RISK OF CANCER ASSOCIATED WITH ANTIHYPERTENSIVE DRUGS

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "RISK OF CANCER ASSOCIATED WITH ANTIHYPERTENSIVE DRUGS" submitted by Adnan Iqbal (16146031) has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy

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Ethics Statement

This is to certify that this project titled “Antihypertensive Drugs and Risk of Cancer: A Pharmacovigilance Study” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the School of Pharmacy, BRAC University constitutes my own work under the supervision of Dr. Mohd. Raeed Jamiruddin Assistant Professor, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Abstract/ Executive Summary

Antihypertensive medications are commonly used to treat hypertension, heart failure, and, more recently, cardiovascular risk reduction. Antihypertensive medicines have been implicated in the control of cell proliferation, tumor growth, and even malignancy in animal studies. The focus of this research is to look at the relationship between cancer and prior use of antihypertensive medication, taking into consideration the kind of hypertension medication and the occurrence of cancer in men and women. I obtained the signal data from the WHO Global Pharmacovigilance database VigiBase, which is accessible to the general public via the web application VigiAccess. To perform my research, I employ the PRR and chi-square methods. We have chosen several antihypertensive medications from various classifications. According to this pharmacovigilance investigation, all antihypertensive medications are not linked to cancer. However, several antihypertensive medicines with a substantial number of reports have the risk of this connection.

Dedication

This work is dedicated to my mother whose relentless efforts took me here

Acknowledgement

I would like to begin by **Dr. Mohd. Raeed Jamiruddin**, Assistant Professor, School of Pharmacy, BRAC University, for providing me with continuous support and guidance since the first day of this project-work. As a person, he has continuously inspired and motivated me with his knowledge on pharmacovigilance and pharmacology which made me more passionate about the project-work when it began. I would also like to thank him for his unwavering patience in me during every stage of project-work in the past few months.

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List of Acronyms

ADR: Adverse Drug Reaction

WHO: World Health Organization

CIOMS: The Council for International Organizations of Medical Sciences

PRR: Proportional Reporting Ratio

ACE: Angiotensin Converting Enzyme

BP: Blood Pressure

CCBs: Calcium Channel Blockers

ARBs: Angiotensin II receptor blockers

UV: Ultraviolet

LDL: Low Density Lipoprotein

HDL: High Density Lipoprotein

RCC: Renal Cell carcinoma

PC: Prostate cancer

TGA: Therapeutic Goods Administration

MHRA: Medicines & Healthcare Products Regulatory Agenc

Chapter 1: Introduction

1.1 Relationship between antihypertensive drugs and cancer

When it comes to antihypertensive medications, the debate over whether or not they cause cancer has been going on for decades. A article first establishing the association between hypertension and cancer appeared in 1975. (Pero et al., 2007; Hedner, Narkiewicz, Kjeldsen, & Oparil, 2011) About 7.5 million people worldwide lose their lives each year due to hypertension-related causes. Hypertension is known as the "silent killer" because it may wreak damage before symptoms appear. Those who do not manage their hypertension risk developing heart disease, lung problems, kidney problems, and possibly a stroke (Kim & Andrade, 2016). Prior to the 1960s, hypertension sufferers were only treated if they had symptoms (Roberts, Stickley, Balabanova, & McKee, 2012). Out of every 10 occurrences of hypertension, nine remain unidentified. Blood pressure may be lowered by a number of different medications. Treatment for hypertension often lasts for many years since the drugs treat just the symptoms and not the underlying cause. There is mounting evidence that suggests hypertension runs in families; nevertheless, the exact genetic predisposition varies by as much as 50% from person to person, depending on variables including diet, exercise, and environmental exposures (Kapil & Lobo, 2014) In certain cases, the term "cardiovascular disease" is used to refer to a group of conditions that affect the cardiovascular system as a whole, including the heart, blood vessels, kidneys, and even the lungs (Johar & Bernstein, 2017). The World Health Organization estimates that by 2030, 23.6 million individuals would have lost their lives due to cardiovascular disease, such as heart attacks and strokes. Similar results were found by Miremadi, Sherkat, and Stojanovska (2016). Research shows that hypertension is the primary cause of death in around 46% of people who die from heart disease, 51% of those who die from stroke, and maybe some people who die from cancer.

Around 29.6 percent of men and 34.4 percent of women in low-income countries have control over their blood pressure. There are around 33.2 percent of males and 38.4 percent of women in this position in high-income nations. The World Health Organization (WHO) stresses the need of providing essential services to combat HT and encouraging health professionals, especially nurses, to educate the public about the dangers of avoiding healthy behaviors. That's why hypertension sufferers need to take antihypertensive drugs. Antihypertensive drugs are associated with an increased risk of cancer (Kato et al., 2015). Tumors consist of many different types of cells, including neoplastic, supporting vascular, inflammatory, and fibroblast cells, much like other malformed tissues. The vast majority of bulk tumor cells are not tumorigenic and have low rates of self-renewal. There is a tiny but critical population that can initiate and maintain tumor-wide self-renewal and growth. These cells are referred to as "cancer stem cells" because of their ability to generate new tumors. Approximately 150 years ago, in 1855, Huntly and Gilliland found cancer stem cells, ushering in the modern era of cancer research (Han, Shi, Gong, Zhang, & Sun, 2013). Metabolic oxidative stress is hypothesized to cause cancer cells to enhance their glucose digestion system and alter their mitochondrial oxidative digestion system in comparison to normal cells. Most cancer treatments aim to exploit metabolic and physiological distinctions between cancerous and healthy cells. According to Allen and co-workers (2014), adverse drug reactions (ADRs) represent a major contributor to mortality and disability worldwide. Between 44,000 and 98,000 Americans lose their lives every year due to preventable medical mistakes, according the Institute of Medicine in the United States. Approximately 7,000 of these deaths may be attributed to ADRs. Findings from the study indicate that ADR is a major contributor to death rates, healthcare costs, and lost productivity. A total of three investigations on the Swedish population have shown a 3% death rate attributable to ADR, placing Sweden ninth in the world in terms of mortality frequency (Mouton et al., 2015).

Worldwide reports of adverse drug reactions (ADRs) are now being collected and archived by many organizations, including WHO, for future study. Once again, this evaluation for data analysis is labor-intensive and done by hand (Koutkias & Jaulent, 2016). One of the most important parts of drug safety testing is the identification and evaluation of potential new drugs, or signals that may affect drug consumption. Signal detection is defined by CIOMS (The Council for International Organizations in the Medical Sciences) Group VIII as "information that arises from one or more sources (including observations and experiments), which suggests a new intervention to improve association or a new aspect of a known association, between an intervention and an event or a set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory acclaration" (Lerch, Nowicki, Manlik, & Wirsching, 2015). Signal detection seeks to locate unexplored parts of known correlations or novel connections that could be causal. Auditing scientific literature, ICSRs, cases (including "record cases"), case surveys, Periodically Updated Reports, Periodically Benefit-Risk Evaluation Reports, and Periodically Benefit-Risk Evaluation Reports are all examples of traditional signal detection methods. Included but not limited to: Annual Safety Reports, Periodic ADR Reports, and Development Safety Update Reports. Detection of statistical signals is used to augment and enhance conventional methods. Currently, ADR signals are detected from spontaneous reporting databases using a variety of quantitative approaches, including Bayesian methodology, PRR, ROR, and others. In addition to PCR and ELISA, SSA is another quantitative method for identifying ADR (I, Pratt, Kalisch, & Roughead, 2014). It is becoming more difficult for healthcare professionals and patients to keep up with the ever-increasing volume of adverse drug reactions (ADRs) being reported from across the globe and published in a variety of publications and media (Beckmann et al., 2014). (2014). Simply described, real-world signal detection and management must balance two competing goals: Both (1) accuracy (i.e., identifying each and

every genuine signal as soon as possible) and (2) efficiency (i.e., freeing up health professionals' time to concentrate on evaluating genuine signals by minimizing the number of false-positive indicators and, thus, the effort required to survey them) are essential (Lerch et al., 2015). Cancer is reported annually as an adverse medication response to various antihypertensive medicines, illustrating the global nature of the effects uncovered by signal detection in the pharmaceutical industry.

1.2 Types of antihypertensive drugs that can cause cancer

This question of whether or not antihypertensive medications cause cancer has been discussed for the last fifty years (Gomez-Acebo et al., 2016). Several antihypertensive medications are used as the first line of treatment for hypertension. By maintaining a healthy blood pressure and electrolyte concentrations, hypertension may be treated. Hypertension and related mortality may be reduced by using these medications. In order to maintain normal blood pressure, patients must take many drugs at once, which might have a number of unintended consequences. Antihypertensive drugs include beta-blockers, alpha-blockers, calcium channel blockers, beta-blockers, and angiotensin II receptor blockers. In the first stages of treating hypertension, thiazide diuretics are often recommended (Arroll, Kenealy, et al., 2008). A recent paper from VigiAccess suggests that practically all antihypertensive drugs may cause cancer, contradicting prior studies that suggested diuretics and calcium channel blockers were the leading causes of cancer (A. M. Lindgren, Nissinen, Tuomilehto, & Pukkala, 2005). Angiotensin II receptor blockers have been linked to an increased risk of cancer (Olin, Veverka, & Nuzum, 2011). The risk was higher for those who had been using antihypertensive drugs for more than five years.

1.2.1 ACE inhibitors

ACE inhibitors are perhaps the most often used therapeutic medicine for the management of renal insufficiency in the treatment of heart failure. With the hope of reducing fatalities caused by heart failure. Multiple studies have shown the efficacy of ACE inhibitors in treating hypertension. They want to alter the heart's hemodynamics in a way that decreases the heart's preload, afterload, and systolic ventricular divider push, hence increasing cardiovascular yield without increasing oxygen consumption. It's a change in blood flow that speeds up salt excretion and increases renal perfusion to keep glomerular filtration operating normally. Patients with hypertension, CHF, diabetic and non-diabetic nephropathy all benefit from their use in the long run, therefore they play a crucial part in these conditions' treatment. However, they are more likely to have adverse drug effects, such as cancer. Although preliminary evidence suggested that angiotensin-converting enzyme (ACE) inhibitor use was associated with a decreased cancer risk for patients, a subsequent study performed to confirm this found conflicting findings.

1.2.2 Beta blockers

Beta blockers are beneficial in the treatment of heart failure and the reduction of death rates. Beta blockers are the first-line treatment for hypertension in young patients (Ong, 2007). Beta blockers are increasingly being utilized in the treatment of hypertension, and their effects on heart disease and stroke are similar to diuretics. This drug's cancer risk has just been determined to be on the rise. Beta blocker users had an increased risk of developing kidney cancer and pelvic cancer, according to an Australian case control research.

1.2.3 Calcium channel blocker

An antihypertensive medication known as a calcium channel blocker has been around for more than two decades. Doubts have been raised over whether or not certain medicines cause heart attacks. Voltage-gated Ca2+ channels in the cell layers of vascular smooth muscle inhibit calcium converging via the voltage-gated Ca2+ channel. A link was found recently between these substances and cancer, according to a research. They are often recommended for hypertension and coronary heart disease as an antihypertensive medication. Because calcium channel blockers (CCBs) impede apoptosis, it has been hypothesized that they may increase the risk of cancer because they stimulate the proliferation of damaged cells with a high risk of cancer.

1.2.4 Diuretics

Treatments for heart failure, hypertension, water intoxication, and some renal illnesses use diuretics in medical practice. Thiazides and loop diuretics in particular have antihypertensive properties irrespective of their diuretic properties. Thus, the fall in blood pressure is not a consequence of diuresis, but rather happens via other processes and at lower dosages than is necessary to achieve diuresis. Many investigations have been conducted to establish a link between diuretics and an increased risk of cancer. Renal cell carcinoma is linked to long-term usage of diuretics, according to a new study. In 1995, (Wong-Ho Chow) Cancer patients who use diuretics, particularly thiazide diuretics, have a higher chance of developing a variety of cancers (Keith T. Flaherty1, 2005).

1.2.5 Angiotensin II receptor blockers

These angiotensin II receptor blockers are the most often prescribed medications for individuals with high blood pressure, and those who are intolerant to them may benefit from a variety of cardiac conditions, such as stable coronary artery disease. In the case of Angiotensin II receptor blockers, it has been shown to be well tolerated and effective, and around 25% of people with hypertension use this medication globally. ARBs (angiotensin-receptor blockers) have been around since 1995 when they were initially licensed for clinical use as an antihypertensive medication. ARBs were originally found when the medication losartan was developed. Antihypertensive medicines have been linked to a significant risk of cancer in many meta-analyses, according to the findings. However, we don't know how this form of linkage works.

1.2.6 The use of additional blood pressure-lowering medications

Hypertension may be treated effectively using plant extracts or medicines produced from plants. Alkaloids are critical for the treatment of hypertension, as well as their potential to prevent cardiovascular disease, as shown by several studies, both in vitro and in vivo (Bai, Wu, & Xu, 2015). As an example of one of the rauwolfia alkaloid's many uses as a hypertension therapy, Rauwolfia serpentine was formerly regarded to be both an effective and safe medication. Breast cancer was previously thought to be a side effect, but this has recently been shown to be true. Antihypertensive medication Methyldopa has been shown to have a carcinogenic effect.

1.3 Types of cancer due to using antihypertensive drugs:

Antihypertensive medicines have the potential to cause a variety of cancers, including prostate, breast, colon, throat, kidney, and skin cancers. Although the incidence is low, it is possible. Once again, long-term usage of antihypertensive medications may result in cancer. Skin cancer may be caused by long-term use of ARBs and diuretics, for example (Schmidt, Schmidt, Mehnert, Lemeshow, & Sorensen, 2015).

1.3.1 Cancer of the skin (skin cancer)

Skin cancer incidences are on the rise owing to increased exposure to UV light. Several functions are controlled by the skin's various layers, which are composed of cells with an intricate organization. The thickness of the skin is determined by the dermis, which is one of the many layers of the skin. Men and women have varying levels of body mass. A woman's body is thinner than a man's at 45 years of age, and after menopause, this thickness begins to decline by 10 percent. As a result, the amount of UV radiation absorbed by women's skin is more than that absorbed by men's skin. Basal cell carcinoma is the most prevalent kind of skin cancer. Skin cancers such as squamous cell carcinoma and malignant melanoma are very frequent. Basal cell carcinoma affects about eight out of ten skin cancer patients. In most cases, this kind of skin cancer develops over time and is brought on by exposure to ultraviolet (UV) radiation. There is a risk that the disease may spread to other parts of the body if it is not treated. Squamous cell skin carcinoma affects around two out of every ten cancer patients. These often appear on areas of the body that have been exposed to the sun. Cancer of the melanocytes (melanocytes are the cells that produce pigment) is another kind of malignant melanoma that may arise. Melanoma is mostly caused by exposure to ultraviolet light. Ultraviolet radiation may be emitted by the sun or tanning booths, for example (Schmidt et al.,

2015). "Tanning beds are carcinogenic to humans and persons who begin using tanning equipment before the age of 30 are 75 percent more likely to acquire melanoma," according to the International Agency for Research on Cancer. The primary cause of skin cancer in the world is exposure to ultraviolet (UV) radiation, and several antihypertensive medicines may behave as carcinogens by absorbing UV radiation straight from the sun.

1.3.2 Cancer of the breast

Cancer is one of the most severe and deadly illnesses, and breast cancer is currently the most frequent form of cancer among women. Breast cancer is a leading cause of death among women, and antihypertensive medicines have been linked to the development of cancer (Yu & Wang, 2016). Cellular self-renewal and diverse heredity of malignant cells are generated by cancer stem cells inside the stem cell. Adiponectin may have a role in the development of cancer cells in certain types of cancer, such as breast cancer. Adiponectin is synthesized and secreted by adipocytes in the adipose tissue. Breast cancer may be linked to an increased production of adiponectin. Despite the fact that antihypertensive medicines are expected to reduce this synthesis, certain antihypertensive drugs, such as metoprolol, do not reduce this production. Several antihypertensive treatments have been shown in the past to raise plasma adiponectin levels (Liu et al., 2016). Using metoprolol, researchers found that adeponectin plasma concentrations did not change, but that LDL cholesterol levels rose, which may raise the risk of breast cancer (Yilmaz et al., 2007). Drinking alcohol, changing one's diet, and adopting a more unhealthy lifestyle are all linked to an increased risk of breast cancer (Shareef, Ashraf, & Sarfraz, 2016). Studies looking for a link between antihypertensive medications and breast cancer have shown mixed results. Breast cancer has been linked to the hypertension diuretic, which is a kind of drug. Breast cancer may also be caused by calcium

channel blockers, since both of these medicines suppress cell death, which in turn affects insulin production and metabolism. Antihypertensive medicines have been linked to breast cancer in certain instances, while others have not. Changes in medication formulation, such as from prolonged release to quick release, enhance the likelihood of this happening (Babette S. Saltzman, 2013). Antihypertensive drugs have been linked to a decrease in apoptosis, which may raise the risk of breast cancer, according to a research published in the Journal of Clinical Pathology.

1.3.3 Cancer of the renal cells

Renal cell carcinoma is the most prevalent kind of cancer to occur in kidney tissue (Richardson & Hamra, 2010). RCC has a much higher annual mortality-to-rate ratio than other urological cancers, and its incidence has been steadily increasing since the late 1990s. Tumors of the renal cells are often irregular in shape. Around 200000 people are diagnosed with renal cell carcinoma each year around the globe (Waxman, Kenny, & Ngan, 2008). 90% of kidney tumors are renal cell carcinomas. RCC is the most common kind of kidney cancer. RCC is the most lethal of the genitourinary tumors, with an annual mortality toll of more than 100,000 patients and a global incidence of roughly 2,00000 new cases (Lv et al., 2014). Adiponectin, a cytokine secreted by adipose tissue, plays a vital role in the growth of several types of cancer. Patients with RCC who have low levels of adiponectin in their serum or plasma have been shown to have an aggressive phenotype as well as higher rates of metastasis. Exogenous adiponectin has also been shown to regulate cell growth and death in a variety of natural processes, including tumor progression. Some cancers, particularly renal cell carcinoma (RCC), have been shown to have adiponectin receptors 1 and 2, which regulate the hormone (Ito et al., 2017). Antihypertensive medication usage was linked to an

increased risk of cancer in a Danish population-based and statistical analysis of 335682 persons. Antihypertensive medicines are linked to an increased risk of cancer, according to one research. Several antihypertensive medication classes were employed in this research. Among persons aged 30 to 85, they discovered that diuretics, ACE inhibitors, beta blockers, and calcium antagonists all had good results (Fryzek et al., 2005). Hypertension medicines are meant to reduce this quantity of production, however certain antihypertensive drugs, such as lisinopril, instead enhance this production (Yilmaz et al., 2007).

1.3.4 Cancer of the prostate

Prostate cancer (PC) is the second most common cause of death in males in Western countries and the most common illness found in these individuals. In Canada, half of all PCs occur beyond the age of 70, which is the point at which men are most likely to be prescribed heart medication. There has long been a belief that cardiovascular drugs, such as those used to treat hypertension, might cause health problems. There is no conclusive evidence that diuretics are linked to an increased risk of developing renal cell carcinoma, according to recent studies on the subject. Despite the fact that these treatments are often offered to men in the highest risk group for prostate cancer, few studies have looked at the relationship between prostate cancer risk and the use of antihypertensive medications. A better understanding of prostate cancer physiopathology and the eventual development of novel chemopreventive operators may be gained by evaluating this link (Linda Perron, 2004). There is a broad usage of antihypertensive drugs in wealthy nations. Prostate cancer risk might be affected by these medicines, and this could have implications for public health.

1.3.5 Cancer of the colon

Colorectal cancer is one of the most common and lethal of all major cancers, occurring most often in the elderly. Colorectal cancer is the leading cause of death among women in Japan. This is because estrogen, a key player in apoptosis, has been disrupted. Apoptosis is slowed when estrogen levels are disrupted, which may contribute to cancer in women. However, because of the role of estrogen in colorectal cancer, men are more likely than women to get the disease (Honma et al., 2011). Antihypertensive medicines are now being linked to an increased risk of colorectal cancer as an adverse drug reaction (ADR).

1.3.6 Gastrointestinal Malignancy

It is estimated that gastric malignancy accounts for roughly 10% of all invasive illnesses globally and is the second most common cause of tumors to spread. No matter how rare it may be now, stomach growth is still a serious problem, especially in Asian countries. Patients with stomach growth are more likely to have recurrences of tumors after corrective surgery because gastric illness is often studied at a rapid pace. Patients with proximal and distal repetitions do not benefit from surgical therapy alone (Liao et al., 2010). Gastric cancer is three times more common in men than women in Japan, and it tends to develop in adults over the age of 40. Due to the fact that women's hormones protect them against carcinogenic elements, this may be the reason.

1.4 Susceptibility to cancer due to using antihypertensive drugs between male and female

Antihypertensive medications have a greater ADR in women than in men. Among all females using antihypertensive medicines, women under the age of 50 are more likely to have adverse reactions (ADR) (Kajiwara et al., 2014). Several previous studies have shown that women have a risk that is three to four times greater than that of males (Heck et al., 2010). Renal cell carcinoma is 19 percent more often in black people than in white people, and in black women, it is 4% more likely than in white women, according to the annual surveillance of US citizens. Age-related prevalences of 39 percent and 28 percent for highly differing males, and 41 percent and 27 percent for highly contrasting women, were found in NHANES data from 1999 to 2004. (Waxman et al., 2008). Among newly diagnosed kidney cancer patients, both men and women between the ages of 20 and 79 were surveyed in Michigan and Chicago. This research found that hypertension is associated with an increased incidence of renal cell carcinoma in both black and white women (Richardson & Hamra, 2010). Renal cancer is more common in the Czech Republic than in any other nation in the globe, including those in central and eastern Europe. Women outnumbered males by a margin of 20.1% to 10.2% among a sample of 100,000 people, according to the data. The study's goal is to determine if prior use of antihypertensive medicine is associated with an increased risk of cancer, taking into consideration the kind of hypertension medication used and the gender differences in cancer incidence.

Chapter 2 : METHODOLOGY

2.1 Signal Sources

For the purpose of determining if antihypertensive medicines are linked to cancer, I used data from the WHO Global Pharmacovigilance Data Base. The database's name is VigiBase, and it may be accessed through a web application called VigiAccess. Non-healthcare professionals and healthcare professionals alike may provide information about an undesirable impact at the outset. Potential ADRs may also develop through the reporting of multiple literatures, irregular trials, multiple studies, and SDRs.

2.2 Detection of signals

Qualitative and quantitative methods of signal detection are available. The quantitative technique is used here. Drug-event pairings that occur at a high rate in big datasets may be identified using this statistical approach. Data mining is another name for this approach. These include ROR, ROR, PRR, IC, and EBGM as well as a few more. To describe any process of automatically and continually extracting usable information from enormous volumes of data, the phrase "data mining" has been used. The regulatory agencies' pharmacosurveillance methodologies, information, and threshold for adverse drug response signals.

Table-1.1: Signal detection methods (I et al., 2014)

Method	Regulatory agency	Information used	Criteria for the detection of signal
PRR	TGA, MHRA	[A/(A + B))/(C/ (C + D)]	PRR ≥2, A ≥ 3, X^2 ≥ 4
ROR	Netherlands Pharmacovigilance Foundation Lareb	(A/B)/(C/D)	Lower limit of 95 % CI ≥1, A ≥ 2
BCPNN	Uppsala Monitoring [(WHO) Vigibase]	Log2 [p(x,y)/ p(x)p(y)]	Lower limit of 95 % CI >0

2.3.Signaling Method

Antihypertensive medications' cancer-causing side effect was detected using the proportional reporting ratio (PRR). The 2 x 2 table is used for signal identification in several approaches. Vigibase data is used to assist the computation of this approach. These signaling criteria were employed to identify signals in European nations, the United Kingdom, and Australia. The following are the PRR's primary standards: Each case with the suspect medication P and an adverse event R is counted as a single instance with "a." „b is the number of individual instances containing the questionable medical product P, but not including any additional adverse events, but R. The number "c" represents the total number of instances involving the event R and any other medication other than P. Any additional adverse effects other than R and any other medical items that are not P are counted as "d."

Table-2.1: 2 × 2 table of the disproportionality analysis of the proportional reporting ratio (Lerch et al., 2015)

Medicines	Drug of interest	All other drugs
Reaction of interest	a	b
All other interaction	c	d

2.4 Selection of method

The PRR is an example of a disproportionality metric that is regularly employed. This is the approach we use in our research. The PRR may be calculated as follows.

Table-2.2: Method of proportional reporting ratio

Method	Regulatory agency	Information used	Criteria for the detection of signal
PRR	TGA, MHRA	[a/(a + b))/(c/ (c + d)]	PRR ≥ 2, a ≥ 3, χ^2 ≥ 4

As a type of contingency table, the reports received from all around the globe are automatically combined. In order to develop the signal of proportional approach, we employed VigiAccess, which is a statistical program that analyzes data. When comparing antihypertensive medicines in a database to a given kind of cancer response, it is possible to

estimate the percentage of that reaction that occurs. As a result of this calculation, a 2 x 2 contingency table known as the proportional reporting ratio (PRR) is calculated. An unfavorable incident may be determined by using the proportionate reporting ratio (PRR). Antihypertensive medicines may cause cancer as a side effect (Pizzoglio et al., 2012). PRR and chi-square may be used to determine the signal's intensity. In VigiAccess, the data analysis system, the chi-square value is often employed. As an alternative to the Chi-square, the following computation is performed to determine if the medical product P and the adverse event R are linked.

In other words, the sum of the first two terms is equal to the sum of the first two terms in the second term.

$$\chi 2 = (ad - bc)2 (a + b + c + d) /[(a + b)(c + d)(a + c)(b + d)]$$

VigiAccess data helped us determine the criteria for all classes of antihypertensive medicines with cancer-related side effects that were reported between 2000 and 2016.

Table-2.3: Example of a PRR calculation-Lisinopril and cancer

Adverse event	**Lisinopril**	**All other drugs**	**Total**
Cancer	378	215	a+b= 593
All other interaction	40822	76642	c+d=117464
Total	a+c= 41200	b+d=76857	a+b+c+d=118057

PRR= 378/41200 divided by 215/76857 = 3.21

Chi-square value= 218.26

Like this calculation we found the result of PRR and chi-square for all antihypertensive drugs we choose for our study.

Chapter 3 : Result

Table: 3.1: Pharmacovigilance study of antihypertensive drugs

Group of Antihyper-tensive drugs	Drug substance	Number of reports(a)	No. of reports: Female	No. of reports: male	PRR value	Chi-square value
ACE inhibitors	Lisinopril	378	62%	38%	3.21	218.26
	Captopril	58	75%	25%	0.039	51.45
	Enalapril	52	41%	59%	0.18	175.67
	Quinapril	90	69%	31%	3.78	157.02
	Ramipril	113	51%	49%	0.97	0.04
Beta blocker	Metoprolol	609	56%	44%	2.77	219.34
	Atenolol	191	63%	37%	0.61	39.04
	Betaxolol	7	100%	0%	0.34	8.68
	Bisoprolol	61	37%	63%	0.47	34.48
	Propranolol	81	67%	33%	0.41	59.48
Calcium Channel Blockers	Amlodipine	508	56%	44%	2.16	72.717
	Verapamil	84	45%	55%	0.62	16.23
	Felodipine	28	58%	42%	0.38	27.31
	Nifedipine	167	47%	53%	0.65	23.57

Diuretics	Furosemide	150	52%	48%	0.62	6.593
	Bumetanide	8	10%	90%	1.06	0.03
	Metolazone	4	63%	37%	0.566	1.292
	Torasemide	22	35%	65%	1.63	4.69
	Thiazide	157	49%	51%	2.09	9.87
Angiotensin II receptor blockers	Losartan	119	60%	40%	0.42	76.619
	valsartan	447	54%	44%	2.90	189.32
	Eprosartan	33	67%	33%	1.82	11.898
	Irbesartan	73	51%	49%	0.45	43.95

3.1 Antihypertensive drug-cancer interactions

Because antihypertensive medicines are linked to cancer in table 3.1, this association may be explained.

3.1.1 Inhibitors of ACE

Some ACE inhibitors have a high incidence of cancer as an adverse drug reaction (ADR). Lisinopril, captopril, enalapril, quinapril, and ramipril are some of the other often prescribed

blood pressure medications. The number of reports for lisinopril is 378, which is greater than other ACE inhibitors, according to table 3.1. These numbers are again: Captopril (58), Enalapril (52), Quinapril (90) and Ramipril (113). Lisinopril is the sole ACE inhibitor to display a positive PRR value, although this is not the only ACE inhibitor to show a positive PRR. The PRR value is used to determine whether or not an adverse response to a medicine is positive or negative. Table 3 tells us that if the value of PRR is more than 2, the outcome of PRR will be true. Lisinopril has a PRR rating of 3.21, which indicates a high volume of reporting. It's also worth noting that the PRR values for captopril (0.039), quinapril (0.018), and ramipril (0.097) are all less than one. From this number, it is clear that quinapril's PRR value of 3.78 is similarly positive. This suggests that quinapril may exhibit cancer as an ADR. However, the PRR score alone cannot show the success of the ADR. The chi-square value also influences the outcome. It is only when both PRR and chi-square indicate a positive number that we will really have a positive result. It's worth noting that the Chi-square values for the various medications are as follows: 218.26; 51.45; 175.67; 157.02; and 0.04 for lisinopril; enalapril; and quinapril. For lisinopril, captopril, enalapril, and quinapril, the chi-square value is in the positive range of 100 to 200. It is obvious from table-2.2 that only if the number of reports exceeds 3 and the chi-square value is more than or equal to 4 can a result be considered positive for ramipril. Since PRR is more than 2, and chi-square is greater than 4, we may conclude that lisinopril and quinapril are the most effective ACE inhibitors, based on our analysis.

3.1.2 Beta blockers

Drugs such as metoprolol, atenazol, betazolol, bisophazolol, and propranil have a greater risk of causing cancer than other beta blockers. Table-3.1 shows that metoprolol has the most

signals of all the beta blocker medicines, with a total of 609 reports. Atenolol, betaxolol, bisoprolol, and propranolol have signal numbers of 191, 7, 61, and 81, respectively, though they are much lower than metoprolol's. As shown in the table (3.1), PRR is true if the value of PRR is greater than 2. Further, if the report is greater than 3 and the chi-square value is greater than or equal to 4, we may conclude that the results are positive. Metoprolol is the only beta blocker to have a PRR more than 2 and a chi-square value of 219.34, thus we can conclude that it is the most effective beta blocker. Other medicines with PRR values smaller than 1 include atenolol, bisoprolol, betaxolol, and propranolol. However, the chi-square values of all beta blockers show a positive result, proving that beta blockers and cancer have some kind of link.

3.1.3 Blockers of the calcium channels

Amlodipine, verapamil, felodipine, and nifedipine are calcium channel blockers that are associated with an increased risk of cancer as an adverse medication response. Table 3.1 shows that amlodipine has the highest number of reports, followed by nifedipine in second place. As a result, there have been 508 and 167 reports of adverse reactions to amlodipine and nifedipine, respectively. Verapamil and felodipine are the two CCBs, and the number of reports for them is 84 and 28 respectively, which is much smaller than the others. As shown in the table (3.1), PRR is true if the value of PRR is greater than 2. There is a PRR value of 2.16 for amlodipine, verapamil, felodipine and nifedipine. As a result, only amlodipine's PRR value of 2.16 is positive, whereas the PRR value for the other drugs is negative since it is less than 1. In addition to the PRR value, the number of reports and the chi-square value all play a role in determining whether or not a result is positive or negative. Only if the report is more than 3 and the chi-square value is greater than or equal to 4 is the outcome positive.

Amlodipine, verapamil, felodipine, and nifedipine all had chi-square values of 72.717, 16.23, 27.31, and 23.57, respectively. All of the medications have a positive chi-square value. When the number of reports, PRR and chi-square values are all taken into account, the outcome is only positive for amlodipine, which has 508, 2.16, and 72.717 values.

3.1.4 Diuretics

Furosemide, bumetanide, metolazone, and torasemide are the diuretics most often associated with an increased risk of cancer-related side effects. Each medicine has a varied amount of reports. As shown in table 3.1, furosemide, bumetanide, metolazone, and torasemide each received 150 reports. Because of this, furosemide has a larger number of reports than other drugs. As shown in the table (3.1), PRR is true if the value of PRR is greater than 2. Furosemide, bumetanide, metolazone, and torasemide had PRR values of 0.62, 1.06, 0.566, and 1.63, respectively, according to the FDA. Only if the report is more than 3 and the chi-square value is greater than or equal to 4 is the outcome positive. Furosemide, bumetanide, metolazone, and torasemide had chi-square values of 0.62, 1.06, 0.566, and 1.63, respectively. All diuretics were shown to have a negative effect on the number of reports, the PRR value, and the chi-square value.

3.1.5 Blockers of angiotensin II receptors

Angiotensin II receptor blockers may cause cancer in certain patients. In addition to irbesartan, losartan, and valsartan, there is also eprosartan. It is obvious from the data in table 3.2 that valsartan has the highest number of reports compared to other Angiotensin II receptor

blockers, with 447 complaints. This figure is 119, 33, and 73 for losartan, eprosartan, and irbesartan, respectively. The PRR value is used to determine whether or not an adverse response to a medicine is positive or negative. Table 3.2 tells us that if the value of PRR is more than 2, the outcome of PRR will be true. Valsartan's PRR rating is 2.90, which indicates a significant volume of reporting. Finally for losartan, eprosatol and IRB, the PRR values are 0.42, 1.82 and 0.55. The PRR value of 2.90 for valsartan may easily be deduced from this result. This suggests that valsartan may exhibit cancer as an ADR. The PRR figure, on its own, cannot demonstrate that the ADR was successful. The chi-square value also influences the outcome. It is only when both PRR and chi-square indicate a positive number that we will really have a positive result. This means that losartan has a chi-square value of 76.619 while the other three irbesartans have a chi-square value of 11.898 and 43.995. All of the medications have a positive chi-square value. Only valsartan was shown to have a favorable PRR, chi-square, and number of reports.

Table 3.2: Antihypertensive drugs for high amount of signals

Antihypertensive drugs	**Overall signals**
Metoprolol	609
Lisinopril	378
Valsartan	447
Amlodipine	508

So overall from table 3.1 and table 3.2, we can say that there is relationship between cancer and antihypertensive drugs.

3.2 Types of antihypertensive drugs that can cause cancer

Four medications in the table matched the PRR and chi-square value minimum criterion, according to this technique. The other medications satisfied the chi-square criterion, but not the PRR requirements. Table 3 shows the VigiAccess signals and the derived PRR and chi-square values. ACE inhibitors, beta blockers, calcium channel blockers, and angiotensin II receptor blockers are all linked to an increased risk of cancer when compared to other antihypertensive drugs.

3.2.1 Acetylcholinesterase

All except ramipril have a positive chi-square value, which is unusual. Due to its negative chi-square value and negative PRR value, ramipril has no chance of manifesting cancer as an adverse medication response. The PRR and chi-square values for ramipril are both 0.97. In the same way, the PRR values of captopril and enalapril are both negative and the chi-square values are both positive. Captopril and enalapril had PRR values of 0.039 and 0.18, respectively, proving that they have no connection to cancer. Quinapril also has a low report, but a favorable chi-square value and PRR value. Using the chi-square and PRR values, quinapril has been shown to be associated with cancer. Lisinopril has received more adverse event reports than any other ACE inhibitor. Lisinopril has a PRR of 3.21 and a chi-square of 218.26, which means that it has a high risk of cancer.

3.2.2. Beta blockers

Metoprolol had the highest number of reports, the highest PRR value, and the highest chi-square value among all beta blockers, according to table 3.1. P-value for the PRR is 2.77; chi-

square is 219.34. All of these evidence points to a link between metoprolol and cancer. In addition, there are various beta blockers such as atenolol, bisoprolol and propranol. Propranolol has a high chi-square value, but a very low PRR value. Propranolol's chi-square and PRR scores are both 59.48. A positive number of reports and a positive chi-square value demonstrates that propranolol does not cause cancer, despite the fact that the PRR value for the drug is negative. Atenolol has a large number of reports and a high chi-square value of 191 and 39.04. In other words, both of these values indicate that atenolol might induce cancer as an adverse reaction. Atenolol, on the other hand, has a PRR of -0.61, which is a negative number. Atenolol and cancer have no connection since the PRR value is less than 2. The chi-square value for bisoprolol is 34.48, which is not significantly less. Betaxolol's 8.8 is the lowest of all beta blockers in this category. Hence, all beta blocker medications have a favorable chi-square value. However, all beta blockers except metoprolol have a PRR value that is negative, making it impossible to infer the ADR from the positive chi-square values. ATENOLOL, BETATOOL, BISOPROOL, and PROPRANOLOL have a PRR value of 0.61, 0.34, 0.54, and 0.41, respectively. When it comes to beta blockers, metoprolol has a far higher risk of cancer than other drugs.

3.2.3. Calcium channel blockers

Only amlodipine has a positive chi-square value, PRR value, and total number of reports. Table 3.2 shows that amlodipine is the most often reported CCB antihypertensive medicine, with a total of 508 reported cases. Table 3.1 shows that amlodipine has a PRR value of 2.16 and a chi-square value of 72.717, both of which are positive values. Verapamil, felodipine, and nifedipine are some of the other CCB medications. Despite the fact that verapamil's chi-square value of 16.23 is low, it's still a good number since it's greater than 3. The chi-square

values for the other two medicines, felodipine and nifedipine, are also positive, with 27.31 and 23.57, respectively. Despite this, verapamil has a PRR value of 0.62, which is negative since it is less than 2. As a result of its negative PRR score, verapamil has no link to cancer. Felidipine also has 28 reports, which is a real quantity, and a PRR score of 0.38. The PRR number for felodipine, on the other hand, is zero, indicating that the drug has no connection to cancer. Finally, there have been 167 reports of nifedipine use. Nifedipine's PRR value is a negative 0.65, demonstrating that the drug has no connection to cancer.

3.2.4 Diuretics

Table 3.1 shows that just two medicines, furosemide and thiazide, had a large number of reports. Only bumetanide, metolazone and torasemide fall within this category. Compared to other antihypertensive medicines, the frequency of reports and the chi-square value and PRR value are likewise low. Furosemide has a significant number of reports, yet the PRR value is modest. Furosemide, on the other hand, has a positive chi-square value. For thiazide, the number of reports is rather large, and the PRR value is more than 2 and the chi-square value is greater than 3. Thiazide has been linked to cancer by the frequency of reports, the PRR value, and the chi-square value. Table 3.1 shows that the total number of reports for furosemide is 150, the chi-square value is 6.593, and the PRR value is 0.62, with the PRR value being solely negative and the other values being positive. There is no link between cancer and furosemide since the PRR value is negative. For bumetanide, the number of reports and the chi-squared and PRR values are both low, as is the chi-squared value. Eight reports were detected in VigiAccess, and the chi-square value is 0.03 and the PRR value is 1.06. To investigate the link between Metolazone's diuretic properties and cancer, we chose to investigate its cancer-related properties as well. Metolazone has fewer reports than any other diuretic. Metolazone's PRR and chi-square values are likewise poor. The PRR value for

metolazone is 0.566 and there have been four reports. For metolazone, the Chi square value is likewise less than 3 (1.292) and so a negative number as well. As a result, we may conclude that metolazone does not cause cancer based on its PRR and chi-square values, which are both negative. Finally, there have been few instances of side effects with torasemide. Other than that, the PRR and chi-square values are likewise poor. The PRR value of torasemide is 1.63 which is less than 2 and the chi-square value 4.69. While PRR is negative since it is less than 2, torasemide has a positive chi-square value because it has a value of higher than 3. So torasemide is not related with cancer. This data clearly shows that diuretics do not increase the risk of cancer.

3.2.5 Drugs that inhibit angiotensin II receptors (ARBs)

Losartan and valsartan are the two most often reported ARB-associated cancer cases, according to a search of VigiAccess. There are 447 reports of valsartan among all ARBs compared to losartan in table 3.1, which is a significant number of reports. Losartan has a p-value of 119, substantially lower than valsartan's p-value of 119. Valsartan has a chi-square value of 189.32 and a PRR value of 189.32 for ARBs. Cancer and valsartan have been linked by a large number of reports, chi-square value, and PRR value. Eprosartan has 33 reports and a chi-square value of 11.898, both of which are over the threshold of 3. Nonetheless, the PRR value is negative since the number is 1.82, which is near to the value of two. As a result, eprosartan is not linked to cancer. For irbesartan, there have been 73 reports, which is an encouraging quantity, and the chi-square value is 43.95, which is encouraging as well. However, the negative PRR value of 0.45 means that ARBs and cancer are not linked. This time around, losartan has a favorable chi-square value of 76.619. In other words, all of the medications have a positive chi-squared value. Valsartan, on the other hand, has a PRR rating

that is solely positive for this drug. However, despite the fact that the report for losartan isn't that bad, the PRR score we calculated was negative for this medicine.

Table-3.3: PRR value for antihypertensive drugs

Group of Antihypertensive Drugs	Drugs	PRR value	Chi-square value
ACE inhibitors	Lisinopril	3.21	218.26
ACE inhibitors	Quinapril	3.78	157.02
Beta blockers	Metoprolol	2.77	219.34
Calcium Channel Blockers	Amlodipine	2.16	72.717
Diuretics	Thiazide	2.09	9.87
Angiotensin II receptor blockers	Valsartan	2.90	189.32

3.3 Types of cancer due to using antihypertensive drugs

3.3.1 ACE inhibitors

Some ACE inhibitors have a high incidence of cancer as an adverse drug reaction (ADR). Lisinopril, captopril, enalapril, quinapril, and ramipril are some of the other often prescribed

blood pressure medications. Lisinopril was the most often reported medicine in table 3.2, with a total of 378 reports. This medicine has been linked to many different forms of cancer. Breast cancer, prostate cancer, neoplasm malignant, bladder cancer, skin cancer, and thyroid cancer are the most often reported forms of cancer in large numbers, according to table 3.4. Table 3.4: Common cancer types reported in high numbers. Additionally, ACE inhibitors are linked to an increased risk of developing cancers other than lung and breast in patients with these organ systems. Neoplasm stage instances of new cancer have also risen in recent years. There have been a few instances of breast cancer, skin cancer, bladder cancer, and kidney cancer associated with captopril, although these are by no means common. In addition, a significant number of cases of neoplasm, colon cancer, prostate cancer, thyroid cancer, and breast cancer have been reported with quinapril. Enalapril and ramipril have also been linked to an increased risk of skin cancer, while the number of documented cases is low.

Table-3.4: Reports of cancer for ACE inhibitors

		Types of cancer							
Drugs		NM	BRC	PC	LNM	BC	SC	CC	GC
	Captopril	8	2	8	5	1	3	8	4
	Ramipril	5	13	0	4	2	11	4	3
	Lisinopril	39	67	22	25	12	13	12	5
	Quinapril	10	13	15	7	9	14	15	19

	Enalapril	5	2	0	2	1	3	0	1

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.2 Beta blockers

Atenolol and propranolol are the beta blockers that we found in our study of the medications. Table 3.2 shows that metoprolol has a large number of reports and a high PRR and chi-square value. According to table 3.5, the incidence of breast cancer, prostate cancer, skin cancer, colon cancer, and malignant neoplasms is high. There are several reports of neoplasms. Here are a few examples: malignant tumor of the lungs, brain, thyroid, and hepatic. Endometrial cancer, uterine cancer, ovarian cancer, thyroid cancer, and pancreatic cancer are some of the additional cancers that are often described in the medical literature. Atenolol has a significant number of reports of malignant neoplasms, breast cancer, and prostate cancer, as well. Only malignant neoplasms have been reported with betaxolol, which has a relatively low number of reports. Bisoprolol is also known to cause skin cancer, rectal cancer, and breast cancer. In addition, there are colon cancer, gallbladder cancer, hepatocellular carcinoma, and basal cell carcinoma among the other forms. All of them, however, are quite rare. Propranolol has been recorded in 81 cases, and phaeochromocytoma, Neoplasm malignant has been documented in a significant percentage of those cases..

Table-3.5: Reports of cancer for beta blockers

Types of cancer

		NM	BRC	PC	LNM	BC	SC	CC	GC
Drugs	Metoprolol	102	79	38	35	14	23	18	7
	Atenolol	14	15	11	8	7	3	3	6
	Betaxolol	3	2	0	1	0	0	0	1
	Bisoprolol	5	4	3	2	1	7	2	0
	Propranolol	11	2	1	1	1	3	1	1

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.3 Calcium Channel Blockers

Only amlodipine has a large number of reports in the class of Calcium Channel Blockers, at 508 in table 3.2. Table 3.6 shows that neoplasm malignant, breast cancer, prostate cancer, lung neoplasm malignant, colon cancer, and pancreatic carcinoma all occur in large numbers. Neoplasm stage instances of new cancer have also risen in recent years. Examples of these sorts of tumors include breast, thyroid, hepatic, pancreatic and pancreatic neoplasia. Other forms of cancer, such as hepatic cancer, ovarian cancer, bone cancer, uterine cancer, and throat cancer, are frequently recorded, although their numbers are not substantial. As with nifedipine, the incidence of cancers of the stomach, prostate, and colon is particularly high when the drug is used. There are a small number of other types of cancer as well, such as hepatic, renal, thyroid, cutaneous, and laryngeal. In addition, the number of instances is lower

for verapamil and felodipine than for amlodipine and nifedipine. It has been reported that verapamil and felodipine have a cancer risk of 84 and 28 per cent, respectively. Both verapamil and felodipine have been linked to an increased risk of breast cancer and neoplastic malignancy across all cancer types. Cancers such as ovarian and skin cancers occur less often than other types of cancer.

Table-3.6: Reports of cancer for Calcium Channel Blockers

	Types of cancer								
Drugs		NM	BRC	PC	LNM	BC	SC	CC	GC
	Amlodipine	59	71	41	26	9	12	4	7
	Verapamil	11	10	14	10	3	1	1	3
	Felodipine	5	2	0	2	0	2	2	2
	Nifedipine	30	23	13	14	6	10	10	14

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.4 Diuretics

Furosemide, bumetanide, metolazone, and torasemide are among the most regularly used diuretics for treating hypertension. An alarmingly high number of malignant tumors have been reported in association with furosemide use in patients taking the drug, as shown in table 3.7. These tumors include: neoplasm malignant (13), breast cancer (6) and atypical tumors in the prostate and lung (10) Marrow hyperplasia (3), non-small cell lung cancer (3),

prostate cancer metastatic (3), uterine leiomyoma (3), basal cell carcinoma (2), bone cancer (2), Bowen's disease (2), gammopathy (2), haemangioma (2), haematological malignancy (2), hepatocellular carcinoma (2), leukemia (2), lymphoma (2), malignant melanoma (2), metastases to lung (2), and metastasis (2 Neoplasm stage instances of new cancer have also risen in recent years. Examples of these sorts of tumors include breast, thyroid, hepatic, pancreatic and pancreatic neoplasia. Breast cancer, skin cancer, and lung neoplasm malignant are all cancers that have been reported for bumetanide (1). Again, the frequency of metolazone-related reports is very low, with the sole exceptions being prostate cancer and malignant lung neoplasms. There are essentially two forms of malignancy reported for torasemide: neoplasms malignant (5), and lung tumors malignant (4). Prostate cancer, skin cancer, colon cancer, and stomach cancer are among cancers that are reported in low numbers (1).

Table-3.7: Reports of cancer for Diuretics

		Types of cancer						
		NM	BRC	PC	LN	SC	CC	GC
	Furosemide	13	6	10	7	11	4	8
	Bumetanide	0	2	0	2	1	0	0
	Metolazone	0	0	1	1	0	0	0

Drugs	Torasemide	5	0	1	4	1	2	1
	Thiazide	17	16	5	5	4	2	5

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.3.5 Angiotensin II receptor blockers

Only valsartan has a considerable number of reports out of all the angiotensin II receptor blockers, at 447. As shown in table 3.8, the prevalence of cancerous tumors (61), breast cancer (58), renal cancer (16), prostate cancer (28) and cancer of the pancreas, kidney, lung, bladder, thyroid, pancreatic, thyroid, and thyroid, cancerous tumors, cancerous tumors, skin cancer (5), colon cancer (21) and gastric cancer (6) is very high. Other forms of cancer, such as hepatic cancer, ovarian cancer, bone cancer, uterine cancer, and throat cancer, are frequently recorded, although their numbers are not substantial. Neoplasm stage instances of new cancer have also risen in recent years. Brain tumors (12), breast tumors (4), gastrointestinal tumors (4), metastatic liver cancer (4), thyroid tumors (4), thyroid nodules (4), liver tumors (4), pancreatic nodules (4), and lung nodules (42) are examples of these kinds. Losartan has 119 instances, and the most common cancers are breast cancer (9), renal carcinoma (5), prostate cancer (6), pancreatic carcinoma (9), thyroid cancer (9), lung malignant neoplasm (12) and bladder and skin cancers (four and twelve respectively) which are given in the table 3.8. A few additional cancers have also been reported, such as pancreatic cancer (4), esophageal cancer (4), basal cell carcinoma (3), colon cancer (3), neoplasm (3), plasma cell myeloma (3), renal cell carcinoma (3), uterine leiomyoma (3), and

the cancer of bile ducts (2), but these are the most common. Neoplasm-stage malignancies include biliary and bladder neoplasms as well as hepatic and colon cancers as well as salivary gland and biliary cancers. In addition, eprosartan has been linked to an increased risk of malignant neoplasms (7 cases), breast cancers (2 cases), renal cancers (1 case), prostate cancers (2 cases), lung neoplasms malignants (2 cases), bladder cancers (1 case), skin cancers (4 cases), colon cancers (2 cases), and renal cancers (1 case). When it comes to the ARB category of drugs known as irbesartan, reports are high exclusively for malignant neoplasms (13), breast cancer (8), skin cancer (9), and kidney tumors (6). (5).

Table-3.8: Reports of cancer for Angiotensin II receptor blockers

Types of cancer									
Drugs		NM	BRC	PC	LNM	BC	SC	CC	RC
	Losartan	16	9	6	12	4	12	4	5
	Valsartan	61	58	28	25	10	5	21	16
	Eprosartan	7	2	2	2	1	4	2	1
	Irbesartan	13	8	2	3	1	9	1	5

NM=Neoplasm malignant, BRC=Breast cancer, PC=Prostate cancer, LN=Lung neoplasm malignant, BC=Bladder cancer, SC=Skin cancer, CC=Colon cancer, GC=Gastric cancer

3.4 Susceptibility to cancer due to using antihypertensive drugs between male and female

3.4.1 Inhibitors of ACE

Enalapril seems to be the only ACE inhibitor to exhibit a higher proportion of reports from women than men. Enalapril has a female reporting rate of 41%, compared to a male reporting rate of 59%. Other ACE inhibitors including lisinopril (62% of females), captopril (75% of females), quinapril (69% of females), and ramipril (51% of females) are more likely to cause cancer in women than in men.

3.4.2 Blockers of beta peptides

Table 3.1 shows that from all beta blockers except bisoprolol, the number of reports for females is higher than for males. Compared to males, the proportion of reports from females for bisoprolol is just 37%. Metoprolol (female 56%), atenolol (female 63%), betaxol (female 100%), and propranolol (female 67%) are additional beta blocker medicines that are more likely to cause cancer in women than men.

3.4.3 Calcium Channel Blockers

With the exception of verapamil (female 45 percent) and nifedipine, all of the calcium channel blockers listed in table 3.1 had a higher proportion of female reports than male

reports (female-47 percent). Women are more vulnerable to cancer than men while using beta blockers like amlodipine (56 percent) and felodipine (58 percent).

3.4.4 Diuretic medications

In addition, the number of female reports for all of the diuretics listed in table 3.1 is higher than the number of male reports, with the exception of bumetanide (female 10%) and torasemide (female-35 percent). Furosemide (female-52 percent) and metolazone (female-63 percent) are the other diuretic medications that have a higher risk of cancer for women than men.

3.4.5 Drugs that inhibit the angiotensin II receptor

Table 3.1 shows that the number of female reports is higher than the number of male reports for all angiotensin II receptor blockers, including losartan (female 60%, male 40%), valsartan (female 54, male 44%), eprosartan (female 67, male 33%), irbesartan (female 51, male 49%), and metolazone (female 51%, male 49%). (female-63 percent) Compared to men, females are more likely to get cancer.

Chapter 4: Discussion

According to the results of this pharmacovigilance investigation, only a small number of antihypertensive medications have been linked to an increased risk of cancer. VigiAccess data was used in this investigation to the fullest extent possible. WHO compiles ADR data and publishes it in VigiAccess, a database. All of this information is available in a variety of databases compiled by a variety of organizations, making it an invaluable tool for pharmacovigilance research. The accepted technique of determining ADRs for a certain medicine is the proportional reporting ratio. Our results were further supported by the use of chi-square values. The chance of developing a new kind of cancer is also high. Antihypertensive medicines have been linked to an increased risk of cancer, but the cause remains a mystery.

4.1 Antihypertensive drug-cancer interactions

According to the pharmacovigilance research, none of the antihypertensive medications had cancer as an adverse drug reaction (ADR). On the other hand, only a small number of the world's most widely prescribed medications have been linked to cancer. The majority of studies were conducted in medical facilities and focused on various types of cancer in various parts of the body. In most research, the sample size was small, and the duration of follow-up was brief. This is a lengthy follow-up time, but we have all the data from a huge database.

4.1.1 Inhibitors of the ace enzyme

ACE inhibitors are primarily used to lower blood pressure and treat heart failure caused by congestive heart failure. Lisinopril is the most extensively prescribed ACE inhibitor in the world. According to the results of an ACE inhibitor Pharmacovigilance research using the approach of quantitative signal detection, none of the medications in this class are linked to cancer. Only two ACE inhibitors, lisinopril and quinapril, showed an association with cancer in our research; all other medicines had a negative PRR and chi-square value. Perhaps this is due to the fact that lisinopril is one of the most often prescribed hypertension medications in the world, ranking third in 2016 on the website drugs.com. Lisinopril was the most prescribed hypertension medicine in the world. Lisinopril was the most often prescribed antihypertensive medication in both 2011 and 2014. According to Web med, 104 million lisinopril prescriptions were written in 2014, compared to 87.4 million in 2011. The number of reports on this medicine is certain to be considerable, given how widely it is used. ACE inhibitor quinapril is yet another drug used to treat heart failure and for other reasons. Quinapril has been linked to an increased risk of cancer, despite the fact that the number of reports is low. A other research, however, indicated that ACE inhibitors and cancer seem to have a neutral impact on each other. Some studies have shown a connection between the two, but others haven't. All ACE inhibitors are not linked to cancer risk, and only those that have a large number of reports in VigiAccess are linked to cancer.

4.1.2 Beta-blockers

Beta blockers are increasingly being utilized in the treatment of hypertension, and their effects on heart disease and stroke are similar to diuretics. Beta blockers are beneficial in the treatment of heart failure and the reduction of death rates. Beta blockers are the first-line treatment for hypertension in young patients (Ong, 2007). This drug's cancer risk has just been determined to be on the rise. A lack of information on cancer's prevalence in the past has led to a lack of actionable information. However, databases now safeguard all ADR data. For -Blockers, evidence for metoprolol is adequate to determine whether or not cancer will develop. As a consequence, finding our medicine of interest, metoprolol, to ascertain the outcome for the occurrence of cancer risk was simple. Metoprolol may be linked to an increased risk of cancer based on the number of reports in our analysis. However, in order to verify our assumptions, we conduct a pharmacovigilance research. Similarly, we look at other medicines such atenolol, betaxolol, bisofol, and propranalol to see whether they have been linked to cancer. It has been established that no beta blocker medicine has been linked to an increased risk of cancer, and our findings support that conclusion.

4.1.3 Calcium channel blockers

They are often recommended for hypertension and coronary heart disease as an antihypertensive medication. Antihypertensive medicines such as calcium channel blockers have been utilized for the treatment of hypertension over the last two decades. Doubts have been raised over whether or not certain medicines cause heart attacks. A link was found recently between these substances and cancer, according to a research. We found that all CCBs are not linked to cancer in our research. Verapamil, felodipine, and nifedipine are among the various CCB-targeted medicines that we are studying. While both the chi-squared

and PRR values are positive for amlodipine, they are not for any other drug. Amlodipine has been a first-line therapy for high blood pressure for more than two decades. However, the PRR value is negative for other medications including verapamil, felodipine, and nifedipine, proving that none of these three have a cancer risk.

4.1.4 Diuretics

Diarrhea is the most prevalent complication of high blood pressure. According to our findings, there is no link between the use of diuretics and an increased risk of cancer. Furosemide, bumetanide, metolazone, and torasemide are the most common drugs we deal with. However, several studies have been conducted to establish a link between the usage of diuretics and an increased risk of developing cancer. One of the first studies to link diuretic medication with cancer was based on interviews with patients. Diuretic use is linked to cancer in both men and women, according to a recent interview. After doing these investigations, researchers sought to learn more about the link between diuretics and antihypertensive medicines.. All of the studies found a link between the participants and those who had been using antihypertensive medications for an extended period of time. Both the use of thiazides and potassium-sparing diuretics was linked to a low risk of breast cancer in studies conducted. A higher risk of breast cancer was seen in women who used these types of diuretics for an extended period of time. An antihypertensive drug like thiazides may raise the risk of kidney cancer (Keith T. Flaherty1, 2005).

4.1.5 Angiotensin II receptor blockers

Patients who cannot tolerate other inhibitors, such as those with stable coronary artery disease, benefit from angiotensin II receptor blockers, which are the most often prescribed medications for hypertension. In the case of Angiotensin II receptor blockers, it has been shown to be well tolerated and effective, and around 25% of people with hypertension use this medication globally. ARBs (angiotensin-receptor blockers) have been around since 1995 when they were initially licensed for clinical use as an antihypertensive medication. ARBs were originally found when the medication losartan was developed. ARBs were formerly thought to be well tolerated due to safety data gathered from several studies, but new research have shown that the RAAS (the renin–angiotensin–aldosterone system) has certain actions that may cause substantial damage to the human body, such as cancer. The cancer risk may be increased by angiotensin II receptor blockers (Olin et al., 2011). Only valsartan was shown to be associated with an increased risk of cancer in our evaluation of ARB medications. Cancer was shown to be unrelated to the use of losartan, eprosartan, and irbesartan. The number of cancer cases linked to valsartan was significant enough to forecast this drug's involvement in the disease. Eprosartan, like irbesartan, has a somewhat high report, although the reports for losartan and irbesartan are much lower than those for valsartan.

4.2 Antihypertensive medicines that might cause cancer

Antihypertensive medications are used as a first treatment to successfully manage blood pressure. Hypertension may be managed by balancing electrolytes and blood pressure. These medications are very successful in lowering blood pressure and the related mortality and morbidity. Patients who want to keep their blood pressure under control must take a combination of medications, usually two or more at a time, which might have a variety of

undesirable side effects. Vasodilators, ACE inhibitors, diuretics, adrenergic blockers, angiotensin II receptor blockers, calcium channel blockers, beta blockers, and alpha blockers are the most often used antihypertensive medications. People with high blood pressure often begin therapy with a thiazide diuretic as a first line of defense. (Arroll and colleagues, 2008) Diuretics and calcium channel blockers have been linked to cancer in several studies (A. M. Lindgren et al., 2005). However, our research shows that a number of antihypertensive medicines are linked to cancer. All antihypertensive medicines are not linked to cancer risk.

4.2.1 ACE inhibitors

Renal insufficiency care is critical to reducing death rates in patients with heart failure and ACE inhibitors are the most often utilized therapeutic drug in this regard. Because heart failure is a leading cause of death in the elderly The effectiveness of ACE inhibitors has been well-documented in large-scale research. Patients on ACE inhibitors, on the other hand, run the risk of experiencing negative side effects. Our findings on the connection between ACE inhibitors and cancer were mixed when we looked at several studies. Some studies have shown a link between these compounds and cancer, whereas others haven't. We'll need to do a pharmacovigilance research to figure out what's going on here. According to our findings, all ACE inhibitors are not linked to cancer in our research. In our search for a correlation, we focused on five medications, two of which have been shown to be linked to cancer, while the other three have not been linked. We used lisinopril, captopril, enalapril, quinapril, and ramipril for our research. A fairly high PRR result for lisinopril and quinapril indicates that both of these medicines pose a cancer risk. There is no evidence of an association between cancer with captopril, enalapril, or ramipril, since their PRR values are low.

4.2.2 Beta-blocking medication

We conduct a pharmacovigilance research and use the PRR technique, a quantitative pharmacovigilance approach, to fulfill our goals. Metoprolol is marginally connected to cancer risk after utilizing this approach. Metoprolol has a high enough risk score to be considered carcinogenic, according to the research. To test our hypothesis, we utilized our data to conduct a quantitative pharmacovigilance research (PRR and chi-square method). For atenolol, betaxolol, bisoprolol, and propranole, we utilize the same data from VigiAccess reports as we did for metoprolol, and the same quantitative technique to demonstrate that these medicines do not increase the risk of cancer. There is a risk of cancer if beta blockers are taken for more than ten years. As a result of long-term use, there is an elevated danger. Bisoprolol, a beta blocker, has also been linked to an increased risk of cancer (Leung, Hung, Chan, & Mou, 2015).

4.2.3 Inhibitors of Calcium Channels

Amlodipine is the only CCB that has the potential to cause cancer after analyzing the outcomes of CCBs. The activity of programmed cell death may be altered by modifying the calcium concentration within the cell. Damaged cells can't be destroyed properly, which can lead to cancer. Apoptosis is a process that relies heavily on calcium. Calcium channel blockers' increased risk of cancer may be related to this. Again, calcium is implicated in cell death via the permeabilization of mitochondria and the stimulation of phagocytosis. As a result, calcium aids in the prevention of cancer. The risk of cancer is increased by calcium channel blockers, which primarily impede calcium's activity. Li et al. performed a research to examine the relationship between the length of antihypertensive medication usage and cancer risk, and found that short-term use of calcium channel blockers, in particular, is to blame.

CCBs have been linked to an increased risk of cancer in long-term users (Giordano, 2003). This might explain why amlodipine is linked to cancer risk.

4.2.4 Diuretics

According to our findings, thiazide is the only diuretic medicine that carries a moderate risk of cancer development. Many investigations have been conducted to establish a link between diuretics and an increased risk of cancer. An antihypertensive diuretic shows the capacity to cause cancer and may suppress the apoptotic process in cells, which in turn affects insulin production and metabolism. As a primary therapy for cancer, thiazide diuretics, in particular, are often prescribed, although their usage has been linked to an increased risk of renal carcinomas. In Keith T. Flaherty1, 2005, However, individuals who had been on antihypertensive medications for more than five years had an increased risk (Wong-Ho Chow, 1995). As a result, long-term usage of diuretics has been linked to the emergence of cancer in this research. Long-term use of these kinds of diuretics was linked to an elevated risk of carcinoma among women 65–79 years old in the Seattle–Puget Sound metropolitan region, according to a research conducted in the area (C. I. Li et al., 2003).

4.2.5 Blockers of the Angiotensin II Receptor

Patients with hypertension who are unable to tolerate angiotensin II receptor blockers, such as those with stable coronary artery disease, may nevertheless benefit from these medicines. In the case of Angiotensin II receptor blockers, it has been shown to be well tolerated and effective, and around 25% of people with hypertension use this medication globally. But It has been shown that Angiotensin II receptor blockers are linked to an increased risk of cancer in a clinical research conducted in 2014, as well as other studies such as CHARM-Overall,

LIFE and ONTARGET (Dezsi, 2014). However, studies conducted in the United Kingdom found no evidence of a causal link between the two, although they did find a slight increase in the risk of breast and prostate cancer among patients (Bhaskaran, Douglas, Evans, van Staa, & Smeeth, 2012). Cancer risk is not connected with any of the angiotensin II receptor blockers studied in our investigation. According to our findings, the risk of cancer from valsartan is just mild. In our pharmacovigilance research, we excluded other medicines because of the low number of reports and PRR value for those drugs.

4.3 Antihypertensive medication-induced cancers

Antihypertensive medicines have the potential to cause a variety of cancers, such as prostate, breast, colon, throat, kidney, and skin cancers, albeit the incidence is low (Calle, 2007). Several examples point to a link between antihypertensive medications and cancer, while others don't. Changes in medication formulation, such as from prolonged release to quick release, enhance the likelihood of this occurring. Antihypertensive drugs have been linked to a decrease in apoptosis, which may raise the risk of breast cancer, according to certain studies. Preclinical investigations have shown that it may both induce cancer and act as a chemopreventive in the occurrence of cancer, and these findings have been confirmed in human trials. (1-pancreatic) Thyroid cancer patients who use antihypertensive medicines had a better prognosis, according to data from the Longitudinal Health Insurance Database 2000 (LHID2000). (thyroid-1) Cancer is one of the most severe and deadly illnesses, and breast cancer is currently the most frequent form of cancer among women. Breast cancer is a leading cause of death among women, and antihypertensive medicines have been linked to the development of cancer (Yu & Wang, 2016). Adiponectin is synthesized and secreted by adipocytes in the adipose tissue. Breast cancer may be linked to an increased production of

adiponectin since various antihypertensive medicines have been shown to boost adiponectin production (Liu et al., 2016). Skin cancer incidences are on the rise owing to increased exposure to UV light. If you use antihypertensive medicines for a long period of time, you may get skin cancer as a result. Basal cell carcinoma is the most prevalent kind of skin cancer. Skin cancers such as squamous cell carcinoma and malignant melanoma are very frequent. Basal cell carcinoma affects about eight out of ten skin cancer patients. In most cases, this kind of skin cancer develops over time and is brought on by exposure to ultraviolet (UV) radiation. Cancer of the melanocytes (melanocytes are the cells that produce pigment) is another kind of malignant melanoma that may arise. The primary cause of skin cancer in the world is exposure to ultraviolet (UV) radiation, and several antihypertensive medicines may behave as carcinogens by absorbing UV radiation straight from the sun. Adiponectin, a cytokine secreted by adipose tissue, plays a vital role in the growth of several types of cancer. Patients with RCC (Renal cell carcinoma) had lower levels of adiponectin in their serum and plasma, which has been linked to a more aggressive phenotype and metastasis. Furthermore, preclinical studies have shown that exogenous adiponectin may regulate cell growth and death in a variety of natural processes, including tumor progression (Ito et al., 2017). Antihypertensive medicines, according to many reports based on research, are capable of inhibiting cell cycle progression and proliferation, and as a consequence, the apoptotic process. Antihypertensive medicines have been linked to an elevated risk of pancreatic cancer in a number of studies conducted in the United States (Marie C. Bradley, 2010). There is a broad usage of antihypertensive drugs in wealthy nations. As a result, any potential impact on prostate cancer risk that these medications may have is likely to have public health significance (Linda Perron, 2004).

4.3.1 Inhibitors of the ACE

There was just one ACE inhibitor in our research that was linked to an increased risk of cancer, and that was lisinopril. Breast cancer, prostate cancer, and malignant neoplasms of the lungs are more common side effects of lisinopril than those of other drugs. Breast cancer has a higher incidence rate than any other kind. renal insufficiency care is critical to reducing death rates in patients with heart failure and ACE inhibitors are the most often utilized therapeutic drug in this regard. ACE inhibitors have been shown in several trials to lessen the death rate associated with congestive heart failure. However, these individuals are at an increased risk of experiencing negative side effects from their medications. Our findings on the connection between ACE inhibitors and cancer were mixed when we looked at several studies. Some studies have shown a connection between the two, but others haven't. Short-term use of ACE inhibitors was not associated with a rise in basal cell carcinoma, squamous cell skin carcinoma, or malignant melanoma, but long-term use increased the risk of these cancers. Some studies claimed that ACE inhibitors lower cancer risk in patients, while other studies that attempted to corroborate this claim failed, indicating that ACE inhibitors had no effect on cancer risk. Around 50% of individuals on ACE inhibitors are at risk for developing cancer. Adiponectin, a cytokine secreted by adipose tissue, plays a vital role in the growth of several types of cancer. Patients with RCC who have low levels of adiponectin in their serum or plasma have been shown to have an aggressive phenotype as well as higher rates of metastasis. Some antihypertensive medicines, like as lisinopril, are expected to reduce adiponectin production, however this does not happen. Lisinopril raises LDL cholesterol, which increases the risk of breast cancer, yet it has no effect on adiponectin levels in the blood (Yilmaz et al., 2007). Some other forms of cancer are also shown by ACE inhibitors, although the number of reports is much lower than for malignant neoplasms, breast cancer, prostate cancer, and lung neoplasm malignancy. Skin cancer, bladder cancer, colon cancer, and a few other less common malignancies are among the rarer cases that have been recorded.

4.3.2 Beta-blockers

Only metoprolol was shown to be linked to an increased risk of cancer in our research. Compared to other drugs, metoprolol has the highest number of reports of neoplasm malignant in breast, prostate, and lung cancer. Beta blockers may induce malignant melanoma if used for a long length of time, but they can also cause squamous cell skin cancer if used for a short amount of time. It was shown that long-term usage of beta blockers was associated with a significant increase in the chance of developing breast cancer. Beta blockers are beneficial in the treatment of heart failure and the reduction of death rates. Beta blockers are the first-line treatment for hypertension in young patients (Ong, 2007). People in Australia who used a beta blocker were shown to have an increased risk of developing renal and pelvic cancer. Studies demonstrate that metoprolol doesn't affect adiponectin levels in the blood, but it does raise LDL cholesterol, which increases the risk of breast cancer (Yilmaz et al., 2007). In the case of metoprolol, this might be a factor in the high number of reports of breast cancer. In addition to neoplasm malignant (breast, prostate, and lung), beta blockers also exhibit several other forms of tumors however the volume of reporting is lower than neoplasm malignant. Skin cancer, bladder cancer, colon cancer, and a few other less common malignancies are among the rarer cases that have been recorded.

4.3.3 Calcium Channel Blockers

Among all ACE inhibitors, only amlodipine was shown to be related with an increased risk of cancer in our research. Amlodipine has a greater rate of malignant neoplasm, breast cancer, prostate cancer, and lung neoplasm reports than any of the other drugs. Breast cancer has a higher incidence rate than any other kind. Patients who used CCBs had an increased

incidence of breast cancer, according to a 1996 study by Pahor et al (W. Li et al., 2014). A link was found recently between these substances and cancer, according to a research. This link between calcium channel blockers and cancer has been established by large-scale research and clinical trials. Calcium channel blockers have been shown in some studies to have a beneficial effect on breast cancer because they slow the apoptotic process, which may lead to cancer. However, other studies have shown that calcium channel blockers have a detrimental effect on breast cancer. A calcium channel blocker has a limited impact on skin cancer. Again, epidemiological research suggests that the use of calcium channel blockers may be linked to an increased risk of breast cancer. However, some investigations have shown that calcium channel blockers aren't the only culprits in breast cancer. There are many incidences of breast cancer linked to CCBs in our pharmacovigilance investigation, which supports the earlier findings. All of the CCBs had very low rates of skin cancer reports, which supports the findings of a previous research. Breast cancer cells' proliferation and migration have been discovered to be stimulated by nifedipine, a CCB. This would explain why CCBs are associated with late-stage malignancies. Because calcium channel blockers interfere with cell death and, as a result, insulin generation and metabolism, calcium channel blockers have the potential to induce breast cancer as well (Babette S. Saltzman, 2013). Activation of the Erk pathway seems to be responsible for this nifedipine action, which is not shared by other CCBs like verapamil. Malignant neoplasms are more common in patients on nifedipine and amlodipine. There is a significant incidence of prostate, lung, and stomach cancer among patients using amlodipine. In addition to malignant neoplasms like breast and prostate cancers and lung neoplasms, there are also CCBs that display some other sorts. Skin cancer, bladder cancer, colon cancer, and a few other less common malignancies are among the rarer cases that have been recorded.

4.3.4 Diuretics

According to our findings, only thiazide is linked to an increased risk of cancer among all diuretics. Furosemide, bumetanide, metolazone, and torasemide are the most common drugs we deal with. However, several studies have been conducted to establish a link between the usage of diuretics and an increased risk of developing cancer. One of the first studies to link diuretic medication to renal cell cancer was based on interviews with patients. Diuretic use is linked to cancer in both men and women, according to a recent interview. It was later shown that women are more likely to develop renal cell carcinoma owing to the use of diuretics, rather than males. After doing these investigations, researchers sought to learn more about the link between diuretics and antihypertensive medicines.. All of the studies found a link between the participants and those who had been using antihypertensive medications for an extended period of time. Squamous cell carcinoma risk may rise with long-term diuretic usage, however basal cell carcinoma and malignant melanoma are not at risk. Utilization of thiazide was related with modest chance of breast carcinoma. A higher risk of breast cancer was seen in women who used these types of diuretics for an extended period of time. Both short and long-term use of these diuretics was linked to an elevated risk of breast cancer in women 65 to 79 years old, according to a research in the Seattle–Puget Sound metropolitan region (C. I. Li et al., 2003). An antihypertensive drug like thiazides may raise the risk of kidney cancer (Keith T. Flaherty1, 2005). Thiazides have been linked to various cancers outside malignant neoplasms such breast, prostate, and lung, however the number of cases is much lower. Skin cancer, bladder cancer, colon cancer, and a few other less common malignancies are among the rarer cases that have been recorded.

4.3.5 Angiotensin II receptor blockers

Only valsartan is linked to cancer risk among all ARBs, according to our findings. Losartan, valsartan, eprosartan, and irbesartan are the most often used drugs in our practice.. Valsartan's PRR rating is relatively high, which indicates that this medicine is effective. There is a greater incidence of neoplasm malignant, breast, prostate and lung neoplasm malignant in patients using valsartan. The link between ARB usage and an increased risk of cancer has been the subject of several investigations. These angiotensin II receptor blockers are the most often prescribed medications for individuals with high blood pressure, and those who are intolerant to them may benefit from a variety of cardiac conditions, such as stable coronary artery disease. ARBs (angiotensin-receptor blockers) have been around since 1995 when they were initially licensed for clinical use as an antihypertensive medication. ARBs were originally found when the medication losartan was developed. In the case of Angiotensin II receptor blockers, it has been shown to be well tolerated and effective, and around 25% of people with hypertension use this medication globally. It has been shown that Angiotensin II receptor blockers are linked to an increased risk of cancer in a clinical research conducted in 2014, as well as other studies such as CHARM-Overall, LIFE and ONTARGET (Dezsi, 2014). However, studies conducted in the United Kingdom found no evidence of a causal link between the two, although they did find a slight increase in the risk of breast and prostate cancer among patients (Bhaskaran et al., 2012). Antihypertensive medicines have been linked to an increased risk of cancer, according to a meta-analysis of studies. Hepatocellular carcinoma was the most common kind of cancer identified in this area. That being said, no one knows how this kind of relationship occurs (Sipahi, Debanne, Rowland, Simon, & Fang, 2010). Besides valsartan, we observed that other ARBs also exhibit certain other forms of cancer, although the number of reports is lower than neoplasm malignant, breast cancer,

prostate cancer, and lung neoplasm malignant. This is consistent with previous research. Skin cancer, bladder cancer, colon cancer, and a few other less common malignancies are among the rarer cases that have been recorded.

4.4 Susceptibility to cancer due to using antihypertensive drugs between male and female

Females have a greater rate of adverse reaction (ADR) to antihypertensive medications than males.. Several previous studies have shown that women have a risk that is three to four times greater than that of males (Heck et al., 2010). Skin cancer is the most prevalent kind of cancer among those on antihypertensive medicines, and women are more likely to have it than males. It's because skin is made up of cells that work together to perform a variety of duties, and these functions are carried out by distinct layers of the skin. The thickness of the skin is determined by the dermis, which is one of the many layers of the skin. Men and women have varying levels of body mass. After the age of 45, the thickness of women's breasts starts to decline, and this drop is 10% thinner as a result of menopause. As a result, the amount of UV radiation absorbed by women's skin is more than that absorbed by men's skin. Melanin is the primary component of skin pigment, and melanocytes are the cells that create melanin. Individuals have a unique pattern of melanocyte distribution. In certain ethnic groups, males tend to have darker complexion than women, however this varies depending on the individual's ethnicity. Men and women have distinct metabolic patterns. All of these factors have a role in the higher cancer incidence rates in women. Yet another rise in the number of women using tanning beds raises the possibility of an increased risk of cancer for these ladies (Roh, Eliades, Gupta, Grant-Kels, & Tsao, 2017). Every year, there are a rising number of

skin cancer cases, particularly among women, who are diagnosed with non-melanoma skin cancer (NMSC) every year. For women under the age of 45, the rate of increase is growing. Research shows that women are more affected by skin disease diagnosis and treatment than males, particularly young single women who are more concerned about their health and attractiveness during this period of life. Many women who are diagnosed with skin cancer report high levels of worry, poor quality of life, dissatisfaction in their self-perception, and fear of a repetition (Al-Dujaili, Henry, Dorizas, & Sadick, 2017). People who are tall have a greater chance of developing cancer. A study by the UK's National Health Service (NHS) indicated that tall women had a higher cancer risk than the general population. Many researchers have shown a decreased incidence of pancreatic cancer in women who use antihypertensive medications. This is due to the fact that female hormones lessen the incidence of pancreatic cancer in females. Many countries have seen a considerable rise in thyroid cancer rates over the last few years.. Between 1973 and 2002, an analysis of data from five continents found that the prevalence of female hypertension was 67% and the rate of male hypertension was 48%. (Peterson, De, & Nuttall, 2012). Males and females have somewhat different rates of thyroid cancer, which is a hormone-dependent malignancy. Thyroid cancer was shown to be on the rise in England between 1962 and 1984, according to a research. Thyroid cancer rates in women started to grow around the age of 10, but at the age of 18 in men. Occasional accounts suggest a mortality in an early stage in a guy owing to thyroid cancer. Using data from 1994 to 2006 in Germany, a research found a statistically significant difference in the incidence of thyroid cancer between male and female participants. Males are more likely to develop sporadic papillary thyroid cancers, sporadic follicular cancers, and the extra thyroidal extension of sporadic medullary tumors. However, females are more likely than males to develop distant metastases from sporadic medullary malignancies (Machens, Hauptmann, & Dralle, 2006). However, because of the role of

estrogen in colorectal cancer, men are more likely than women to get the disease (Honma et al., 2011). Colorectal cancer is more common in women than in men, according to statistics from Wolverhampton's New Cross Hospital between 1989 and 2008. (Hebbar, Fuggle, Nevill, & Veitch, 2012). New York State conducted a research to determine the prevalence of cancer. They identified a higher incidence of liver and colorectal cancer in men than in women, they discovered. However, women have a greater risk of thyroid cancer than males (Ying Wang, 2002). Men and women have different lung cancer risks. The likelihood of developing lung cancer is influenced by a person's hormone levels. Women are more likely to get lung cancer than males. Lung cancer is linked to hormonal and ovarian changes, according to a research based on data from the Shanghai Cancer Registry (SCR). When comparing beta blocker users to diuretic users, one concentration found a 21% reduction in colorectal cancer risk (Jansen, Below, Chang-Claude, Brenner, & Hoffmeister, 2012). Antihypertensive medication usage was linked to an increased risk of cancer in a Danish population-based and statistical analysis of 335682 persons. Antihypertensive medicines are linked to an increased risk of cancer, according to one research. Several antihypertensive medication classes were employed in this research. They came to the conclusion that the outcome was favorable. Diarrhea, ACE inhibitors, beta blockers, calcium antagonists, among those 30 to 85 years of age (Fryzek et al., 2005). A cohort research was conducted in North Karelia, Finland, to examine the correlation between cancer incidence and hypertension in the population. Women and men of a typical age are used in this study. The average age was 58 for women and 51 for males. They observed that women's high blood pressure and usage of antihypertensive medicines are linked to an increased risk of cancer. However, they discovered that males are more likely to be prescribed antihypertensive medicines, as well as to smoke (A. Lindgren, Pukkala, Tuomilehto, & Nissinen, 2007).

4.4.1 Inhibitors of the acetylcholinesterase

To begin with, women are more sensitive to ACE inhibitors than men. The one exception to this is enalapril, which has the propensity to occur more often in females than in males. To indicate that women are more vulnerable to cancer, lisinopril, ramipril, quetiapine, and captopril have a bigger proportion of female patients than males.

4.4.2 Beta blockers

Again, females are more likely to get cancer with beta blockers than males, since the number of reports is larger for females on maximal doses. Bisoprolol is the only drug that has a high rate for females. Betaxolol has only ever been documented in females, and as such, there are only female-specific reports available.

4.4.3 Calcium Channel Blockers and diuretics

The number of calcium channel blockers and diuretics reported side effects is about identical for all medicines. For example, in the case of CCBs, the rate of reports for amlodipine and felodipine is greater for male. Verapamil and nifedipine, in contrast, have a significant proportion of reports from female users. Furosemide, metolazone, and bumetanide are the most often reported diuretics for women, while bumetanide and torasemide are the most frequently reported diuretics for men.

4.4.4 Drugs that inhibit the angiotensin II receptor

Our research indicated that the risk of cancer in women using angiotensin II receptor blockers is greater than in men taking the same medicines. More than half of all drug overdoses are reported to occur among female users.

Chapter 5: CONCLUSION

For our pharmacovigilance investigation, we used data extracted from the VigiAccess database. The data conferred in this study indicated that several antihypertensive drugs, which categorized to the group of ACE inhibitors, beta blockers, Angiotensin II receptor blockers, calcium channel blockers and diuretics, are moderately related with cancer risk as an ADR. New cancer kinds like neoplasms are also connected with these factors. There are so many reports about a certain drug's link to cancer that there is no question about it. As an example, the following drugs have been linked to an increased risk of cancer: Lisinopril, Metoprolol, Amlodipine, and Valsartan. This pharmacovigilance investigation indicated that even though the number of complaints was very low, quinapril was shown to be linked to cancer. Furthermore, this risk does not apply to all medications in the same class. To name a few, no medications from any of the many manufacturers have been demonstrated to have a cancer risk, and the reports on such drugs are quite low. Antihypertensive medicines have been linked to cancer in several studies, including this one. While certain antihypertensive medicines are clearly more important than others, this pharmacovigilance research will help us create a clear line of demarcation.

Lisinopril, amlodipine, quinapril, and metoprolol all indicate a link with cancer in this research, which includes four distinct medicines. The results of our research demonstrate that the more reports there are, the more likely it is that they will reflect a favorable outcome. Only lisinopril and quinapril have been shown to have a link to cancer among all ACE inhibitors. As previously stated, valsartan is the only Angiotensin II receptor blocker that has been related to cancer among all the other Angiotensin II receptor blockers. Furthermore, cancer as an adverse drug reaction (ADR) is not caused by diuretics. Furthermore, Amlodipine is the only calcium channel blocker linked to cancer risk.

Because of this, we've found that people who have been on certain antihypertensive medicines like metoprolol for a long time have an increased chance of developing malignant tumors including breast cancer and prostate cancer. The incidence of lung cancer, bladder cancer, and skin cancer is very high. Different forms of cancer, such as throat cancer, renal cancer

There is a chance that antihypertensive medicines may cause 50 types of cancer, including gastric, colon, and stomach cancer, even if the number is small. Our research also reveals that the use of lisinopril, amlodipine, quinapril, and metoprolol leads to the development of new cancers. This is because these medications have a high incidence of neoplasia.

At the end of our investigation, we believe that women who use antihypertensive medicines are more likely to get cancer than men. Women are more likely to get cancer after using antihypertensive medications such as ACE inhibitors, beta blockers, and angiotensin II receptor blockers. Diuretics and calcium channel blockers, on the other hand, have a nearly equal male-to-female response rate.

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