFDF1FD4269F79CD47453E03D15FE3FA7&FORM=IQFRBA[38]

Approximately 90% of cancer of the cervix are squamous cell carcinomas.[34, 35,39] This form of malignancy starts at the thin, flat, squamous cells on the surface of the ectocervix, the portion of the cervix that is close to the birth canal (vagina). About 10% of cervical tumors are of the adenocarcinoma form. This type of cervical cancer originates from the glandular cells which are in mucus-producing cells located in the endocervix, near the uteri corpus (that is the body of the uterus[34, 35, 39]. Sometimes, cancer of the cervix may have features of both groups, and this is known as the mixed carcinoma or adenosquamous carcinoma.[34, 35,39]

2.2 Causal Association of Human Papillomavirus (HPV) and Cancer of the Cervix

It is important to have a clear understanding of how the etiology of cancer of the cervix was established which eventually enabled the development of HPV vaccines, one of the major breakthroughs in the history of cervical cancer. For decades, the etiology of cancer of the cervix remained unknown and there were several attempts by past scientists to establish the cause of cervical cancer without much success. However, the earliest breakthroughs came in the 1930s while Dr. Richard Shope of the Rockefeller University was working on wild rabbits that had developed “horn”, which upon further analysis, was caused by a virus that could be transmitted. This discovery played a crucial part in the subsequent studies by Dr Zur Hausen.[40]

The late 1980s and early 1990s had witnessed the emergence of mounting and somewhat irrefutable evidence associating HPV to cervical cancer. In fact, the 1990s saw the largest series of cases of invasive cervical cancer investigated by the International agency for Research on Cancer (IARC) in 22 countries around the world involving about 1000women with histologically verified cancer of the cervix.[41,42] HPV-DNA was

detected in 99.7% of the tumors leading to the conclusion that HPV is a necessary cause of cervical cancer.

The almost established nature of this hypothesis encouraged more studies into other related epidemiological factors involved such as high parity, early sexual debut, multiple sexual partners, low socioeconomic status, oral contraceptives and other factors featured prominently in different studies[43-45]. Also, accumulated case control and cohort studies' results had progressed to the stage of delineating different strains of HPV and establishing their association to cervical cancer and other malignancies with HPV 16 and HPV 18 featuring prominently in the case of cancer of the cervix[43,44]. Palpably, "in 1995, the IARC monograph working group concluded that there was sufficient evidence for the carcinogenicity of HPV-16 and HPV-18 and limited evidence for carcinogenicity of HPV-31 and HPV-33." [41].

Evidently, in the 1990s the relationship between HPV and cervical neoplasia was confirmed.[46] According to Bosch et al., the 1990s produced the key results of case-control and cohort studies, and witnessed an increasing number of results on the clinical uses of HPV-DNA testing in screening and triage,[47] and, as Liaw et al. (1995) noted in their case control studies, it was also becoming apparent that those with multiple HPV infections have a higher risk of developing cancer of the cervix.[45]

With the changing dimension of research studies having confirmed that HPV was a necessary cause of cervical cancer, epidemiological studies advanced to associating different strains of HPV to different anogenital pathologies, categorizing different histological forms of cervical cancer in relation to HPV strains and highlighting other risk factors that may play a prominent role or catalyze the carcinogesis process. For instance,

Ngelangel et al. in their hospital-based case control studying the Philippines detected HPV-DNA in 93.8% case subjects with squamous cell carcinoma, 90.9% in case subjects with adenocarcinoma/adenosquamous carcinoma as opposed to just 9.2% of control subjects.[48]

They observed the presence of 6 HPV types in adenocarcinoma, and 15 HPV types in squamous cell carcinoma while noting that, apart from HPV 16 and HPV 18, HPV45 had the strongest association with squamous cell carcinoma. The same year saw the publication of the results of the Morocco-based case control studies by Chaoki et al. which, among other observations, added to the mounting evidence associating high parity, oral contraceptive, multiple sexual partners and low socioeconomic status to the HPV-cervical cancer link.[49]

On the same note, the results of a nested study in Sweden by Ylitalo and colleagues found a strong relationship between HPV viral load and cervical cancer when it concluded that women with high HPV 16 viral loads were at least 30 times the relative risk of HPV-16-negative women in terms of developing cancer of the cervix.[50,51] Franceschi et al. (2003), after reviewing their case control study results even suggested that a vaccine against HPV 16 and 18 may be effective in more than 75% cases of invasive cervical carcinoma.[52]

The early 2000s witnessed the supplementation of facts and extension of dimensions of studies heralded by the emergence of results of longitudinal studies, which provides information on the dynamics of cumulative or persistent exposure to HPV infection, commenced mostly in 1990s and the drive to intervention studies. One of such

papers was the result of the Ludwig-McGill cohort study in Brazil conducted between November 1993 and March 1997 with follow-up until June 2000 with a total of 1611 women. The paper asserted that there was a strong relationship between persistent infection with HPV and the incidence of squamous intraepithelial lesion (SIL), especially for HPV 16 and 18 types.[53]

Furthermore, over the years, triage studies have shown that HPV testing is more sensitive than repeated cytology in identifying underlying high grade lesions in females with atypical squamous cells of undetermined significance (ASCUS). [46] In terms of causality assessment these studies showed that it is possible to predict the concurrent presence of neoplastic disease or the risk of developing it, by means of HPV-DNA detection. This property of the HPV test offers an indirect measurement of the strength of the association and of the temporal relationship. From different types of studies, it is clearly evident that HPV infection precedes cervical intraepithelial neoplasia and cancer of the cervix by some years. The result is that clinical use of HPV-DNA testing in screening has been validated by epidemiological studies over the years: cross-sectional design and large randomized trials.

Overall, the etiological role of HPV infection in cancer of the cervix has been greatly documented without any doubt. The association occurs in almost every case of cancer of the cervix all over the world including developed and developing countries.[7]

2.2.1 Human Papillomavirus

HPVs are now identified as the etiological factors in nearly all types of cervical intraepithelial neoplasia (CIN) and invasive cancer of the cervix. In fact, based on laboratory, clinical, and epidemiological evidence HPVs have been recognized as the

'necessary cause' of cervical cancer that is cancer of the cervix will not develop in the absence of persistent HPV infection.[10] The relationship is stronger than that between lung cancer and cigarette smoking; but, the progression of cancer of the cervix from HPV infection is not inevitable. Studies have shown that only 100 000 or 10% of every one million women who are infected, progress to cervical dysplasia (that is pre-cancerous changes in cervical epithelial cells). Out of these, about 8000 (8%) will progress to early cervical cancer (often referred to as carcinoma in situ). This is usually confined to the external covering of the cervical cells and around 1600 of these women will progress to invasive cancer of the cervix (see figure 4).[4]

There are over 80 kinds of HPV. Approximately 30 of these HPVs are transmitted through sexual intercourse, together with those that cause papilloma (genital warts). It has been well documented that over 6 million females in the United States of America have persistent HPV infection. However, most women infected with HPV do not progress to cancer of the cervix.[39] About half of the sexually transmitted HPVs are linked to cancer of the cervix. These are divided into two main groups, the high and low risks. The "high-risk" HPVs16, 18, 31, and 33 make a protein which can cause epithelial cells of the cervix to proliferate excessively.[39] The high risk HPV viruses make a second protein which interferes with tumor suppressor genes that are produced by the human immune system. These high-risk types have viral oncogenes E7 (binds to Rb) and E6 (binds to p53).[39] The HPV-16 strain is thought to account for over 60% of cancer of the cervix cases (see figure 5).[4]

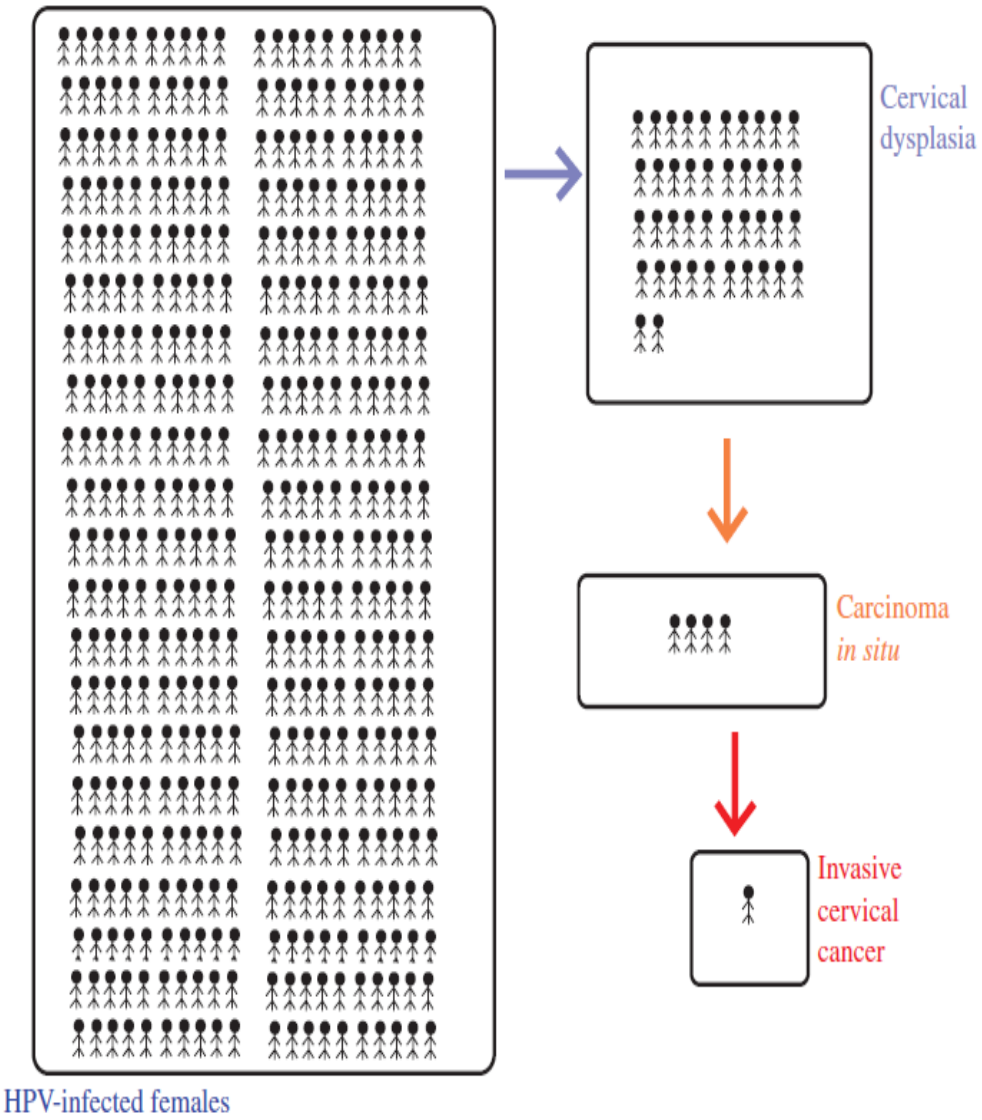


FIGURE 4: Natural history of oncogenic HPV infection. Adapted from Galani and Christodoulou 2009.[4]

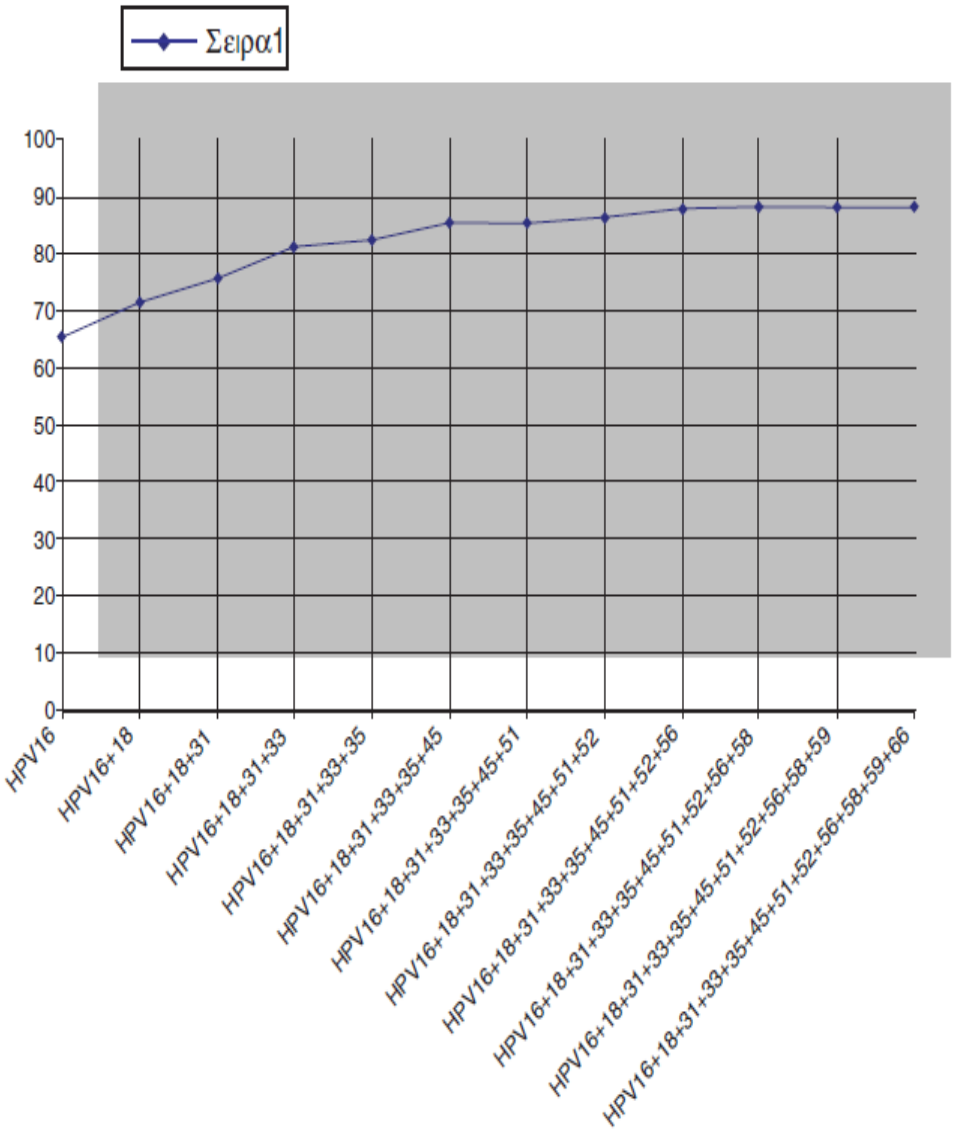


FIGURE 5: HPV types characterized as oncogenic and their relative contribution to cervical cancer development. Values are shown as percentages Adapted from Galani and Christodoulou 2009.[4]

2.3 Other Risk Factors of Cervical Cancer

Additionally, other risk factors have been identified for developing cancer of the cervix. These include cigarette smoking, prolonged use of oral contraceptives, dietary habits, specifically, diets deprived of vegetables and fruits, high parity, coinfection with other sexually transmitted organisms, such as herpes simplex virus type 2, and a Chlamydia trachomatis and co-infection with more than one HPV type[9, 12]. Moreover, human immunodeficiency virus (HIV) infection and other immunosuppressive conditions are associated with an increased risk of disease persistence as well as progression, signifying a hypothetical background for long term viral persistence in a dormant stage which ultimately progresses when immune guard permit it. In view of the fact that HPV is a sexually transmitted infection (STI), certain sexual behaviors put females at risk of HPV infection and cancer of the cervix. Some of these sexual behaviors include:

- Multiple sexual partners: HPV infection may not produce any symptoms, so sexual partners may not know that they are infected.
- Sexual intercourse at age 16 or younger: the cells lining the cervix do not fully mature until age 18. These immature cells are more susceptible to cancer-causing agents and viruses.
- High-risk males (Sexual partners who have had multiple partners)
- Partners who began having intercourse at a young age
- A partner who has had a previous sexual partner with cervical cancer

2.3.1 Immunosuppression

Infection with the HIV, the etiological agent that causes (AIDS) acquired immunodeficiency syndrome, is also one of the risk factors for cancer of the cervix.[39, 40] Women who test positive for HIV may have impaired immune systems that cannot correct precancerous conditions. In addition, sexual behaviors that put females at risk for HIV infection also puts them at risk for HPV infection.[39,40] There is some evidence suggestive of involvement of genital herpes virus, another sexually transmitted virus, in cancer of the cervix.[39]

2.3.2 Smoking

Studies have shown that cigarette smoking double the risk of cancer of the cervix. In fact, evidence suggests that about half of women diagnosed with cancer of the cervix smoke.[39,40] Chemicals produced by tobacco smoke damage the DNA of cervical cells. The risk increases with the amount a woman smokes and the number of years she smokes. A study conducted in 2003 also associates smoking with lower survival rates and poorer outcomes in patients diagnosed with cervical cancer. [39,40]

2.3.3 Diet and Drugs

Another identified risk factor is diet. Diets that lack the adequate amount of vegetables and fruits make people more susceptible to cancer of the cervix. [39,40] A study conducted in 2003 also links obesity to increased risk for certain cervical cancer especially cervical adenocarcinoma. [39,40] The authors stated further that even women who were overweight had a higher incidence of cervical cancer. [39,40] The association appears to be due to high estrogen levels in overweight and obese women. Estrogen and other sex hormone levels are influenced by excessive fat tissue. Females also have an enhanced

risk of cancer of the cervix if their mothers took DES (diethylstilbestrol) drug while they were pregnant. This medication was given to pregnant women between 1940 and 1971 to prevent miscarriages. Similarly, studies have indicated that the long-term use of oral contraceptives to some extent increase the risk of cancer of the cervix. [39,40]

2.4 Cervical Intraepithelial Neoplasia: A Premalignant Lesion to Cervical Cancer

The precursor lesion is cervical intraepithelial neoplasia (CIN), which is commonly occurs at the squamocolumnar junction (transformation zone or T-zone). [34, 35] The CIN is classified as follows:

I.CIN I (mild dysplasia) corresponds to low grade SIL (squamous intraepithelial lesion). From the base of epithelium to one-third (see figure 6 below).[54] Dysplasia is an abnormal proliferation of cells characterized by changes in cell size, shape, and loss of cellular organization.

II. CIN II (moderate dysplasia) corresponds to high grade SIL. From the base of epithelium to two-third (see figure 6 below)

III. CIN III (severe dysplasia) also corresponds to high grade SIL. From the base of epithelium up to the surface (see figure 6 below)

CIN III can be used with.CIS (carcinoma in situ or stage 0); and finally invasive squamous cell carcinoma

Both CIN l and CIN ll are reversible while CIN lll or CIS is irreversible

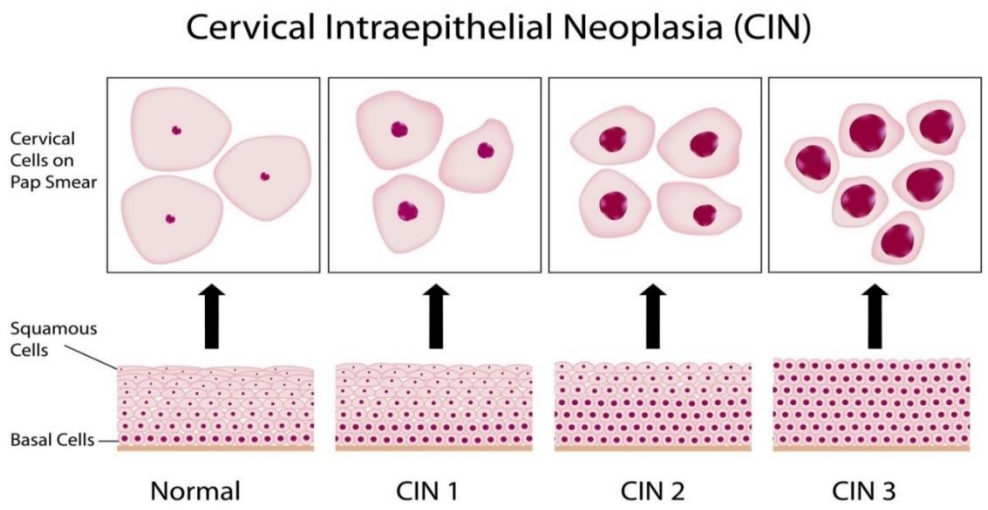
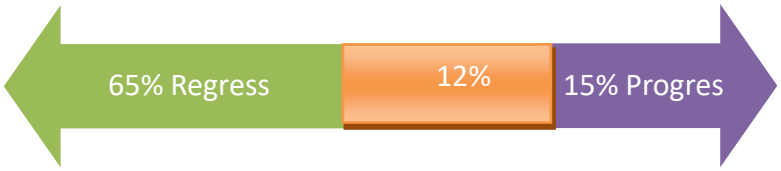


Figure 6: Cervical intraepithelial neoplasia progression changes

http://intimatehealthhelp.net/wp-content/uploads/2012/08/cervical-cancer2.jpg[54]

The premalignant lesions of the cervix are generally asymptomatic.[34, 35] The evolution from the precancerous stage to invasive cervical cancer has been reported to be around 8-10 years.[34] While some lesions remain static, a majority will spontaneously regress: leaving only a minority to progress toward the cancer stage (see figure 7). [34, 35]



HPV types	HPV types
6,11	16, 18, 30s

FIGURE 7: Response to HPV Types: Natural History of Cervical Dysplasia[35]

2.5 Clinical Presentation

Often times, there are no symptoms or signs of early cancer of the cervix but it can be detected early with regular screening and follow-up.[12, 36, 39] The most common symptoms of cervical cancer are:

1. Post-menopausal bleeding, if the woman is not on Hormone Replacement Therapy (HRT) or has stopped it for 6 weeks
2. Abnormal bleeding: after or during sexual intercourse, or between menstrual periods
3. Abnormal or malodorous vaginal discharge
4. Dyspareunia (pain during sex)
5. Lower back pain.[34-36]

However in certain cases there may be no noticeable indication until the cancer has progressed to an advanced stage. [34-36]

2.6 Diagnostic Tests

- **Cervical biopsy:** The first diagnostic investigation must be biopsy of the cervix, squamous cell carcinoma is usually the most commonly diagnosed type from biopsy procedures
- **Metastatic workup.** A metastatic workup is performed once a pathological diagnosis of cancer of the cervix is established. This usually includes chest x-ray, pelvic examination, cystoscopy, intravenous pyelogram (IVP), and sigmoidoscopy.

- Imaging studies. It should be noted that an abdominal pelvic MRI or CT is not useful in clinical staging of cancer of the cervix as staging is done clinically.

2. 7 Staging of Cervical Cancer

Cancer of the cervix begins on the surface of the cervix and tends to grow slowly. Before it shows in the cervix, the cervical cells undergo series of change referred to as cervical dysplasia. This stage is heralded by the appearance of abnormal cells in the cervical tissue. With time, the atypical cells can become malignant cells and begin to proliferate uncontrollably and extend more deeply into the cervical tissue and to nearby organs or structures. Stage is the clinical estimate of the extent of spread of a malignant tumor.[34] Low stage means a localized tumor; stage rises as tumor spread locally then metastasize. Staging is cervical cancer is purely clinical, and it is based on pelvic examination, and it might involve an IVP.[34]

The followings are the identified cervical cancer stages (see figure 8).[55]

Stage 0: Carcinoma in-situ (CIS) Abnormal cell are found in the innermost lining of the cervix. The basement membrane is intact.

Stage 1: Spread is limited to the cervix. This is the most common stage at diagnosis.

Ia1: Invasion is ≤3 mm deep (minimally invasive)

Ia2: Invasion is >3 but ≤5 mm deep (micro invasion)

IB: Invasion is >5 mm deep (frank invasion)

Stage II: Spread **adjacent** to the cervix

IIa: Involves upper two-thirds of vagina

IIb: Invasion of the parametria

Stage III: Spread **further** from the cervix

IIIA: Involves lower one-third of vagina

IIIB: Extends to pelvic side wall blocking ureter and causing urinary obstruction

Stage IV: Spread furthest from the cervix

IVA: Involves bladder or rectum or beyond true pelvis

IVB: Distant metastasis

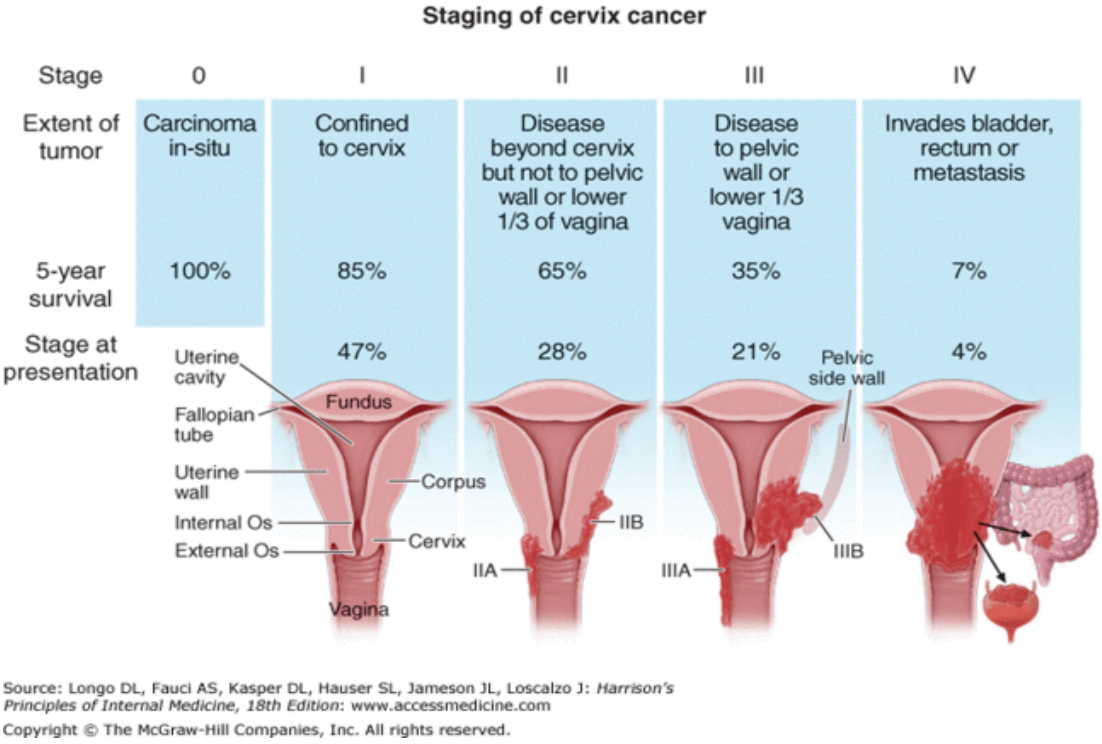


Figure 8 Adapted from Longo et al.[55]

http://cancercervical.wikispaces.com/file/view/loadbinary.gif/389993458/644x459/loadbinary.gif

2.8 Prevention of Cervical Dysplasia by HPV Vaccination

With so much evidence gathered over the years and the results of cohort studies reaffirming the already known, the scientific community and the pharmaceutical companies joined in the race to find a therapeutic intervention to the virus-cancer link. The early results of Randomized Controlled Trials (RCT) with vaccines targeted at the causative virus proved promising: Koutsky et al., in their double-blind RCT with 2392 women published in The New England Journal of Medicine in 2002, found that the incidence of persistent HPV-16 infection was 3.8% per 100 woman-years at risk in their placebo group compared to zero per 100 woman-years at risk in the vaccine group.[56] This discovery, even though somewhat anticipated, was remarkable.

The results of other RCTs strengthened this position proving that therapy/prevention was possible. For instance, significant vaccine efficacy was observed against HPV-16 and HPV-18 according to the RCT results by Harper and colleagues.[57] The study showed a vaccine efficacy of 100% (42.4-100) against CIN lesions associated with vaccine types.[57]

Again, in a randomnized, placebo-controlled, double-blind trial with 5455 women in multiple centres over a three year period using a quadrivalent vaccine against HPV type 6, 11, 16 and 18, vaccine efficacy was 100% for each of the coprimary end points (Garland et al. 2007).[58]

The advent of effective preventive vaccines prove the etiological role of persistent HPV infections in cancer of the cervix development.[59]

HPV vaccination provides the scientific and public health community an unprecedented opportunity to reduce the burden of cancer of the cervix.[60]

A bivalent vaccine (GlaxoSmithKline or Cervarix) containing HPV 16 and 18 and a quadrivalent vaccine (Merck or Gardasil) containing HPV 6, 11, 16, and 18 antigens are in use in immunization programs all around the globe. Clinical research trials have shown that 3 doses of HPV vaccine delivered 90-100% protection against HPV infection as well as pre-malignant stage associated with HPV 16 and 18 in females between 15–26 years old who did not have the HPV infections at immunization.[61] Evidence further showed that there were partial cross-protection against other HPV types has been reported but its duration is unknown.[60] Studies have also reported that HPV vaccines are effective in prevention of HPV 16 and 18 infections at other structural parts of the body in both girls and boys.[61,62] Immunobridging studies have provided strong evidences that allowed licensing of the HPV vaccination in both sexes beginning from age nine.[61] Studies also showed that 2 doses of the vaccine 2-dose schedules stimulate production of high concentration of antibodies, which in turn guide the decision on the approval of a 2-dose schedule for both girls and boys aged 9–14 years (See Table 1a).

Before-licensure and after-licensure research have provided evidence supportive of the HPV vaccine safe use in human beings. HPV immunization began in the USA in 2006 and 2011 for girls and boys respectively aged 11–12 years. For age 15 or more three doses of quadrivalent HPV recombinant vaccine are given initially, then 2 months later, then 6 months later, for an approximate cost of $300. A nonavalent (9) HPV vaccine containing HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antigens was approved by the United States Food and Drug Administration (FDA) in 2014.

A nationwide study on the prevalence of HPV immunization coverage between 2008 and 2010 has shown that 32.0% (95% confidence interval [CI] = 30.3% to 33.6%)

of girls aged 13 to 17 years in 2010 had received three doses of the HPV vaccine, and coverage was statistically significantly lower among the uninsured (14.1%, 95% CI = 9.4% to 20.6%) and in a number of Southern states where cancer of the cervix rates were highest and recent Pap testing prevalence was the lowest.[63] For instance, 20.0% of girls in Mississippi [95% CI = 13.8% to 28.2%]) and Alabama [95% CI = 13.9% to 27.9%], The authors reported overall low vaccination coverage among adolescents. HPV vaccination rates varied significantly among subpopulations (Figure 9 and Figure 9a).[63]

HPV Vaccination* Recommendations for Males & Females

Population	HPV Vaccination
Boys & Girls, ages 9-14 years	2-dose series
Males & Females ages 15-26	3-dose series
Persons with weakened immune systems	

Table 1a Adapted from the American Cancer society Cancer Facts and Statistics http://www.cancer.org/research/cancerfactsstatistics/index#[63]

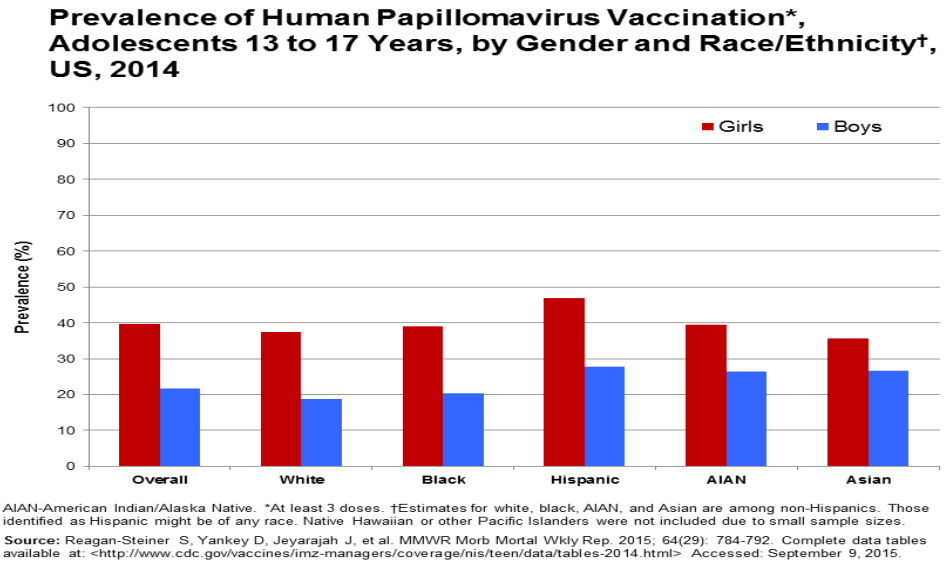


Figure 9 Adapted from the American Cancer society Cancer Facts and Statistics http://www.cancer.org/research/cancerfactsstatistics/index#[63]

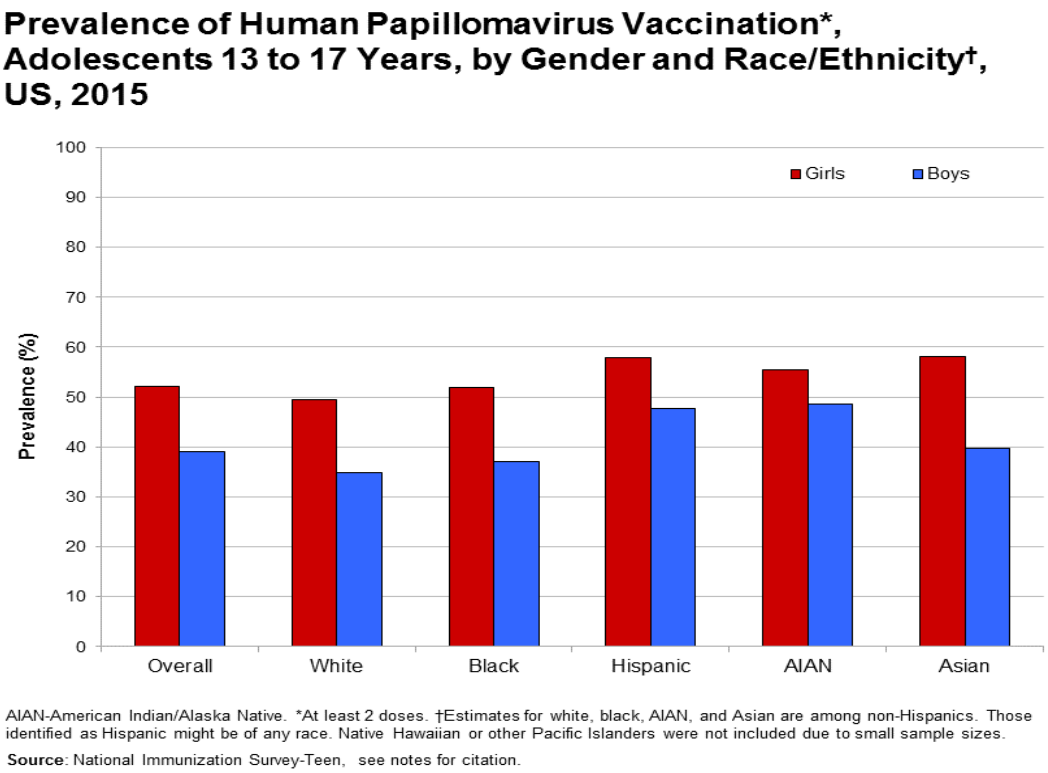


Figure 9a Adapted from the American Cancer society Cancer Facts and Statistics http://www.cancer.org/research/cancerfactsstatistics/index#[63]

2.9 Cervical Cancer Screening

The ultimate aim of cancer of the cervix screening is to preclude the disease and death from cancer. The best screening approach must be able to identify those cervical cancer premalignant cases with likelihood of progression to invasive malignancy (that is maximize the advantages of screening) Additionally, a good screening procedure should be able to prevent the unnecessary detection and treatment of transient HPV infection and its associated benign lesion without possibility of progression to cancer (that is minimize the likely problems related to screening).[64, 65] The two recommended procedures for cervical cancer screening are Papanicolaou (Pap) test or cytology or Pap smear and Human papillomavirus (HPV) test. [64,65]

Pap smear is a method for collecting cells from the surface of the cervix. The cells are examined under a microscope to see if they are normal or abnormal cells.[12] Pap smear screening for cervical cancer premalignant stage has played significant roles in reducing cancer of the cervix incidence as well as mortality in nations where high-quality screening is offered, however false-positive outcomes are not uncommon, because majority of atypical cytology (ASC-US) is not connected with simultaneous CIN3 or cancer, and is thus still a concern.[12]

The second recognized cancer of the cervix screening method is HPV test. This is a laboratory diagnostic procedure to detect presence of commonly implicated HPV DNAs in cervical cancer. The sample collected for cervical cytology could be used for this molecular laboratory test. This test may also be done if the results of a Pap test show certain abnormal cervical cells.[12] HPV DNA laboratory test could provide a better prediction which person may develop CIN3 over the next five to fifteen years than pap smear.[44-46] HPV DNA test was incorporated into the cervical cancer screening program in 2002 by the American Cancer Society (ACS) [64-67] The incorporation of the HPV DNA laboratory test into the screening program is beneficial as it allows both increased disease detection (improving benefits) and increased length of screening intervals (decreasing harms such as the psychosocial impact of screening positive, treatment of lesions with likelihood of resolving, and added clinic follow-up and tests).[12]
Table 1 summarizes the recommended age and frequency of the cervical cancer screening. A number of published studies supported the adopted of the screening's age and frequency[64-66].

TABLE 1 Cervical Cancer Screening Recommendation Summary

Population	Test or Procedure	Frequency
21 – 29 years	Pap test	Every 3 Years
30 – 65 years	HPV and Pap test	Every 5 Years (preferred)
	Pap test only	Every 3 Years (acceptable)

2.10 Cervical Cancer Screening Rates in the United States

The study conducted by Horner in 2011 on the geographical distribution of cervical cancer screening, incidence of cervical cancer, staging of the cancer, and mortality identified the following areas as having low usage of traditional cervical cancer screening methods: regions of Appalachia (from the southern tier of New York to northern Alabama, Mississippi, and Georgia), the central Mississippi Valley (including Missouri, Kentucky, and Tennessee), West North Central states (spanning North and South Dakota, Nebraska), Texas, Florida, and the lower Mountain states of Arizona, New Mexico, and Utah (see figure 10).[68]

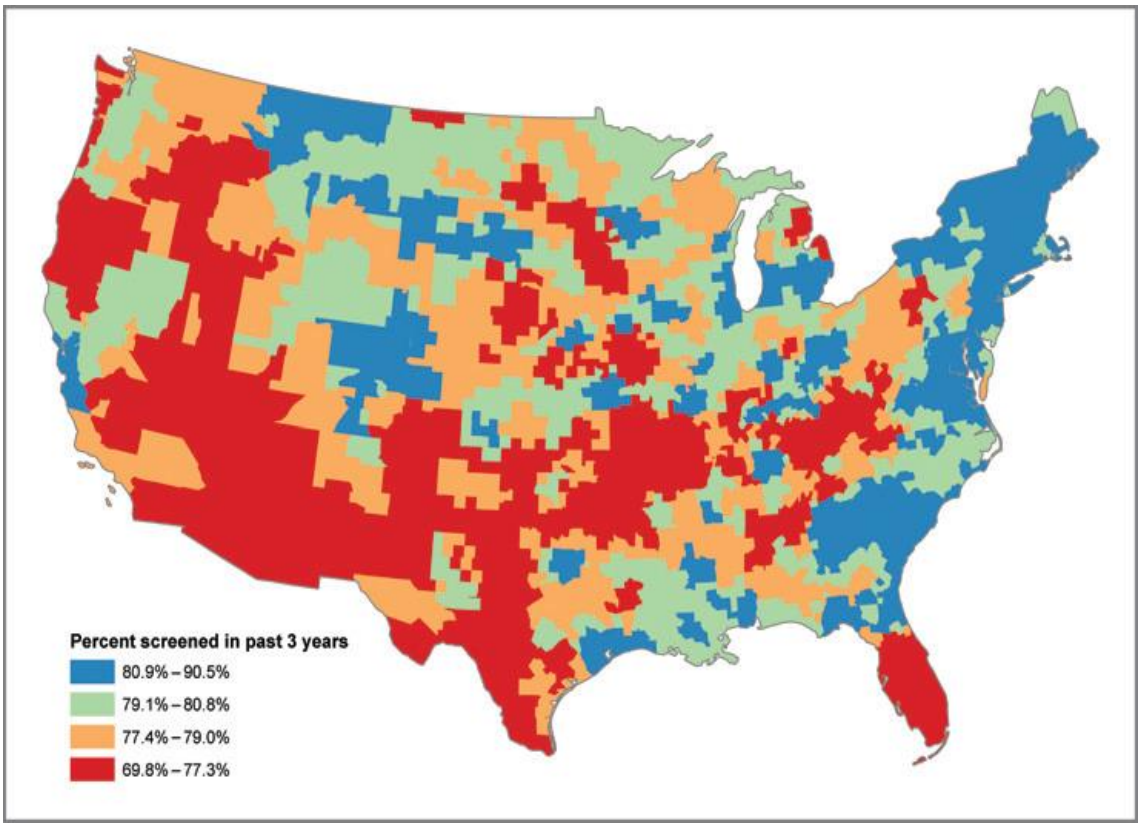


Figure 10: Percentage of women ages 18 years and more who reported having had a Pap smear test within the last three years by county in the United States, 2000 to 2003.[68]

Similarly, the study conducted on cervical cancer screening and follow-up in 4 geographically diverse US health care systems, 1998 Through 2007 revealed that cytology screening test rates declined (from 483 per 1000 person-years in 2000 to 412 per 1000 person-years in 2007) and HPV DNA laboratory test rates go up over the study period. The frequency of screening differed across healthcare systems.[61]

Further study on disparities of cancer of the cervix showed racial differences in cervical screening rates in the United States (See Figure 11 and Figure 11a).[69] In 2001 the California Health Interview Survey, a randomized telephone survey with over 25,000

respondents, collected data showing that Asian women are less probable to report ever having a cytology test or a recent (within three years) pap smear compared to other racial and ethnic groups (See Table 2).[69,70] There were no significant differences in screening rates among White, American Indian (AI)/ Alaska Native (AN), African American, or Hispanic women.[71-82] However, cervical cancer screening rates varied significantly among subpopulations. For instance, the study conducted by analyzing the 2001 California Health Interview Survey data revealed that among Asian American, Filipino women had the maximum screening rates (81.1%) while Vietnamese women had the minimum screening rates (62.3%).[73]

Table 2 Cancer of the cervix screening rates by ethnic and racial groups [69]

	% Ever had a Pap test	% Pap test within 3 years
Healthy People 2010 goal	97	90
Non-Hispanic white	95	79
Hispanic	88	74
African American	94	80
Asian	79	60
AI/AN	97	71

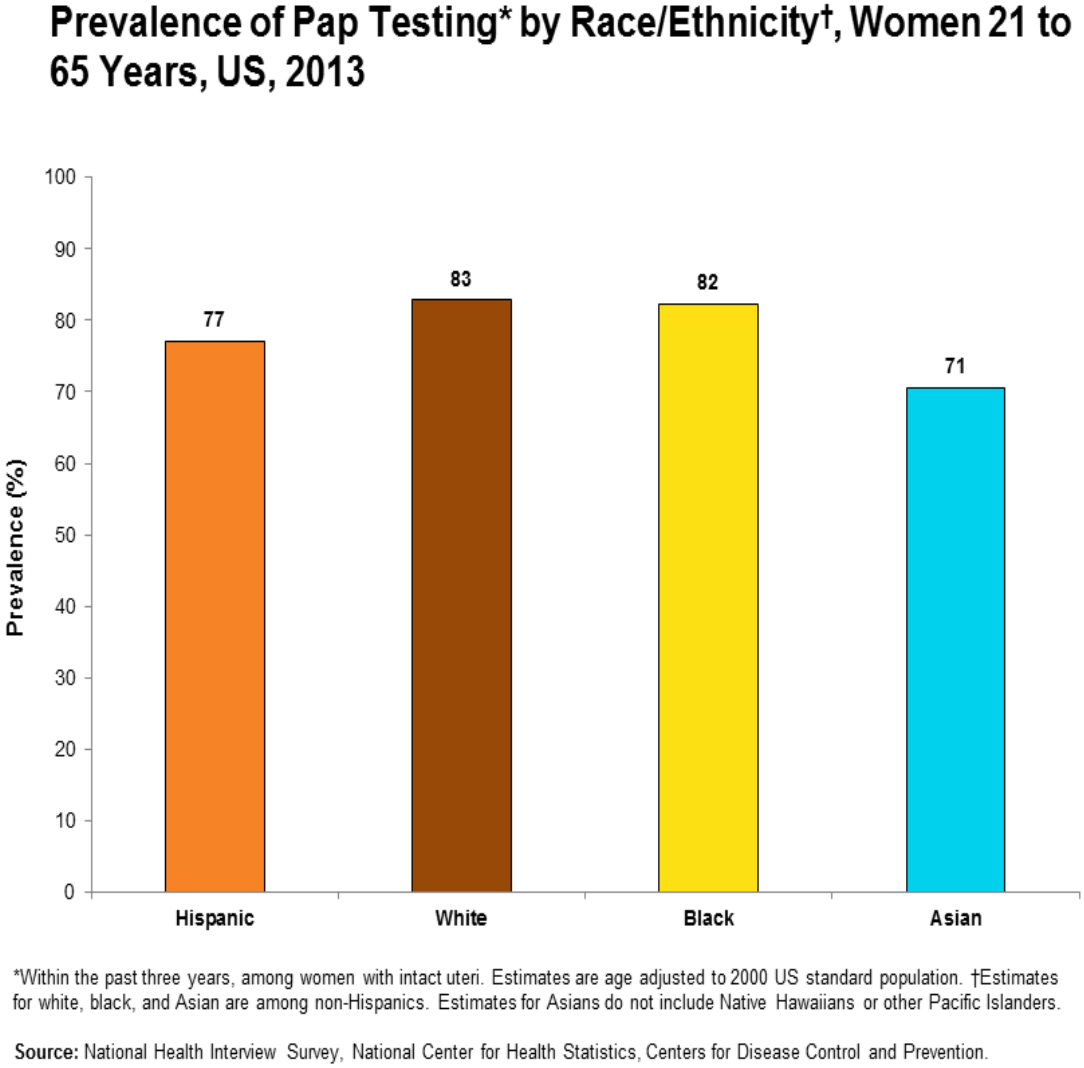


Figure 11: Adapted from the American Cancer society Cancer Facts and Statistics http://www.cancer.org/research/cancerfactsstatistics/index#[63]

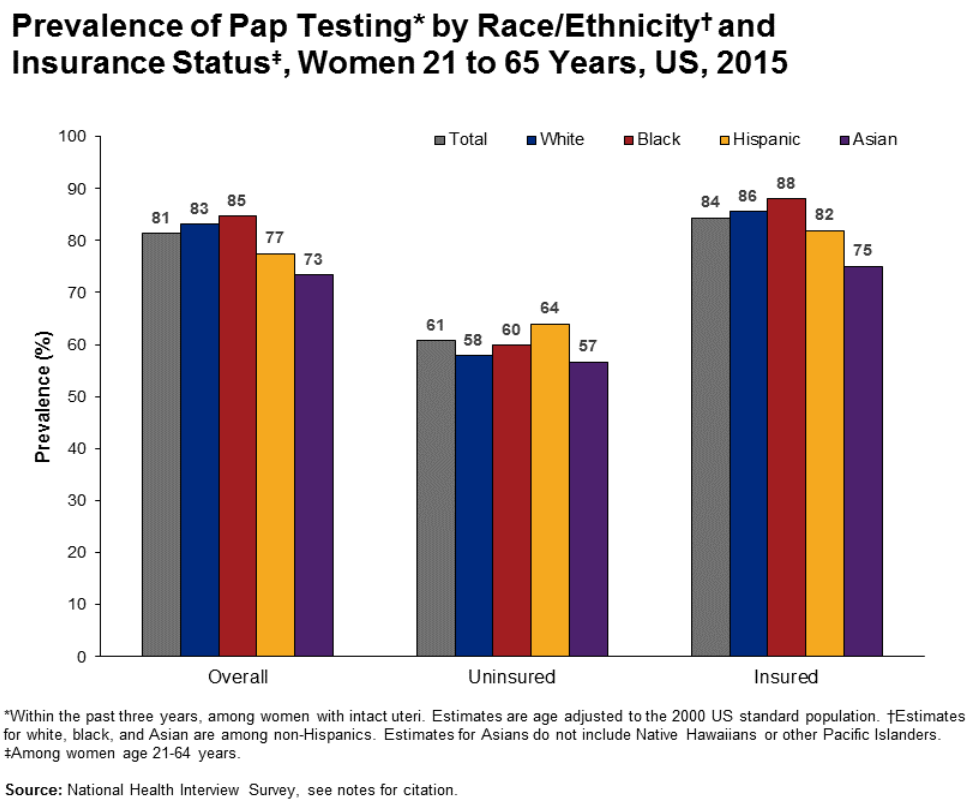


Figure 11a: Adapted from the American Cancer society Cancer Facts and Statistics http://www.cancer.org/research/cancerfactsstatistics/index#[63]

United States Demographics and Projected Population Changes

A larger number of unscreened minority women will result if present screening trends continue as these populations age. By the year 2050, the US Census Bureau projects that the Hispanic population will have experience growth by 188% of its 2000 estimate, and will then make up 24.4% of the US population.[74] Furthermore, increases are projected for Asian Americans, African Americans, and other minority groups (including AI/AN and those who identified themselves as belonging to two or more groups) (Figure 12a, 12b).[75]

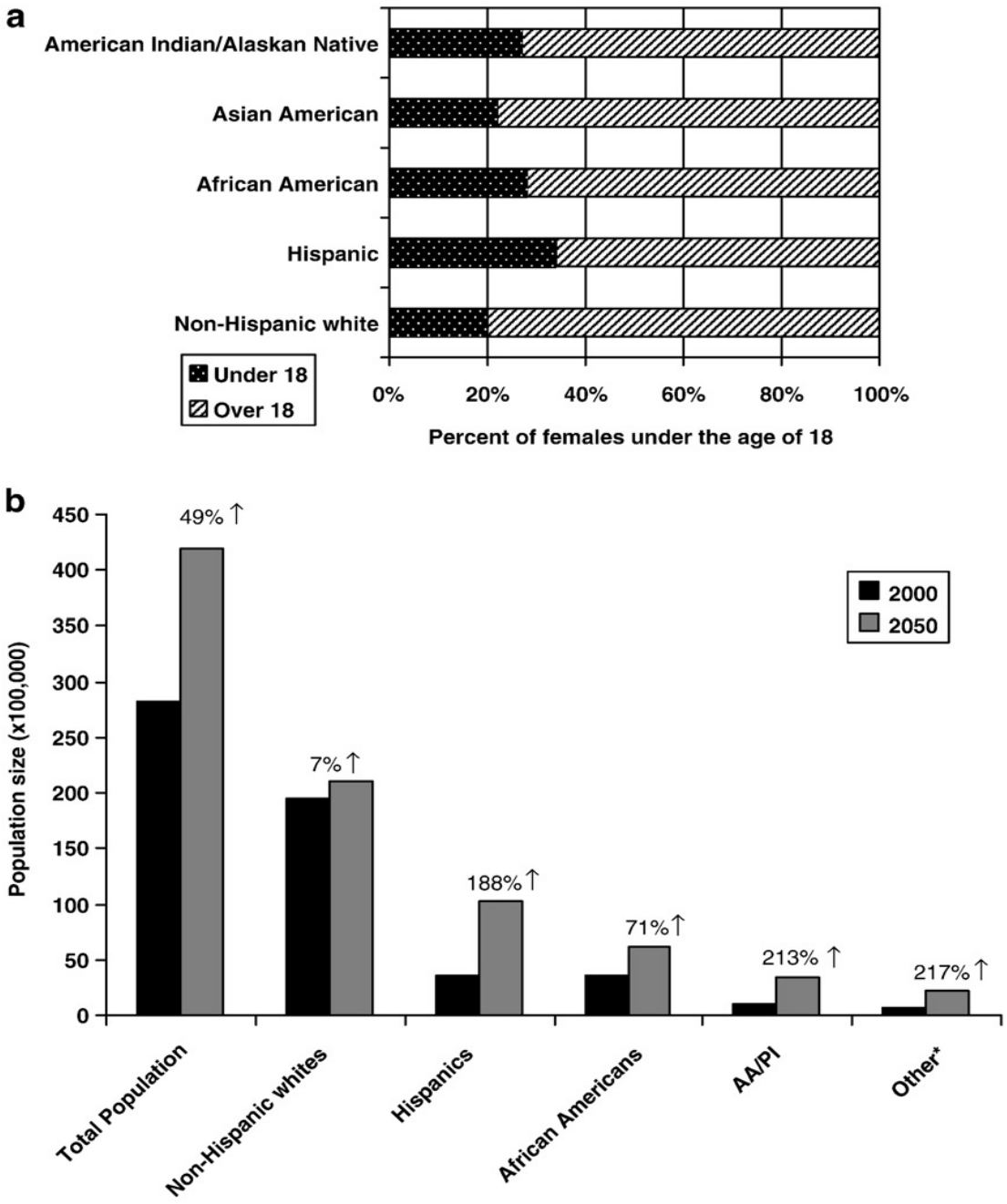


Figure 12 a: Distribution of US females under the age of 18 by racial group, 2006. [75]

Figure 12 b: Estimated change in US population demographics, according to racial and ethnic group, 2000–2050.[75]

Persistence of the current disparities in cervical cancer screening may cause a reversal in the general national decline in mortality and incidence rates.[75] In the next few decades, minority groups will grow in size and will constitute a larger portion of the US population. Hispanics consist of 20% of the total US female population under the age of 18 years as of July 2006.[75] Analysis of each population individually shows that non-Hispanic whites have the lowest percentage of females under the age of 18 years (20.4%) when compared with Asian Americans (21.7%), AI/AN (27%), African Americans (28%), and Hispanics (34%). [75]

The report of the National Health Interview Survey (NHIS) administered yearly by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) to examine the prevalence of several cancer screening practices reported by adults in the year 2000, with a focus on differences in screening among subgroups of the United States population that historically have been underserved has shown that screening use for most groups has increased since 1987, but major disparities remain.[76]

2.11 Review of Relevant Literature

Several studies have shown that racial disparities exist in cervical cancer outcomes such as mortality rate[75, 77, 78], survival rate, incidence, and prevalence. For instances, One of the earliest studies conducted using data from the Surveillance, Epidemiology, and End Results (SEER) Program for 1988–1994 to determine the associations between race and treatment, and race and stage revealed that race remains an independent predictor of cancer of the cervix survival after accounting for treatment patterns, stage of disease, and age. The authors mentioned further that the adjusted hazard ratio (1.30 (95% CI 1.14, 1.48)) for death was high for the African American in a comprehensive model including International Federation of Gynecology and Obstetrics (FIGO) stage of disease, histology, grade, lymph node status, treatment, and demographic factors.[77]

Another study has shown that racial disparities in cervical cancer death exist and the death rate difference between the white and black races is significant.[79] African American women have twice to thrice risk of dying from cancer of cervix (6.9 compared with 2.6 per 100,000) and two times the risk of being diagnosed of having cancer of cervix when compared to white women (14.3 compared with 7.9 per 100,000 person-years).[80] Earlier research on racial disparities in cancer of the cervix mortality have pointed out that the higher death rate in African American women was due to an advanced clinical stage at presentation.[17,81] It has been suggested that the advanced stage at presentation and the higher death rate of African American women with cancer of the cervix is due to inadequate access to screening services and barriers to care. Similarly, when compared to white women, Chen et al found that African American women had notably lower percentages of early stage diagnoses of cervical cancer[17]. Furthermore, the percentage of cancer of the cervix cases diagnosed at the advanced stage for white

women reduced from 7.2% in 1976 to 5.5% in 1990.[19] However, from 1976 to 1990 the percentage for advanced diagnoses increased from 8.7% to 13.6%[19].

Several studies support the findings that African American women have a higher percentage of cancer of the cervix diagnosis at later stages[18,82-85]. Across the different ethnic/racial groups, there are differences regarding the stage of the cancer at diagnosis. Advanced clinical stage at presentation could provide an explanation as to why death rates don't often parallel to the rate of incidence of cancer of the cervix.

The average yearly cancer of the cervix death rate between 2000 and 2004 for African American women was twice as large for white women with cervical cancer (2.2 deaths per 100,000).[69] Additionally, studies have shown that African Americans women with cancer of the cervix have a five-year lower survival rate (56%) compared to non-Hispanic (68%) and Hispanic (71%) white women.[84]

Moreover, the population based study of ethnic and racial disparities in survival rate among patients with invasive cancer of the cervix conducted by Patel and others indicated that after adjusting for stage and age at diagnosis, histology, and cancer treatment (surgery, chemotheraphy, and radiation therapy) Hispanic Caucasian women were at 26% decreased risk of death from any cause (hazard ratio (HR) = 0.74, 95% confidence interval (CI): 0.66–0.83) and non-Hispanic African American women were at 19% increased risk of death (HR = 1.19, 95% CI:1.06–1.33) compared to non-Hispanic Caucasian women over the follow-up period.[84] Investigation of population based SEER data displayed large differences for women with invasive cancer of the cervix that correlated with their respective race/ethnicity was the conclusion made by the authors.

When put side by side to non-Hispanic African American or non-Hispanic Caucasian women, Hispanic Caucasian women in SEER had improved survival. [84]

In addition, the study by Alejandro Rauh-Hain and colleagues on the racial differences in cancer of the cervix survival over time which used the SEER Program data from 1985 to 2005 indicated that in comparison with whites, African American women had a hazard ratio (HR) of 1.41 (95% confidence interval 51.32-1.51) of cervical cancer mortality. After accounting for race, SEER registry, stage, age, histology, grade, treatment, and marital status, African American women had an HR of 1.13 (95% confidence interval51.05-1.22) of CC-related mortality. Furthermore, regulating for the same variables presented a significant difference in CC-specific mortality from 1985 to 1989 and 1990 to 1994, but not after 1995.[24]

Another important factor that was frequently mentioned in the literature as a major contributor to cervical cancer incidence and mortality disparities is socioeconomic status. A study conducted on widening socioeconomic differences in cancer of the cervix death among females in twenty-six states, using cervical cancer mortality data (1993-2005) from the National Vital Statistics System administered by the Centers for Disease Control and Prevention, National Center for Health Statistics found that decrease in death rate was greatest for the patients with the highest level of education (6.8% per year for African American women and 3.2% per year for Caucasian women). Therefore, the education disparity widened between the periods 1993 to 1995 and 2005 to 2007 from 3.8 (95% CI, 2.0-7.0) to 5.6 (95% CI, 3.1-10.0) for African Americans and from 3.1 (95% CI, 2.4-3.9) to 4.4 (95% CI, 3.5-5.6) for Caucasian.[86] Uninsured women experienced an increase in the risk of late-stage diagnosis over time versus privately insured women.

Eliminating socioeconomic status (SES) disparities would avert 74% of the deaths attributed to cancer of the cervix in 2007. The authors, therefore, concluded that SES disparities in cervical cancer mortality and the risk of late-stage diagnosis increased over time. Eliminating SES disparities may also have averted the deaths during 2006.[86]

Similarly, the study that involved analyzing population-based SEER incidence and U.S. mortality data between 1975 and 2000 has displayed significant socioeconomic disparities in cancer of the cervix, that have continued to remain as the rates of mortality and incidence continue to reduce. Although the magnitude of the association varied by ethnicity, the large association between lower SES and higher mortality and incidence rates and lower likelihoods of survival and early-stage diagnoses was generally observed for each racial/ethnic group.[30] These patterns are in line with the literature.[87-97]

The study conducted by Odekunle on racial and socioeconomic disparities in cervical cancer mortality indicated that the Black race (3.0%) had the highest death rate followed by Native Americans (1.5%) and White (1.4%) races while the Asian or Pacific Islanders race (1.1%) had the lowest death rate. The chi-squared test showed statistically significant ($x^2 = 23.067$ and $P = 0.000$) racial differences in those who died during hospitalization at alpha ($P < 0.05$).[3] In terms of median household income levels; the mortality rate distribution showed that the lowest income category (median household income less than $39,000) had the highest death rate (2.0%) while the highest income category (median household income equal or greater than $63,000) recorded as having the lowest death rate (1.3%). The chi-squared test indicated that there was statistically significant ($x^2 = 17.26$ and $P = 0.001$) income differences in died during hospitalization.[3]

CHAPTER III

RESEARCH METHODOLOGY

3.1 Overview

The following section presents a detailed description of the methodology employed for the study on the association of genetic alterations (mutations and CNAs) with cervical cancer mortality, tumor recurrence, and racial differences. This study made use of the TCGA (The Cancer Genome Atlas) database.

3.2 The Cancer Genome Atlas Dataset

The TCGA database is a publicly available database that was created by a joint effort between the National Cancer Institute and the National Human Genome Research Institute. The TCGA database has comprehensive key genomic changes in 33 types of malignancy, including cervical cancer.[98] The TCGA cervical cancer (TCGA CESC) data were accessed. The two CESC genomic profiles used were mutation data from whole exome sequencing and putative copy-number alteration data from GISTIC 2.0. The clinical variables used were: disease status, patient's vital status, cervical cancer type detailed, clinical stage, diagnosis age, lymphovascular involvement, and race category (see table 4). The CESC clinical and genomic profiles were submitted to the TCGA between 2011 and 2014. These were accessed through the cBioPortal for Cancer Genomics analytic tool.

The cBioPortal is an open-access analytic tool that allows visualization, downloading, and analyzing of TCGA datasets.[99,100] The SPSS statistical software and

Excel were also utilized for the analysis. The Fisher's exact test was used to test for associations between the categorical variable, race, and gene mutation status as well as gene amplification status. Logistic regression analysis was used to quantify the strength of associations. Binary logistic regression model was adopted to examine the association of identified genetic (PIK3CA and PTEN) alterations with racial groups, cervical cancer mortality, and tumor recurrence. Multivariable logistic regression was performed to the test effects of stage, diagnosis age, and race on the presence of PIK3CA-PTEN genetic alterations. Statistical significance was defined as $P < 0.05$.

3.3 Logistic regression analysis

Block 0 (beginning block/step 0) means only constant is in the model and our predictions are not in the equation yet.

Block 1 (step 1) indicates that our predictors are entered the model simultaneously. The method used is Enter.

3.3.1 Variables in the equation

1. Wald Test: It tests the effect of individual predictor while controlling other predictors

2. "Sig" is the significance level of the coefficient: "

3. Exp(B) is the "odds ratio (OR)" of the individual coefficient.

3.4. Interpretation of 95% Confidence Interval of OR (Exp(B))

- An Odds Ratio= 1 indicates 'no association' between the exposure and the outcome or disease. [101]

- If the 95% confidence interval for the OR does not contain 1.0 we can conclude that there is a statistically significant association between the exposure and the outcome or disease.
- If the 95% confidence interval for the OR contains 1.0, the association is not significant at the 0.05 level. [101]

Table 3: TCGA Data Variables Used for Analysis:

Study Variables	Original Variable Name in the TCGA Data Set	Variable Description
Patient's Vital Status	Patient's Vital Status	Dead Alive Categorical (binary) Variable
Disease Status	Disease Status	Recurred/Progressed Disease Free Categorical (binary) Variable
Race Category	Race Category	White Black or African American American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Asian N/A (not available) Categorical Variable
PIK3CA Gene Mutation	PIK3CA Gene Mutation	Present Absent Categorical Variable
PIK3CA Gene CNA	PIK3CA Gene CNA	Present

		Absent Categorical Variable
PTEN Gene Mutation	PTEN Gene Mutation	Present Absent Categorical Variable
PTEN Gene CNA	PTEN Gene CNA	Present Absent Categorical Variable
MECOM Gene Mutation	MECOM Gene Mutation	Present Absent Categorical Variable
MECOM Gene CNA	MECOM Gene CNA	Present Absent Categorical Variable
TP63 Gene Mutation	TP63 Gene Mutation	Present Absent Categorical Variable
TP63 Gene CNA	TP63 Gene CNA	Present Absent Categorical Variable
Cervical Cancer Type Detailed	Cervical Cancer Type Detailed	Cervical Squamous Cell Carcinoma Endocervical Adenocarcinnma Mucinous Carcinoma Cervical Adenoquamous Carcinoma Endometrioid Carrcinoma
Clinical stage	Clinical Stage	Stage l Stage ll

		Stage lll Stage 1V
Diagnosis Age	Diagnosis Age	1<20 ll= 20-34 lll=35-44 lV=55-64 V=55-64 Vl>6

Inclusion criteria for PIK3CA and PTEN genes:

- Mutations involving PIK3CA, PTEN, or both genes
- CNAs involving PIK3CA, PTEN, or both genes excluding amplification in PTEN gene

CHAPTER IV

RESULTS

4.1 Overview

The following section presents the findings from the analysis of data from the TCGA CESC dataset for 2011, 2012, 2013, and 2014. This section is divided into five subsections. These include: the TCGA CESC summary findings, findings from mutation profiled data, findings from copy number alteration data, measure of associations, and multivariable analysis.

4.2 Descriptive Findings from TCGA Dataset

Table 4a: Sample distribution summary

Cancer Study	All Cases	Cases with Mutation Data	Cases with Copy Number Alteration Data
Cervical Cancer	309	194	295

Table 4a shows a sample distribution summary. There were 309 cervical cancer cases. Mutation analysis was done in 194 cases and copy number alteration analysis was done in 295 cases.

Figure 13: Number of samples with/without gene mutations data.

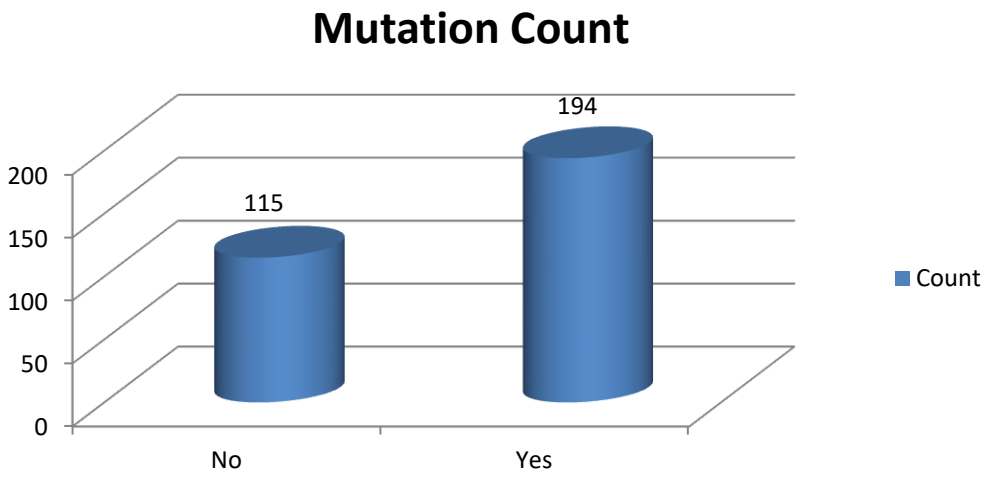


Figure 13 shows the number of samples with/without gene mutations. There were 194 samples with gene mutations and 115 samples without gene mutations.

Figure 14: **Number of samples with/without gene copy number variations data**.

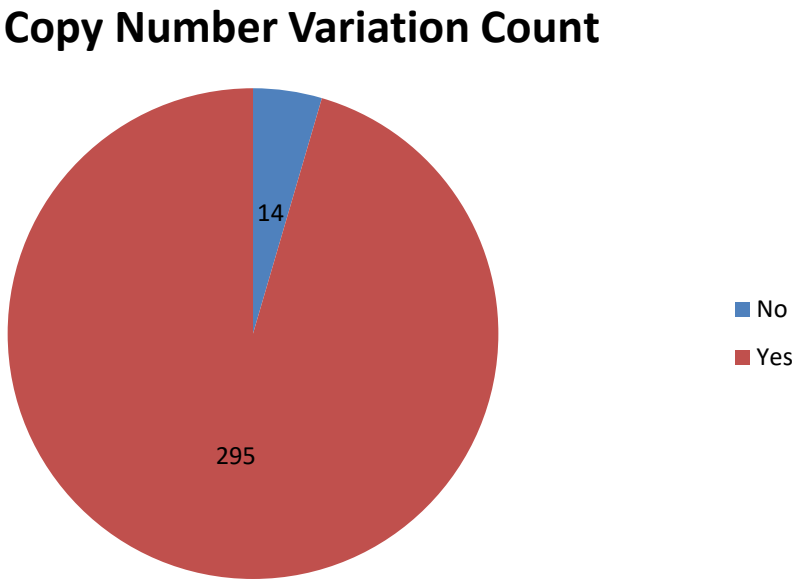


Figure 14 shows the number of samples with/without gene copy number variations. There were 295 samples with gene copy number variations and 14 samples without gene copy number variations.

Figure 15 Sample Distributions by Race.

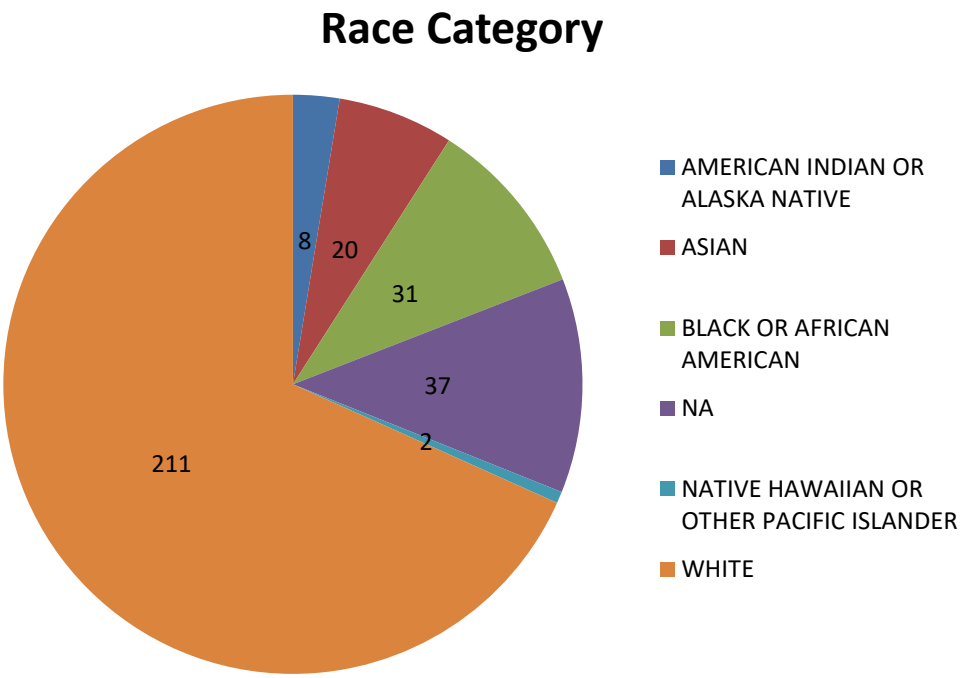


Figure 15 shows the sample distribution by race. White has the highest number of samples (211), followed by the N/A (not available) group (37), Black or African American (31), Asian (20), American Indian or Alaska native (8) while native Hawaiian or other Pacific Islander close off with having the lowest number of samples.

Figure 16: Total Sample Distribution by Patient's Vital Status

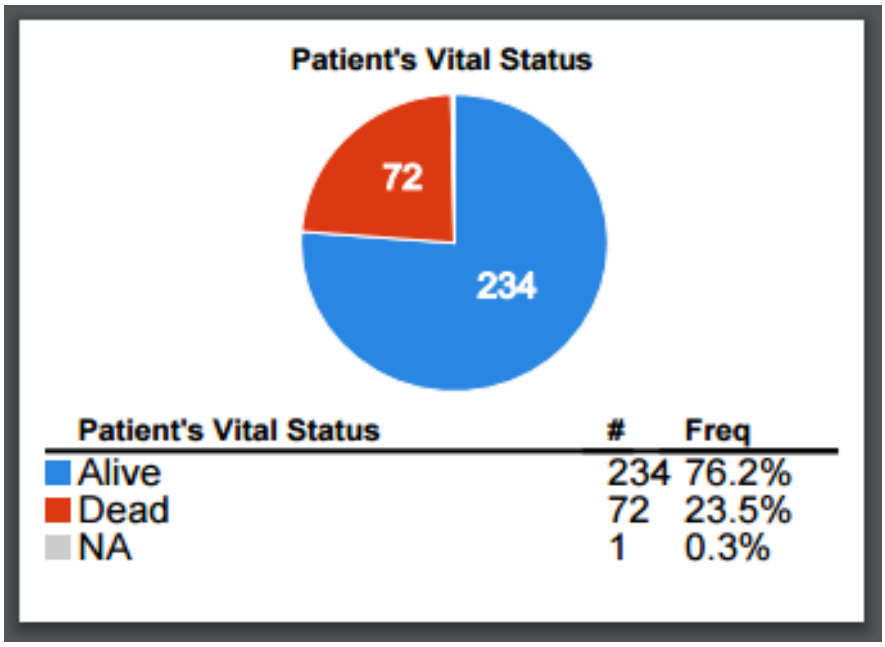


Figure 16 shows the total sample distribution by patient's vital status. 234 patients with cervical cancer were alive while 72 out of the 309 patients died.

Figure 17: Total Sample Distribution by Disease Free Status

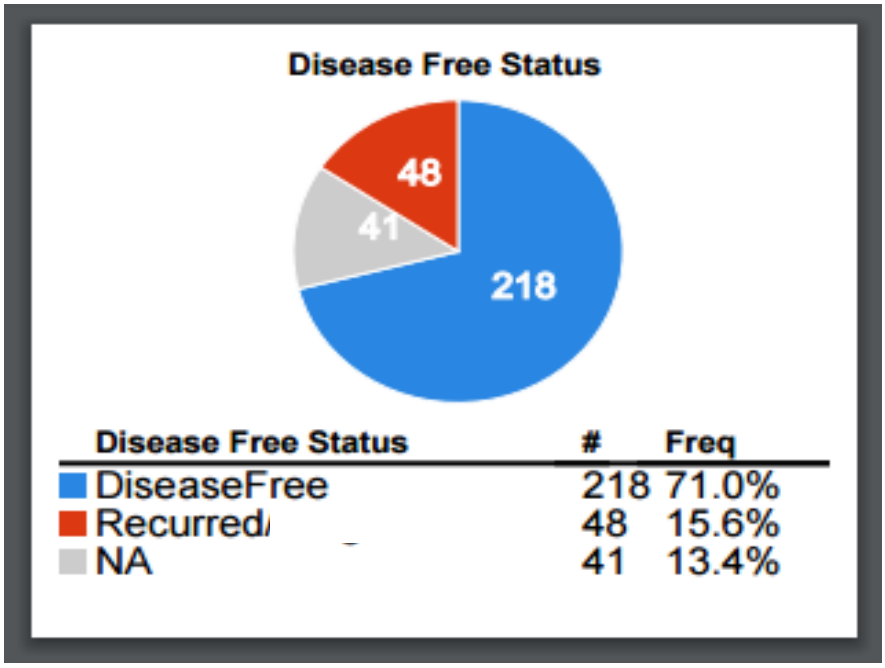


Figure 17 shows the total sample distribution by disease free status. 218 patients with cervical cancer were disease free while 48 out of the 309 patients had tumor recurrence.

Figure 17a: Age at Diagnosis

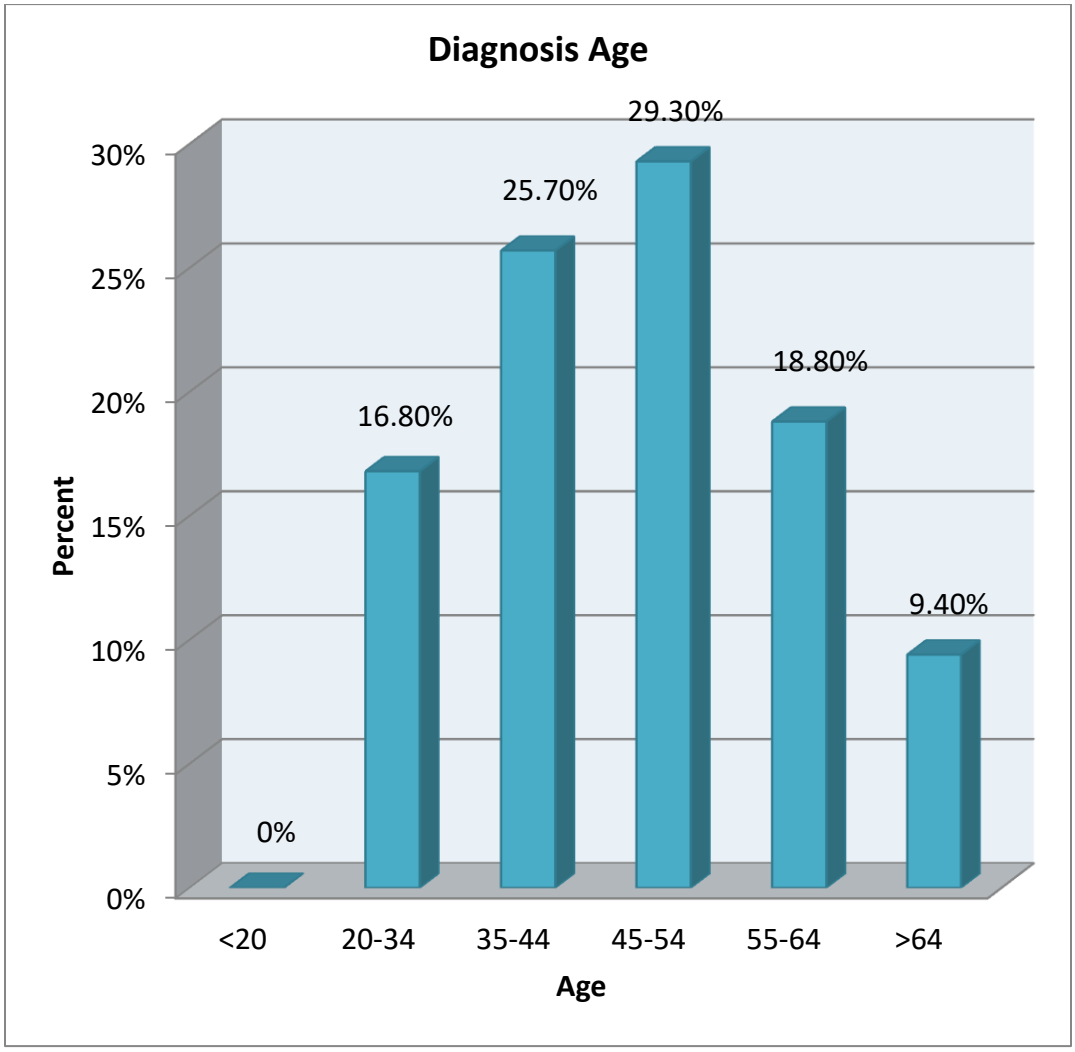


Figure 17a shows that 29.30% of patients were diagnosed between the ages 45 and 54. 25.70% of patients were diagnosed between the ages 35 and 44 and 18.80% were diagnosed between the ages 55 and 64. 16.80% of patients were diagnosed between the ages 20 and 34 and 9.40% of patients were diagnosed above the age of 64. No patients were diagnosed under the age of 20.

Figure 17b: International Classification of Diseases (ICD) for Oncology.

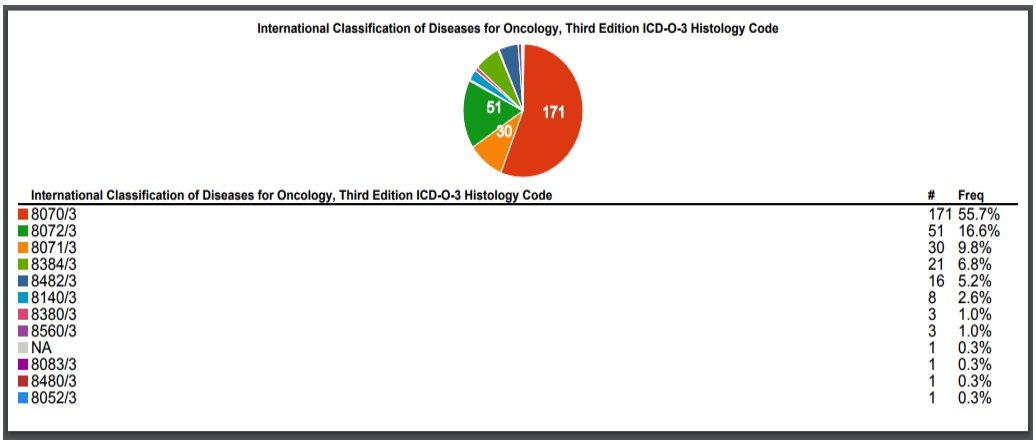


Figure 17b shows that most cervical cancer cases have ICD code classification 8070/3 which is 55.7% of the cases followed by classification 8072/3 accounting for 16.6%, 8071/3 with 9.8% and 8384/3 with the fourth most cases with 6.8% of cervical cancer cases.

Table 4b: Cervical Cancer Clinical Stage

Clinical Staging			
	Frequency	**Percent**	**Cumulative Percent**
Stage I	116	60.7	60.7
Stage II	34	17.8	78.5
Stage III	30	15.7	94.2
Stage IV	11	5.8	100.0

Table 4b shows that most of the cervical cancer cases were Stage I which accounted for 60.7% of the cases followed by Stage II accounting for 17.8%, Stage III with 15.7% and Stage IV accounting for 5.8% of the cervical cancer cases..

Figure 18: Cervical Cancer Histological Type

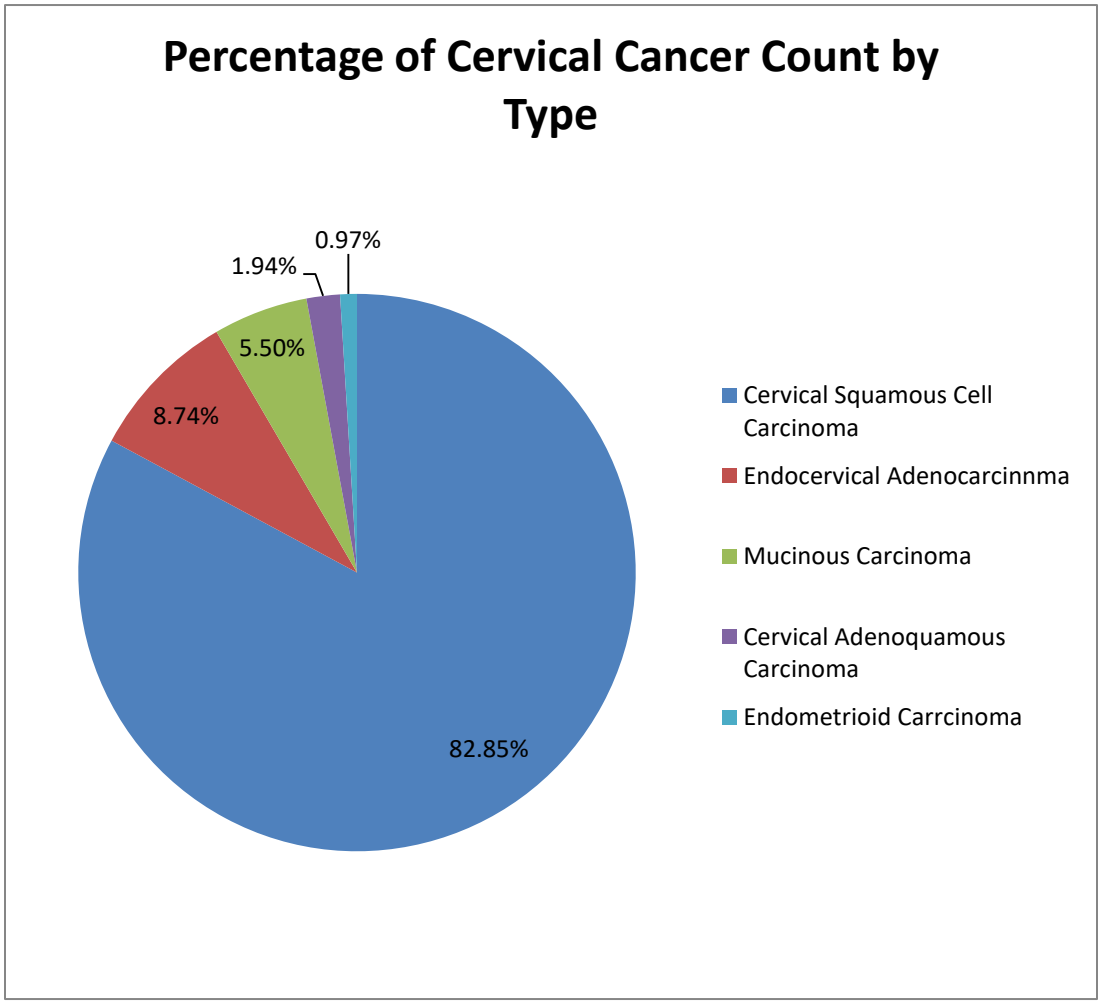


Figure 18 shows the distributions of cervical cancer type. Cervical squamous cell carcinoma was the commonest cervical cancer type (82.85%), followed by Endocervical Adenocarcinma (8.74%), Mucinous Carcinoma (5.5%), Cervical Adenoquamous Carcinoma (1.94%), and Endometrioid carcinoma (0.97%).

4.3 Findings from Mutation Profiled Samples

The top eleven mutated genes in the TCGA dataset were PIK3CA, MUC4, KMT2C, SYNE1, KMT2D, EP300, RYR2, FLG, DMD, and FBXW7, and PTEN. Appendix 1 shows the list of genes with at least 8 mutations. Table 5 shows the top eleven mutated genes in 194 profiled samples. Table 5 was compared with the list of genes in appendices 2 to 5 to identify tumor suppressor genes and oncogenes. The PIK3CA gene has the highest numbers of mutations with 53 mutation counts and 23.7% frequency. The PTEN gene, the eleventh frequent mutated gene has 15 mutation counts and 7.7 % frequency.

Table 5: Top eleven mutated genes in 194 profiled samples

TOP ELEVEN MUTATED GENES IN 194 PROFILED SAMPLES								
GENE SYMBOL	MUTATION COUNT	FREQUENCY N=194	AFRICAN AMERICAN N=16		WHITE N=138		OTHER N=40	
			COUNT	FREQUENCY	COUNT	FREQUENCY	COUNT	FREQUENCY
PIK3CA	53	27.3%	6	37.50%	35	25.36%	12	30.00%
MUC4	37	19.1%	4	25.00%	23	16.67%	10	25.00%
KMT2C	29	14.9%	2	12.50%	20	14.49%	7	17.50%
SYNE1	23	11.9%	2	12.50%	11	7.97%	10	25.00%
KMT2D	22	11.3%	2	12.50%	14	10.14%	6	15.00%
EP300	21	10.8%	3	18.75%	17	12.32%	1	2.50%
RYR2	21	10.8%	1	6.25%	17	12.32%	3	7.50%
FLG	20	10.3%	2	12.50%	11	7.97%	7	17.50%
DMD	20	10.3%	1	6.25%	14	10.14%	5	12.50%
FBXW7	19	9.8%	1	6.25%	13	9.42%	5	12.50%
PTEN	15	8.0%	3	18.75%	11	7.97%	1	2.50%

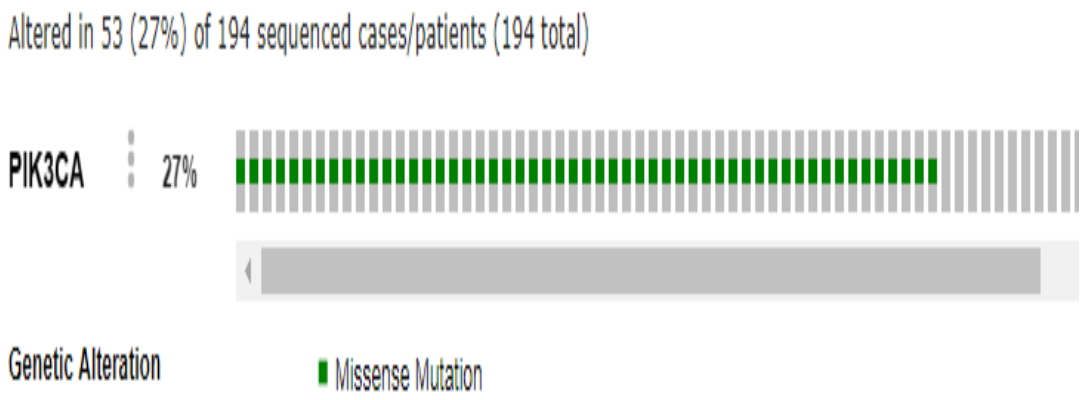
PIK3CA and PTEN genes are identified as the most common oncogene and tumor suppressor genes respectively. Many of the PIK3CA mutations were known have an oncogenic effect (i.e. the mutated PIK3CA proteins have increased catalytic activity resulting in enhanced downstream signaling and oncogenic transformation). Table 6 shows the different types of PIK3CA mutations in the dataset. The two most common PIK3CA missense mutations in the dataset are E545K (E545K mutation results in an amino acid substitution at position 545 in PIK3CA, from a glutamic acid (E) to a lysine (K)) and E542K (E542K mutation results in an amino acid substitution at position 542 in PIK3CA, from a glutamic acid (E) to a lysine (K)).

Table 6: Type of Genetic Alterations across All 53 Cases with PIK3CA Gene Mutations:

	Case ID	PIK3CA: MUTATION (AA CHANGE)	CLINICAL IMPLICATION	BIOLOGICAL EFFECT
1.	TCGA-C5-A1BE-01	MUT: E726K;	ONCOGENIC	GAIN-OF FUNCTION
2.	TCGA-C5-A1BJ-01	MUT: E600K,E545Q;	ONCOGENIC	GAIN-OF-FUNCTION
3.	TCGA-C5-A1BM-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
4.	TCGA-C5-A1BQ-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
5.	TCGA-C5-A1MH-01	MUT: E545K,E726K;	ONCOGENIC	GAIN-OF-FUNCTION
6.	TCGA-C5-A1MK-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
7.	TCGA-C5-A1ML-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
8.	TCGA-C5-A2M1-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
9.	TCGA-C5-A3HE-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
10.	TCGA-C5-A7CJ-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
11.	TCGA-C5-A7CO-01	MUT: E81K;	ONCOGENIC	GAIN-OF-FUNCTION
12.	TCGA-C5-A7UH-01	MUT: R93W;	ONCOGENIC	GAIN-OF-FUNCTION
13.	TCGA-DG-A2KK-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
14.	TCGA-DG-A2KL-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
15.	TCGA-DS-A5RQ-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
16.	TCGA-DS-A7WF-01	MUT: H1047Q;	ONCOGENIC	GAIN-OF-FUNCTION
17.	TCGA-EA-A3HT-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
18.	TCGA-EA-A3QE-01	MUT: H1047R;	ONCOGENIC	GAIN-OF-FUNCTION
19.	TCGA-EA-A4BA-01	MUT: K111E;	ONCOGENIC	GAIN-OF-FUNCTION
20.	TCGA-EA-A50E-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION

21.	TCGA-EA-A5FO-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
22.	TCGA-EK-A2PG-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
23.	TCGA-EK-A2PM-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
24.	TCGA-EK-A2RD-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
25.	TCGA-EK-A2RN-01	MUT: E545K,E726K;	ONCOGENIC	GAIN-OF-FUNCTION
26.	TCGA-EK-A2RO-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
27.	TCGA-EK-A3GJ-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
28.	TCGA-EK-A3GM-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
29.	TCGA-FU-A23K-01	MUT: V344G;	INCONCLUSIVE	INCONCLUSIVE
30.	TCGA-FU-A3HY-01	MUT: H1047L;	ONCOGENIC	GAIN-OF-FUNCTION
31.	TCGA-FU-A3HZ-01	MUT: L339I;	UNKNOWN	UNKNOWN
32.	TCGA-FU-A3WB-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
33.	TCGA-FU-A57G-01	MUT: Q546R;	ONCOGENIC	GAIN-OF-FUNCTION
34.	TCGA-HG-A2PA-01	MUT: G106V;	ONCOGENIC	GAIN-OF-FUNCTION
35.	TCGA-IR-A3LF-01	MUT: E542K,G1007R;	ONCOGENIC	GAIN-OF-FUNCTION
36.	TCGA-IR-A3LH-01	MUT: C90R;	UNKNOWN	UNKNOWN
37.	TCGA-IR-A3LI-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
38.	TCGA-IR-A3LK-01	MUT: Q75E;	UNKNOWN	UNKNOWN
39.	TCGA-JW-A5VH-01	MUT: R38H;	ONCOGENIC	GAIN-OF-FUNCTION
40.	TCGA-JW-A5VJ-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
41.	TCGA-JW-A5VL-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
42.	TCGA-JW-A69B-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
43.	TCGA-JW-A852-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
44.	TCGA-JX-A3Q0-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
45.	TCGA-LP-A4AV-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
46.	TCGA-LP-A7HU-01	MUT: E542K,E545K;	ONCOGENIC	GAIN-OF-FUNCTION
47.	TCGA-MY-A5BD-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
48.	TCGA-MY-A5BE-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
49.	TCGA-Q1-A5R1-01	MUT: E545K;	ONCOGENIC	GAIN-OF-FUNCTION
50.	TCGA-Q1-A5R3-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
51.	TCGA-Q1-A6DV-01	MUT: G118D;	ONCOGENIC	GAIN-OF-FUNCTION
52.	TCGA-Q1-A73P-01	MUT: E542K;	ONCOGENIC	GAIN-OF-FUNCTION
53.	TCGA-R2-A69V-01	MUT: A399T;	UNKNOWN	UNKNOWN

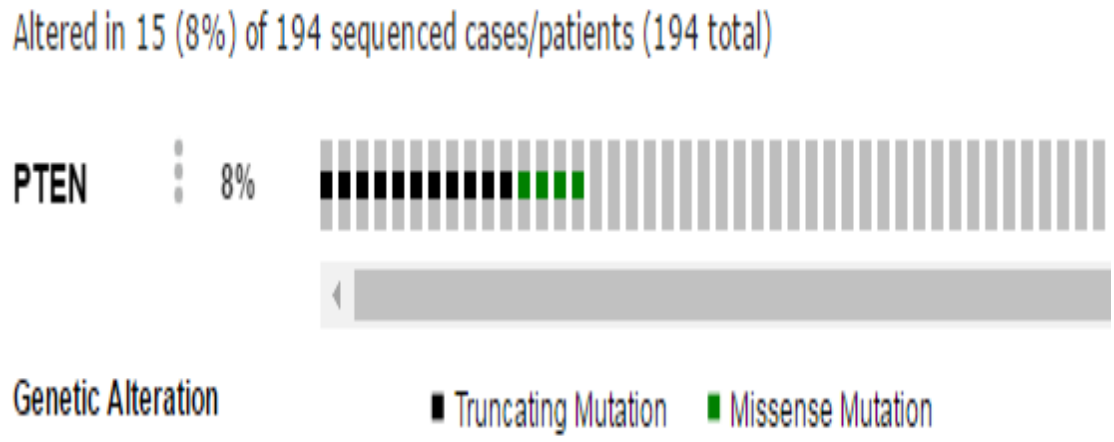
Figure 19: PIK3CA gene mutations by type



Adapted from cBioportal for Cancer Genomics [99, 100]

Figure 19 shows that the 53 PIK3CA gene mutations were all missense point mutations

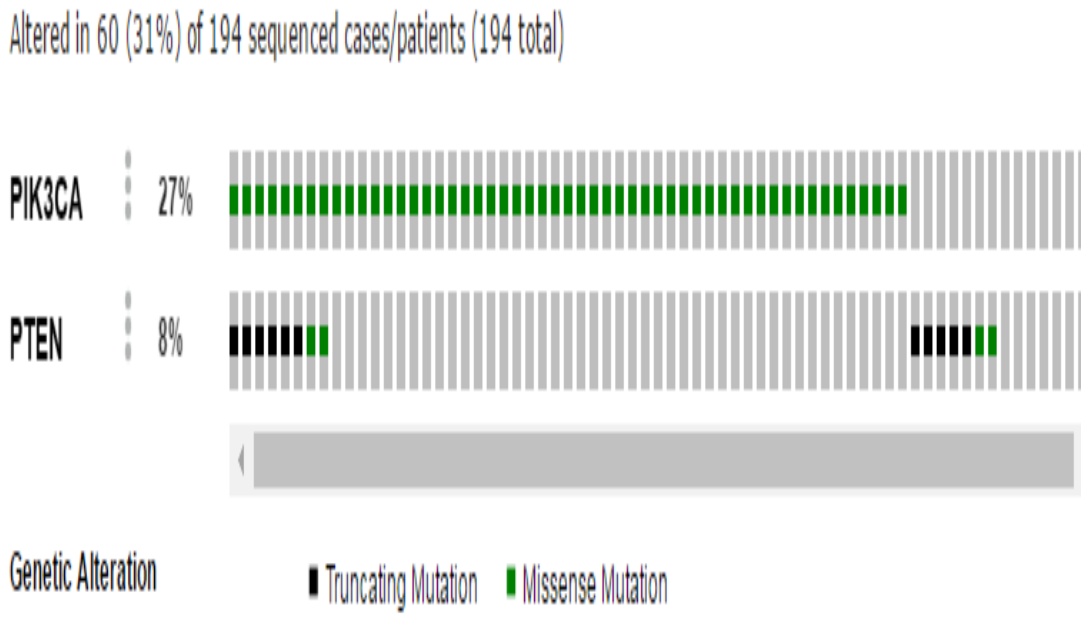
Figure 20: PTEN gene mutations by type



Adapted from cBioportal for Cancer Genomics [99, 100]

Figure 20 shows that the PTEN gene mutations were both missense and nonsense (truncating) types

Figure 21: PIK3CA and PTEN mutations by type



Adapted from cBioportal for Cancer Genomics [99, 100]

Figure 21 shows the different types of PIK3CA and PTEN mutations in the TCGA CESC dataset. PTEN gene mutations were both missense and nonsense types while the PIK3CA gene mutations were only in missense form.

Table 7: Type of Genetic Alterations across all 15 Cases with PTEN Gene Mutations

	Case ID	PTEN: MUTATION (AA CHANGE)	TYPE OF MUTATIONS	CLINICAL IMPLICATION	BIOLOGIC EFFECT
1.	TCGA-BI-A0VR-01	MUT: Q214*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
2.	TCGA-C5-A1BM-01	MUT: Y65*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
3.	TCGA-C5-A1BQ-01	MUT: Q171*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
4.	TCGA-C5-A3HL-01	MUT: N323K*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
5.	TCGA-C5-A7CL-01	MUT: S229*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
6.	TCGA-EA-A4BA-01	MUT: R130Q	MISSENSE	ONCOGENIC	LOSS-OF-FUNCTION
7.	TCGA-EA-A556-01	MUT: Y68I*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
8.	TCGA-EA-A5FO-01	MUT: R233*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
9.	TCGA-EK-A2PM-01	MUT: X343*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
10.	TCGA-EK-A2RK-01	MUT: D252N, D312N	MISSENSE	ONCOGENIC	LOSS-OF-FUNCTION
11.	TCGA-FU-A23K-01	MUT: X212*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
12.	TCGA-FU-A3HZ-01	MUT: R130Q, L325F	MISSENSE	ONCOGENIC	LOSS-OF-FUNCTION
13.	TCGA-FU-A3TQ-01	MUT: R15*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
14.	TCGA-JW-A5VH-01	MUT: X85*	NONSENSE	ONCOGENIC	LOSS-OF-FUNCTION
15.	TCGA-Q1-A6DW-01	MUT: R130Q	MISSENSE	ONCOGENIC	LOSS-OF-FUNCTION

Table 7 shows the different types of PTEN mutations in the TCGA CESC dataset. All the fifteen PTEN gene mutations (missense and nonsense) were known to be oncogenic.

Figure 22: TP63 mutations by type

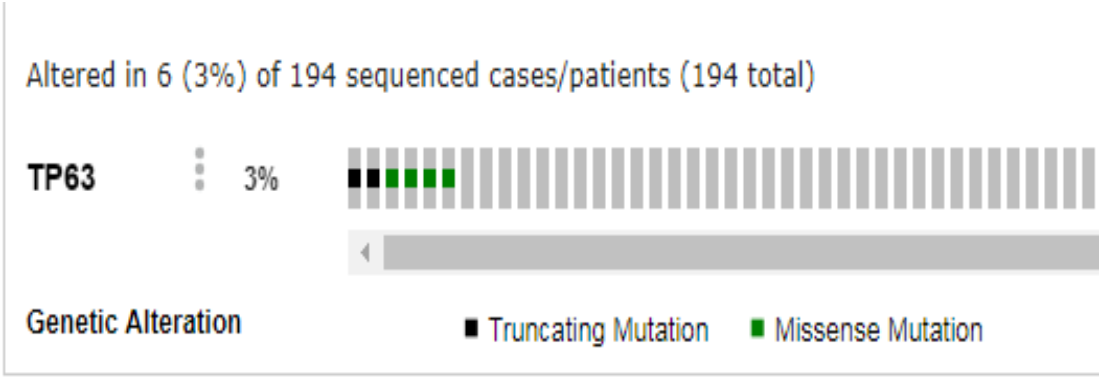


Figure 22 shows that the TP63 gene mutations were both missense and truncating types

Figure 22a: TP53 mutations by type

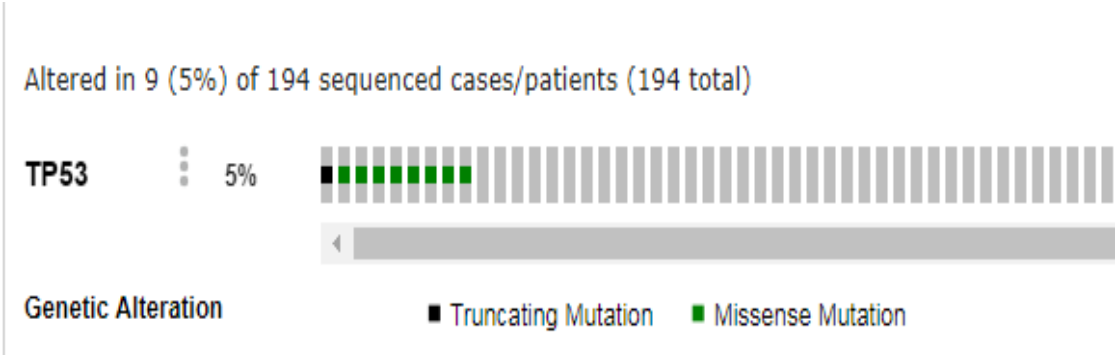


Figure 22a shows that the TP53 gene mutations were both missense and truncating types

Figure 22b: MECOM mutations by type

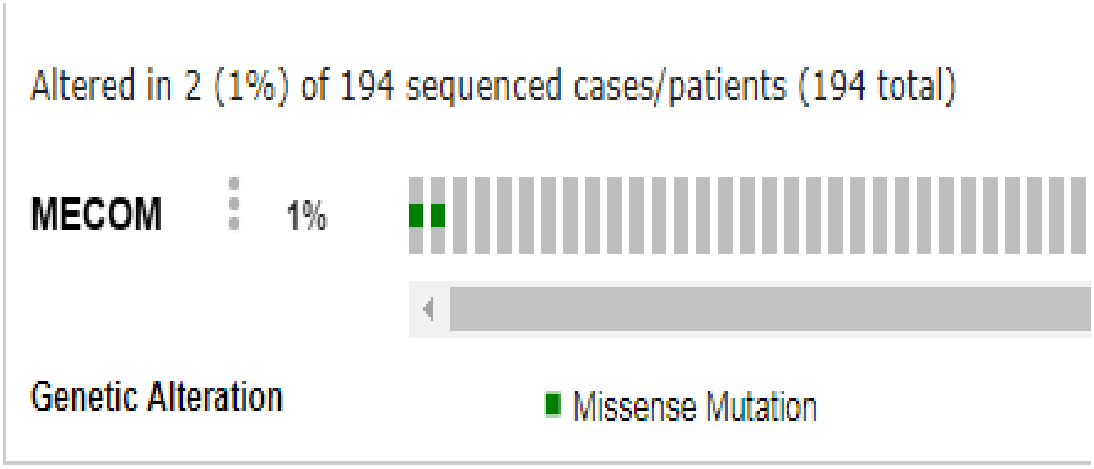


Figure 22b shows that the MECOM gene mutations were missense type

Figure 22c: PRKC1 mutations by type

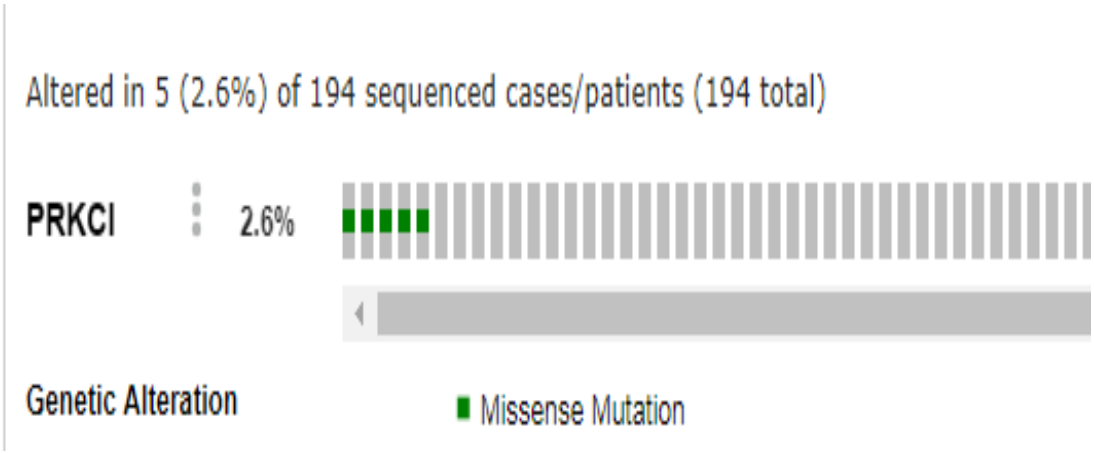


Figure 22c shows that the PRKC1 gene mutations were missense type

Figure 23: Mutation data distribution by patient's vital status

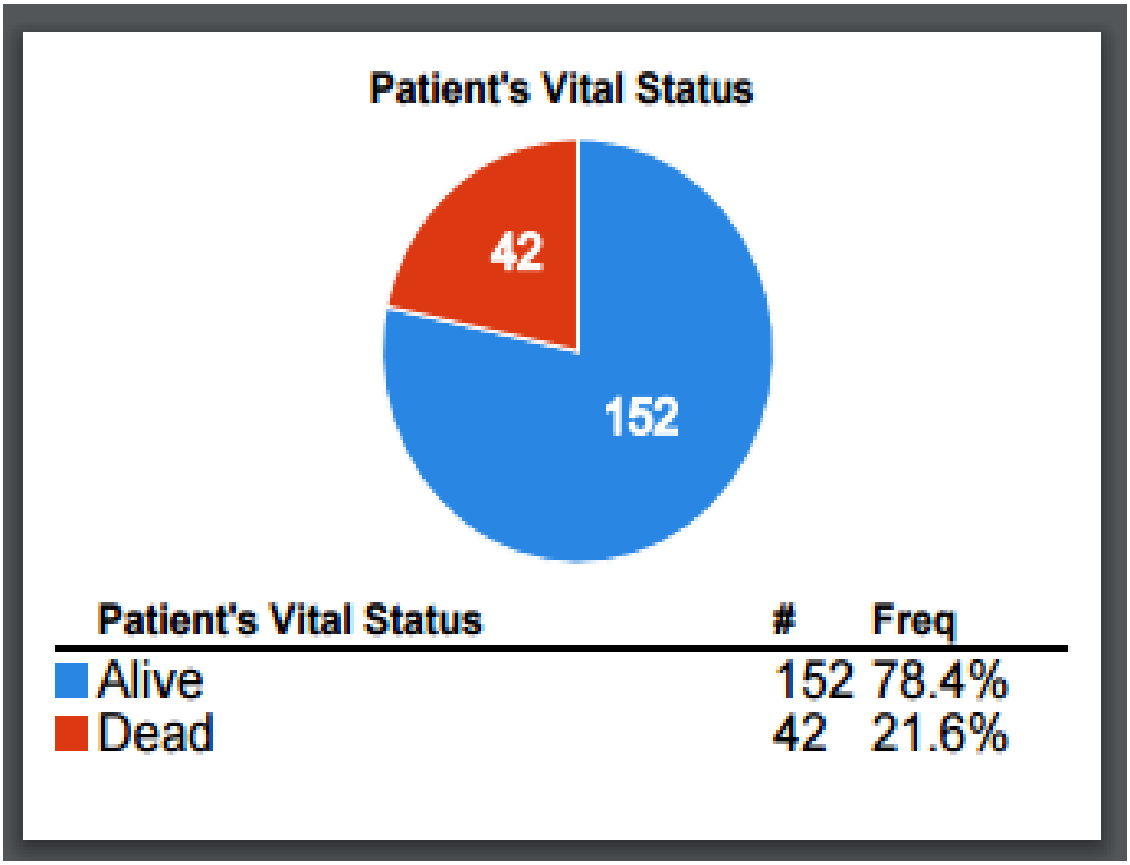


Figure 23 shows mutation data distribution by patient's vital status. There were 194 patients with mutation data, 152 (78.4%) patients were alive and 42 (21.6%) patients died.

Figure 24: Mutation data distribution by disease free status

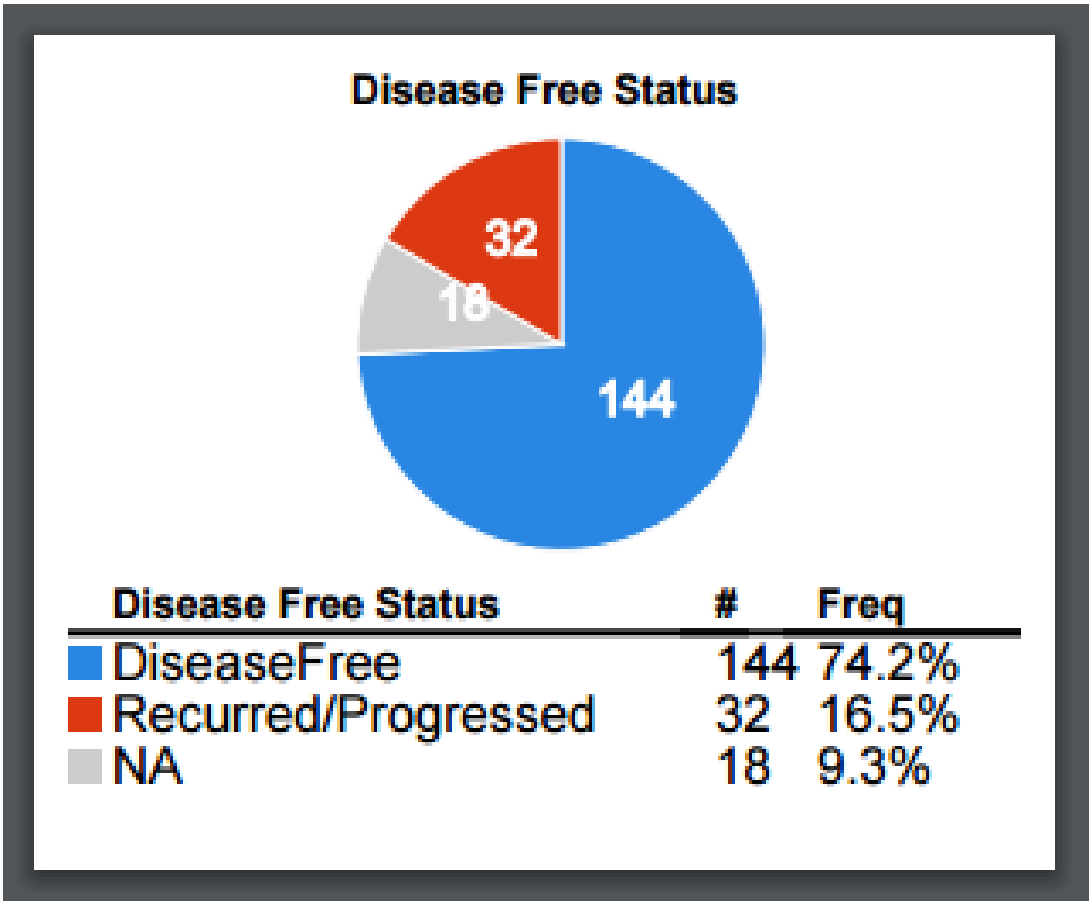


Figure 24 shows mutation data distribution by disease free status. There were 194 patients with mutation data, 144 (74.2%) patients were disease free and 32 (16.5%) had recurrence.

Table 8: PIK3CA gene mutation status by race

Race	PIK3CA Mutation Present		PIK3CA Mutation Absent		Total
	Count	%	Count	%	Sample Profile
White	35	25.4	103	74.6	138
Asian	4	21.1	15	78.9	19
Black or African American	6	37.5	10	62.5	16
American Indian or Alaska Native	5	62.5	3	37.5	8

Table 8 shows the comparison of PIK3CA gene mutation status by race. The racial group with the highest mutation rate was the American Indian or Alaska Native (62.5 %) followed by Black or African American (37.5 %), White (25.4 %), and Asian (21.1 %).

Table 9: PIK3CA-PTEN Mutation Status by Patient's Vital Status, Disease Status, and Race Category

	Patient's Vital Status				Disease Status				Race Category			
	Dead		Alive		Recurred		Free		Black		White	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
PIK3CA-PTEN Mutations Present	22	52	38	25	15	47	38	26	6	37	41	30
PIK3CA-PTEN Mutations Absent	20	48	114	75	17	53	106	74	10	63	97	70

Table 9 shows that 22 patients with PIK3CA-PTEN mutations died and 38 patients with PIK3CA mutation were alive. While 20 patients without PIK3CA-PTEN mutations died and 114 patients without PIK3CA mutation were alive. While 17 patients without PIK3CA-PTEN mutations had recurrence and 106 patients without PIK3CA-PTEN mutations were disease free.

4.4 Findings from Copy Number Alteration Profiled Samples

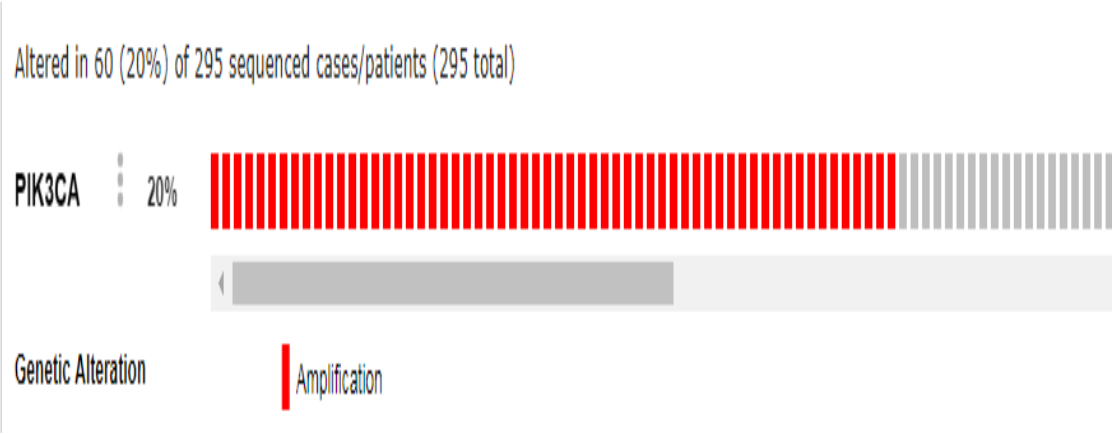
Table 10: Top Twelve Genes with CNA in 295 Profiled Samples

TOP TWELVE GENES WITH CNA IN 295 PROFILED SAMPLES										
GENE SYMBOL	CYTO-BAND	COU-NT	FREQ-UENCY N = 295	AFRICAN AMERICAN N = 28			WHITE N=201		OTHER N = 66	
				COUNT	FREQ-UENCY	CNA	COUNT	FREQ-UENCY	COUNT	FREQ-UENCY
TP63	3q28	62	21.0%	7	25.00%	AMP	39	19.40%	16	24.24%
MECOM	3q26.2	62	21.0%	8	28.57%	AMP	40	19.90%	14	21.21%
PIK3CA	3q26.3	60	20.3%	9	32.14%	AMP	38	18.91%	13	19.70%
PRKCI	3q26.3	60	20.3%	7	25.00%	AMP	39	19.40%	14	21.21%
TRFC	3q29	59	20.0%	7	25.00%	AMP	37	18.41%	15	22.73%
RPL35A	3q29	59	20.0%	7	25.00%	AMP	37	18.41%	15	22.73%
LPP	3q28	58	19.7%	7	25.00%	AMP	38	18.91%	13	19.70%
TBL1XR1	3q26.32	58	19.7%	7	25.00%	AMP	38	18.91%	13	19.70%
FGF12	3q28	57	19.3%	7	25.00%	AMP	37	18.41%	13	19.70%
SOX2	3q26.3	57	19.3%	7	25.00%	AMP	37	18.41%	13	19.70%
LIFR	5p13.1	18	6.1%	1	3.57%	AMP	13	6.47%	4	6.06%
PTEN	10q23.3	17	6.0%	5	17.86%	DEL	8	3.98%	4	6.06%

Table 10 shows the top twelve genes with CNA in 295 profiled samples. The top twelve genes with CNA in the TCGA dataset were TP63, MECOM, PIK3CA, PRKCI, TRFC, RPL35A, LPP, TBL, FGF12, SOX2, LIFR, and PTEN. Table 10 was compared with the list of genes in appendices 1 to 4 to identify tumor suppressor genes and oncogenes. The

PIK3CA gene had 60 counts and a 20.3% frequency and PTEN was deleted in 15 cases and amplified in 2. Appendix 6 shows the list of genes with at least 5 CNAs.

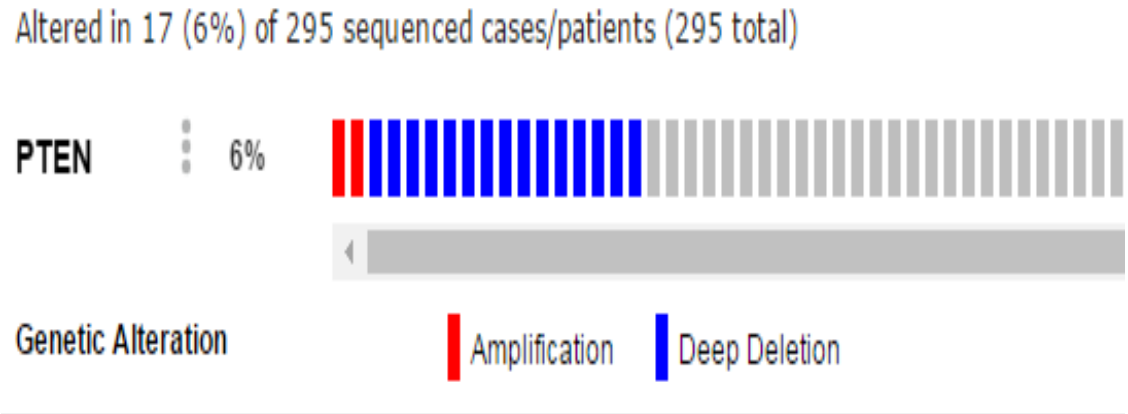
Figure 25: PIK3CA Copy Number Variations by type



Adapted from cBioportal for Cancer Genomics [99, 100]

Figure 25: shows that the 60 PIK3CA Copy Number Variations were all due to the amplification of PIK3CA gene. PIK3CA gene amplifications are known to have oncogenic effects.

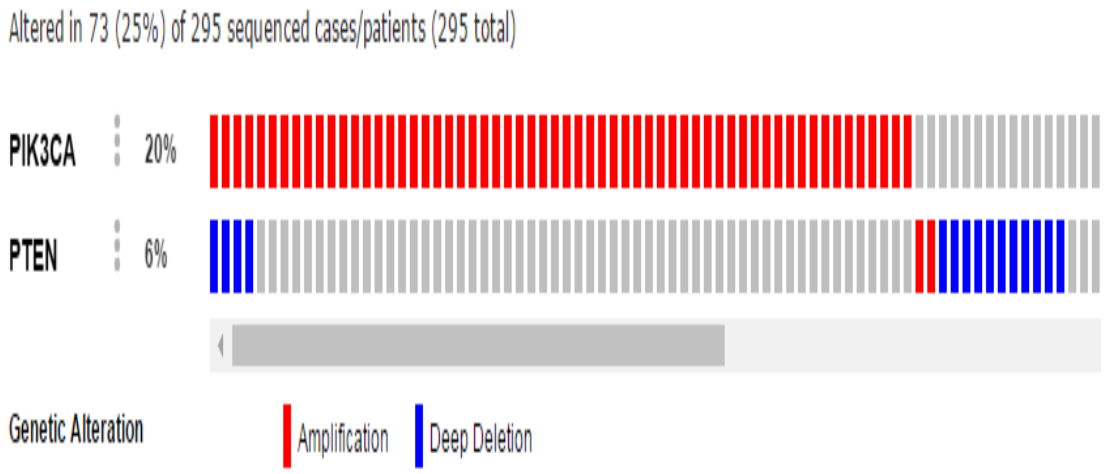
Figure 26: PTEN Copy Number Variations by type



Adapted from cBioportal for Cancer Genomics [99, 100]

Figure 26 shows the types of PTEN CNAs in the TCGA CESC dataset. 15 patients had PTEN deletion while 2 patients had amplified PTEN gene. PTEN gene deletions have been shown to have oncogenic effects.

Figure 27: PIK3CA and PTEN Copy Number Variations by type



Adapted from cBioportal for Cancer Genomics [99, 100]

Figure 27 shows the different types of PIK3CA and PTEN CNAs in the TCGA CESC dataset. PTEN gene CNAs were both amplification and deletion types while the PIK3CA gene CNAs were only in amplification form.

Figure 28: TP63 Copy Number Variations by type

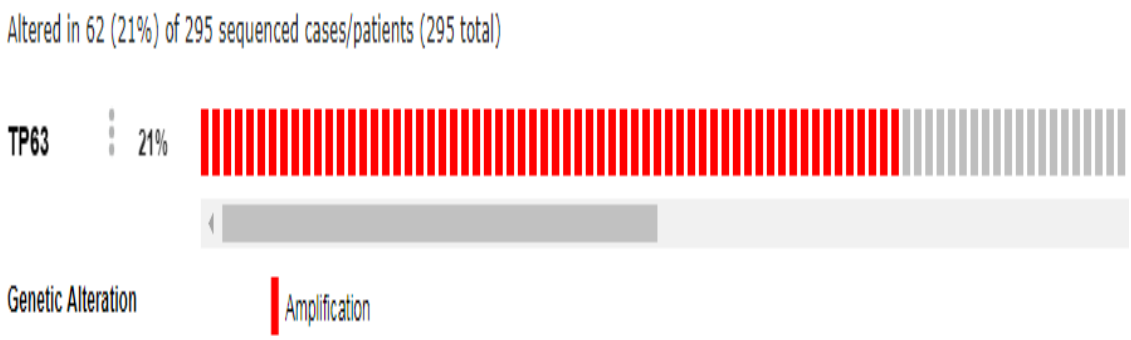


Figure 28: shows that the 62 TP63 Copy Number Variations were all due to the amplification

Figure 29: TP53 Copy Number Variations by type

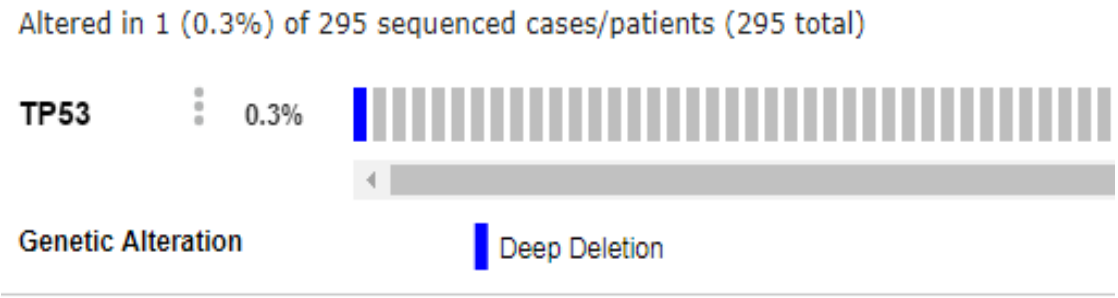


Figure 29 shows that the TP63 CNAs were due to deletion

Figure 29 a: MECOM Copy Number Variations by type

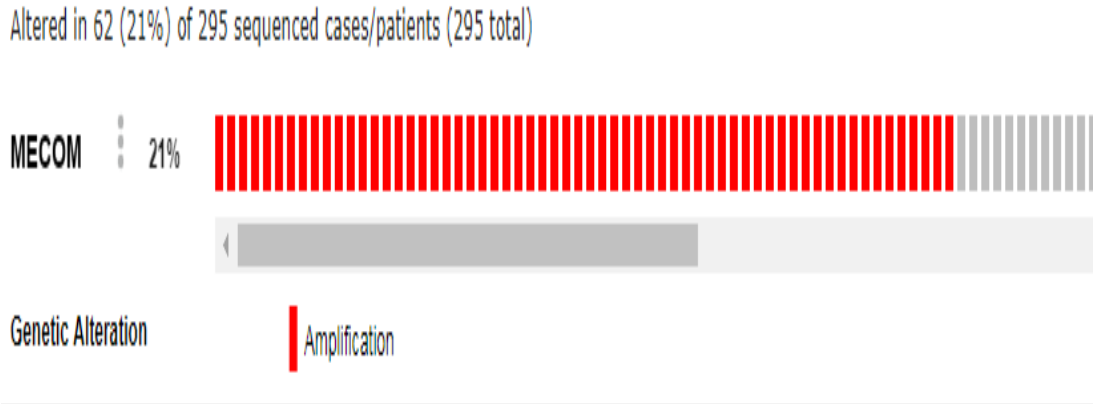


Figure 29a shows that the 62 MECOM CNAs were all due to the amplification

Figure 29b: PRKC1 Copy Number Variations by type

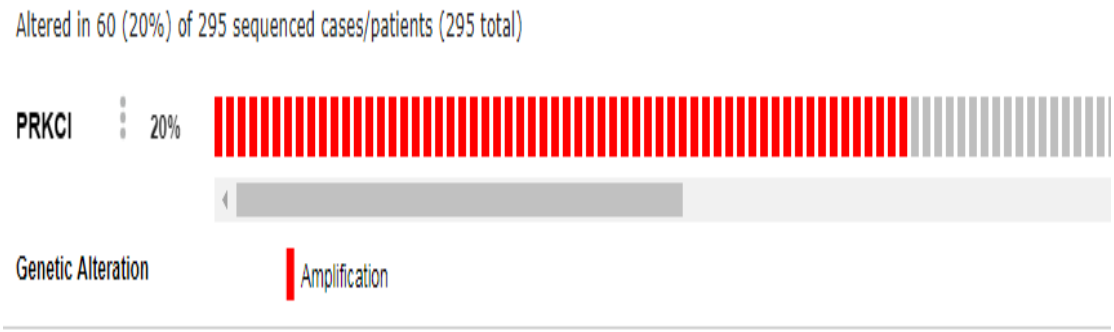


Figure 29b shows that the PRKC1 CNAs were due to the amplification

Figure 30: CNA data distribution by patient's vital status

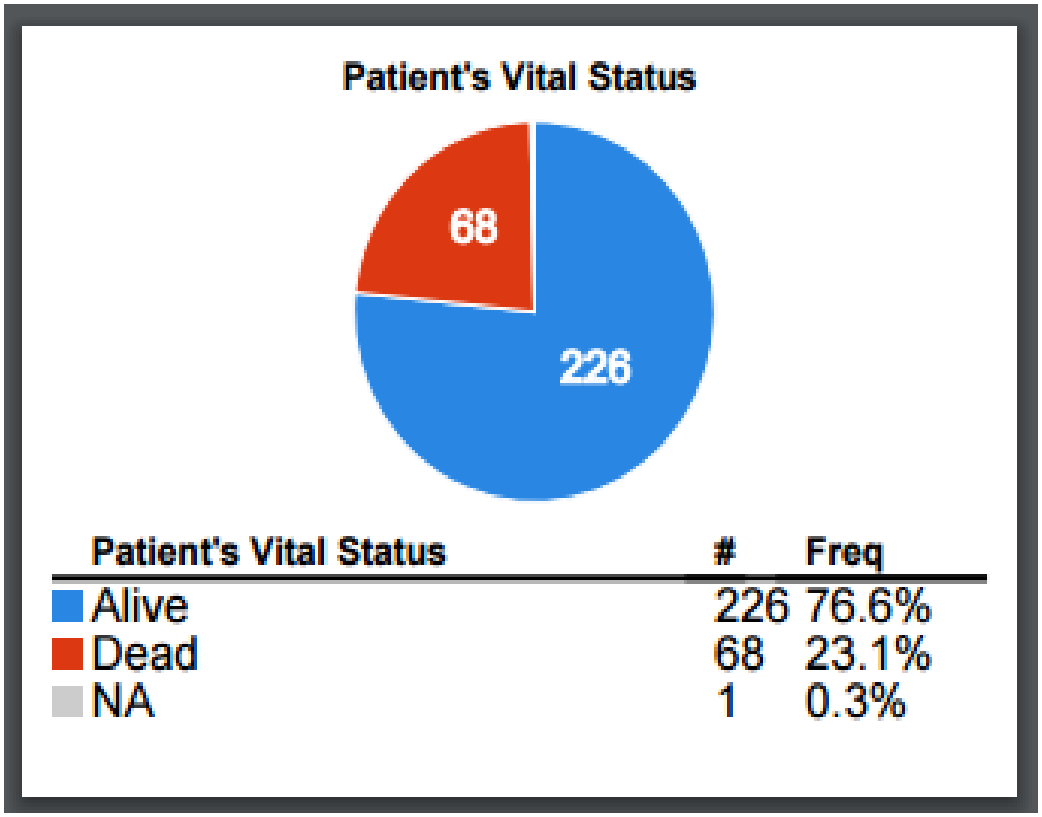


Figure 30 shows CNA data distribution by patient's vital status. There were 295 patients with CNA data, 226 (76.6%) patients were alive and 68 (23.1%) patients died.

Figure 31: CNA data distribution by disease free status

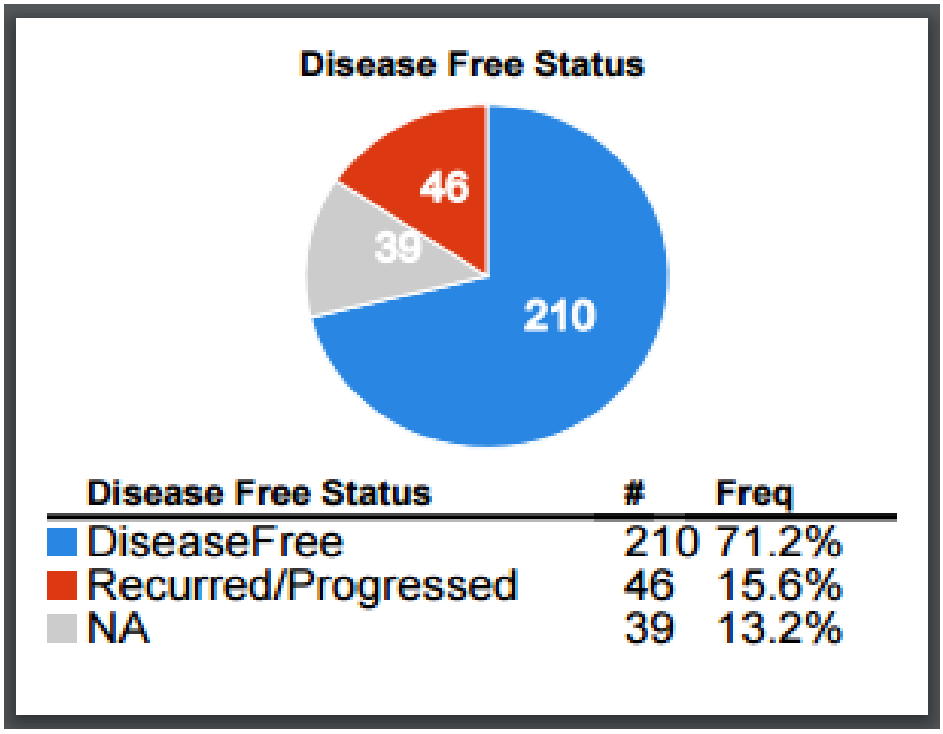


Figure 31 shows CNA data distribution by disease free status. There were 295 patients with CNA data, 210 (71.2%) patients were disease free and 46 (15.6%) patients had recurrence.

Table 11: Comparison of PIK3CA Gene amplification status by race

Race	PIK3CA Amplification Present		PIK3CA Amplification Absent		Total
	Count	%	Count	%	Profiled Samples
White	38	18.9	163	81.1	201
Asian	4	21.1	15	78.9	19
Black or African American	9	32.1	19	67.9	28
American Indian or Alaska Native	1	12.5	7	87.5	8

Table 11 shows the comparison of PIK3CA gene amplification status by race. The racial group with the highest rates of PIK3CA amplification was the Black or African American (32.1 %) followed by the Asian (21.1 %), White (18.9 %), and American Indian or Alaska Native (12.5%).

Figure 32: Comparison of PIK3CA gene amplification rates by race

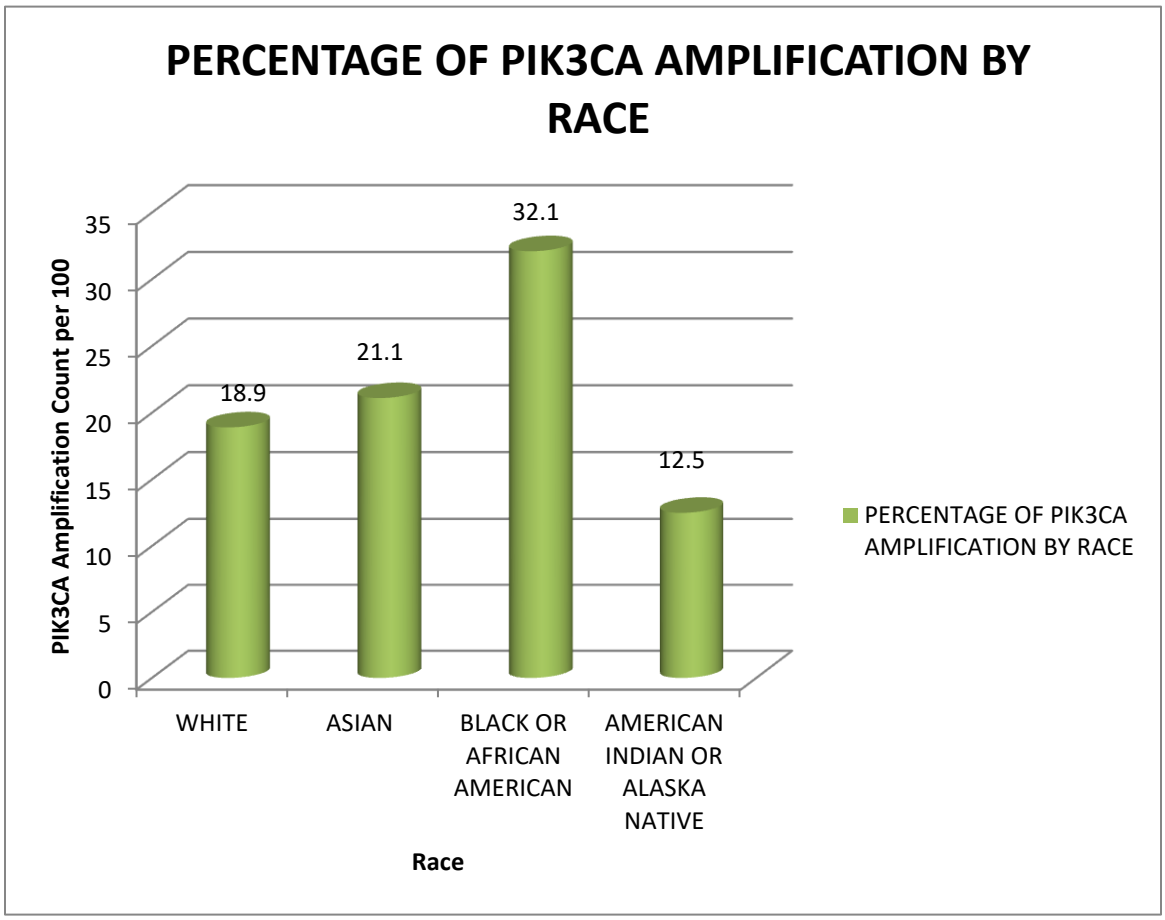


Figure 32 shows the comparison of PIK3CA gene amplification rates by race. The racial group with the highest rates of PIK3CA amplification was the Black or African American (32.1 %) followed by the Asian (21.1 %), White (18.9 %), and American Indian or Alaska Native (12.5%).

Table 12: PIK3CA-PTEN CNA Status by Patient's Vital Status, Disease Status, and Race Category

	Patient's Vital Status				Disease Status				Race Category			
	Dead		Alive		Recurred		Free		Black		White	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
PIK3CA-PTEN CNAs Present	25	37	46	20	20	43	51	24	11	39	43	21
PIK3CA-PTEN CNAs Absent	42	63	179	80	26	57	158	76	17	61	158	79

Table 12: shows that 25 patients with PIK3CA-PTEN CNAs died and 46 patients with PIK3CA-PTEN CNAs were alive. PIK3CA-PTEN CNA status by disease status findings revealed that 20 patients with PIK3CA-PTEN CNAs had tumor recurrence and 51 patients with PIK3CA-PTEN CNAs were disease free. 11 patients with PIK3CA-PTEN CNAs were African American women and 43 patients with PIK3CA-PTEN CNAs were White women.

4.5: Measure of Association

4.5 1: Measure of Association of Cervical Cancer Mortality and PIK3CA-PTEN Mutation Status

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
PIK3CA_PTEN_MUTATION * PATIENT_VITAL_STATUS	194	100.0%	0	0.0%	194	100.0%

Table 13: PIK3CA-PTEN Mutation Status by Patient's Vital Status

PIK3CA_PTEN_MUTATION * PATIENT_VITAL_STATUS Crosstabulation

			PATIENT_VITAL_STATUS		
			DEAD	ALIVE	Total
PIK3CA_PTEN_MUTATION	POSITIVE	Count	22	38	60
		% within PIK3CA_PTEN_MUTATION	36.7%	63.3%	100.0 %
	NEGATIVE	Count	20	114	134
		% within PIK3CA_PTEN_MUTATION	14.9%	85.1%	100.0 %
Total		Count	42	152	194
		% within PIK3CA_PTEN_MUTATION	21.6%	78.4%	100.0 %

Table 13 shows the PIK3CA-PTEN mutation status by patient's vital status; 22 patients with PIK3CA-PTEN mutations died and 38 patients with PIK3CA mutation were alive. While 20 patients without PIK3CA-PTEN mutations died and 114 patients without PIK3CA mutation were alive.

Figure 33: PIK3CA-PTEN mutation status by patient's vital status

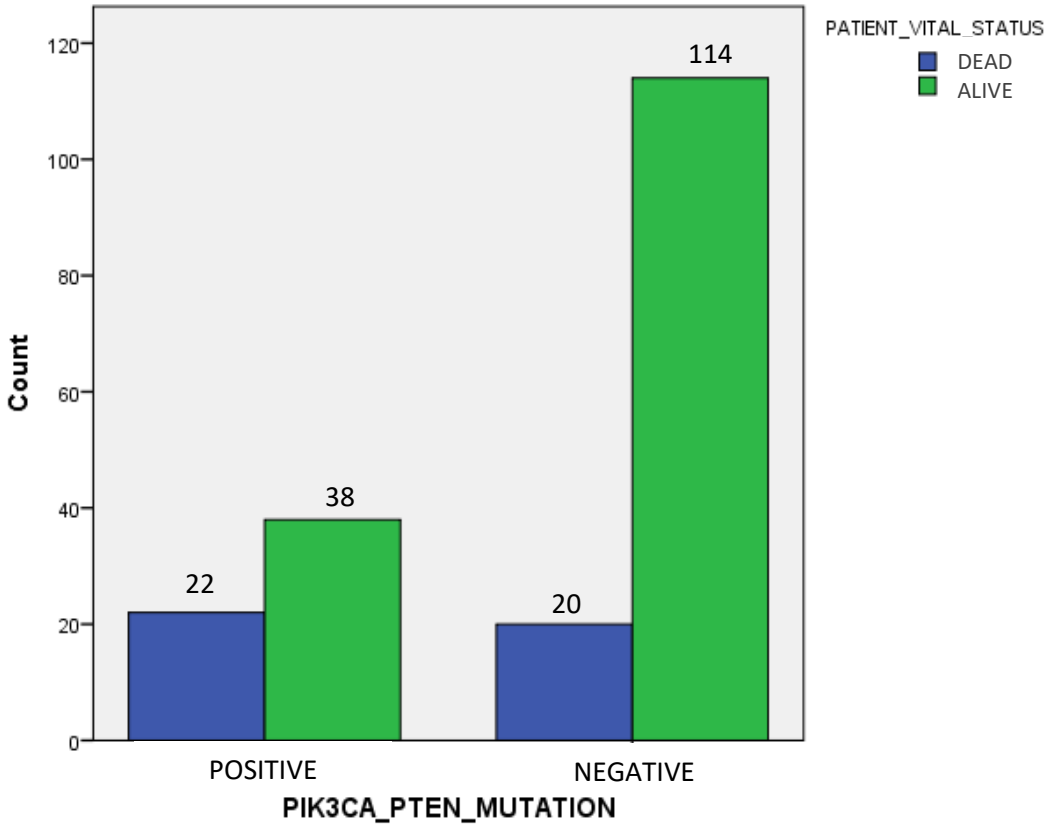


Figure 33 shows the PIK3CA-PTEN mutation status by patient's vital status; 22 patients with PIK3CA-PTEN mutations died and 38 patients with PIK3CA mutation were alive. While 20 patients without PIK3CA-PTEN mutations died and 114 patients without PIK3CA mutation were alive.

Table 14: Inferential Statistics for PIK3CA-PTEN mutation status by patient's vital status

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	11.549[a]	1	.001		
Continuity Correction[b]	10.303	1	.001		
Likelihood Ratio	10.908	1	.001		
Fisher's Exact Test				.001	.001
N of Valid Cases	194				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 12.99.

b. Computed only for a 2x2 table

Table 14 shows the inferential statistics value for comparison of PIK3CA-PTEN gene mutation status by patient's vital status. The Fisher's Exact Test showed that there was significant difference (0.001) in the PIK3CA-PTEN mutation status by patient's vital status at alpha ($P<0.05$).

50% of African Americans with mutations died while 33.3% were alive. P-value = 0.550

37% of Caucasians with mutations died while 27.9% were alive. P-value = 0.352

Table 15: Binominal Logistic Regression Analysis PIK3CA-PTEN Mutation Status by Patient's Vital Status

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	PIK3CA_PTEN_MUTATION	.654	.642	10.908	1	.001	3.300	1.625	6.700
	Constant	.147	.313	.219	1	.640	.864		

a. Variable(s) entered on step 1: PIK3CA_PTEN_MUTATION

Table 15 shows the OR (EXP (B)) and CI for Cervical Cancer Mortality and PIK3CA-PTEN Mutations. The odds ratio for cervical cancer mortality for PIK3CA-PTEN mutations present compared to the PIK3CA-PTEN mutations absent is 3.300 indicating increased odds of death for cervical cancer patients with positive PIK3CA-PTEN mutations. The 95% Confidence Interval of the Odds Ratio was 1.625-6.700.

4.5.2: Measure of Association of Cervical Cancer Recurrence and PIK3CA-PTEN Mutation Status

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
PIK3CA_PTEN_MUTATION * DISEASE_STATUS	176	100.0%	0	0.0%	176	100.0%

Table 16: PIK3CA-PTEN Mutation Status by Disease Status

PIK3CA_PTEN_MUTATION * DISEASE_STATUS Crosstabulation

			DISEASE_STATUS		
			RECURRED	FREE	Total
PIK3CA_PTEN_MUTATION	POSITIVE	Count	15	38	53
		% within PIK3CA_PTEN_MUTATION	28.3%	71.7%	100.0%
	NEGATIVE	Count	17	106	123
		% within PIK3CA_PTEN_MUTATION	13.8%	86.2%	100.0%
Total		Count	32	144	176
		% within PIK3CA_PTEN_MUTATION	18.2%	81.8%	100.0%

Table 16 shows the PIK3CA-PTEN mutation status by disease status; 15 patients with PIK3CA-PTEN mutations had tumor recurrence or progression and 38 patients with PIK3CA-PTEN mutations did not have recurrence or progression. While 17 patients without PIK3CA-PTEN mutations had recurrence and 106 patients without PIK3CA-PTEN mutations were disease free.

Figure 34: PIK3CA-PTEN mutation status by disease status

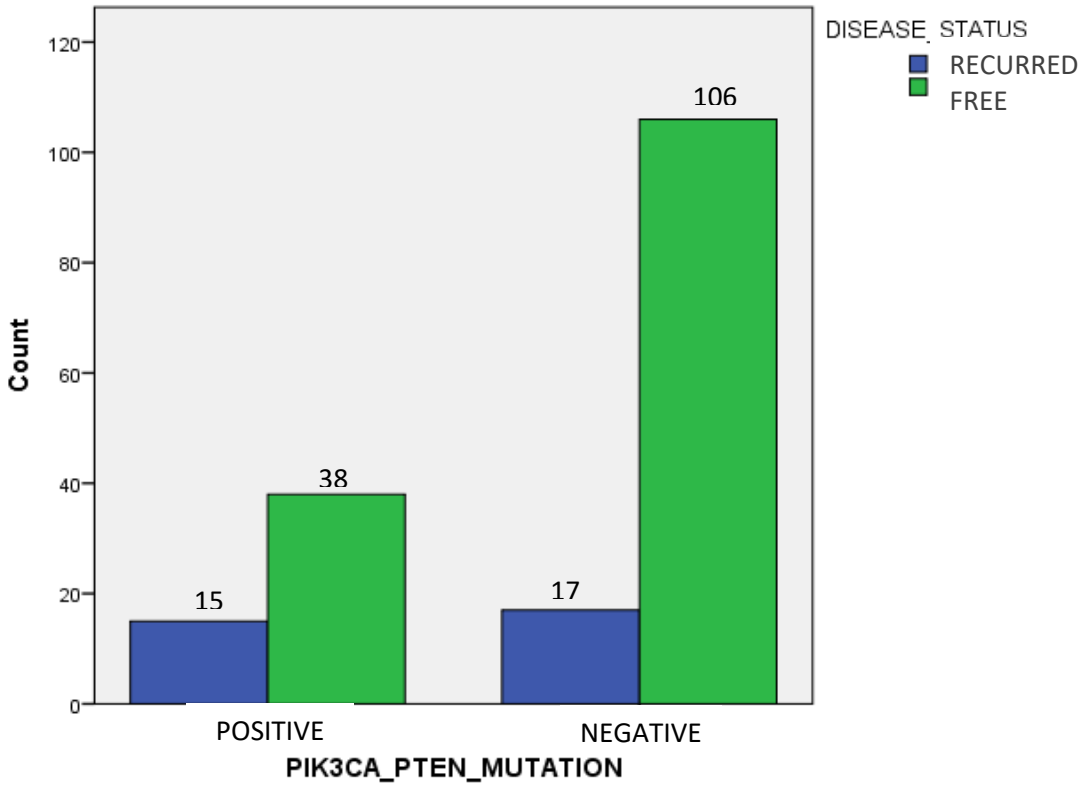


Figure 34 shows the PIK3CA-PTEN mutation status by disease status; 15 patients with PIK3CA-PTEN mutations had tumor recurrence or progression and 38 patients with PIK3CA-PTEN mutations did not have recurrence or progression. While 17 patients

without PIK3CA-PTEN mutations had recurrence and 106 patients without PIK3CA-PTEN mutations were disease free.

Table 17: Inferential Statistics for PIK3CA-PTEN mutation status by disease status

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.221[a]	1	.042		
Continuity Correction[b]	4.293	1	.038		
Likelihood Ratio	4.925	1	.026		
Fisher's Exact Test				.032	.021
N of Valid Cases	176				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 9.64.

b. Computed only for a 2x2 table

Table 17 shows the inferential statistics value for comparison of PIK3CA-PTEN gene mutation status by disease status. The Fisher's Exact Test showed that there was significant difference (0.032) in PIK3CA-PTEN mutation status by disease free status at alpha (P<0.05). 40% of African Americans with mutations had recurrence while 36.4% did not have recurrence. P-value=1.000. 40% of Caucasians with mutations had recurrence while 28% did not have recurrence. P-value=0.276

Table 18: Binominal Logistic Regression Analysis forPIK3CA-PTEN mutation status by disease status

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	PIK3CA_PTEN_MUTATION	.654	.642	4.925	1	.042	2.461	1.120	5.407
	Constant	.147	.313	.219	1	.640	.864		

a. Variable(s) entered on step 1: PIK3CA_PTEN_MUTATION

Table 18 shows the OR and CI for Cervical Cancer Recurrence and PIK3CA-PTEN Mutations. The odds ratio for cervical cancer recurrence/progression for PIK3CA and PTEN

mutations present compared to the PIK3CA and PTEN mutations absent is 2.461 indicating increased odds of recurrence for cervical cancer patients with positive PIK3CA and PTEN mutations. The 95% Confidence Interval of the Odds Ratio was 1.120- 5.407.

4.5.3: Measure of Association of Race and PIK3CA-PTEN Mutation Status

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
PIK3CA_PTEN_MUTATION * RACE	154	100.0%	0	0.0%	154	100.0%

Table 19: PIK3CA-PTEN Mutation Status by Race

PIK3CA_PTEN_MUTATION * RACE Crosstabulation

			RACE		
			BLACK	WHITE	Total
PIK3CA_PTEN_MUTATION	POSITIVE	Count	6	41	47
		% within PIK3CA_PTEN_MUTATION	12.8%	87.2%	100.0%
	NEGATIVE	Count	10	97	107
		% within PIK3CA_PTEN_MUTATION	9.3%	90.7%	100.0%
Total		Count	16	138	154
		% within PIK3CA_PTEN_MUTATION	10.4%	89.6%	100.0%

Table 19 shows the PIK3CA-PTEN mutation status by RACE; 6 patients with PIK3CA-PTEN mutations were African American women and 41 patients with PIK3CA-PTEN mutations were White women. While 10 patients without PIK3CA-PTEN mutations were

African American women and 97 patients without PIK3CA-PTEN mutations were White women.

Figure 35: PIK3CA-PTEN mutation status by race

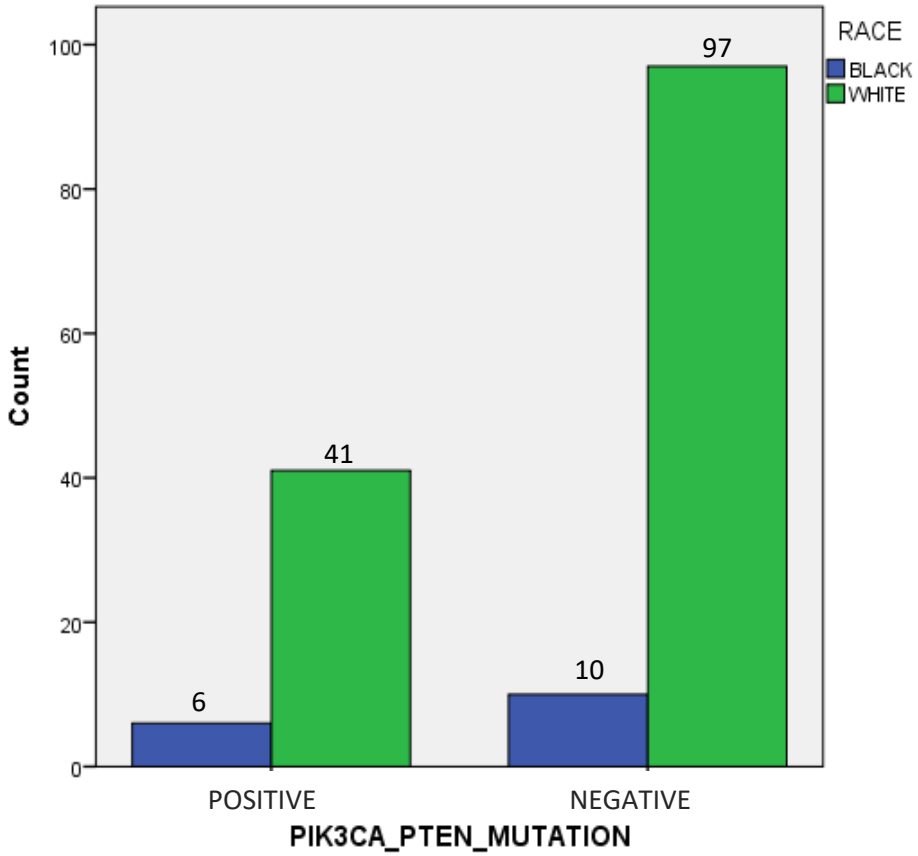


Figure 35 shows the PIK3CA-PTEN mutation status by RACE; 6 patients with PIK3CA-PTEN mutations were of the black race and 41 patients with PIK3CA-PTEN mutations were of the white race. While 10 patients without PIK3CA-PTEN mutations were of the black race and 97 patients without PIK3CA-PTEN mutations were of the white race.

Table 20: Inferential Statistics for PIK3CA-PTEN mutation status by race

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.410[a]	1	.570		
Continuity Correction[b]	.125	1	.723		
Likelihood Ratio	.397	1	.529		
Fisher's Exact Test				.550	.352
N of Valid Cases	154				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.88.

b. Computed only for a 2x2 table

Table 20 shows the inferential statistics value for comparison of PIK3CA-PTEN gene mutation status by race. The Fisher's Exact Test showed that there was no significant difference (0.550) in PIK3CA-PTEN mutation status by race at alpha ($P<0.05$).

Table 21: Binominal Logistic Regression Analysis for Race by PIK3CA-PTEN mutation status

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Step 1[a]	Race	.154	.642	.397	1	.570	1.420	.484	4.163
	Constant	.147	.313	.219	1	.640	.864		

a Variable(s) entered on step 1: Race

Table 21 shows the PIK3CA-PTEN mutation status by race; Odds ratio was 1.420. This indicates that there is an increase in the odds of PIK3CA-PTEN mutations in the Black race. The 95% Confidence Interval of the Odds Ratio was 0.484-4.163.

4.5.4: Measure of Association of Cervical Cancer Recurrence and PIK3CA-PTEN CNA Status

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
PIK3CA_PTEN_CNA * DISEASE_STATUS	255	100.0%	0	0.0%	255	100.0%

Table 22: PIK3CA-PTEN CNA Status by Disease Status

PIK3CA_PTEN_CNA * DISEASE_STATUS Crosstabulation

			DISEASE_STATUS		
			RECURRED	FREE	Total
PIK3CA_PTEN_CNA	POSITIVE	Count	20	51	71
		% within PIK3CA_PTEN_CNA	28.2%	71.8%	100.0%
	NEGATIVE	Count	26	158	184
		% within PIK3CA_PTEN_CNA	14.1%	85.9%	100.0%
Total		Count	46	209	255
		% within PIK3CA_PTEN_CNA	18.0%	82.0%	100.0%

Table 22 shows the PIK3CA-PTEN CNA status by disease status; 20 patients with PIK3CA-PTEN CNAs had tumor recurrence and 51 patients with PIK3CA-PTEN CNAs were disease free. While 26 patients without PIK3CA-PTEN CNAs had tumor recurrence and 158 patients without PIK3CA-PTEN CNAs were disease free.

Figure 36: PIK3CA-PTEN CNA status by disease status

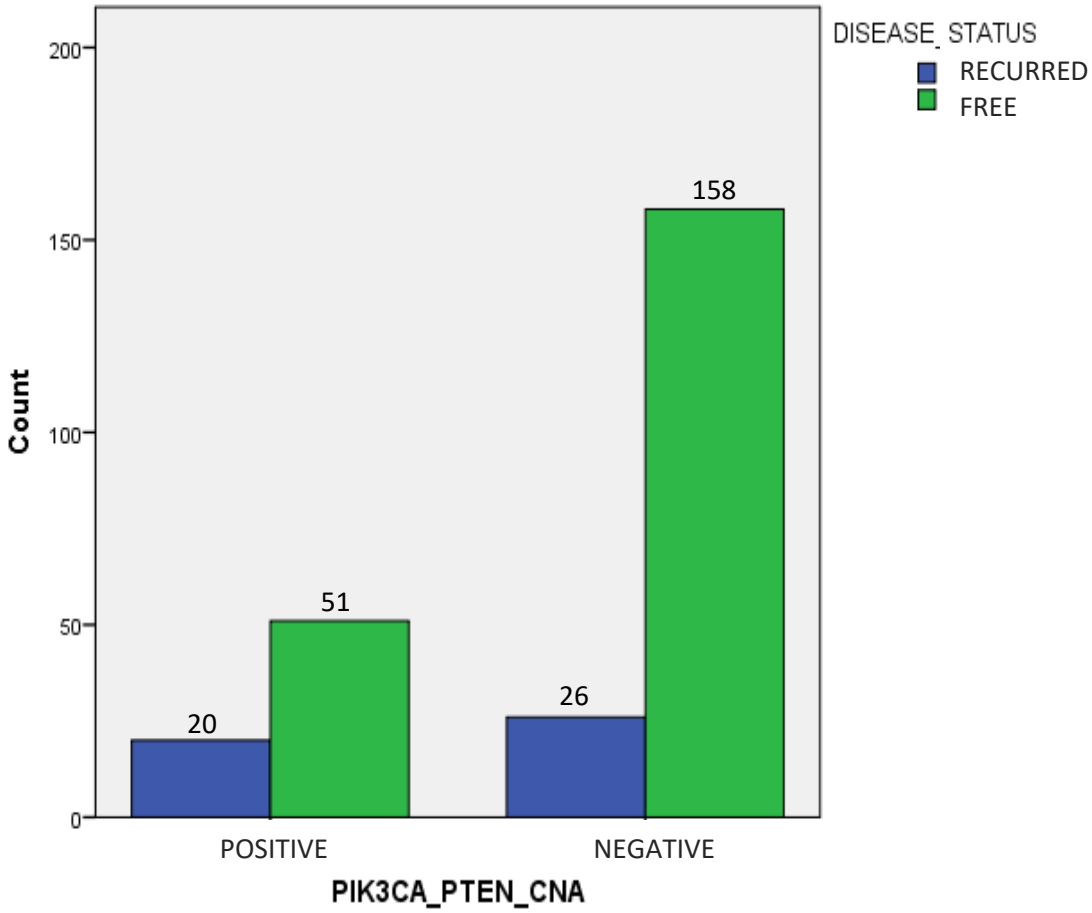


Figure 36 shows the PIK3CA-PTEN CNA status by disease status; 20 patients with PIK3CA-PTEN CNAs had tumor recurrence and 51 patients with PIK3CA-PTEN CNAs were disease free. While 26 patients without PIK3CA-PTEN CNAs had tumor recurrence and 158 patients without PIK3CA-PTEN CNAs were disease free.

Table 23: Inferential Statistics for PIK3CA-PTEN CNA status by disease status

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.829[a]	1	.034		
Continuity Correction[b]	5.913	1	.015		
Likelihood Ratio	6.393	1	.011		
Fisher's Exact Test				.011	.009
N of Valid Cases	255				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 12.81.

b. Computed only for a 2x2 table

Table 23 shows the inferential statistics value for comparison of PIK3CA-PTEN CNA status by disease status. The Fisher's Exact Test showed that there was significant difference (0.011) in PIK3CA-PTEN CNA status by disease status at alpha ($P<0.05$). 55.6% of African Americans with CNA had recurrence while 31.6% did not have recurrence. P-value= 0.225. 35.5% of Caucasians with CNAs had recurrence while 18.8% did not have recurrence. P-value= 0.037

Table 24: Binominal Logistic Regression Analysis for PIK3CA-PTEN CNA status by disease status

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	PIK3CA_PTEN_CNA	.654	.642	6.393	1	.034	2.383	1.228	4.624
	Constant	.021	.258	.530	1	.936	1.021		

a Variable(s) entered on step 1: PIK3CA_PTEN_CNA

Table 24 shows the OR and CI for Cervical Cancer Recurrence and PIK3CA-PTEN CNAs. The odds ratio for cervical cancer recurrence/progression for PIK3CA-PTEN CNAs positive compared to the PIK3CA-PTEN CNAs negative was 2.383 indicating increased odds of recurrence for cervical cancer patients with positive PIK3CA-PTEN CNAs. The 95% Confidence Interval of the Odds Ratio was 1.228-4.624.

4.5.5: Measure of Association of Cervical Cancer Mortality and PIK3CA-PTEN CNA Status

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
PIK3CA_PTEN_CNA * PATIENT_VITAL_STATUS	292	100.0%	0	0.0%	292	100.0%

Table 25: PIK3CA-PTEN CNA Status by Patient's Vital Status

PIK3CA_PTEN_CNA * PATIENT_VITAL_STATUS Crosstabulation

			PATIENT_VITAL_STATUS		
			DEAD	ALIVE	Total
PIK3CA_PTEN_CNA	POSITIVE	Count	25	46	71
		% within PIK3CA_PTEN_CNA	35.2%	64.8%	100.0%
	NEGATIVE	Count	42	179	221
		% within PIK3CA_PTEN_CNA	19.0%	81.0%	100.0%
Total		Count	67	225	292
		% within PIK3CA_PTEN_CNA	22.9%	77.1%	100.0%

Table 25 shows the PIK3CA-PTEN CNA status by patient's vital status; 25 patients with PIK3CA-PTEN CNAs died and 46 patients with PIK3CA-PTEN CNAs were alive. While 42 patients without PIK3CA-PTEN CNAs died and 179 patients without PIK3CA-PTEN CNAs were alive.

Figure 37: PIK3CA-PTEN CNA Status by Patient's Vital Status

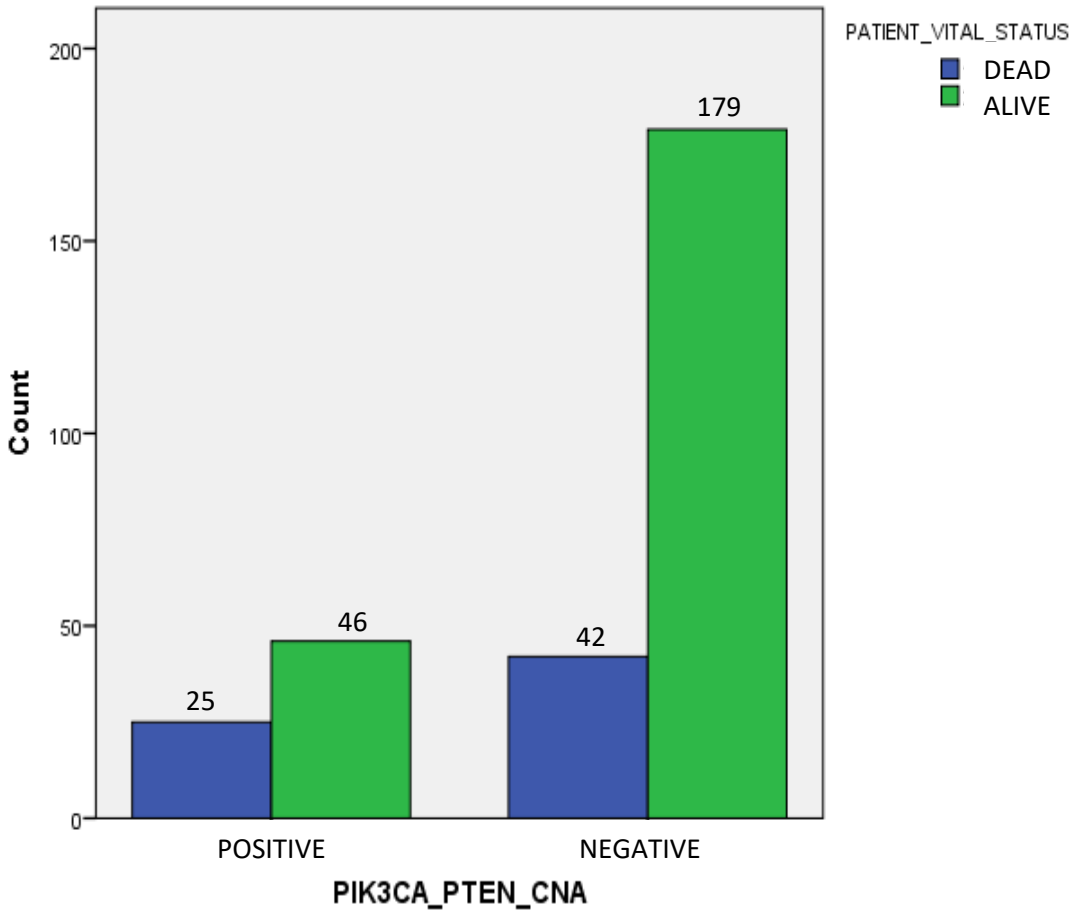


Figure 37 shows the PIK3CA-PTEN CNA status by patient's vital status; 25 patients with PIK3CA-PTEN CNAs died and 46 patients with PIK3CA-PTEN mutations were alive. While 42 patients without PIK3CA-PTEN CNAs died and 179 patients without PIK3CA-PTEN CNAs were alive.

Table 26: Inferential Statistics for PIK3CA-PTEN CNA status by patient's vital status

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.983[a]	1	.025		
Continuity Correction[b]	7.093	1	.008		
Likelihood Ratio	7.489	1	.006		
Fisher's Exact Test				.009	.005
N of Valid Cases	292				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 16.29.

b. Computed only for a 2x2 table

Table 26 shows the inferential statistics value for comparison of PIK3CA-PTEN CNA status by patient's vital status. The Fisher's Exact Test showed that there was significant difference (0.009) in PIK3CA-PTEN CNA status by patient's vital status at alpha ($P<0.05$). 62.5% of African Americans with CNAs died while 30% were alive. P-value = 0.111. 30% of Caucasians with CNAs died while 18.5% were alive. P-value = 0.086

Table 27: Binominal Logistic Regression Analysis for PIK3CA-PTEN CNA status by patient's vital status

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	PIK3CA_PTEN_CNA	.454	.442	7.489	1	.025	2.316	1.282	4.186
	Constant	.021	.258	.530	1	.936	1.021		

a Variable(s) entered on step 1: PIK3CA_PTEN_CNA

Table 27 shows the OR and CI for Cervical Cancer Death and PIK3CA-PTEN CNAs. The odds ratio for cervical cancer mortality for PIK3CA –PTEN CNA positive compared to the PIK3CA- PTEN CNA negative is 2.316 indicating increased odds of dead for cervical cancer

patients with positive PIK3CA-PTEN CNAs. The 95% Confidence Interval of the Odds Ratio was 1.282- 4.186.

4.5.6: Measure of Association of Race and PIK3CA-PTEN CNA Status

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
PIK3CA_PTEN_CNA * RACE	229	100.0%	0	0.0%	229	100.0%

Table 28: PIK3CA-PTEN CNA status by race

PIK3CA_PTEN_CNA * RACE Crosstabulation

			RACE		
			BLACK	WHITE	Total
PIK3CA_PTEN_CNA	POSITIVE	Count	11	43	54
		% within PIK3CA_PTEN_CNA	20.4%	79.6%	100.0%
	NEGATIVE	Count	17	158	175
		% within PIK3CA_PTEN_CNA	9.7%	90.3%	100.0%
Total		Count	28	201	229
		% within PIK3CA_PTEN_CNA	12.2%	87.8%	100.0%

Table 28 shows the PIK3CA-PTEN CNA status by race; 11 patients with PIK3CA-PTEN CNAs were of the black race and 43 patients with PIK3CA-PTEN CNAs were of the white race. While 17 patients without PIK3CA-PTEN CNAs were of the black race and 158 patients without PIK3CA-PTEN CNAs were of the white race

Figure 38: PIK3CA-PTEN CNA Status by Race

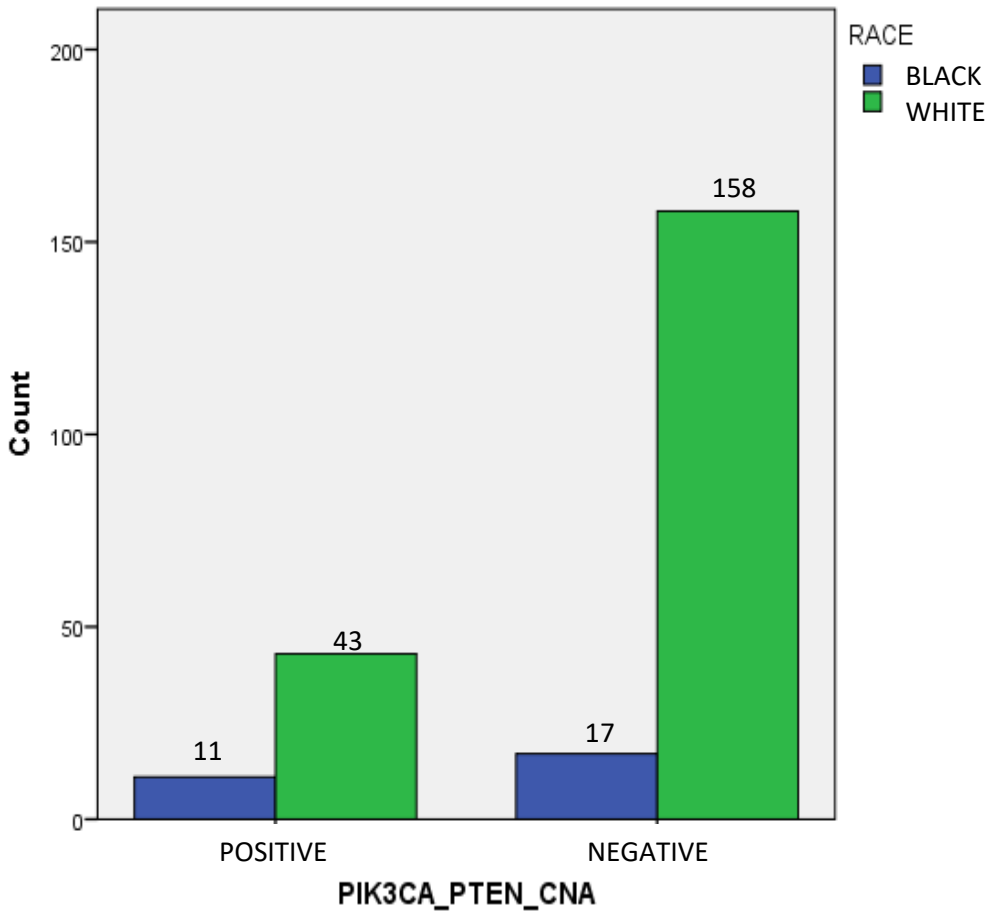


Figure 38 shows the PIK3CA-PTEN CNA status by race; 11 patients with PIK3CA-PTEN CNAs were of the black race and 43 patients with PIK3CA-PTEN CNAs were of the white race. While 17 patients without PIK3CA-PTEN CNAs were of the black race and 158 patients without PIK3CA-PTEN CNAs were of the white race.

Figure 39: Percentage of PIK3CA, PTEN, or both genes CNAs by Race Category

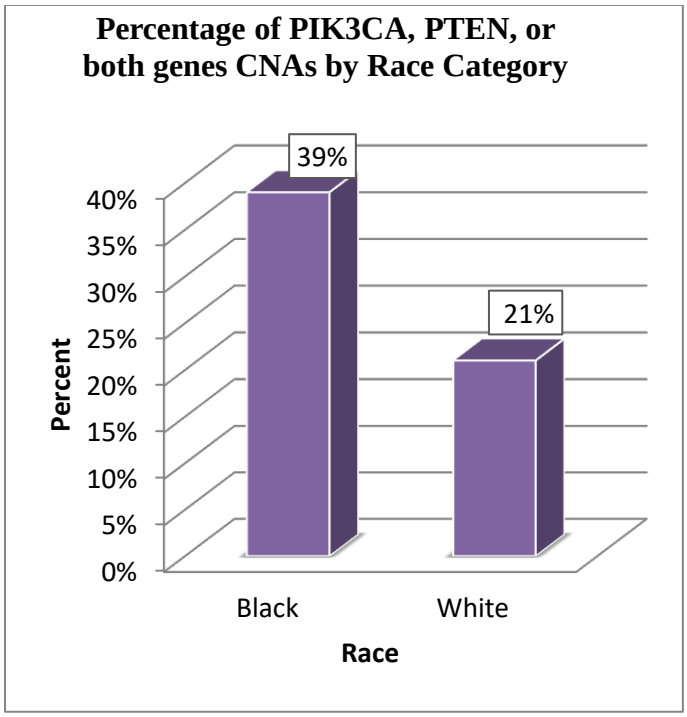


Table 29: Inferential Statistics for PIK3CA-PTEN CNA by race

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.366[a]	1	.044		
Continuity Correction[b]	3.430	1	.064		
Likelihood Ratio	3.953	1	.047		
Fisher's Exact Test				.043	.036
N of Valid Cases	229				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.60.

b. Computed only for a 2x2 table

Table 29 shows the inferential statistics value for comparison of PIK3CA-PTEN CNA status by race. The Fisher's Exact Test showed that there was significant difference (0.043) in PIK3CA-PTEN CNA status by race at alpha ($P<0.05$).

Table 30: Binominal Logistic Regression Analysis for Race Category

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Race	.254	.242	3.953	1	.044	2.378	1.137	5.452
	Constant	.021	.258	.530	1	.936	1.021		

a Variable(s) entered on step 1: Race

Table 30 shows the PIK3CA-PTEN CNA status by race; Odds ratio was 2.378. This indicates that there is an increase in the odds of PIK3CA-PTEN CNAs in African-American women. The 95% Confidence Interval of the Odds Ratio (1.137, 5.452) indicates that the odds of PIK3CA-PTEN CNAs in African-American women are significantly higher for the PIK3CA-PTEN CNA positive group compared to the PIK3CA- PTEN CNA negative.

Table 31: Staging * Race Crosstabulation

			RACE	
			AFRICAN AMERICAN	WHITE
Stage	Stage I	Count	11	114
		% within RACE	39.29%	56.72%
	Stage II	Count	5	44
		% within RACE	17.86%	21.89%
	Stage III	Count	6	31
		% within RACE	21.43%	15.42%
	Stage IV	Count	4	9
		% within RACE	14.29%	4.48%

Table 31 shows that a greater percentage of African American women presented at a later stage than Caucasian women. For instance, 14.29% of African American presented at stage four while only 4.48% of Caucasian women presented at stage four.

Table 32: Diagnosis_Age * Race Crosstabulation

			RACE	
			AFRICAN AMERICAN	WHITE
Diagnosis_age	20-34	Count	3	42
		% within RACE	10.71%	20.90%
	35-44	Count	4	50
		% within RACE	14.29%	24.88%
	45-54	Count	8	70
		% within RACE	28.57%	34.83%
	55-64	Count	7	27
		% within RACE	25.00%	13.43%
	>64	Count	6	12
		% within RACE	21.43%	5.97%

Table 32 shows that a larger percentage of African American women were diagnosed at later ages when compared to Caucasian women. For instance, 25.00% of African American women were diagnosed between the ages 55 and 64 while only 13.43% of Caucasian women were diagnosed between the ages 55 and 64.

4.6: Multivariable Logistic Regression Analysis

Table 33: Multivariable Logistic Regression Analysis

	Sig.	Exp(B)	95% C.I. for Exp(B)	
			Lower	Upper
Stage II	.773	1.178	0.387	3.584
Stage III	.044	2.206	1.687	5.854
Stage IV	.015	4.606	1.218	17.424
35-44	.886	1.120	0.237	5.288
45-54	.502	1.600	0.402	6.366
55-64	.037	3.629	1.863	15.263
>64	.006	7.000	1.520	32.237
Race	.043	2.378	1.137	5.452

The logistic regression was performed to test the effects of stage, diagnosis age, and race on the presence of PIK3CA-PTEN CNAs. The model showed that stages III and IV, diagnosis age groups 55-64 and > 64, and race predictors significantly predicted PIK3CA-PTEN genetic alteration (CNA) status.

CHAPTER V

DISCUSSION AND CONCLUSIONS

5.1 DISCUSSION

This section discusses the findings of the study. The top eleven mutated genes in the TCGA cervical cancer dataset were the PIK3CA, MUC4, KMT2C, SYNE1, KMT2D, EP300, RYR2, FLG, DMD, FBXW7, and PTEN genes. The top twelve genes with CNAs were the TP63, MECOM, PIK3CA, PRKCI, TRFC, RPL35A, LPP, TBL, FGF12, SOX2, LIFR, and PTEN genes.

PIK3CA and PTEN genes were identified as the most common oncogene and tumor suppressor gene respectively. The PIK3CA gene is one of the most commonly implicated genes in human cancer.[33, 102-107] It is located on the long (q) arm of chromosome 3 at position 26.3 (3q26.3).[108] The PIK3CA gene provides information for making the p110α (p110 alpha) protein, which is the catalytic subunit of the PI3K (phosphatidylinositol 3-kinase) enzyme.[(33, 108)] This is an important enzyme in the PI3K pathway.[108] The PI3K pathway is essential for several cellular activities such as cell metabolism, cell survival, cell growth, and proliferation. [104,108] The PI3K enzyme phosphorylates PIP2 (Phosphatidylinositol-4,5-biphosphate) to PIP3 (Phosphatidylinositol-3,4,5- triphosphate) (See figure 40) through a process termed phosphorylation.[108] PIK3CA gene amplifications and mutations are two common causes of excessive activation of this pathway in cancer. [104, 108]

Additionally, Yen-Ying et al.'s study on PIK3CA as an oncogene in cancer of the cervix highlighted that in cancer of the cervix cell lines harboring amplified PIK3CA; the expression of the gene product (p110a) of PIK3CA was enlarged, consequently becoming associated with the high kinase activity. Also, changing phenotypes in these lines, including decreased apoptosis and increased cell growth, proved to be notably affected by the treatment of specific PI 3-kinase inhibitor, symptomatic of increased expression of PIK3CA in cancer of the cervix may result in reducing apoptosis and advancing cell proliferation. Moreover, these aforementioned evidence support PIK3CA amplification may be connected to cervical tumorigenesis.[104]

The PTEN is also one of the most commonly implicated genes in the development of many cancers. [108] The PTEN gene is located on the long (q) arm of chromosome 10. [108] The PTEN gene provides instructions for making a phosphatase (PTEN) enzyme. The PTEN enzyme directly opposes the activity of the PI3K enzyme by removing phosphate groups from molecules (see figure 40). The PTEN enzyme acts as a tumor suppressor this means that PTEN helps regulate cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way.

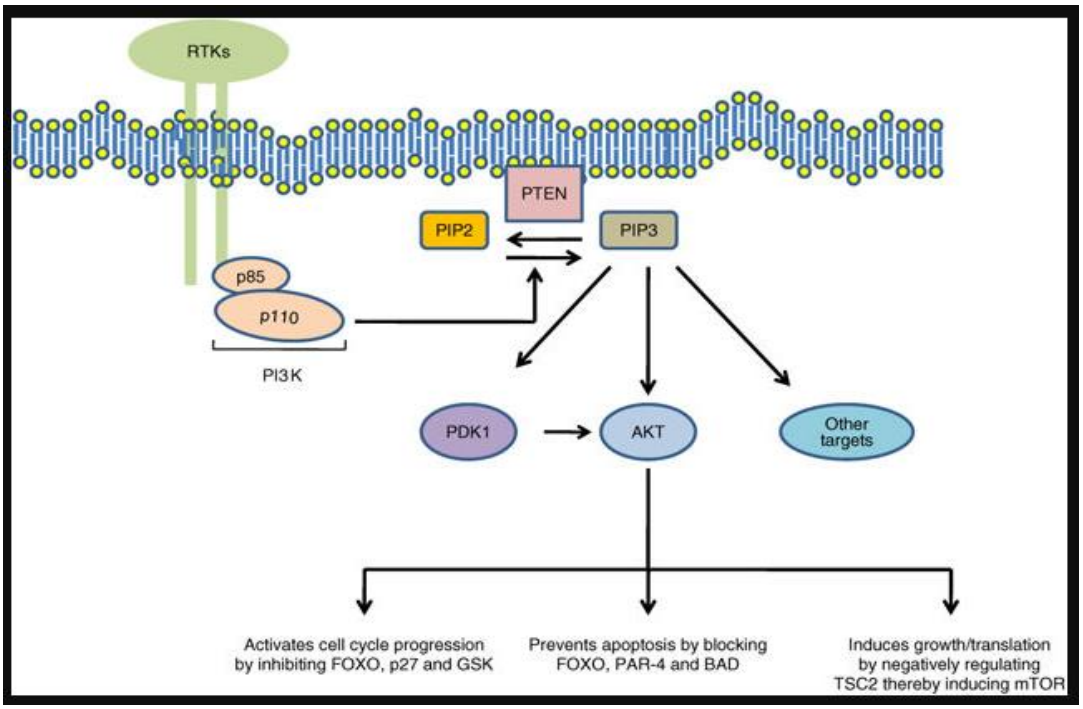


FIGURE 40: PI3K Pathway showing the position of PTEN action

Adapted from: http://www.nature.com/onc/journal/v27/n41/images/onc2008248f1.jpg . [109]

- PIK3CA Mutations – increased kinase activity
- PTEN mutations – decreased phosphatase activity
- Net effects – increased prolonged signaling for proliferation
- PIK3CA Amplifications– increased kinase activity
- PTEN deletions – decreased phosphatase activity
- Net effects – increased prolonged signaling for proliferation

The finding that PIK3CA is the most frequently mutated gene in this study is similar to the result of the study conducted by Wright and colleagues,[107] however, in addition to the PIK3CA gene they also found the KRAS and EGFR genes.[107] Similarly, Xiang et al. (2015), Lou H et al. (2015) ,and other researchers found the PIK3CA gene as the highest mutated gene in cervical cancer.[33, 106,110]

The risk, Exp (B), of dying for patients with genetic alterations (PIK3CA mutations, PTEN mutations, PTEN deletions and PIK3CA amplifications) in PIK3CA, PTEN, or both is 3.300 (1.625– 6.700). This indicates an increased risk of death for cervical cancer patients with these genetic alterations. The odds ratio of tumor recurrence for patients with these genetic alterations is 2.461 (1.120–5.407) indicating increased risk of tumor recurrence for cervical cancer patients with these genetic alterations. Furthermore, the adjusted odds ratio for genetic alterations status by race (African American and White women) is 2.378 (1.137, 5.452). This shows a higher prevalence of these genetic alterations in African American women compared to Caucasian women.

The study conducted by McIntyre and colleagues to determine the frequency of PIK3CA mutations in patients with cervical cancer treated with radical chemoradiotherapy (CRT) and to observe the result of tumor PIK3CA mutational status in pre-treatment biopsies on overall survival (OS) and progression-free survival (PFS) showed that PIK3CA mutation status was strongly associated with overall survival (OS) in FIGO stage IB/II cervical cancers, unadjusted HR 6.0 (95% CI 2.1-17.5), p=0.0002.[102]

Furthermore, a major association connected the level of pAKT expression and local recurrence was determined by a demonstration review that made use of 27 women's records who received primary radiation therapy as a result of locally advanced cervical cancer (LACC) with FIGO stage IIB–IVA revealed. The authors concluded that signaling from phosphatidylinositide 3-kinase/pAKT could lead to radiation resistance, and that evaluation of pAKT may be a prognostic indicator for a reaction to radiotherapy in LACC. [103] Further studies on oncogenic mutations in cervical cancer by Wright and colleagues pointed out that PIK3CA mutation was associated with shorter survival (67.1

months vs 90.3 months; hazard ratio, 9.1; 95% confidence interval, 2.8-29.5 months; P < .001). [107]

5.2 CONCLUSIONS

PIK3CA and PTEN genes are identified as the most common oncogene and tumor suppressor genes, respectively, in cervical cancer. 63 patients had mutations in PIK3CA, PTEN or both and 70 patients had CNAs. Genetic alterations (mutations or CNAs) in PIK3CA, PTEN, or both are associated with a higher risk of cervical cancer mortality and tumor recurrence. There is no statistically significant difference in death and recurrence rates between African American and Caucasian women with these genetic alterations. The generalization of this racial finding should be done with caution because the available TCGA cervical cancer data for African Americans was small. Further evaluation with a larger dataset will be required to validate these findings.

There is no significant difference between the prevalence of mutations involving these genes in African American and White women. African American women have a higher risk of having CNAs in these genes but this may be due to the fact that a larger percentage of African Americans presented at a later stage than Caucasian women as stages III and IV and diagnosis age groups 55-64 and >64 are significant predictors of the presence of CNAs in PIK3CA, PTEN, or both.

FUTURE DIRECTION

- To explore PIK3CA and PTEN genetic alterations as therapeutic targets to improve cervical cancer treatment
- To investigate further, other genes that may be involved in cervical cancer in the PI3K pathway.

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APPENDICES

Appendix 1: A list of genes with at least 8 mutations

Gene	# Mut	Freq
PIK3CA	53	27.32%
MUC4	37	19.07%
KMT2C	29	14.95%
SYNE1	23	11.86%
KMT2D	22	11.34%
EP300	21	10.82%
RYR2	21	10.82%
FLG	20	10.31%
DMD	20	10.31%
FBXW7	19	9.79%
PTEN	15	7.73%
ARID1A	15	7.73%
ABCA12	15	7.73%
PCLO	15	7.73%
DST	14	7.22%
CREBBP	14	7.22%
GOLGB1	14	7.22%
LRP2	14	7.22%
NAV3	14	7.22%
MUC17	14	7.22%
CSMD1	14	7.22%
CSMD3	13	6.70%
LRP1B	13	6.70%
PLEC	13	6.70%
FAT3	13	6.70%
DNAH3	13	6.70%
TRRAP	13	6.70%
DNAH2	13	6.70%
NBEAL1	13	6.70%
ANK2	12	6.19%
VCAN	12	6.19%
MYH9	12	6.19%
NFE2L2	12	6.19%
NHS	12	6.19%
CMYA5	12	6.19%
CHD7	12	6.19%
VPS13A	12	6.19%
WDFY4	12	6.19%
DCHS1	12	6.19%
HUWE1	12	6.19%
POLQ	12	6.19%

SRCAP	12	6.19%
FRAS1	12	6.19%
AHNAK2	12	6.19%
DNAH10	12	6.19%
HFM1	11	5.67%
ANK3	11	5.67%
ZFHX3	11	5.67%
ATM	11	5.67%
ADGRB3	11	5.67%
DNAH5	11	5.67%
EYS	11	5.67%
MYO15A	11	5.67%
ERBB3	11	5.67%
BPTF	11	5.67%
FAT2	11	5.67%
HLA-B	11	5.67%
KRAS	11	5.67%
NOTCH1	11	5.67%
MED1	11	5.67%
RYR3	11	5.67%
SI	11	5.67%
MYH15	11	5.67%
SPEN	11	5.67%
ABCA13	11	5.67%
FSIP2	11	5.67%
CUBN	11	5.67%
ADGRG4	11	5.67%
BSN	11	5.67%
MXRA5	11	5.67%
PDE4DIP	11	5.67%
TENM1	11	5.67%
PKHD1L1	11	5.67%
BOD1L1	11	5.67%
ADAMTS20	11	5.67%
CHD4	10	5.15%
COL6A3	10	5.15%
COL11A1	10	5.15%
DYNC1H1	10	5.15%
DSP	10	5.15%
ERBB2	10	5.15%
FAT1	10	5.15%
GTF3C1	10	5.15%
HIVEP1	10	5.15%
HELZ2	10	5.15%
MAP3K5	10	5.15%
PKD1	10	5.15%

PKHD1	10	5.15%
PARP14	10	5.15%
PRKDC	10	5.15%
ANKHD1	10	5.15%
PTPRD	10	5.15%
RYR1	10	5.15%
RGPD4	10	5.15%
SPTAN1	10	5.15%
SSPO	10	5.15%
PLCB1	10	5.15%
TEX15	10	5.15%
MACF1	10	5.15%
TPR	10	5.15%
FMN2	10	5.15%
ALMS1	10	5.15%
PREX1	10	5.15%
DNAH11	10	5.15%
DNAH1	10	5.15%
KNTC1	10	5.15%
DOPEY2	10	5.15%
VPS13B	10	5.15%
HRNR	10	5.15%
FAT4	10	5.15%
DYNC2H1	10	5.15%
ZNF750	10	5.15%
GPR179	10	5.15%
NSD1	10	5.15%
ATRX	9	4.64%
CACNA1B	9	4.64%
CASP8	9	4.64%
CHD3	9	4.64%
COL19A1	9	4.64%
DCC	9	4.64%
DNAH9	9	4.64%
F8	9	4.64%
FBN2	9	4.64%
UBR5	9	4.64%
KIAA1109	9	4.64%
FLNA	9	4.64%
FLNC	9	4.64%
HSD17B4	9	4.64%
AFF3	9	4.64%
LAMA2	9	4.64%
MAP2	9	4.64%
KIAA0754	9	4.64%
MYH2	9	4.64%

BRWD1	9	4.64%
PPL	9	4.64%
MAPK1	9	4.64%
HYDIN	9	4.64%
UHRF1BP1	9	4.64%
FAM208B	9	4.64%
PTPRC	9	4.64%
RB1	9	4.64%
KIF26B	9	4.64%
ATG2B	9	4.64%
PLXNA3	9	4.64%
CEP162	9	4.64%
TNIK	9	4.64%
SMG1	9	4.64%
NBEAL2	9	4.64%
MGA	9	4.64%
DMXL2	9	4.64%
TCF20	9	4.64%
ICE1	9	4.64%
DNAH7	9	4.64%
YLPM1	9	4.64%
TP53	9	4.64%
TP53BP1	9	4.64%
DSCAML1	9	4.64%
BRWD3	9	4.64%
RNF213	9	4.64%
MYH13	9	4.64%
DOCK11	9	4.64%
IQGAP1	9	4.64%
FCGBP	9	4.64%
HERC2	9	4.64%
HERC1	9	4.64%
MGAM	9	4.64%
THSD7A	9	4.64%
LATS1	9	4.64%
NIPBL	9	4.64%
USP34	9	4.64%
ZNF536	9	4.64%
MED12	9	4.64%
AKAP13	9	4.64%
ASPM	9	4.64%
CPSF1	9	4.64%
FREM2	9	4.64%
ZFHX4	9	4.64%
LRRC37A3	9	4.64%
CDH23	9	4.64%

MAST4	9	4.64%
THSD7B	9	4.64%
ADAMTS12	9	4.64%
ABL1	8	4.12%
ADCY9	8	4.12%
FHAD1	8	4.12%
AR	8	4.12%
ARHGAP6	8	4.12%
ASTN1	8	4.12%
CACNA1C	8	4.12%
COL7A1	8	4.12%
COL12A1	8	4.12%
DNAH8	8	4.12%
EPHA2	8	4.12%
CHD6	8	4.12%
MTOR	8	4.12%
TNRC18	8	4.12%
GOLGA4	8	4.12%
ARHGAP35	8	4.12%
FREM3	8	4.12%
HSPG2	8	4.12%
SPAG17	8	4.12%
KTN1	8	4.12%
LAMA5	8	4.12%
LRP5	8	4.12%
MKI67	8	4.12%
KMT2A	8	4.12%
MT-CO1	8	4.12%
MYH3	8	4.12%
NF1	8	4.12%
NOTCH3	8	4.12%
HECTD4	8	4.12%
PCNT	8	4.12%
PCSK5	8	4.12%
DCHS2	8	4.12%
PSD	8	4.12%
VPS13C	8	4.12%
GON4L	8	4.12%
KDM5A	8	4.12%
ROBO1	8	4.12%
ZGRF1	8	4.12%
WDFY3	8	4.12%
PLCH1	8	4.12%
BDP1	8	4.12%
HECW1	8	4.12%
MYCBP2	8	4.12%

SPTA1	8	4.12%
KIF1B	8	4.12%
CIC	8	4.12%
ADAMTS16	8	4.12%
ADGRL3	8	4.12%
KLHL4	8	4.12%
UBR4	8	4.12%
TDRD1	8	4.12%
TG	8	4.12%
TCHH	8	4.12%
PARD3	8	4.12%
NPAP1	8	4.12%
TAF1L	8	4.12%
UTRN	8	4.12%
ZNF236	8	4.12%
NAV2	8	4.12%
CLTCL1	8	4.12%
USP9X	8	4.12%
AK9	8	4.12%
BIRC6	8	4.12%
TENM2	8	4.12%
TDRD6	8	4.12%
EP400	8	4.12%
CHD8	8	4.12%
CACNA1H	8	4.12%
AHCTF1	8	4.12%
NCOR2	8	4.12%
CNTNAP2	8	4.12%
TANC2	8	4.12%
ARHGEF11	8	4.12%
ZEB2	8	4.12%
CEP350	8	4.12%
COL24A1	8	4.12%
MAGEC1	8	4.12%
USP43	8	4.12%
LRPPRC	8	4.12%
NBEA	8	4.12%
ARPP21	8	4.12%
KIAA2026	8	4.12%
PRUNE2	8	4.12%
CNTRL	8	4.12%
DIDO1	8	4.12%
PTPRT	8	4.12%
FLG2	8	4.12%
FRMPD2	8	4.12%
ERICH3	8	4.12%

SPATA31D1	8	4.12%
CFAP54	8	4.12%
SVEP1	8	4.12%
NAA15	8	4.12%
XIRP2	8	4.12%
AKNA	8	4.12%
YTHDC2	8	4.12%
INTS3	8	4.12%
WNK3	8	4.12%

Appendix 2: A list of oncogenes used in the comparison of gene functional groups[111]

Gene Symbol - Oncogenes		
ABL1	EVI1	MYC
ABL2	EWSR1	MYCL1
AKT1	FEV	MYCN
AKT2	FGFR1	NCOA4
ATF1	FGFR1OP	NFKB2
BCL11A	FGFR2	NRAS
BCL2	FUS	NTRK1
BCL3	GOLGA5	NUP214
BCL6	GOPC	PAX8
BCR	HMGA1	PDGFB
BRAF	HMGA2	PIK3CA
CARD11	HRAS	PIM1
CBLB	IRF4	PLAG1
CBLC	JUN	PPARG

Appendix 3: A list of oncogenes used in the comparison of gene functional groups[111]

Gene Symbol - Oncogenes		
CCND1	KIT	PTPN11
CCND2	KRAS	RAF1
CCND3	LCK	REL
CDX2	LMO2	RET
CTNNB1	MAF	ROS1
DDB2	MAFB	SMO
DDIT3	MAML2	SS18
DDX6	MDM2	TCL1A
DEK	MET	TET2
EGFR	MITF	TFG
ELK4	MLL	TLX1
ERBB2	MPL	TPR
ETV4	MYB	USP6
ETV6		

Appendix 4: A list of tumor suppressors used in the comparison of gene functional groups[111]

Gene Symbol – Tumor Suppressors		
APC	IL2	TNFAIP3
ARHGEF12	JAK2	TP53
ATM	MAP2K4	TSC1
BCL11B	MDM4	TSC2
BLM	MEN1	VHL
BMPR1A	MLH1	WRN
BRCA1	MSH2	WT1
BRCA2	NF1	
CARS	NF2	
CBFA2T3	NOTCH1	
CDH1	NPM1	
CDH11	NR4A3	
CDK6	NUP98	
CDKN2C	PALB2	
CEBPA	PML	

Appendix 5: A list of tumor suppressors used in the comparison of gene functional groups[111]

Gene Symbol – Tumor Suppressors	
CHEK2	PTEN
CREB1	RB1
CREBBP	RUNX1
CYLD	SDHB
DDX5	SDHD
EXT1	SMARCA4
EXT2	SMARCB1
FBXW7	SOCS1
FH	STK11
FLT3	SUFU
FOXP1	SUZ12
GPC3	SYK
IDH1	TCF3

Appendix 6: List of genes with at least 5 CNAs

Gene	Cytoband	CNA	#	Freq
TP63	3q28	AMP	62	21.02%
MECOM	3q26.2	AMP	62	21.02%
PIK3CA	3q26.3	AMP	60	20.34%
PRKCI	3q26.3	AMP	60	20.34%
TFRC	3q29	AMP	59	20.00%
RPL35A	3q29	AMP	59	20.00%
LPP	3q28	AMP	58	19.66%
TBL1XR1	3q26.32	AMP	58	19.66%
FGF12	3q28	AMP	57	19.32%
SOX2	3q26.3	AMP	57	19.32%
LIFR	5p13.1	AMP	18	6.10%
PTEN	10q23.3	DEL	15	5.08%
ERBB2	17q12	AMP	15	5.08%
STK11	19p13.3	DEL	15	5.08%
ASXL1	20q11.21	AMP	14	4.75%
HDAC4	2q37.3	DEL	14	4.75%
FAT1	4q35.2	DEL	14	4.75%
DDX10	11q22.3	DEL	14	4.75%
ZBTB16	11q23.2	DEL	14	4.75%
CHEK1	11q24.2	DEL	14	4.75%
ETS1	11q24.3	DEL	14	4.75%
FLI1	11q24.3	DEL	14	4.75%
MYC	8q24.21	AMP	14	4.75%
TFG	3q12.2	AMP	14	4.75%
BTLA	3q13.2	AMP	14	4.75%
GSK3B	3q13.33	AMP	14	4.75%
POFUT1	20q11.21	AMP	13	4.41%
ABCG4	11q23.3	DEL	13	4.41%
CBL	11q23.3	DEL	13	4.41%
ATM	11q22.3	DEL	13	4.41%
POU2AF1	11q23.1	DEL	13	4.41%
SDHD	11q23.1	DEL	13	4.41%
ARHGEF12	11q23.3	DEL	13	4.41%
KCNJ5	11q24.3	DEL	13	4.41%
EPHA6	3q11.2	AMP	13	4.41%
POGLUT1	3q13.33	AMP	13	4.41%
DNMT3B	20q11.21	AMP	12	4.07%
CD22	19q13.12	AMP	12	4.07%
DKC1	Xq28	AMP	12	4.07%
MTCP1	Xq28	AMP	12	4.07%
SNED1	2q37.3	DEL	12	4.07%
D2HGDH	2q37.3	DEL	12	4.07%
PDCD1	2q37.3	DEL	12	4.07%

KMT2A	11q23.3	DEL	12	4.07%
DDX6	11q23.3	DEL	12	4.07%
PAFAH1B2	11q23.3	DEL	12	4.07%
PCSK7	11q23.3	DEL	12	4.07%
RB1	13q14.2	DEL	12	4.07%
CKS1B	1q21.3	AMP	11	3.73%
RIT1	1q22	AMP	11	3.73%
PBX1	1q23.3	AMP	11	3.73%
CCNQ	Xq28	AMP	11	3.73%
DUSP9	Xq28	AMP	11	3.73%
ACKR3	2q37.3	DEL	11	3.73%
PASK	2q37.3	DEL	11	3.73%
EPPK1	8q24.3	AMP	11	3.73%
PLEC	8q24.3	AMP	11	3.73%
BCL3	19q13.32	AMP	11	3.73%
CBLC	19q13.32	AMP	11	3.73%
INPP5D	2q37.1	DEL	11	3.73%
FHIT	3p14.2	DEL	11	3.73%
CBLB	3q13.11	AMP	11	3.73%
FOXP1	3p13	DEL	11	3.73%
MUC1	1q22	AMP	10	3.39%
YY1AP1	1q22	AMP	10	3.39%
KMT2B	19q13.12	AMP	10	3.39%
FSTL3	19p13.3	DEL	10	3.39%
TCF3	19p13.3	DEL	10	3.39%
AFF2	Xq28	AMP	10	3.39%
CYSLTR2	13q14.2	DEL	10	3.39%
PRKN	6q26	DEL	10	3.39%
AGO2	8q24.3	AMP	10	3.39%
PTK2	8q24.3	AMP	10	3.39%
RECQL4	8q24.3	AMP	10	3.39%
AKT2	19q13.2	AMP	10	3.39%
ERBB4	2q34	DEL	10	3.39%
APH1A	1q21.2	AMP	9	3.05%
MCL1	1q21.2	AMP	9	3.05%
ARNT	1q21.3	AMP	9	3.05%
MLLT11	1q21.3	AMP	9	3.05%
TPM3	1q21.3	AMP	9	3.05%
PRCC	1q23.1	AMP	9	3.05%
NTRK1	1q23.1	AMP	9	3.05%
INSRR	1q23.1	AMP	9	3.05%
NCSTN	1q23.2	AMP	9	3.05%
B4GALT3	1q23.3	AMP	9	3.05%
SDHC	1q23.3	AMP	9	3.05%
FCGR2B	1q23.3	AMP	9	3.05%
DDR2	1q23.3	AMP	9	3.05%

BAP1	3p21.1	DEL	9	3.05%
FGF19	11q13.3	AMP	9	3.05%
FGF4	11q13.3	AMP	9	3.05%
FGF3	11q13.3	AMP	9	3.05%
RAD51B	14q24.1	AMP	9	3.05%
H3F3B	17q25.1	AMP	9	3.05%
SERP2	13q14.11	DEL	9	3.05%
LCP1	13q14.13	DEL	9	3.05%
FOXO1	13q14.11	DEL	9	3.05%
NDRG1	8q24.22	AMP	9	3.05%
FANCI	15q26.1	AMP	9	3.05%
IDH2	15q26.1	AMP	9	3.05%
CRTC3	15q26.1	AMP	9	3.05%
BLM	15q26.1	AMP	9	3.05%
CHD2	15q26.1	AMP	9	3.05%
CUL3	2q36.2	DEL	9	3.05%
IKZF3	17q12-q21.1	AMP	9	3.05%
WWOX	16q23.1-q23.2	DEL	9	3.05%
CTLA4	2q33.2	DEL	9	3.05%
BARD1	2q35	DEL	9	3.05%
EPHA3	3p11.1	DEL	9	3.05%
MITF	3p13	DEL	9	3.05%
RYBP	3p13	DEL	9	3.05%
FCRL4	1q23.1	AMP	8	2.71%
NUF2	1q23.3	AMP	8	2.71%
IGF1R	15q26.3	AMP	8	2.71%
MEF2A	15q26.3	AMP	8	2.71%
GRIN2A	16p13.2	AMP	8	2.71%
CIITA	16p13.13	AMP	8	2.71%
RMI2	16p13.13	AMP	8	2.71%
SOCS1	16p13.13	AMP	8	2.71%
DOT1L	19p13.3	DEL	8	2.71%
GADD45B	19p13.3	DEL	8	2.71%
TYMS	18p11.32	AMP	8	2.71%
YES1	18p11.32	AMP	8	2.71%
CCND1	11q13.3	AMP	8	2.71%
CD274	9p24.1	AMP	8	2.71%
PDCD1LG2	9p24.1	AMP	8	2.71%
MDC1	6p21.33	AMP	8	2.71%
NOTCH2	1p12	AMP	8	2.71%
BCL9	1q21.2	AMP	8	2.71%
HIST2H3C	1q21.2	AMP	8	2.71%
HIST2H3D	1q21.2	AMP	8	2.71%
PDE4DIP	1q21.2	AMP	8	2.71%
EGR3	8p21.3	DEL	8	2.71%
AFDN	6q27	DEL	8	2.71%

CREB1	2q33.3	DEL	8	2.71%
IKZF2	2q34	DEL	8	2.71%
ATIC	2q35	DEL	8	2.71%
AAMP	2q35	DEL	8	2.71%
EPHA4	2q36.1	DEL	8	2.71%
PAX3	2q36.1	DEL	8	2.71%
ACSL3	2q36.1	DEL	8	2.71%
IRS1	2q36.3	DEL	8	2.71%
FEV	2q35	DEL	8	2.71%
INHA	2q35	DEL	8	2.71%
SHQ1	3p13	DEL	8	2.71%
PPP4R2	3p13	DEL	8	2.71%
DNAH12	3p14.3	DEL	8	2.71%
SRC	20q11.23	AMP	7	2.37%
SMYD3	1q44	AMP	7	2.37%
CEBPA	19q13.11	AMP	7	2.37%
DMD	Xp21.2-p21.1	DEL	7	2.37%
MAML2	11q21	AMP	7	2.37%
GNA11	19p13.3	DEL	7	2.37%
MAP2K2	19p13.3	DEL	7	2.37%
JAK2	9p24.1	AMP	7	2.37%
FBXW7	4q31.3	DEL	7	2.37%
SMAD4	18q21.2	DEL	7	2.37%
FAT3	11q14.3	DEL	7	2.37%
LHFPL6	13q13.3-q14.11	DEL	7	2.37%
TUSC3	8p22	DEL	7	2.37%
RAD21	8q24.11	AMP	7	2.37%
EXT1	8q24.11	AMP	7	2.37%
RSPO2	8q23.1	AMP	7	2.37%
NTRK3	15q25.3	AMP	7	2.37%
RPS19	19q13.2	AMP	7	2.37%
CD79A	19q13.2	AMP	7	2.37%
CIC	19q13.2	AMP	7	2.37%
CDK12	17q12	AMP	7	2.37%
MAP3K4	6q26	DEL	7	2.37%
FGFR1OP	6q27	DEL	7	2.37%
CPS1	2q34	DEL	7	2.37%
SF3B1	2q33.1	AMP	7	2.37%
AXIN2	17q24.1	AMP	7	2.37%
POU5F1	6p21.33	AMP	7	2.37%
NOTCH4	6p21.32	AMP	7	2.37%
STK19	6p21.33	AMP	7	2.37%
TAP1	6p21.32	AMP	7	2.37%
TAP2	6p21.32	AMP	7	2.37%
TGFBR2	3p24.1	DEL	7	2.37%
PICALM	11q14.2	AMP	7	2.37%

EED	11q14.2	AMP	7	2.37%
PTPRD	9p24.1-p23	DEL	7	2.37%
SMARCA4	19p13.2	AMP	6	2.03%
PICALM	11q14.2	DEL	6	2.03%
EED	11q14.2	DEL	6	2.03%
FH	1q43	AMP	6	2.03%
AKT3	1q43-q44	AMP	6	2.03%
NLRP3	1q44	AMP	6	2.03%
SH3GL1	19p13.3	DEL	6	2.03%
TICAM1	19p13.3	DEL	6	2.03%
PTPRS	19p13.3	DEL	6	2.03%
MLLT1	19p13.3	DEL	6	2.03%
TNFSF9	19p13.3	DEL	6	2.03%
CD70	19p13.3	DEL	6	2.03%
INSR	19p13.2	DEL	6	2.03%
KDM4C	9p24.1	AMP	6	2.03%
NFE2L2	2q31.2	AMP	6	2.03%
KDM6A	Xp11.3	DEL	6	2.03%
SRSF2	17q25.1	AMP	6	2.03%
SEPT9	17q25.3	AMP	6	2.03%
RBMX	Xq26.3	AMP	6	2.03%
CCDC160	Xq26.2	AMP	6	2.03%
PHF6	Xq26.2	AMP	6	2.03%
MRE11	11q21	DEL	6	2.03%
SESN3	11q21	DEL	6	2.03%
MAML2	11q21	DEL	6	2.03%
TRAF3	14q32.32	DEL	6	2.03%
FAS	10q23.31	DEL	6	2.03%
PML	15q24.1	AMP	6	2.03%
CD276	15q24.1	AMP	6	2.03%
SIN3A	15q24.2	AMP	6	2.03%
ERF	19q13.2	AMP	6	2.03%
COP1	1q25.1-q25.2	AMP	6	2.03%
CRIPAK	4p16.3	DEL	6	2.03%
ESR1	6q25.1-q25.2	DEL	6	2.03%
TNKS	8p23.1	DEL	6	2.03%
PCM1	8p22	DEL	6	2.03%
ESCO2	8p21.1	DEL	6	2.03%
DUSP4	8p12	DEL	6	2.03%
WRN	8p12	DEL	6	2.03%
ASMTL	Xp22.33 and Yp11.2	AMP	6	2.03%
CRLF2	Xp22.33 and Yp11.2	AMP	6	2.03%
P2RY8	Xp22.33 and Yp11.2	AMP	6	2.03%

ZRSR2	Xp22.2	AMP	6	2.03%
EIF1AX	Xp22.12	AMP	6	2.03%
CASP8	2q33.1	DEL	6	2.03%
ARID1B	6q25.3	DEL	6	2.03%
EZR	6q25.3	DEL	6	2.03%
IDH1	2q34	DEL	6	2.03%
DIS3	13q21.33	AMP	6	2.03%
ABCA9	17q24.2	AMP	6	2.03%
ERCC2	19q13.32	AMP	6	2.03%
SESN3	11q21	AMP	6	2.03%
JUN	1p32.1	AMP	6	2.03%
MST1R	3p21.31	DEL	6	2.03%
PARP3	3p21.2	DEL	6	2.03%
PBRM1	3p21.1	DEL	6	2.03%
EGFR	7p11.2	AMP	6	2.03%
CCNE1	19q12	AMP	6	2.03%
DNMT1	19p13.2	AMP	5	1.69%
KEAP1	19p13.2	AMP	5	1.69%
DNM2	19p13.2	AMP	5	1.69%
CARM1	19p13.2	AMP	5	1.69%
CALR	19p13.13	AMP	5	1.69%
PTPN2	18p11.21	AMP	5	1.69%
GATA1	Xp11.23	AMP	5	1.69%
LRP5	11q13.2	AMP	5	1.69%
BRD4	19p13.12	DEL	5	1.69%
TNFRSF17	16p13.13	AMP	5	1.69%
SNX29	16p13.13-p13.12	AMP	5	1.69%
ZNF217	20q13.2	AMP	5	1.69%
SS18L1	20q13.33	AMP	5	1.69%
ARFRP1	20q13.33	AMP	5	1.69%
RTEL1	20q13.33	AMP	5	1.69%
RPS6KB2	11q13.2	AMP	5	1.69%
MAFB	20q12	AMP	5	1.69%
PTPRT	20q12-q13.11	AMP	5	1.69%
TSHZ2	20q13.2	AMP	5	1.69%
AURKA	20q13.2	AMP	5	1.69%
GNAS	20q13.32	AMP	5	1.69%
PTPRD	9p24.1-p23	AMP	5	1.69%
NFIB	9p23-p22.3	AMP	5	1.69%
CREBBP	16p13.3	AMP	5	1.69%
CHN1	2q31.1	AMP	5	1.69%
HOXD13	2q31.1	AMP	5	1.69%
HOXD11	2q31.1	AMP	5	1.69%
ICK	6p12.1	AMP	5	1.69%
TCL6	14q32.13	AMP	5	1.69%
TRIP11	14q32.12	AMP	5	1.69%

GOLGA5	14q32.12	AMP	5	1.69%
DICER1	14q32.13	AMP	5	1.69%
TCL1A	14q32.13	AMP	5	1.69%
KAT6A	8p11.21	AMP	5	1.69%
ABCB1	7q21.12	AMP	5	1.69%
GPC3	Xq26.2	AMP	5	1.69%
FBXO31	16q24.2	DEL	5	1.69%
PGR	11q22.1	DEL	5	1.69%
BCL2L2	14q11.2	AMP	5	1.69%
ELOC	8q21.11	AMP	5	1.69%
COX6C	8q22.2	AMP	5	1.69%
AXL	19q13.2	AMP	5	1.69%
TPR	1q31.1	AMP	5	1.69%
ABL2	1q25.2	AMP	5	1.69%
FGFR3	4p16.3	DEL	5	1.69%
NSD2	4p16.3	DEL	5	1.69%
TSHZ3	19q12	AMP	5	1.69%
PRRX1	1q24.2	AMP	5	1.69%
MYCN	2p24.3	AMP	5	1.69%
TNFAIP3	6q23.3	DEL	5	1.69%
ECT2L	6q24.1	DEL	5	1.69%
LATS1	6q25.1	DEL	5	1.69%
SYNE1	6q25.2	DEL	5	1.69%
NUTM2A	10q23.2	DEL	5	1.69%
EP300	22q13.2	DEL	5	1.69%
PRKAR1A	17q24.2	AMP	5	1.69%
CUL4A	13q34	AMP	5	1.69%
CD79B	17q23.3	AMP	5	1.69%
DDX5	17q23.3	AMP	5	1.69%
GNA13	17q24.1	AMP	5	1.69%
SOX9	17q24.3	AMP	5	1.69%
TFPT	19q13.42	AMP	5	1.69%
BRSK1	19q13.42	AMP	5	1.69%
FAT3	11q14.3	AMP	5	1.69%
MRE11	11q21	AMP	5	1.69%
SETD2	3p21.31	DEL	5	1.69%
NCKIPSD	3p21.31	DEL	5	1.69%
RHOA	3p21.31	DEL	5	1.69%
MST1	3p21.31	DEL	5	1.69%
PAK1	11q13.5-q14.1	AMP	5	1.69%