Association of Vitamin D Receptor Gene Polymorphisms with Risk of Cancer: A Comprehensive Review

By

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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 "Association of Vitamin D Receptor Gene Polymorphisms with Risk of Cancer: A Comprehensive Review" submitted by Billal Hossain Tusher (19146030) of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

Recently, there has been considerable interest in the fat-soluble vitamin D, which is essential for the proper formation of bones, for its potential role in cancer prevention as it operates through the vitamin D receptor (VDR) which is a nuclear transcription factor regulating several physiological processes like immune modulation, and cellular growth and differentiation.

VDR genetic polymorphisms, or variations of the VDR gene, may cause abnormal functional performance of the VDR which may also predispose an individual to a particular type of cancer. Despite multiple studies having been linked with these polymorphisms including racial factors, and differences in lifestyle that may affect vitamin D metabolism, the association of these polymorphisms with susceptibility of specific types of cancers particularly; colorectal, breast and prostate cancer have actually been documented. This paper focuses upon the work done demonstrating the association of the VDR gene polymorphisms as a risk factor for cancer and attempts to evaluate important polymorphisms along with known biological mechanisms of their action, the emerging barriers to interpretation of results in the context of the present literature. Keeping in mind the complex nature of such relationships, the analysis attempts to highlight why future research should focus on how preventive strategies could leverage the cancer-preventive potential of vitamin D.

Keywords: Vitamin D, Vitamin D receptor (VDR), VDR polymorphisms (FokI, BsmI, TaqI), cancer risk, gene-environment interaction, personalized medicine, calcium homeostasis, cell proliferation, differentiation, apoptosis

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Table of Contents

List of Acronyms

VDR - Vitamin D Receptor

SNP - Single Nucleotide Polymorphism (not included in the text but relevant to the topic of polymorphisms)

rs - Reference SNP cluster identifier (used in SNP databases)

DNA - Deoxyribonucleic acid

APA - American Psychological Association (referencing style)

Pubmed - Public Medline database (literature search engine)

RCT - Randomized Controlled Trial

Chapter 1

Introduction

1.1 Importance and Synthesis of Vitamin D

Vitamin D, commonly known as the “sunshine vitamin,” is a vital fat-soluble nutrient essential for numerous biological processes in the human body. It is synthesized in the skin in response to exposure to ultraviolet B (UVB) radiation from sunlight. Upon exposure, 7-dehydrocholesterol in the skin converts to pre-vitamin D3, which is subsequently converted to vitamin D3. This precursor is then hydroxylated in the liver to form 25-hydroxyvitamin D (25(OH)D), the primary circulating form of Vitamin D and a common marker for assessing Vitamin D status in the body. A final hydroxylation step occurs in the kidneys, producing the biologically active form, calcitriol, or 1,25-dihydroxyvitamin D (1,25(OH)2D). Through this transformation, Vitamin D becomes capable of exerting significant biological effects by interacting with specific cellular receptors.

Vitamin D is primarily known for its role in calcium and phosphorus regulation, essential for maintaining strong and healthy bones. It aids in the absorption of these minerals from the gut, ensuring adequate bone mineralization, which prevents bone diseases such as rickets in children and osteomalacia in adults. In case of adults, adequate amount of Vitamin D levels in their body can help them prevent osteoporosis and reduce the risk of fractures. However, beside its well-established role in skeletal health, according to research it has shown that Vitamin D also has potential roles in various other physiological functions, especially in the immune system. According to studies Vitamin D can modulate immune responses and can exert anti-inflammatory effects, suggesting a protective role against autoimmune diseases, infections, and inflammatory conditions. Moreover, Vitamin D also has anti-proliferative and pro-

differentiation effects, that are relevant with the context of chronic diseases like cancer, site cellular proliferation is often uncontrolled (Holick, 2016).

1.2 The Vitamin D Receptor (VDR) and Its Role in Mediating Vitamin D's Effects

The mechanisms of Vitamin D mainly work via binding to a specific target receptor. Which is also known as the Vitamin D Receptor (VDR). This receptor functions as a ligand-gated transcription factor. VDR can be widely revealed in various tissues and cells all over the body and further reach bone tissue and also towards organs with Vitamin D targets. It can also be found in areas such as non-skeletal tissues for example, the intestine, immune cells, pancreas, and epithelial cells lining organs like the breast, colon, and prostate. Due to this much flexible spread of VDR, it can be determined that many physiological processes are directly or indirectly linked in one way or another. Be it baseline cellular activities or it can also be any response to environmental and physiological actions.

After the activation process begins, the binding of Vitamin D to VDR occurs that forms a Vitamin D-VDR complex molecule. This complex then relocates to the cell nucleus and it binds to specific areas which are known as Vitamin D response elements (VDREs) on target genes. By going through this process, the VDR plays a key role as a transcription regulator. As a result, the expression of target specific genes that are involved in critical cellular activities. Such activities include cell proliferation, differentiation, apoptosis, and even various immune functions etc. The organism heavily relies on this because it is directly involved in specific critical bodily parameter regulations like maintaining cellular homeostasis, preventing abnormal cell growth that could lead to cancer and regular removal of damaged or dysfunctional cells through apoptosis that can obstruct new and fresh cell growth. The interaction between VDR and Vitamin D is quite significant and impactful in tissues that are very prone to cellular turnover, For instance, the skin and epithelial linings of organs. It

essentially assists in regulation of the cellular homeostasis. If somehow this pathway becomes dysregulated, this will lead to uncontrolled cellular proliferation. That as a result indicates the initial mark of cancer and other hyperplastic disorders (Wang et al., 2008).

1.3 Cancer: A Global Health Challenge with Rising Incidence

One of the most devastating and challenging illnesses is cancer as it is a leading cause of death worldwide. According to the World Health Organization (WHO), cancer was responsible for approx. 10 million deaths in the year 2020. Almost 19.3 million new cases were also diagnosed globally in the same year. This disease can initiate from an irregular behavior of genetic errors, environmental impact, and other lifestyle factors. The actual identification of cancer is mainly uncontrolled cell growth. There can often be cases of metastasis to distant sites in the body. This growth may come from genetic mutations and alterations that dysregulates normal regulatory mechanisms governing cell division and death (Cellular Homeostasis).

Cancer is associated with many stages. It initiates with genetic mutations which cause abnormal cells to evade all the checkpoints that can prevent any abnormal genetic alterations and due to this evasion, the cycle of cell proliferation is imbalanced. Furthermore, these cells continue to accumulate causing more mutations, they gain a selective growth advantage, forming a tumor. In the advanced stages, cancer cells may gain the ability to invade surrounding tissues and enter the bloodstream or lymphatic system, allowing them to spread to other parts of the body, a process known as metastasis. The process of cancer development and progression is highly influenced by genetic susceptibility, environmental exposures, lifestyle factors, and immune system interactions. Due to the diverse and multifactorial nature of cancer, effective prevention and treatment strategies remain a critical area of ongoing research (Institute of Medicine, 2011).

1.4 Rationale for the Review: Investigating the Association between VDR Gene Polymorphisms and Cancer Risk

Vitamin D exhibits anti-proliferative properties and stimulates differentiation and apoptotic effects, which indicates that it has potential as a protective factor in cancer. Vitamin D may be able to prevent uncontrolled cell growth which is characteristic of cancer. Variation in VDR gene can lead to different effects. VDR gene polymorphism leads to genetic variation within the VDR receptor family. These variations can influence the binding of vitamin D with its receptor. Polymorphisms may lead to decreased expression or may change the structure of the VDR protein. This can lead to reduced biological activity.

This review will analyse the link between VDR gene polymorphism and the risk of cancer. It will be done by reviewing current articles on this topic. This review can provide valuable insights into cancer prevention and may help in diagnosis. If we are able to establish a connection, then populations at risk could be identified early on and early intervention could be ensured. This can be used to develop novel drugs and could be used in the field of precision medicine for cancer prevention. These treatments may be developed based on individual's genetic profile. This article will give a comprehensive overview based on evidence and contribute to our current understanding (Li et al., 2013).

Chapter 2

Method & Materials

Thirty articles were analysed and evaluated to extract information for this topic, this provided me with sufficient information to cover all aspects of my topic. All relevant papers were gathered from reliable sources, including Google Scholar, PubMed, Sci-hub, Rochester, Research Gate, and others. These sources were carefully searched to get all the material required to guarantee the validity of my review query. I used keywords such as vitamin D, vitamin D receptor (VDR), VDR polymorphisms (FokI, BsmI, TaqI), etc. to discover the relevant publications and obtain the information I needed. My review paper uses an APA 7th citation, and I have given the writers the appropriate credit. Reading all of the materials I've gathered has improved my understanding of the process underlying the relationship between polymorphisms in the Association of Vitamin D Receptor Gene and Cancer Risk. I learned how the essential mechanism of vitamin D receptors functions in both early and older stages from the review study.

Chapter 3

Vitamin D and Cancer

3.1 Biological Mechanisms by Which Vitamin D May Influence Cancer Risk

The mechanism of cancer formation through the route of multiple cellular activities such as cell division, differentiation, programmed cell death, and immune functions has led to due consideration being given to the role of Vitamin D as a potential factor in cancer risk. These processes emphasize the ability of Vitamin D to modulate the development and progression of cancer through the maintenance of normal cellular activities and immunological processes.

3.1.1 Cell Growth and Proliferation

The ability of Vitamin D to combat the development of cancer lies in the dose-dependent inhibition of growth and expansion of cells, which are the two main evolutionary properties of a malignant phenomenon. Furthermore, Vitamin D improves regulation of essential cell functions by facilitating cell cycle cessation at specific points within the cycle. Such an action helps prevent unregulated proliferative growth, which is typical to cancerous growths. In addition, it has been demonstrated that vitamin D can decreased expression of certain genes involved in cellular signaling networks that promote cell growth as well as some oncogenes, while increasing expression of some genes associated with inhibition of the cell cycle. This controlling function is particularly important for these tissues where rapid growth or stress is present and more susceptible to the oncogenic change. As a result, the interference of cellular proliferation by Vitamin D is a major antagonism against the consequences created by genetic alterations that promote cancers cell´s division.

3.1.2 Differentiation and Apoptosis

Vitamin D is best known for its role in promoting cellular differentiation, that is, the process by which immature or stem-like cells acquire specialized, mature cell types. It plays a great role in cancer prevention since undifferentiated cells are prone to uncontrolled proliferation and invasion. Vitamin D facilitates the differentiation of cancer cells and inhibits their malignant properties, thereby encouraging them to take on a more stable and less proliferative phenotype. Furthermore, Vitamin D induces apoptosis or programmed cell death, through which damaged or neoplastic cells are eliminated. By energizing apoptotic pathways, Vitamin D assists in the extermination of cancerous cells from the body before they can exude into tumours or spread onto other tissues. All these may become very crucial in situations when DNA damage is likely to occur repeatedly due to agency factors in life, like ultraviolet exposure or smoking tobacco

3.1.3 Immune Function

Vitamin D enhances both innate and adaptive immunity while playing a crucial role in the immunological response. It aids in the maturation and activation of antigen-presenting cells APCs, which include macrophages and dendritic cells responsible for presenting cancer antigens to T-lymphocytes. Activated T-lymphocytes are known as "defenders" of the immune system possess great potential to recognize and destroy malignant cells. Vitamin D also regulates cytokine production, which comprises signalling molecules that affect the immune response and promote inflammation. By regulating cytokine levels, Vitamin D helps maintain a balance between pro-inflammatory responses and anti-inflammatory responses; this equilibrium is necessary for influencing the course of cancer. A well-balanced immune

environment is required to attack tumour cells with minimal risks of chronic inflammation, often considered a significant risk factor for cancer (Sung et al., 2021b).

3.2 Evidence from In Vitro and In Vivo Studies

Analysis of Vitamin D interactions with cancer development and potential therapies has recently received a boost as a result of detailed studies conducted both in in vitro and in vivo models. These investigations have revealed valuable information on how Vitamin D and VDR signalling pathways are implicated in or may slow down various types of cancers notably. Thus, the focus here is the role of vitamin D, or more specifically, its deficiency, in the context of the cancer prevention.

3.2.1 In Vitro Studies

In vitro research has profoundly impacted elucidating the cellular mechanisms through which Vitamin D acts on cancer cells. Studies done on several cancer cell lines, including those of breast, prostate, colon, and melanoma, have shown that Vitamin D treatment reduces cell growth increases differentiation and induces apoptosis in these cells. For example, studies on breast cancer cell lines have shown that Vitamin D treatment downregulates genes associated with cell proliferation while upregulating markers related to differentiation. Like effects have been noted in prostate and colon cancer cells, reinforcing the concept that Vitamin D may inhibit malignant behavior in various types of cancers. These findings underscore the reasoning behind considering Vitamin D as an adjunct therapeutic agent in strategies of treating cancers, especially when the pathway involving the Vitamin D receptor is functional.

3.2.2 In Vivo Studies

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3.3 Methodology and Materials Used in Vitamin D Research on Cancer

A number of ranges of methodologies and materials designed for stimulating the condition of cancer development of vitamin D.

3.3.1 Cell Culture Studies

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3.3.2 Animal Models

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3.3.3 Human Epidemiological Studies

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3.4 Limitations and Future Directions

In vitro research has profoundly impacted elucidating the cellular mechanisms through which Vitamin D acts on cancer cells. Studies done on several cancer cell lines, including those of breast, prostate, colon, and melanoma, have shown that Vitamin D treatment reduces cell growth increases differentiation and induces apoptosis in these cells. For example, studies on breast cancer cell lines have shown that Vitamin D treatment down regulates genes associated with cell proliferation while upregulating markers related to differentiation. Like effects have been noted in prostate and colon cancer cells, reinforcing the concept that Vitamin D may inhibit malignant behavior in various types of cancers. These findings underscore the reasoning behind considering Vitamin D as an adjunct therapeutic agent in strategies of treating cancers, especially when the pathway involving the Vitamin D receptor is functional.

Chapter 4

Vitamin D Receptor (VDR) Gene Polymorphisms

4.1 Common VDR polymorphisms and their functional effects

One of the ways our bodies use vitamin D is to help keep our bones healthy and also as a key player in immune system regulation. Vitamin D does its thing by binding the Vitamin D Receptor (VDR), a protein that is expressed in cells. This ligand-receptor complex functions in the cell as a molecular switch to turn on (or off) genes resulting in biological effects of vitamin D. (Garland et al., 2014)

Single Nucleotide Polymorphisms (SNPs) are variations in the DNA sequence of a gene and, as such, some may be surrounding or within VDR. They can do several things to the structure or function of the Vitamin D receptor (VDR) protein. This change in the structure or function might affect its interaction with vitamin D. (Institute of Medicine, 2011

Here's how VDR gene polymorphisms might be linked to cancer risk:

Altered VDR function: If one of the SNPs decreases activity in VDRPAR, that cell with potentially decreased ability to respond vitamin D signals. Uncontrolled cell growth is a hallmark of cancer; imbalances in the regulation of such processes as proliferation, programmed cell death (apoptosis), and passage through the stages that comprise what is known as the CELL CYCLE can engender malignant transformations (Cantorna et al., 2000)

Gene-environment interaction: The effects of the VDR gene may interact with environmental factors such as sunlight or vitamin D intake. These data suggest that the protective influence of 25(OH)D is modified by VDR genotype, such that individuals with certain genotypes may be more susceptible to its effects or lack thereof (56). (Sung et al., 2021a)

4.2 Current Research Landscape

The association of various VDR polymorphisms (such as FokI, BsmI, Taq1) in cancer risk including breast lung and colorectal cancers are currently under investigations by the researchers. Results of these studies, however, have been inconclusive; some reports suggest an association between particular VDR genotypes and increased cancer risk but others do not consistently demonstrate such a link.

4.3 Future Directions

Further studies on larger and more heterogeneous samples are needed to determine the association between the VDR gene polymorphisms and the risk of cancer. It is important to understand the effect of VDR gene polymorphisms in relation to these external factors such as photonic exposure and dietary intake of vitamin D. Giovannucci et al. pointed out in 2019 that functional studies are important to explain how cancer initiating events may be influenced by VDR gene polymorphisms.

4.4 Potential Implications

The possibility of cancer prevention through individualized strategies may come true in case a robust association between VDR polymorphisms and cancer susceptibility is established.Targeted interventions to achieve maximum vitamin D levels or exposure to the sun (with appropriate sun protective practices of course) may be useful in reducing cancer risk among individuals with particular VDR genes: (Ohyama and Nakagawa 2013)

Chapter 5

Association Studies: VDR Polymorphisms and Cancer Risk

5.1 Focus on specific cancer types (e.g., breast cancer, lung cancer)

5.1.1 Breast Cancer

- **Breast Cancer:** It is expected that 2.3 million new cases of breast cancer will be diagnosed in 2020 and therefore represent the most common malignancy among women worldwide. Many studies explored the association of VDR polymorphisms with susceptibility to breast cancer.
- **FokI polymorphism:** There are conflicting results about the relation of risk of breast cancer and the FokI polymorphism: some show an increased risk related to the ff genotype, whereas others do not. Such correlations could be modified by sun exposure and ethnicity.
- **BsmI polymorphism:** Similar to the FokI polymorphism, BsmI shows variable results related to the risk of breast cancer, presenting as BB versus bb genotypes. Whereas some studies reported no significant association, others have reported an association with an increased risk associated with the bb genotype.
- **Gene-environment interaction:** Research points to a possible interplay between environmental variables including vitamin D consumption and sun exposure and VDR polymorphisms in the risk of breast cancer. For example, when it comes to lowering the risk of breast cancer, people with specific VDR genotypes may benefit more from getting enough sun exposure or taking vitamin D supplements. (Heaney and others, 2011)

5.1.2 Lung Cancer

- **Lung Cancer:** Lung cancer is the leading cause of death due to cancer, which is projected to account for 1.8 million deaths in the year 2020 worldwide. While genetic risk factors exist, the major modifiable risk factor for lung cancer is smoking. Other studies have also focused on how VDR polymorphisms may contribute to susceptibility to lung cancer. Lung cancer is the primary cause of tumour deaths worldwide, with an estimated 1.8 million ung cancer deaths occurring in 2020. While genetic mechanisms can play a role in the development of lung cancer, smoking is generally considered the major risk factor for the disease. The relationship between VDR polymorphisms and the risk of developing lung cancer has been explored.
- **FokI polymorphism:** Consideration of the possible association between the FokI polymorphism and lung cancer risk reveals a conflict in studies' results. Some researchers believe that the ff genotype can enhance lung cancer risk, particularly among smokers (Garland et al., 2014).
- **TaqI polymorphism:** Other studies have explored the TaqI polymorphism, such as TT versus TT in relation to lung cancer; some found that carriers of the genotype TT had an increased risk, especially among smokers (Langdahl et al., 2009).
- **Confounding factors:** Smoker status is one of the major confounding variables in lung cancer studies. Given the overwhelming risk of cigarette smoking, the independent effects of VDR polymorphisms may sometimes be hard to tease out.

5.2 Geographic variations in VDR polymorphisms and cancer risk

The frequencies of VDR polymorphisms can substantially differ among different populations. For instance, the genotype FokI ff is more frequent among Asians and Africans compared with Europeans. Indeed, such a difference in the distribution of the alternative VDR genotypes may contribute to the inconsistent findings on the associations between VDR polymorphisms and cancer risk among various geographical populations.

5.3 Gene-environment interactions (e.g., sun exposure, Vitamin D intake)

Certain VDR polymorphisms are thought to interact with sun exposure and dietary intake of vitamin D. The carriers of certain VDR genotypes may be specifically susceptible to protection afforded by sun exposure or vitamin D. As such, for example, studies indicate that individuals with genotypes linked to lower VDR activity would likely benefit from sun exposure or supplementation with vitamin D in attempts to reduce the risk of cancer.

Because the relations between genes and environment are complex, as are the ways in which these interactions affect tumorigenesis in diverse populations, substantial additional research will be required to understand such interrelations fully.

Chapter 6

Challenges and Limitations

The number of studies that have analysed the association of Vitamin D receptor polymorphisms with the risk of cancer has grown immensely. This may show the growing impact that VDR genetics can have on strategies related to the prevention and treatment of cancer. While research in this area has advanced, a number of challenges and limitations still casts a shadow on the precision and relevance of research findings. Such limitations are important to acknowledge, and thus further advancement of this field with better approaches in future research will give more conclusive findings. In this regard, we discuss the major impediments to this field of research.

6.1 Heterogeneity of Studies

One of the key challenges regarding research into the association between VDR polymorphisms and the risk of cancer is the marked heterogeneity across different studies. Variability occurs for several reasons: differences in the design and methodologies of studies, sample sizes, and demographic features among the populations assessed. The research on the VDR polymorphisms is quite variable regarding both the specific cancer types that were investigated, the different VDR polymorphisms tested, and testing methods applied for these genetic changes. For example, some focused solely on investigating either breast or prostate cancers, while other studies have included cancers of many types. Furthermore, diversity in the populations of different studies, represented by different ethnicities, geographic locations, and genetic backgrounds, imposes a limitation on generalizing the findings. In addition, the sample sizes vary from small cohort studies to the larger population-based investigations, implying a limitation on statistical power and reliability of results due to the fact that smaller studies may lack the statistical power to detect clinically significant associations. In consequence, such

discrepancies obviate definitive conclusions and may obscure the real effect of VDR polymorphisms on the risk of cancer.

6.2 Confounding Factors

The association study of VDR polymorphisms with cancer risk is complicated by many potential confounding factors that can influence VDR activity and cancer susceptibility. The major confounders are dietary habits, lifestyle factors, and sun exposure-all of which are known to affect Vitamin D metabolism, the circulating levels of Vitamin D, and overall cancer development. X For example, the dietary source of a person greatly influences Vitamin D intake, and that food sources rich in Vitamin D may themselves influence the functions of VDRs irrespective of any genetic predisposition. Similarly, lifestyle factors such as smoking, exercise, and alcohol consumption are well-documented to exert very powerful influences on the risk of cancer and can obscure the associations between VDR polymorphisms and cancer. Moreover, sun exposure-the major source of Vitamin D in its endogenous synthesis-varies greatly in each individual depending on geographical location, frequency of outdoor activities, and skin type, which will eventually result in heterogeneous levels of serum Vitamin D. This makes it difficult to distinguish between independent effects of VDR polymorphisms and all these environmental and lifestyle influences. For this reason, without consideration of these confounding factors, there is a great risk of having spurious associations, and this might prevent the clear establishment of an association between VDR polymorphisms and the susceptibility of cancer.

6.3 Limitations of Association Studies

Much of the information regarding VDR polymorphisms and their association with the risk of cancer come from observational studies, which by their nature have inadequacies in establishing cause and effect. While they may determine that there is an association of VDR

polymorphisms with the incidence of a particular form of cancer, it cannot be established with certainty by observational studies that such variants represent one cause of cancer. Given that the majority of these association studies are of a correlational nature, one must note that the relationships reported could be due to either confounding or chance rather than any biological effect. In order for a relationship to extend beyond just correlations, studies of function are required to define exactly what the mechanism is whereby VDR polymorphisms could influence cancer biology. In fact, such functional analyses, including in vitro and in vivo studies, are absolutely necessary in the study of how these genetic variants alter VDR activity, gene expression, and cellular behaviour in relationship to tumorigenesis. These studies allow an investigator to delineate whether specific polymorphisms result in an altered VDR signalling, altered Vitamin D binding, or disruption in the downstream consequences of VDR activation, such as regulation of cell cycle or modulation of immune response. In the absence of such insights, it therefore remains difficult to define accurately the true relevance of VDR polymorphisms in cancer risk, and thus constrained is the potential for development of targeted therapeutic or preventive strategies.

6.4 Challenges in Genotyping and Variability in Polymorphisms

Other problems are more technical and pertain to the genotyping of VDR polymorphisms. The quality and accuracy of the genotyping methods can vary substantially between studies; some also employ older, less reliable methods that may not have the resolution to correctly identify all genetic variants. In addition, different studies may investigate different numbers and types of VDR polymorphisms, which makes it hard to compare the findings from one study with those of another. Whereas some review common polymorphisms such as FokI, BsmI, TaqI, and ApaI, others may consider less common or less understood genetic variations. This then further creates some inconsistency in the scope and focus of the VDR polymorphism review, adding some level of complexity to probably cause divergence in findings and difficulties in

performing meta-analyses, which require some level of standardization in comparing results among studies

6.5 Population-Specific Variations in VDR Polymorphisms

These VDR polymorphisms are known to vary in prevalence between populations, and there are variants that might be linked with ethnic groups. This variable distribution is an added problem in the evaluation of the association of VDR polymorphisms with cancer risk. For this reason, the frequency and importance of VDR polymorphisms can vary among populations due to genetic background. It is not surprising to find an association in a population that is absent in another one. Besides, aspects related to environmental and cultural particularities of populations, like dietary habits, lifestyle conditions, and herbal practices, may interact with genes related to VDR in a very complicated way, thereby perplexing the interpretation of research findings. Also, without considering such population-specific differences, it will be tough to generalize the findings to larger populations. It therefore calls for more representative and diverse research samples.

6.6 Ethical and Practical Considerations in Human Studies

Working with VDR polymorphisms and their relations to the risk of cancer brings about both ethical and practical complications while studying them in human populations. Most studies in genetics need informed consent, which requires the clear explanation of purpose to the participants and protection of privacy, especially in genetic testing and data sharing. Besides, cancer is a complex disease, and only large sample sizes and longitudinally collected data can ensure the results are valid. These are resource-intensive pre-requisites, though, which prevent comprehensive investigations of these latter types in resource-poor settings or amongst marginalized communities.

6.7 Future Directions and Recommendations

Several strategies can be utilized to help overcome some of the limitations and challenges of VDR polymorphisms and cancer risk. First, improving standardization of methodologies, the genetic markers investigated, and demographics of study populations should help to lessen some of the problems of study heterogeneity. Second, strong control for potential confounding by incorporating comprehensive dietary, lifestyle, and environmental exposure assessments will aid in teasing out the independent effect of VDR polymorphisms on cancer risk. It would also be very important to shift from observational studies to functional research in order to take the mechanistic insights forward. This could come through CRISPR-Cas9 gene editing or in vitro study of the VDR pathway in elucidating how a particular polymorphism affects VDR functionality and cellular behaviour.

Only large-scale, population-based multi-ethnic studies and meta-analyses considering genetic and environmental diversity will play an important role in explaining the variation of VDR polymorphisms across different populations. Further, more advanced statistical approaches-like Mendelian randomization-will have better capabilities to establish causality in association studies with a minimum impact of confounding variables.

Overall, substantial challenges exist in the investigation of the association between VDR polymorphisms and cancer risk. Removal of such barriers will translate into information that is far more precise, inclusive, and translatable. Future discoveries will facilitate strategies pertaining to precision medicine wherein diverse manners of cancer prevention and management are tailor-made based on the genetic constitution of an individual to ultimately achieve superior cancer-related outcomes in disparate populations.

Chapter 7

Conclusion

Gene polymorphisms with cancer susceptibility are complex and widely studied. While several studies indicate the association of some VDR polymorphisms with the increased susceptibility in certain types of cancer, the findings are often inconsistent. Heterogeneity among studies, confounding factors, and implicit limitations of association studies hamper definitive conclusions being drawn. (Institute of Medicine, 2011)

Several notabilities deserve attention, if not all:

Further research will be required to understand the functional implications that VDR polymorphisms have on Vitamin D signalling. It is also important to consider that the interaction of the VDR polymorphisms with sun exposure and Vitamin D intake may not have been completely explored. More detailed research is possible when the focus is on specific kinds of cancer and populations that vary. This would require functional studies to elucidate the mechanisms by which VDR polymorphisms may act to impact cancer progression

7.1 Public health implications

While the evidence in relation to a conclusive role of VDR polymorphisms in cancer risk remains unclear, there is general recognition of benefits for Vitamin D in general health and in the prevention of diseases. Public health recommendations commonly encourage adequate levels of Vitamin D from sun exposure, along with relevant sun protection measures, and through nutrition (Garland et al., 2014).

7.2 Future directions and research needs

1. Personalized medicine may investigate how VDR polymorphisms interact with individual Vitamin D levels and other environmental factors to perhaps allow for personalized approaches

in cancer prevention. For example, individuals with specific VDR genotypes may particularly benefit from selective strategies of Vitamin D supplementation.

2. Functional studies: Extensive investigations into the molecular mechanisms of how the VDR polymorphisms influence Vitamin D signalling and influence pathways of cancer have been very useful. Findings from such studies will likely prove helpful in devising new therapeutic approaches targeting the VDR pathway in cancer prevention or treatment.

3. Epigenetic Constitutions: Whether epigenetics-play-ing a hereditable modification of gene expression without actual changes in the DNA sequence-on the expression of VDR, or interacting with the VDR polymorphisms, remains to be seen.

4. Larger, Well-Designed Studies: To strengthen the present evidence for elucidating the real impact of the association between VDR polymorphisms and cancer risk, comprehensive, prospective studies involving larger numbers of subjects from diverse ethnic backgrounds and long-term follow-ups should be conducted.

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