# IMMUNOSUPPRESSANT-INDUCED THYROID TUMORIGENESIS IN KIDNEY TRANSPLANT PATIENTS

By

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A thesis submitted to the School of Pharmacy in partial fulfilment 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 original work while completing my 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 project titled “Immunosuppressant-Induced Thyroid Tumorigenesis in Kidney Transplant Patients” submitted by Owowo Wisdom Chikaodiri (22146104) of Spring, 2022 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 29th May 2025.

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## Ethics Statement

The project does not involve any animal trials or clinical trials on humans.

## Abstract

Renal transplantation is a life-saving procedure for patients with end-stage renal disease. However, the introduction of a transplanted kidney triggers an immune response due to differences in human leukocyte antigens (HLAs) between the donor and the recipient. This immune reaction identifies the transplanted kidney as a foreign body, leading to potential graft rejection. To mitigate this, immunosuppressive agents are administered to suppress the immune response. These agents are typically used at higher doses during the initial post-transplant phase and are gradually tapered during the maintenance phase. While immunosuppressants are essential for preventing graft rejection, their long-term use has been linked to an increased risk of malignancies, including thyroid cancer. This review aims to investigate the oncogenic potential of immunosuppressive therapy in renal transplant recipients, with a specific focus on the thyroid gland. By exploring existing studies and clinical data, this review aims to provide insights into the relationship between immunosuppressant use and thyroid malignancies, thereby contributing to the optimization of post-transplant care strategies.



**Keywords:** Immunosuppressant; renal transplant; thyroid cancer; immune response; malignancies; graft rejection.

## Dedication

This thesis is dedicated to my beloved family; the family of Mr. Jacob Chikaodiri Owowo and Mrs. Lovelyn Chikaodiri Owowo for their unwavering love, support, and sacrifices. To my dear siblings, Chioma, Ruth, Peter, and Peace, your strength and encouragement have been my constant inspiration. And to myself, for the resilience and determination that carried me through this journey.

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## List of Acronyms

| | |
|---|---|
| ESRD | End-Stage Renal Disease |
| eGFR | Estimated Glomerular Filtration Rate |
| GFR | Glomerular Filtration Rate |
| BP | Blood Pressure |
| HR | Hazard Ratio |
| HLA | Human Leukocyte Antigen |
| MHC | Major Histocompatibility Complex |
| CNIs | Calcineurin Inhibitors |
| mTOR | Mammalian Target of Rapamycin |
| mTORi | mTOR Inhibitors |
| AZA | Azathioprine |
| NFAT | Nuclear Factor of Activated T cells |
| TPO | Thyroid Peroxidase |
| NIS | Sodium-Iodide Symporter |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TSH | Thyroid Stimulating Hormone |
| PTMC | Papillary Thyroid Microcarcinoma |

| | |
|---|---|
| PTC | Papillary Thyroid Carcinoma |
| BTA | Benign Thyroid Adenoma |
| VEGF | Vascular Endothelial Growth Factor |
| ROC | Receiver Operating Characteristic |
| RTx | Renal Transplantation |
| CsA | Cyclosporine A |
| EBV | Epstein-Barr Virus |
| HPV | Human Papillomavirus |
| HHV-8 | Human Herpesvirus 8 |
| SCID | Severe Combined Immunodeficiency |
| TH | Thyroid Hormone |
| TF | Transcription Factor |
| FNAb | Fine Needle Aspiration Biopsy |
| CTL | Cytotoxic T Lymphocyte |
| PI3K-AKT | Phosphoinositide 3-Kinase – Protein Kinase B Pathway |
| NFATc | Cytoplasmic Form of NFAT |
| HSF1 | Heat Shock Factor 1 |
| CREB | cAMP Response Element-Binding Protein |
| HIF-1 | Hypoxia-Inducible Factor 1 |

| | |
|---|---|
| NFKB | Nuclear Factor Kappa-light-chain-enhancer of Activated B cells |
| EGR1 | Early Growth Response Protein 1 |
| TH | Thyroid Hormone |
| MIC | Minimally Invasive Cancer |
| NFI | Nuclear Factor I |
| FOXP3 | Forkhead Box P3 |
| CTLA4 | Cytotoxic T-Lymphocyte Antigen 4 |
| PDCD1 | Programmed Cell Death 1, encodes PD-1 |
| IL2RA | Interleukin-2 Receptor Alpha |

# Chapter 1

## Introduction

Renal transplantation offers the most feasible option for combating end-stage renal disease (ESRD) in terms of expenses for developing or underdeveloped countries and for opting for a better quality of life. Recipients of renal transplants prefer the state of having a live donor to avoid the harmful effects of dialysis while waiting for a cadaver donor. Renal transplantation offers a potential breakthrough in terms of its magnitude, scope, and reach; it is one of the quickest reconstructive surgeries because it enhances the survivors' quality of life, irrespective of their state of health (Etxebarria, 2022; Groth, 2023).

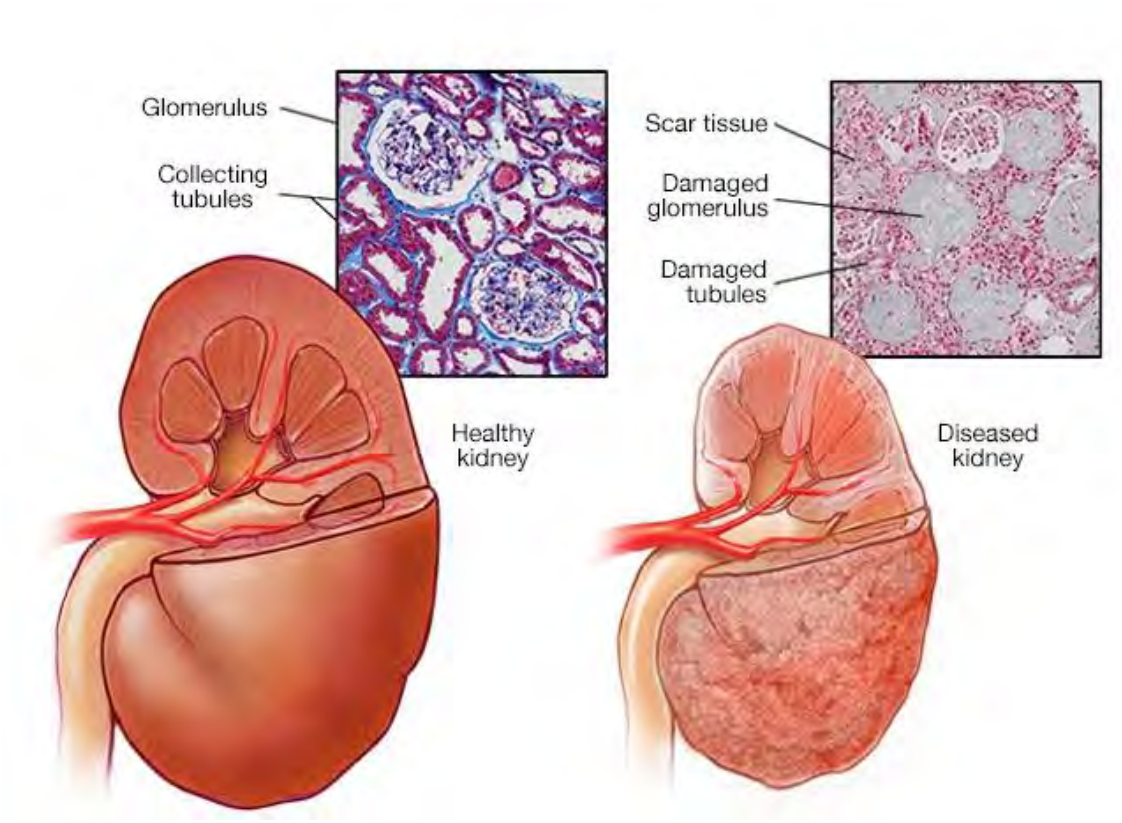


*Figure 1: Histological and Structural Comparison between Healthy and Diseased Kidneys*

Renal transplantation offers patients with ESRD a significantly improved quality of life, both physically and mentally. Successful transplantation requires stringent protocols, including

careful selection of recipients and donors- whether live or deceased- and thorough evaluation of organ viability and infectious diseases. Organ procurement is performed by specialised surgeons using techniques equivalent to non-transplant procedures, aiming to minimise intraoperative complications. Precise surgical methods are essential to avoid vascular or structural damage and ensure optimal graft function. Timely organ extraction is critical to prevent tissue deterioration (Groth, 2023).

During donor nephrectomy, adjacent tissues are preserved, and vascular anastomosis is performed efficiently to maintain perfusion. Though live kidney donation is generally safe, it may lead to long-term risks such as increased blood pressure and proteinuria due to compensatory renal changes. Kidney transplantation eliminates the need for dialysis and helps normalise blood pressure, improving both survival and quality of life (Bai, 2022; Dahle, 2022).

## 1.1 Overview of End-Stage Renal Disease

End-stage renal disease (ESRD) is the final stage of chronic kidney disease, wherein the kidney functions are compromised with an estimated glomerular filtration rate (eGFR) < 15.0 mL/min/1.73 $m^2$, resulting in persistent uremia. It is subdivided into two types: Acute and chronic end-stage renal disease (Palevsky PM, 2013).

**Acute renal end-stage disease:** Acute ESRD is characterised by a sudden decline in glomerular filtration rate (GFR) to below 15 mL/min/1.73 $m^2$. This condition is often reversible and typically presents with elevated serum creatinine levels and/or a marked reduction in urine output. Common etiologies include volume depletion (dehydration), infections, exposure to nephrotoxic agents, urinary tract obstruction, and significant haemorrhage (Palevsky PM, 2013).

**Chronic end-stage renal disease:** Chronic ESRD is the gradual irreversible end-stage renal disease which is usually caused by diabetes mellitus, hypertension and glomerulonephritis. It progresses over months to years and a result requires dialysis or renal transplant. (Palevsky PM, 2013).

Common causes of ESRD include diabetes and hypertension, and the magnitude of the problem is reflected in its prevalence rates. 19% of patients on hemodialysis and those on peritoneal dialysis suffer from ESRD due to diabetes, while 36% and 67% undergo dialysis for ESRD due to hypertension (Bai, 2022; Gusev, 2021)

Clinically, ESRD is characterised by the development of various clinical manifestations, including fatigue, easy bruising, nausea, vomiting, anorexia, weight loss, and generalised swelling. Uremia in general also worsens these symptoms, lowering the overall quality of life significantly. Disease management implies the maintenance of exquisite intake and output records with periodic intake of drugs: antihypertensive therapy aiming for a systolic blood pressure of 120-140 mm Hg and diastolic blood pressure < 90 mm Hg; end organ disease control to overcome a twenty percent incidence of cardiovascular diseases resulting in myocardial infarction and symptoms such as retinopathy and painful neuropathy; oral hypoglycemia with glycemic index monitoring and dietary guidance, and insulin injections to control an HbA1c of < 7.5%. Thus, considering the fact that ESRD is unmodifiable and a universal challenge in the absence of a definite cure, the only available therapeutic approach aims at regaining renal function through renal replacement therapy options including dialysis and renal transplantation (Debnath, 2021; Gregg, 2021).

## 1.2 Renal Transplantation

Each year, nearly 1,000 individuals in Australia initiate renal replacement therapy, with the majority commencing dialysis (Abdelmalak, 2024; Wyld, 2021). While dialysis sustains life, it remains a suboptimal modality compared to kidney transplantation, which offers the opportunity to replace irreversibly lost renal tissue- tissue that the body cannot regenerate. Without transplantation, progression to end-stage renal disease (ESRD) represents a clinical point of no return. Compared to transplantation, dialysis is associated with significantly higher mortality, particularly among younger patients and those receiving peritoneal dialysis. Moreover, dialysis often fails to fully restore renal function, and prolonged treatment is frequently accompanied by chronic inflammation, immunosuppression, and progressive fibrosis (Béguin, 2021; Vinson, 2023).

Renal transplantation is both life-saving and life-enhancing, offering substantial advantages over dialysis that persist even 20 years post-transplant. Compared to dialysis, transplant recipients experience significantly improved survival and quality of life, including greater psychological well-being, fewer dietary restrictions, improved fertility, and enhanced social and economic reintegration. Despite the lifelong need for immunosuppression and potential complications, the benefits are sustained. National registry data from Australia show graft survival rates of over 90% at 1 year, 84% at 5 years, 64% at 10 years, and 38% at 20 years (Abdelmalak, 2024; Wyld, 2021).

## 1.3 Rationale of the Study

Renal transplantation enhances the survival and quality of life of patients with end-stage renal disease. However, this clinical success depends on the lifelong administration of immunosuppressive therapy to prevent graft rejection. While indispensable, long-term use of

immunosuppressive agents has been consistently linked to an increased risk of post-transplant malignancies, particularly involving lymphoid tissues, skin, and the gastrointestinal tract. Among these, thyroid cancer remains relatively underexplored, despite emerging clinical and epidemiological evidence suggesting a possible association with immunosuppressive exposure (Al-Adra et al., 2021; Eccher et al., 2020).

Understanding the oncogenic risk specific to the thyroid gland is critical. Early detection of thyroid malignancy may improve outcomes through timely intervention, especially in immunosuppressed populations who may present with atypical tumour progression. Despite this, thyroid cancer screening is not a routine component of post-transplant surveillance, underscoring a crucial gap in patient care protocols. This review aims to address this gap by critically evaluating existing evidence on the association between immunosuppressive therapy and thyroid malignancies in renal transplant recipients.

Although a growing body of epidemiological studies has linked immunosuppression to increased cancer risk, the underlying biological mechanisms remain insufficiently characterised. The most robust evidence implicates certain classes of drugs- particularly calcineurin inhibitors, antimetabolites, and corticosteroids- alongside factors such as immune status, duration and dosage of therapy, individual genetic susceptibility, and concurrent viral infections (Murakami et al., 2021). These agents may act directly through mutagenic or immortalising effects on thyroid tissue, or indirectly by impairing tumour immunosurveillance and disrupting graft-versus-cancer effects.

Given that drug regimens, screening strategies, and monitoring protocols can be modified, a clearer understanding of these risks offers actionable insights. Tailored interventions, such as immunosuppression minimisation, drug substitution, or enhanced thyroid monitoring, could significantly improve patient outcomes. However, the heterogeneity of immunosuppressants,

variability in cancer subtypes, and interplay of individual risk factors make this an ongoing area of concern and highlight the need for targeted, evidence-informed approaches in transplant oncology (Murakami et al., 2021).

# Chapter 2

# Methodology

This review adopted a structured and systematic approach to examine the oncogenic potential of immunosuppressive therapy on the thyroid gland in renal transplant recipients. It integrates a comprehensive literature review with a retrospective cohort analysis using national-level health data.

## 2.1 Literature Review Strategy

A thorough search was conducted across PubMed, Scopus, Web of Science, Embase, and Google Scholar for articles published between January 2000 and April 2025. Keywords included “immunosuppressants,” “thyroid cancer,” “renal transplantation,” and “oncogenic risk,” combined using Boolean operators. Peer-reviewed English-language studies involving human renal transplant recipients and reporting thyroid malignancies were included. Animal studies, non-renal transplant cohorts, and abstract-only publications were excluded. Titles, abstracts, and full texts were screened independently by two reviewers, with data extracted on study design, therapy type, and thyroid outcomes.

## 2.2 Retrospective Cohort Design

A cohort study was conducted using Taiwan’s National Health Insurance Research Database (NHIRD), encompassing over 22 million individuals. We included renal transplant recipients from 2000 to 2011 who initiated immunosuppressive therapy within 30 days of transplantation. Patients with prior organ transplants or baseline thyroid dysfunction were excluded. The index date was defined as the transplant date.

## 2.3 Exposure and Outcome Assessment

Exposure to immunosuppressive agents- classified into seven major drug classes- was assessed based on prescription records, including drug type, dosage, and duration. The primary outcome was histologically confirmed thyroid cancer. Follow-up extended to cancer diagnosis, death, graft failure, re-transplantation, or study end date.

## 2.4 Data Sources and Variables

Data were drawn from NHIRD, cancer registries, and hospital electronic records, including demographics, comorbidities, diagnostics, and biopsy confirmations. Additional thyroid-specific data were retrieved from a dedicated research clinic.

## 2.5 Statistical Analysis

Kaplan–Meier estimates were used to calculate incidence rates. Multivariate Cox regression models estimated adjusted hazard ratios (HRs) with 95% confidence intervals, controlling for age, sex, comorbidities, and lifestyle factors. Subgroup and dose-response analyses were conducted to assess potential effect modifiers and mediators.

## 2.6 Research Questions

This study explores the oncogenic potential of immunosuppressive therapy on the thyroid gland in renal transplant recipients, addressing the clinical incidence, pharmacological mechanisms, and pathophysiological implications. Despite well-established associations between long-term immunosuppression and cancer risk, thyroid malignancies remain under-investigated in this context. The research was done based on these five key questions:

1. **What is the incidence of thyroid cancer in renal transplant recipients on long-term immunosuppressive therapy?**

Renal transplant recipients exhibit a higher incidence of thyroid cancer compared to the general population, particularly aggressive subtypes such as T3 and follicular thyroid carcinoma (Fuhrmann, 2023; Jung, 2022). Routine post-transplant ultrasound has been proposed to improve early detection and outcomes.

2. **Which immunosuppressive agents have the highest oncogenic potential in the thyroid gland?**

Cyclosporine and tacrolimus are implicated in thyroid carcinogenesis via upregulation of cAMP signalling and expression of thyroid peroxidase (TPO) and sodium-iodide symporter (NIS), both of which are involved in hormone biosynthesis and tumour growth (Chu, 2020; Ghafouri-Fard, 2022; Pani, 2022).

3. **How do the dosage and duration of immunosuppressive therapy influence thyroid cancer risk?**

Both factors are critical, with higher malignancy risks observed in the early post-transplant period and with increasing cumulative doses of agents like cyclosporine and prednisone. The risk peaks within the first year and correlates with thyroid proliferative abnormalities (Rojulpote, 2022; Tsuji, 2020; Tönshoff, 2020).

4. **What mechanisms may explain the oncogenic effects of immunosuppressants on the thyroid?**

   Immunosuppressants reduce immune surveillance by impairing T-cell–mediated tumour clearance, induce oxidative stress, and may disrupt DNA repair pathways (Ma et al., 2021; Liu, 2022). The inhibition of clonal expansion in lymphocytes, while therapeutically useful, also increases susceptibility to malignant transformation (Serkies et al., 2023).

5. **Can iodine deficiency or altered thyroid function modulate the oncogenic risk?** Altered I-131 uptake and subclinical hypothyroidism in transplant patients suggest that chronic iodine deficiency may interact with immunosuppressive exposure to elevate thyroid cancer risk. Identifying these conditions could improve prophylaxis and timing of surgical interventions (Hayes, 2021; Rollan, 2022).

By addressing these questions, the study aims to inform clinical surveillance strategies, individualised immunosuppressive protocols, and early thyroid cancer detection among renal transplant recipients.

# Chapter 3

## Human Leukocyte Antigens (HLA) in Transplant Rejection

Human leukocyte antigens (HLA), encoded by the highly polymorphic major histocompatibility complex (MHC) on chromosome 6, play a critical role in transplant rejection. These antigens, inherited from both parents, determine tissue compatibility between donor and recipient. A complete HLA match—particularly for HLA-A, -B, and -DR loci-significantly reduces the risk of graft rejection, as observed in matched siblings or identical twins (Bedford, 2022; Legaz, 2022).

Mismatch in HLA molecules can trigger immune responses leading to both early and late graft dysfunction. While immunological and non-immunological factors contribute to rejection, the presence of specific anti-HLA antibodies and the degree of mismatch are key determinants. Advances in HLA class I and II molecular typing and antibody detection have improved graft survival outcomes. However, even permissible mismatches, though sometimes unavoidable, elevate the risk of rejection and allograft vasculopathy. Therefore, precise HLA matching remains essential in transplantation, particularly in procedures like bone marrow transplants (Abou-Jaoudé, 2021; J. J. , F. S. V. , & M. S. D. Kim, 2021).

When a graft is transplanted between two individuals, the recipient's immune system recognises alloantigens from the donor organ as foreign. This immune recognition is primarily mediated by the highly polymorphic HLA molecules expressed on all nucleated cells and platelets. Donor HLA molecules present both self and foreign peptides to the recipient's immune system, triggering T and B cell responses. CD4+ helper and CD8+ cytotoxic T cells, along with activated B cells, generate alloantibodies that initiate immune responses leading to graft rejection.

## 3.2 Immunosuppressive Therapy in Renal Transplantation

Immunosuppressive therapy is essential for preventing graft rejection in kidney transplantation, but long-term use is a known risk factor for malignancies. Despite matching donor-recipient ABO blood types and minimising donor-specific antibodies, immune suppression remains necessary due to unavoidable HLA mismatches that trigger rejection. Modern immunosuppressants not only inhibit immune responses but also interfere with various cellular and hormonal pathways.

These drugs function by suppressing lymphocyte activation, cytokine production, antigen presentation, and antibody formation. Therapy must be tailored to the patient's immunologic risk, medical history, and graft prognosis. The goal is to preserve graft function while minimising adverse effects such as infection and cancer. Advances in personalised medicine, risk modelling, and drug combinations continue to refine treatment strategies (Shen et al., 2022; Tie, 2022; Li, 2020).

## 3.3 Key Classes of Immunosuppressive Drugs

Immunosuppressants in renal transplantation fall into seven categories: corticosteroids, calcineurin inhibitors (CNIs), mTOR inhibitors, co-stimulation blockers, T-cell depleting agents, antiproliferative agents (e.g., mycophenolate mofetil, azathioprine), and newer tapering/induction-based protocols. CNIs and mTOR inhibitors are commonly used to minimise steroid exposure. Drug combinations are selected based on patient-specific factors, with ongoing research into optimised and individualised regimens (Parlakpinar, 2021).

### 3.4 Dosing Strategies

Dosing is adjusted for age, weight, renal function, and infection risk. Drugs like Tacrolimus, which have a narrow therapeutic window, require careful monitoring to balance efficacy and toxicity. Dosage modifications are made during infections, in EBV-negative recipients, or when adverse effects occur. Adherence is critical, as non-compliance can lead to graft failure or increased mortality (Bergan, 2021; Malpica, 2020).

## 3.5 Immunosuppression and Cancer Risk

Immunosuppressive therapy impairs tumour immunosurveillance, increasing the risk of malignancy in transplant recipients. The cumulative dosage and duration of therapy are more predictive of cancer development than individual drug exposure. Polypharmacy complicates the ability to isolate the oncogenic risk of specific agents, and ethical constraints limit trial-based evidence. Nonetheless, certain drug classes are associated with distinct malignancy profiles, and cancer surveillance remains a cornerstone of post-transplant care (Blosser, 2021; Shen et al., 2022).

## 3.6 Thyroid Cancer in Renal Transplant Recipients

Renal transplant recipients exhibit a three to four-fold higher incidence of thyroid cancer compared to the general population. This risk is influenced by long-term immunosuppression, pre-existing ESRD-related immune dysfunction, and factors like radiation exposure and goitre. Studies, particularly in Asian populations, report significantly elevated standardised incidence ratios, with some indicating a 9- to 100-fold increase. One large case-control study confirmed higher thyroid cancer rates among those on immunosuppressants, with mammalian target of

rapamycin (mTOR) inhibitors showing variable associations with hypothyroidism and cancer risk.

Late detection due to the absence of screening protocols often results in advanced-stage diagnoses. Regular monitoring of thyroid function, imaging, and attention to subclinical dysfunction are critical. While some evidence suggests ESRD itself may predispose individuals to thyroid malignancy, immunosuppression likely compounds this risk. Further research into drug-specific oncogenic potential and the role of immune restoration in cancer progression is warranted (Buxeda, 2021; Canossi, 2022; Cicalese, 2023).

HLA mismatches, even at a single antigen, can trigger CD4/CD8 T cell responses, increasing the risk of antibody-mediated and T cell–mediated rejection. Matching at HLA-A, -B, -DRB1, and -DQ loci reduces rejection and improves graft outcomes. Poor HLA compatibility is linked to de novo donor-specific antibodies and worse clinical results. Pre-transplant crossmatching and zero-mismatch prioritisation, especially for sensitised recipients, enhance survival and remain key in donor selection (Gramkow, 2024; Osorio-Jaramillo, 2020; Senev, 2020; Wiebe, 2022).

# Chapter 4

# Immunosuppressive Agents and Cancer Risk: Focus on Thyroid Malignancy

Immunosuppressive agents, essential for preventing graft rejection in transplant recipients, impair immune surveillance, increasing the risk of malignancies, including thyroid cancer. This risk is linked to both the type and cumulative exposure to agents such as calcineurin inhibitors (CNIs), mTOR inhibitors, corticosteroids, and antiproliferative agents like azathioprine and mycophenolate mofetil. CNIs (e.g., cyclosporine, tacrolimus) inhibit T-cell activation via NFAT suppression but are associated with increased skin and solid organ cancers. mTOR inhibitors (e.g., sirolimus, everolimus) regulate cell growth and immune responses and have shown both protective and adverse oncologic effects. Corticosteroids exert broad immunosuppressive effects, including T-cell depletion and reduced antigen presentation, and may increase susceptibility to infections and certain malignancies (Hiam-Galvez, 2021; Pellegrino, 2021)..

## 4.1 Calcineurin Inhibitors (CNIs)

CNIs are powerful inhibitors of the nuclear factor of activated T cells (NFAT), a critical molecule responsible for T-cell activation. NFAT regulation is controlled through the action of calmodulin and calcineurin, a calcium-dependent phosphatase that promotes NFAT import to the nucleus. In the absence of NFAT, T-cell activation is significantly decreased, and psoriasis or other autoimmune diseases are reduced. CNIs have become the mainstay of oral immunosuppressive agents used to prevent and treat graft rejection in transplant recipients. However, long-term use of CNIs is associated with significant side effects and is often avoided when possible (Marin, 2021; Vergara-Rejante, 2023).

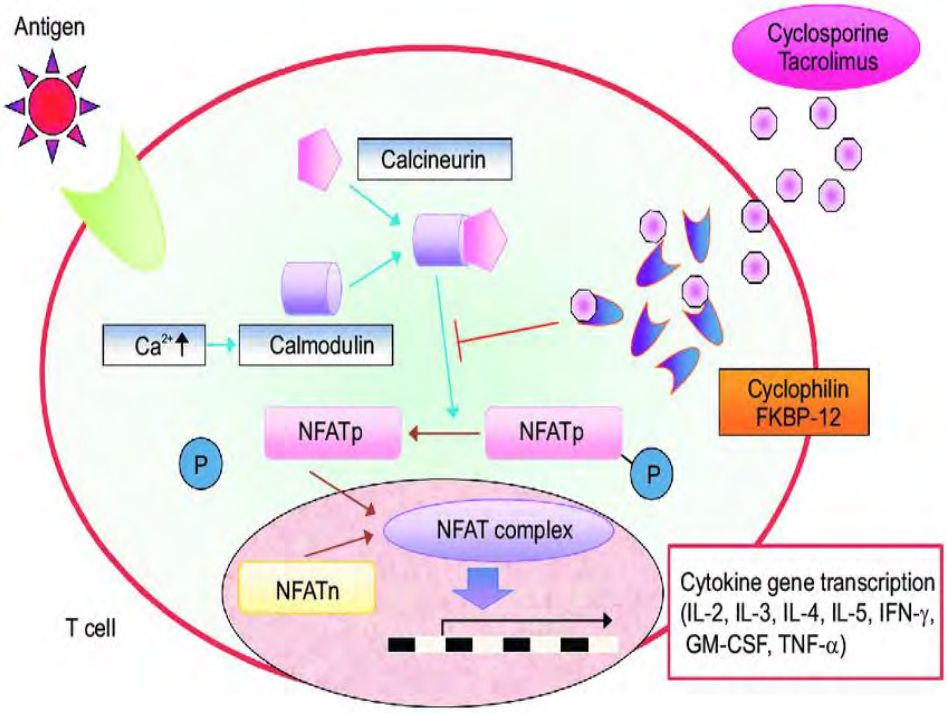


*Figure 2: Mechanism of Action of Calcineurin Inhibitors (Cyclosporine and Tacrolimus) in T Cell Signalling*

Calcineurin is known to be a tumor suppressor that acts by dephosphorylating and activating the apoptosis-inducing factor Bad, a member of the Bcl-2 pro-apoptotic protein family, leading to cell apoptosis. In addition, calcineurin can also activate the NFATc transcription factor, leading to increased FasL expression in T cells, promoting alloimmune killing of activated T cells. An analysis of a kidney transplant registry suggested a significantly higher risk of cancer with CsA-based immunosuppressive therapy, particularly for nonmelanoma skin cancer. Moreover, the risk of solid organ malignancies appeared to be three times higher than in the general population. Since then, numerous reports on the higher risk of various malignancies following CNI-based immunosuppression have been published, most of which supported the increased skin cancer risk with CNI therapy, particularly the combination of CNI and AZA treatment(Kreher, 2023; Kulbat, 2023).

## 4.2 Immunosuppressive Agents: Mechanism of Action and Common Drugs

Disruption of the natural progression of T cells from G1 to S phase alters the immune response of an organism. Such a blockage is associated with the generation of a population of immature cells containing reduced numbers of both cytotoxic and suppressor T lymphocytes, reduced levels of natural suppressor cells, and, in some instances, decreased antibody production. All these effects contribute in some way to the immunosuppression of the drugs. Cyclosporine, the most powerful of the agents that block the progression of T cells from G1 to S phase, was originally developed as an immunosuppressive agent to prevent the rejection of transplanted organs. Other drugs of the same class have been developed more recently from Streptomyces species. Because of their powerful immunosuppressive effects, they have also found use in controlling autoimmune responses associated with a wide variety of diseases such as systemic lupus erythematosus and rheumatoid arthritis. Their other powerful medical applications are in suppressing the immune response in transplantation and reducing inflammation and slowing the progression of fibrosis in various organ systems. Some common immunosuppressive agents used in transplantation include cyclosporine and tacrolimus. These drugs work by suppressing the immune response to prevent rejection of the transplanted organ. Common drugs used as immunosuppressive agents include cyclosporine and tacrolimus. These drugs work by suppressing the immune response to prevent rejection of the transplanted organ, but they may also have implications for thyroid cancer risk (Aiyegbusi, 2022; Parlakpinar, 2021)

## 4.3 mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is a critical effector of the PI3K-AKT pathway, a signaling cascade that is frequently activated in human cancers, including thyroid carcinoma. Two distinct mTOR complexes, mTORC1 and mTORC2, both contribute to various signaling events and biologic activities in cancer cells. mTOR inhibitors exhibit anticancer activities by

inducing features of autophagy and apoptosis, as well as by inhibiting cell cycle progression, angiogenesis, migration, invasion, and tumor stem cell self-renewal. As a consequence, mTOR inhibitors have demonstrated efficacy and safety in advanced thyroid cancer, starting from results of preclinical studies. Since numerous studies have identified a relationship between mTOR and immune regulators, multiple studies have aimed to determine the role of mTOR in immunosuppression. In T cell lines, mTOR inhibition can reverse the tumor-induced suppression of the cytokines.

However, the antiproliferative effect exhibited significantly faster kinetics than the reestablished cytokine secretion. In nude and SCID mice, exposure to mTOR inhibitors for two weeks also reversed the tumor-induced reduction of thymic cellularity. These investigations suggest that mTOR represents one of the common signaling nodes that regulate the T-cell suppressive function. An increased understanding of the mTOR/tumor suppression signaling network will provide valuable insights for the design of future immunotherapies. Furthermore, mTOR inhibitors may combine with immunomodulatory antibodies to enhance the efficacy of cancer immunotherapy while overcoming its resistance (Glaviano, 2023; Pappa, 2021).

## 4.4 Mechanism of action and common drugs (e.g., sirolimus, everolimus).

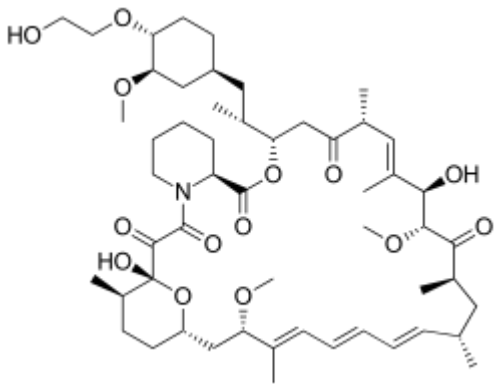


*Figure 3: Structure of Everolimus*

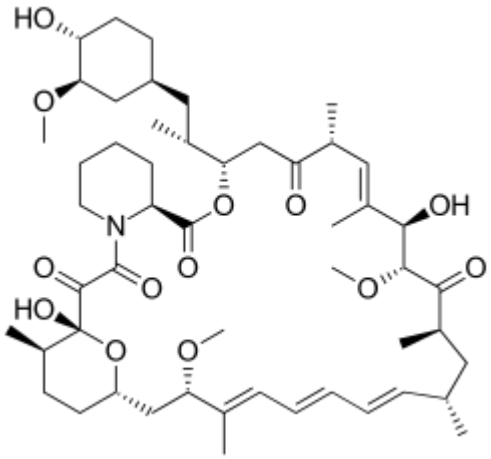


*Figure 4: Structure of Sirolimus*

Immunosuppressive agents such as sirolimus and everolimus are potent inhibitors of the mammalian target of rapamycin and have been introduced into clinical solid-organ transplantation to avoid calcineurin inhibitor toxicity, among them an increased cancer risk, particularly for nonmelanoma skin cancers and lymphomas. This concept is reviewed with special emphasis on their effect on thyroid cancer because, paradoxically, most data indicate a reduced cancer protective role in thyroid carcinogenesis. Such data from large clinical studies in solid-organ transplantation recipients suffering from thyroid cancer or benign thyroid nodules is revised and possible mechanisms for an immunosuppressive agent-dependent cancer risk and protective action in thyroid function and carcinogenesis are re-evaluated (Gheorghe, 2021; Gianchecchi, 2020; Maier, 2024).

The mammalian target of rapamycin represents an important signaling pathway for multiple biological processes, including cell growth, differentiation, angiogenesis, and immune responses. Small-molecule inhibitors of the mammalian target of rapamycin such as the macrolides sirolimus and everolimus largely serve as immunosuppressive agents or anticancer drugs since the approval for treatment of advanced renal cell carcinoma(Panwar, 2023; Xu, 2022).

## 4.5 Corticosteroids

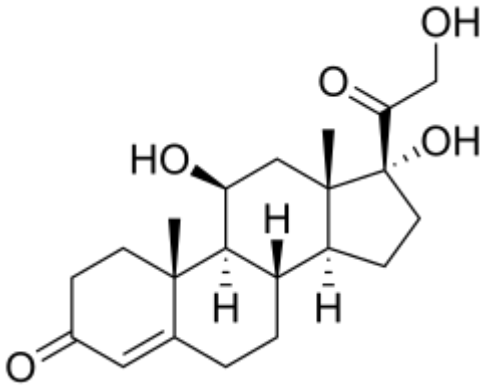


*Figure 5: Structure of Hydrocortisone*

Corticosteroids like hydrocortisone have a large spectrum of effects on the immune system and have been used to inhibit inflammation and the immune response to different diseases. They affect a variety of immune cell populations such as macrophages, monocytes, dendritic cells, neutrophils, basophils, mast cells, eosinophils, T helper cells, T regulatory cells, and T cytotoxic cells. Very high doses of systemic corticosteroids have an almost immediate effect on T lymphocytes, resulting in extensive lymphopenia, in particular of CD4+ T lymphocytes. Corticosteroids are cytotoxic for CD4+ and CD8+ T lymphocytes, largely affecting the mature memory T lymphocyte population. High-dose systemic corticosteroids also affect the cellular components of the innate immune system, first and foremost the monocyte-macrophage system. Corticosteroids can have pleiotropic immunomodulatory effects on dendritic cells, both in their phenotype and in their ability to present antigens and/or stimulate T cells (Ikuta, 2022; Taves, 2021).

It is quite clear that corticosteroids reduce immune system responses and the ability of the organism to mount effective immune defenses. Chronically administered high doses of corticosteroids may inhibit growth of lymphoid tissue and affect humoral immunity. High and prolonged exposure to these drugs predisposes individuals to develop latent or primary infections and reactivate existing chronic infections. These powerful immune-modulatory

agents have been applied in the treatment of numerous clinical conditions by inhibiting inflammation and the immune response. In recent years, corticosteroids have been suggested as a savior from the profound pro-inflammatory cytokine storm developed during the course of treatment of severe acute respiratory syndrome, Middle East respiratory syndrome, and other respiratory disease pandemics (Borkar, 2022; Singh, 2022).

## 4.6 Adverse Outcomes and Mechanisms

Immunosuppressants facilitate oncogenesis by disrupting immune surveillance, promoting viral reactivation (e.g., EBV, HPV), and impairing apoptosis and DNA repair. The risk is notably higher for virally mediated cancers but is increasingly recognised in thyroid malignancies, particularly among long-term transplant recipients. Thyroid cancer risk may also reflect the combined effects of ESRD, immunosuppression, and pre-existing thyroid dysfunction.

## 4.7 Thyroid Cancer in Transplant Patients

Renal transplant recipients show a higher incidence of thyroid cancer than the general population, with female patients disproportionately affected. This elevated risk is influenced by cumulative drug exposure, delayed diagnosis, and complex interactions between immunosuppression and thyroid pathology. While some agents like sirolimus show protective potential, evidence is inconclusive and highlights the need for further research.

Long-term immunosuppressive therapy increases cancer risk through impaired immune surveillance and potential drug-specific mechanisms. While associations with thyroid cancer are emerging, more targeted, longitudinal research is required to define causality, stratify risk, and guide personalized immunosuppressive strategies in renal transplant recipients.

## 4.8 Overview of malignancies associated with long-term immunosuppression in transplant patients

The transplant patient cohort has posed an interesting question to the medical world. Decades of immunosuppression are associated with a plethora of problems, one of which is de novo malignancies. These are divided into early-onset and late-onset. The present chapter is an attempt to delve deeper into the cancer risk for transplant patients and to better understand what the shared pathways with solid organ cancer patients are, and then introduce data gathered on cancer risk factors, etiologic data, and organ-specific cancer data. Since both cancer and the use of immune-modulating agents can be immune system responses, the shared pathway effect also becomes even more interesting. Tissue invasion and evasion of immune surveillance can allow the immune system to become less effective and, again, increase risk (Altieri, 2021; Zwart, 2021).

In summary, the underlying risk for any specific cancer is manifold; however, the role of chronic immune modulation contributes to several noted and important pathways. In conclusion, long-term immune modulation increases the risk of de novo cancer in solid organ transplant patients due to impaired immunosurveillance and activation or synergistic effects of both pro-growth of dysplastic cells, as well as the activation of other tumor progression pathways. Future questions remain: How can we study the long-term effects of anti-rejection drugs on immune cells in human test systems? Do immune cells from solid organ transplant patients express biologically relevant markers before cancer initiation, and what are the caveats for longitudinal prospective studies for any organ site even after transformation? (Mudigonda, 2022; Zwart, 2021).

## 4.9 Mechanisms through which Immunosuppressants increase Cancer Risk

While immunosuppressive agents have greatly advanced transplantation and treatment of autoimmune conditions, they are increasingly linked to elevated cancer risk. This is primarily due to impaired immune surveillance, which allows malignant cells to escape detection. Immunosuppressants particularly raise the risk of virus-associated cancers, such as Kaposi's sarcoma (HHV-8), Merkel cell carcinoma (polyomavirus), lymphomas (EBV), and cervical cancer (HPV). Recent concerns also highlight a growing association between long-term immunosuppression and thyroid cancer, especially as transplant numbers rise across all age groups (Kempen, 2023).

# Chapter 5

## Thyroid Gland, Cancer and Immunosuppressants

The thyroid gland, located in the neck and shaped like a butterfly, plays a crucial role in regulating metabolism via T3 and T4 hormones, under TSH control from the pituitary (Basolo et al., 2022; Teixeira et al., 2020). It contains follicular and parafollicular cells, requires iodine for hormone synthesis, and includes immune cells that may respond to injury or inflammation (Al-Suhaimi, 2017; Ali & Majeed, 2022; Salman, 2024).

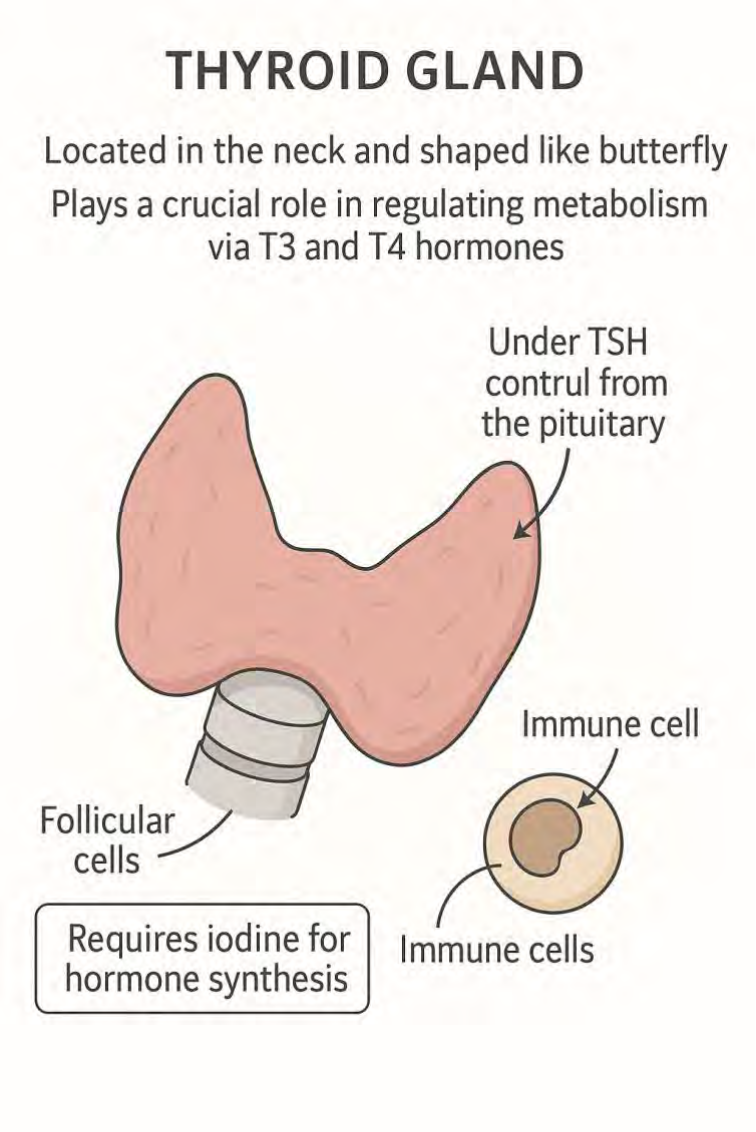


*Figure 6: Location of Thyroid Gland*

Thyroid cancer incidence has increased globally, with ionising radiation being a major risk factor, particularly in women and children (Kitahara et al., 2020; Li et al., 2021; Morton et al., 2021). Improved diagnostics, such as ultrasonography and fine-needle aspiration, have contributed to higher detection rates, especially of small differentiated thyroid cancers (Kim et al., 2020).

Several studies have linked long-term immunosuppressive therapy—especially steroids, azathioprine, and cyclosporine—to an elevated risk of thyroid malignancies, though data on anaplastic and medullary types remain limited (Kitahara & Schneider, 2022; Petranović Ovčariček et al., 2021; Cunha, 2022; Shobab et al., 2022).

# Chapter 6

# Presentation of the Demographic Characteristics of the Patient Cohort (age, gender, duration post-transplant)

A retrospective study to describe the incidence of thyroid cancer, the pathology and treatment of the tumors, and patient survival at a single university renal transplant center was conducted. The potential risk factors, such as dialysis duration, age, gender, renal transplant duration, donor type, pre-existing thyroid disease, and the time interval after the transplant to the diagnosis were identified. The demographic characteristics of the patient cohort, including age, gender, and duration post-transplant, were extracted from a prospectively maintained renal transplant database. The remaining data in this retrospective single-center study were collected from electronic medical records. The renal transplants performed during the 16-year interval were reviewed. A pathologist reviewed all the biopsy reports from the excised thyroid masses to determine the histological type of thyroid cancer. To determine the prevalence of post-transplant thyroid masses, reports of thyroid image findings or biopsies obtained during the study period were recorded. Based on these data, we determined the incidence of thyroid cancer as well as the characteristics of the thyroid masses in our cohort (Jeong, 2020).

## 6.1 Incidence of Thyroid Cancer

A population-based cohort study of de novo malignancy in Taiwanese renal transplant recipients was conducted. The study found that the standardized incidence ratio for subsequent thyroid cancer was significantly elevated among renal transplant recipients (5.44). The study showed renal transplant certainly carried a longer-than-lifetime risk of thyroid carcinoma. The overall incidence of new thyroid cancers was 4.2% for males and 13.0% for females, with a ratio of 3.10:1 for females to males. The age-adjusted incidence was 1.51 per 10,000 for males

and 4.64 per 10,000 for females, still only about 0.05% per year in the United States. After receiving renal allografts and associated immunosuppressive agents, thyroid cancer risk appears to be increased three-fold or potentially higher. These two studies seem to contradict each other, but not exactly. It may suggest that the increased risk is in patients whose immunity has been relatively low for a long period of time (Delman, 2022; Feodoroff, 2024; Taborelli, 2022).

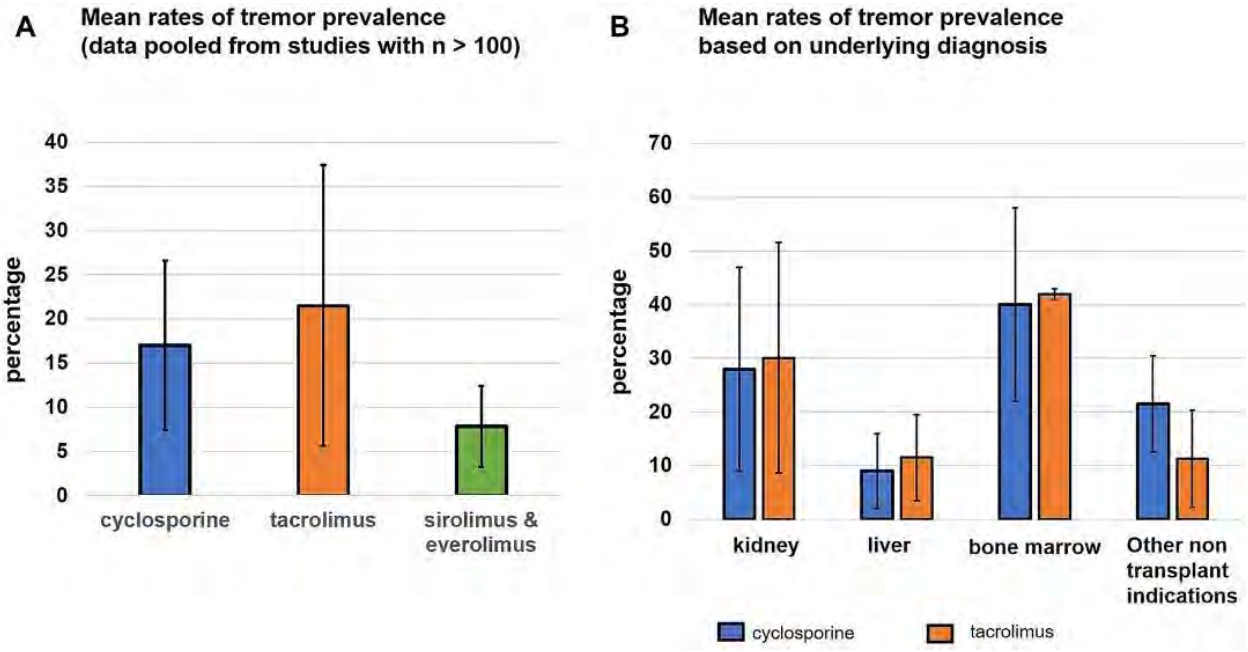


*Figure 7: Mean Prevalence of Tremor Associated with Immunosuppressants by Drug Type and Clinical Indication*

In a retrospective cohort study, the association between thyroid carcinoma and solid organ transplant was further explored. Among 21 recipients (11 females and 10 males; range 14-69 years) who received the first cadaveric kidney transplant and died before 1 January 1973, only two males developed thyroid carcinoma. The potential pitfalls for such reinterpretation of the study data if wellness has been ignored, and it may not be the immune deficiency that resulted in cancers. Thyroid carcinoma and its risk mode in renal transplant recipients have not been studied thoroughly and represent an area worth exploring, and maybe preventing (Fuhrmann,

2023; Jung, 2022; Pyrża, 2022). Thyroid cancer incidence in renal transplant patients is influenced by various factors such as age, gender, and exposure to radiation. Studies have shown that the incidence of thyroid cancer is higher in transplant recipients compared to the general population.

## 6.2 Frequency of thyroid malignancies among renal transplant patients

Renal transplant patients are a group with an increased incidence of malignant tumors. The most common histologic types are skin and other types of malignancies—lymphoma, Kaposi sarcoma, etc. Malignant neoplasms of the kidneys, ureter, and bladder predominate in the urinary tract, while basal cell carcinoma, squamous cell carcinoma, and melanoma are the most common skin malignancies. Increased risk of developing malignancy is due to prolonged immunosuppressive treatment to prevent renal rejection. Many researchers have noted that thyroid cancer tends to occur much more frequently in patients after kidney transplantation. To date, there are only five published studies in which the incidence of thyroid cancer resulting from malignancy in patients after renal transplant was studied. Thyroid cancer was detected in 9 patients of the total number of patients treated during the first 10 years after renal transplantation. The data obtained give grounds for considering patients after kidney transplantation as individuals of a group who are at increased risk of developing thyroid cancer (Bilha, 2023b; K. Serkies et al., 2023; Sigman, 2023).

## 6.3 Comparison with the general population or non-immunosuppressed transplant patients

Patients undergoing solid organ transplantation and who are on chronic immunosuppressive therapy are at higher risk of developing a malignancy. Renal transplant patients have a higher incidence of malignancy compared to the general population or non-immunosuppressed

transplant patients. This is due to the use of immunosuppressive agents and chronic viral illnesses. There are very few studies regarding thyroid cancer in renal transplant patients. These do not document demographics, risk factors, and a comparison with the general population or non-immunosuppressed patients. They are treated in the same manner as non-end-stage renal disease patients. The records of 27 renal transplant patients treated at a medical center for thyroid malignancy were retrospectively reviewed for demographics, preexisting thyroid disorders, risk factors, tumor characteristics, management, and follow-up. Data analysis was performed using descriptive statistics (Shen et al., 2022).

Compared to the general population, the gender distribution, age at treatment, types of thyroid malignancy, coexistence of type 2 diabetes mellitus, smoking history, prior radiation exposure, stage at presentation, management, disease-free survival, and overall survival were comparable. However, the time of observation was short, and three patients were diagnosed with thyroid malignancy within twelve months of renal transplantation. The patient demographics, risk factors, tumor characteristics, and management were comparable to those reported in the literature. To the best of our knowledge, this report represents the largest case series regarding the demographic characteristics, risk factors, and management considerations for renal transplant patients who develop thyroid malignancy. It is unclear if patients who undergo renal transplantation are at a higher risk of developing viral-induced malignancy, or if they simply undergo closer observation for their underlying pretransplant coexisting disorders and receive the same beneficial effects that their immunosuppressive course confers upon a failed graft. Further research and an increased time of observation are warranted (Zivaljevic, 2023).

## 6.4 Oncogenic Potential of Different Immunosuppressants

There are a number of elements that make up human cancer. Most of the genes such as FOXP3 (Forkhead Box P3), CTLA4 (Cytotoxic T-Lymphocyte Antigen 4), PDCD1 (Programmed Cell Death 1, encodes PD-1) and IL2RA (Interleukin-2 Receptor Alpha, also known as CD25) which was not identified for their role in cancer initially. The original discovery of immunosuppression cohort genes helped point to the oncogenic potential of the drug classes they represent. Cyclosporine is a small cyclic polypeptide of 11 amino acids. It belongs to the group of drugs commonly known as calcineurin inhibitors. This family of drugs is common in all types of organ transplantation. Both cyclosporine A and tacrolimus are highly effective targets in inhibiting T-cell responses. Cyclosporine has formed the cornerstone of immunosuppression in organ transplantation. However, it is also a strong T-lymphocyte mitogen, promotes cytokine expression, induces nuclear oncogenes, and enhances the assembly of proto-oncogene proteins. These observations support potential tumorigenic features of cyclosporine (Andras, 2023; Moldvai, 2024; Wang, 2022).

There are very few pure oncogenic transformed calcineurin substrate systems defined. Calcineurin inhibitors have been shown to inhibit the dephosphorylation of a variety of substrates such as transcription factor NFAT, fructose-1, 6-macate, plasma membrane Ca(2+)-ATPase, pyruvate dehydrogenase, and a group of heat shock protein-1, heat-shock transcription factor-1, CREB, and glycogen synthase kinase 3b. Inhibitors of calcineurin cause an inhibition of HSF1 translocation to the nucleus. It seems that the substrates of this protein are tissue specific and the oncogenic action of this protein is unknown. However, apart from these, the information available about the status of TF genes in transplant patients at the time of diagnosis with thyroid cancer and at the time of transplant is limited. To the best of my knowledge, there are limited publications available related to the genomics of these transcription factors. Is it

interesting to know the impact of potential nonbacterial infectious diseases such as viruses, fungi, and protozoan parasites in the immunosuppressive gene regulation system?(Dhuli, 2023; Ding, 2023; Sunder-Plassmann, 2023; Wang, 2022; Yang, 2023). The oncogenic potential of different immunosuppressants in renal transplant patients has been a topic of interest in research. Some studies have suggested that certain medications may increase the risk of developing thyroid cancer, while others have not found a significant association. It is important for healthcare providers to consider these factors when determining the best treatment approach for patients.

Considering the important roles of cyclosporine and tacrolimus in solid organ transplantation in direct and indirect interactions with HIF-1, estrogen, NFI, NFKB, and EGR1, it becomes critically important to identify how patients' transcription factor genes can be targeted for the successful therapeutic prevention of the adverse incident of cancers. It has been reported that the disruption of the binding of key cofactors to the transcription factors of cancer is a new approach to overcome the problem of cancer. A small number of small molecules that cause transcription factor functionality disruption are currently discovered by the fields dedicated to studies on protein-protein interaction inhibitors. It is, however, interesting to note that the oncogenic potential of these drugs was not appreciated when they were introduced as immunosuppressants in the clinic but were only realised much later. More than 30 years have passed, and only a few hundred drugs are being used as inhibitors in the clinical practice of oncology (Garofalo, 2022; Lasek, 2022; Xu, 2022).

## 6.5 Stratified results based on the type of immunosuppressive therapy

In conclusion, our study suggests that the incidence of TCA is significantly higher among renal transplant patients treated recurrently or for long periods of time with tacrolimus/CTL-based regimens, especially among men. The higher risk for TCA was particularly pronounced for

PTC and among long-term recipients of the immunosuppressive therapy. The use of mTORi alone or in combination with tacrolimus/CTL confirms the safety. These data suggest that specific patient subsets receiving immunosuppressive therapy, especially aged patients and men, who show some early TCA signs, need stricter and specific tacrolimus/CTL/mTORi immunosuppressive therapy surveillance that would necessitate laboratory and/or imaging TCA testing and possibly discontinuing the therapy if the signs continue to worsen (Griveas, 2023, van Oosten, 2022).

## 6.6 Dose-response relationship between immunosuppressants and thyroid cancer

The context of this study is culturally unique, namely the United Arab Emirates, specifically the city of Al Ain, Abu Dhabi, at the Tawam Hospital Kidney Care Centre. It describes the demographics, risk factors, and treatment of thyroid cancer following renal transplantation. The patients had a disparity in thyroid cancer tissue diagnosis, mostly either papillary or follicular carcinoma, unlike the higher percentage of benign thyroid diseases treated and followed in the current literature. The receiver operating characteristic curve achieved an area under the curve value of 80%. The PTap was within the acceptable value of 5%. From this novel robust ROC curve, acquired PTap clinical factors of native dialysis vintage, CNIm dose, FK506 dose, gender, and use of spironolactone and tacrolimus had the highest predictive associations, respectively. Our findings were similar to the literature, namely the dose-response relationship to thyroid cancer with CNIm and PTS agents, and their biological sex dichotomy. In conclusion, it is important to understand the clinical context and local risk profiles of the UAE. This knowledge will assist the medical team of RTx patients who will have long-term follow-up and pressing other post-RTx issues to address, either within the RTx clinic or other hospital clinics and admissions. All had aggressive thyroid cancer histology findings and

demographic association differences with the literature, and the majority were extremely immunosuppressed with traditional agents. Furthermore, it is an important step to recognise the linked phenotypes, PTap clinical factors, including for patients to participate in their modifiable risk factors and thyroid cancer surveillance monitoring processes. Knowledge dissemination will serve to heighten public knowledge, local health policies, and enhanced healthcare during RTx pathophysiology and general (Griveas, 2023, van Oosten, 2022).

6.7 Case Studies which accounted for thyroid cancer from immunosuppressants in renal transplant patients:

**Case 1:**

A large-scale study analyzed data from over 229,000 U.S. solid organ transplant recipients between 1987 and 2012. It found that the incidence of thyroid cancer was 2.5 times higher in transplant recipients compared to the general population, with kidney transplant recipients showing a distinctive increase. Among renal transplant patients, the increased incidence of virus-related cancers is mainly attributed to the immunosuppressants used to prevent graft rejection. (Kitahara et al., 2017).

**Case 2:**

The Federico II University retrospectively conducted a median follow-up of 10 years and an average graft survival of 8 years on 1,200 kidney transplant patients, comprising 745 males and 455 females, between 1980 and 2012. Among patients aged 18 to 65, 6.4% of males and 4.7% of females developed cancer, emphasizing the potential for renal transplant recipients to develop cancers such as thyroid cancer.(Santangelo et al., 2015).

**Case 3:**

A recent study on the incidence of thyroid disease evaluated via ultrasound-guided FNAb in 44 kidney transplant recipients found that all patients presented with various degrees of goitre, with a thyroid nodule present in 43% of patients and thyroid cancer in 11.4%. Furthermore, there was a significant association between cyclosporine levels and the occurrence of goitre, confirming that higher levels of immunosuppression may increase the risk of developing thyroid cancer.(Veroux et al., 2019).

**Case 4:**

A study conducted between January 2000 and October 2017 on 760 kidney transplant recipients at a single centre found that 16.8% (240) of patients developed thyroid disease, while 18 patients developed thyroid cancer. The study suggests that the cumulative dose a patient receives over time, irrespective of the specific type of immunosuppressant, can increase the risk of developing thyroid cancer.(Veroux et al., 2019).

## 6.8 Other Observations

Other information noted in this study was that all patients were transplant recipients of kidneys from cadaveric donors, a reflection of the high endemic chronic kidney disease in Qatar. The natural history of thyroid cancer in ESRD is not known. The prevalence of incidental thyroid cancer in thyroidectomy specimens for benign disease was found to be 1%. The prevalence in autopsy cases of ESRD patients unexpectedly was 38% for MIC and cancer. Over time, more pre-ablation diagnostic studies, improved imaging modalities, and a well-defined role for suppressive therapy may help further define this disease process. Furthermore, studies in this and other post-ESRD settings might help to determine the role and true significance of ceruloplasmin and possibly of other yet-to-be-specified inflammatory markers in these new patient populations (Al-Sabbagh, 2024; Gillis, 2024; LeClair, 2021; Rodrigues, 2022

## 6.9 Correlation between duration of immunosuppressant therapy and malignancy risk

Long-term immunosuppressive therapy in organ-transplanted patients has been associated with an increased risk of developing malignancies. It is thought that the duration and intensity of immunosuppression are directly related to this risk. However, despite increasing reports of post-transplant lymphoproliferative disorder and so-called post-transplant lymphomas, only isolated cases of differentiated thyroid cancer have been reported. Here, we report two cases of differentiated thyroid cancer occurring in long-term immunosuppressed renal transplant patients from a single kidney transplant center. Both patients had been treated with mycophenolate mofetil, cyclosporine, and prednisolone. Recipients of renal transplantation have an increased risk of developing thyroid tumors because of their chronic immunosuppressive therapy. The incidence of malignant disease varies widely. According to the analysis, female subjects have a higher incidence of thyroid carcinoma than males, and those subjects in the year following the transplantation procedure are at high risk: the so-called 'immunodeficiency period' more than doubles the risk of developing cancer, particularly in either the neck or the genitourinary system (Massicotte-Azarniouch, 2024).

## 6.10 Other potential factors influencing thyroid cancer development

Increased incidence of noncutaneous cancer in transplant recipients is well described, and the increase in the reported risk of thyroid cancer is not limited to renal transplant patients alone. The mechanism of increase in cancer risk in renal transplant patients is multifactorial. Renal transplant patients have unique associated factors including uremia and its treatment, immunosuppression, increased screening, coinfections, and malnutrition and anemia. Renal transplant patients are at increased risk of developing chronic viral hepatitis with resultant

increased risk of viral hepatitis–associated hepatocellular carcinoma. Known risk factors for hepatitis such as age and male sex have been established (Granata, 2023; Khaddour, 2024; Peleva, 2024). Other potential factors influencing thyroid cancer development may include exposure to radiation, family history of thyroid cancer, and certain genetic mutations.

Immunosuppression as a risk factor and its interaction with other risk factors must be considered in an attempt to understand the complex clinical scenario leading to the multiple cancers that occur in renal transplant patients. Some cancers such as Kaposi sarcoma and nonmelanocytic skin cancer have a clear causative and preventive role of certain viruses and ultraviolet light exposure, respectively, in the immunosuppressive state. Other cancers such as hepatocellular carcinoma have an interaction between the oncogenic viruses and the immunosuppressive state of the patient. The hepatitis B virus tumor contains a predicted T-lymphocyte epitope and in the setting of low T-lymphocyte levels along with immunosuppression, the virus escapes control from the immune system, resulting in uncontrolled replication of the virus. Viral load is consequently markedly increased, and risk of neoplastic transformation is significantly greater than in immunocompetent patients. Renal transplant recipients have a higher risk of developing chronic viral infections from hepatitis B as compared with patients with chronic kidney disease.

In summary, renal transplant patients are at increased risk of developing chronic viral hepatitis compared with immunosuppressed individuals only or with immunosuppressed patients on different types of immunosuppression who are not patients with chronic kidney disease who are immunocompetent. Thymus-derived lymphocytes play multiple roles in immunity and cancer surveillance, and the decreased cell-mediated immunity from coexisting chronic viral infections makes patients more prone to malignancies, either as immune suppression-induced tumors or as opportunistic infections-induced cancer. The use of immunosuppressants is

another proposed risk factor for cancer, with certain medications associated with malignancies in renal transplant recipients. At present, no vaccination strategy has been proven to affect post-transplantation cancer incidence. Whether vaccination strategies should be more aggressive preemptively in patients awaiting transplant, or perhaps be mandatory for transplant candidates, or perhaps be administered in ways to boost host immunity requires further investigation (Borriello, 2022; Gandolfini, 2022; Kotton, 2024; Oweira, 2022).

## 6.11 Interpretation of Results

The multivariate analyses performed to investigate the independent predictive factors of PTMC indicated that only the use of tacrolimus was an independent predictive factor. The results indicated that the use of cyclosporine did not increase the risk of PTMCs, but the number of patients using cyclosporine was also small to confirm this hypothesis. It is noteworthy that no previous study has presented associations between the use of immunosuppressants and thyroid neoplasm, but some studies have demonstrated the involvement of the immune system in the carcinogenesis of thyroid neoplasm. Previous studies have reported that the immune response is associated with the development of thyroid autoimmune diseases, which are important risk factors for PTC (Skala, 2024).

The immune system plays a significant role in cancer surveillance, as it can recognise tumor cell santigens selectively. Several studies have shown an association between organ transplantation and malignancy, and the interactions between immunosuppressants and tumor development have been previously demonstrated in hepatocellular carcinoma and other solid organ malignancies. In contrast to the conventional belief that the immunosuppressed immune system is likely to suppress tumor growth, recent studies have suggested that the immune system likely interacts with the tumor until the tumor eventually progresses and affects the immune system to induce an immunosuppressive state. Our study showed that the tacrolimus

group had an increased risk of PTMCs. In addition, the cumulative dosage of tacrolimus increased the risk of PTMCs. In conclusion, we discovered that solid organ transplant recipients using tacrolimus had a high risk of PTMCs. This result warrants additional prospective research on the potential link between PTMCs and immunosuppressant therapy (Basté Rotllan, 2022; Devon, 2024; Giovanella, 2022).

## 6.12 Discussion of the main findings regarding the oncogenic potential of immunosuppressants in the thyroid gland

A growing body of evidence suggests that organ transplant patients and individuals on long-term immunosuppressant therapy, especially when started at a young age, have a markedly increased risk for the development of some types of cancer. Furthermore, patients with autoimmune disorders treated with immunosuppressants are also considered at higher risk for the development of some tumors. In the case of the thyroid gland, several retrospective studies have shown an increased cancer prevalence in patients receiving chronic or even short-term immunosuppressant combination therapy. Most of these studies concern cyclosporine A and/or rapamycin, two immunosuppressants inhibiting the mTOR signaling pathway, that are administered to patients after organ transplantation to suppress immune reaction. Epidemiological studies have shown that solid cancers, including thyroid cancer, are major causes of morbidity and mortality after renal transplantation, revealing higher standardised incidence ratios in cohort studies (Friman, 2022; Jin, 2024; Murray, 2020; Shen, 2022).

Although the increased prevalence of cancer cells in transplanted patients was widely accepted, the underlying molecular and cellular mechanisms are not completely understood. In the thyroid gland, mTOR inhibitors, such as cyclosporine A, tacrolimus, or rapamycin, have been shown to fluctuate intracellular iodide uptake, leading to thyroid dysfunction. Under both physiological and pathological conditions, thyrocytes, forming the functional unit of the

thyroid gland, adjacent to intracellular colloid, regulate the intrathyroid iodine metabolism in response to circulating iodide. The synthesis of thyroid hormones, subjected to the negative feedback exerted by plasma TH concentration, involves specific proteins making up iodide transporters. Dysfunction of sodium/iodide symporter, thyroglobulin, thyroid transcription factor 1, or the associated deiodinases is well-recognised genetic variations affecting the sensitivity of the thyroid to endogenous or exogenous compounds influencing iodide uptake. In addition, more recent better in vitro drug evaluation, which provides mid-infrared or synchrotron radiation Fourier-transform infrared microscopy as tools to evaluate the effect of drugs on thyroid cells, has indicated that inhibition of iodide dynamics and thyroid cell activity could be further used to detect drug-induced dormancy of thyroid cancer cells. However, only a few reports have specifically investigated the thyroid function in patients receiving chronic or short-term combination therapy. Furthermore, how exposure to any individual or combination of immunosuppressants affects the iodide tumor-suppressive function in normal or cancer cells has not been experimentally addressed. Although the risk of cancer development is known to increase after kidney transplantation, several mediators of these effects have been proposed, such as long-term immunosuppressant exposure or chronic uremia and dialysis, creating a complex metabolic environment. Although several tumors, including thyroid cancer, are believed to stem from the long-term post-transplant inflammation, more mechanistic evidence is needed (Oh, 2021; Ratajczak, 2021; L. C. Zhang, 2023).

## 6.13 Comparison with previous research findings

The occurrence of non-Hodgkin lymphoma and posttransplant lymphoproliferative disease in patients treated with immunosuppressive drugs has been recognised for many years. Other types of cancer, such as bladder, lung, kidney, and skin cancer also occur at an increased rate in this population. Several clinical studies have demonstrated an increased frequency of thyroid

cancer in kidney transplant recipients. In vitro investigations have shown that the immunosuppressive drugs enhance the mutagenicity of environmental pollutants, which could accelerate thyroid carcinogenesis. The aim of this review is to present the potential mechanisms underlying the supportive effect of immunosuppressive drugs on thyroid carcinogenesis and to describe the current knowledge of the clinical manifestation and prognosis of thyroid cancer in this particular group of patients. Our final goal was to highlight the most relevant areas in which additional studies are needed to answer open questions and to identify alternative therapeutic solutions in patients undergoing immunosuppressive therapy (Davies, 2021; C. M. Kitahara, Schneider, 2022).

## 6.14 Mechanisms Behind Immunosuppressant-Induced Thyroid Cancer

Long-term immunosuppression may increase the risk of papillary thyroid carcinoma (PTC) and benign thyroid adenomas (BTA) due to immune dysregulation. Sirolimus and temsirolimus, which modulate mTOR signalling, contrast with tacrolimus, a SIRT1 inhibitor causing broader T-cell suppression. While mTOR inhibitors paradoxically stimulate immunity and may reduce cancer risk, tacrolimus leads to more profound immunosuppression, potentially elevating risk (Bizzarri, 2023; Frostadottir, 2024; Spini, 2024).

Tyrosine kinase inhibitors (e.g., pazopanib, sunitinib, bevacizumab) reduce thyroid cancer risk by blocking VEGF pathways and raising TSH levels, which stimulate immune function and inhibit tumor growth (Cuomo, 2022; Hong, 2024; Koehler et al., 2021; Puliafito, 2022).

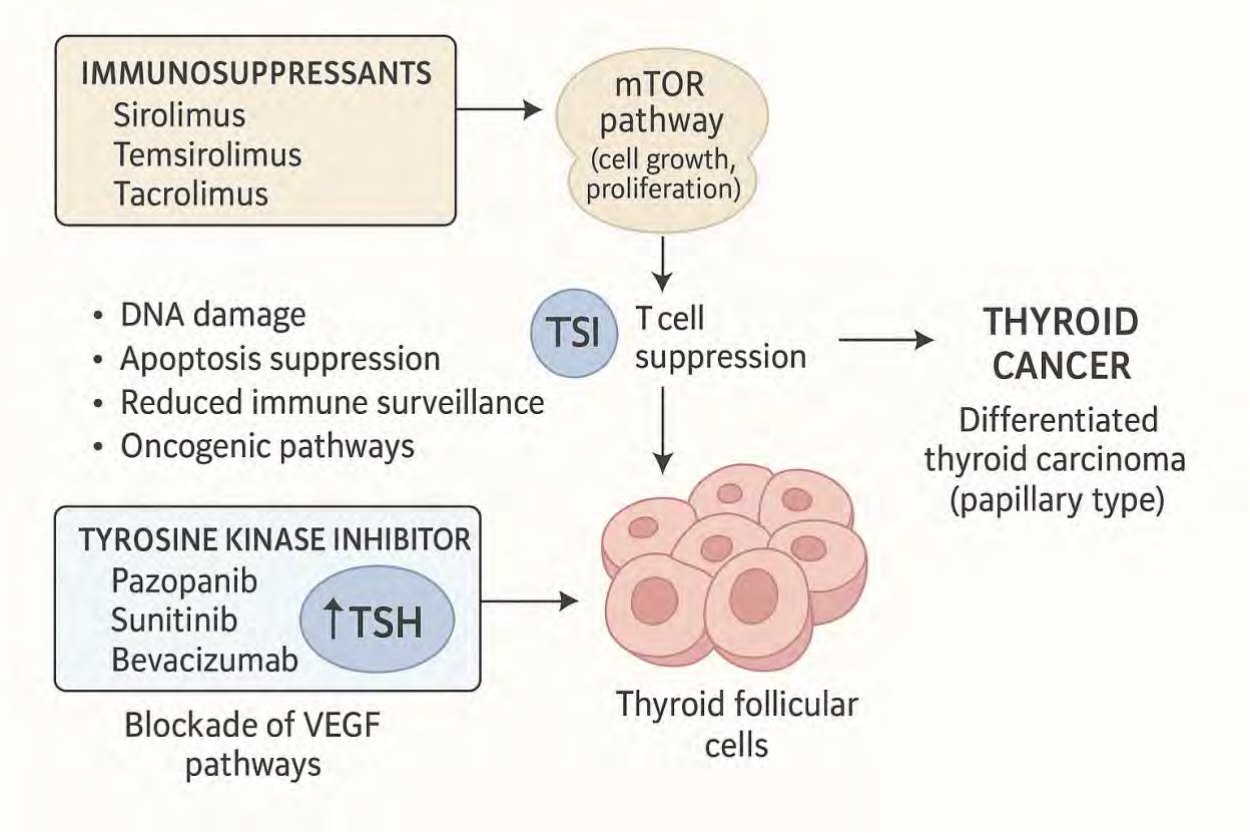


*Figure 8: Mechanisms by Which Immunosuppressants and Tyrosine Kinase Inhibitors Promote Thyroid Cancer Development*

## 6.15 Proposed Biological Mechanisms

Immunosuppressants may promote thyroid cancer through immune suppression (e.g., T-cell inhibition), impaired cytokine production, and DNA repair disruption. Some agents, such as corticosteroids and calcineurin inhibitors, may also elevate oxidative stress or alter hormone signalling (Cappelli & Shah, 2020; Reyes, 2022; Tison, 2022). Factors like radiation exposure, iodine deficiency, or obesity may compound these risks. Chronic immune suppression, unlike cumulative immune stimulation from allergies, may reduce immune surveillance and increase malignancy risk (Masetti, 2021; Megwalu & Moon, 2022; Wang et al., 2022).

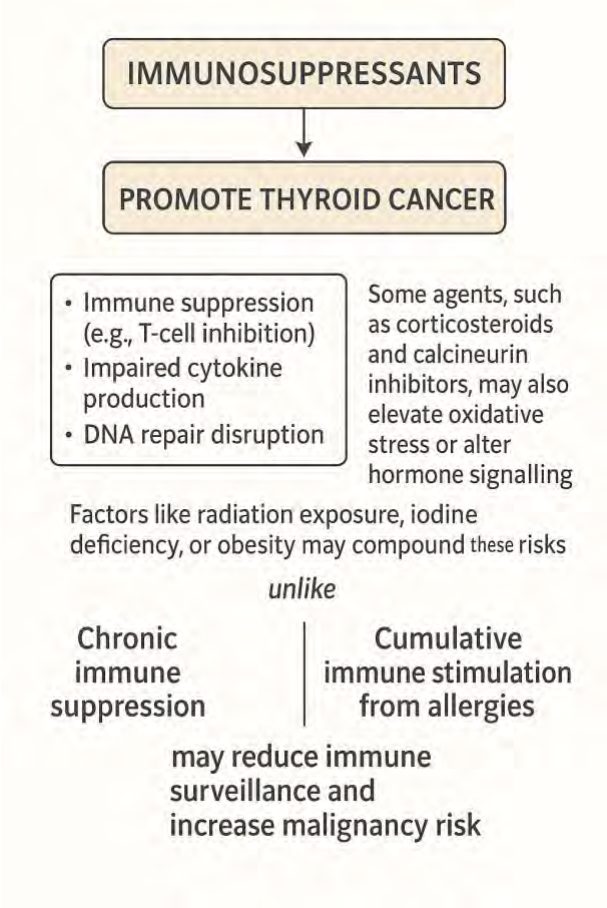


*Figure 9: Potential Mechanisms Linking Immunosuppressant Use to Increased Thyroid Cancer Risk*

## 6.16 Clinical Implications

Understanding these mechanisms suggests that immunosuppressive levels may modulate thyroid cancer risk. Thus, less aggressive immunosuppressive regimens may be favourable for at-risk patients. While immunotherapy shows promise in other cancers, it may trigger thyroid neoplasia in immunosuppressed individuals. Monitoring and biopsy-based evaluations are critical to detect emerging thyroid pathology (Cunha, 2022; Karwacka, 2021; Neto, 2024; Wojtukiewicz, 2021). More research is needed, especially regarding the safety of immunotherapy in thyroid or neuroendocrine cancers among transplant patients (Abdelrahim, 2024; Etxebarria, 2022; Portuguese, 2022).

## 6.17 Monitoring Considerations

Given the impact of drugs like tacrolimus and corticosteroids on thyroid function, regular screening of transplant recipients is recommended. Thyroid dysfunctions may be transient or permanent and are often linked to immune suppression. Therefore, careful dose regulation and thyroid monitoring should be integral to post-transplant care (Andrade-Sierra, 2021; Girardin, 2023; Scott, 2023).

## 6.18 Screening Recommendations

Thyroid cancer risk is elevated among organ transplant recipients, particularly with long-term corticosteroid or immunosuppressive exposure. The biological plausibility stems from disrupted immune surveillance, hormonal modulation, and viral oncogenesis. As such, routine thyroid evaluation (e.g., ultrasound) for transplant recipients may aid early detection (Andersen, 2022; Bruera, 2021; Haanen, 2020; Javed, 2024; Wunderlich, 2024). Associations with UV exposure and HPV-related cancers further highlight the role of broader immunosuppressive risks in endocrine malignancies (Boucai, 2024; Peled, 2020).

## 6.19 Limitations

This study's retrospective design limits access to complete medication histories and cumulative dosages, preventing dose-response analysis. Findings may not generalise beyond Taiwanese populations. Selection bias and unmeasured confounders remain concerns despite careful adjustments. Moreover, the role of immunosuppressants in modulating thyroid cancer stage or aggressiveness could not be assessed (Ko, 2020; Wei, 2021; Yu, 2020).

# Chapter 7

# Conclusion and Future Directions

Renal transplant recipients face a distinctly elevated risk of developing thyroid malignancies, largely attributable to the long-term use of immunosuppressive agents that compromise immune surveillance, alter thyroid physiology, and disrupt DNA repair mechanisms. This risk is particularly pronounced with calcineurin inhibitors and antimetabolites, while mTOR inhibitors may offer protective effects. Given the rising prevalence of kidney transplants and the lifelong need for immunosuppression, thyroid cancer in this population is emerging as a significant clinical concern.

Despite epidemiological associations, the precise oncogenic mechanisms of immunosuppressants remain incompletely understood. Future research must move beyond correlative data to explore causality through longitudinal and mechanistic studies. Integrated approaches, combining in vitro cell models, animal studies, and multi-centre human cohorts, are essential to elucidate the underlying pathways and patient-specific risk factors.

Moreover, advancements in genomics and proteomics can facilitate biomarker discovery for early detection and risk stratification. Innovations in imaging and real-time monitoring could further enable preemptive intervention before malignancy develops. Addressing these challenges through multidisciplinary collaboration will be critical to inform tailored therapeutic regimens and preventive protocols for renal transplant patients.

## 7.1 Recommendations

1. **Implement Routine Thyroid Screening**

Incorporate thyroid function tests (TSH, fT3, fT4) and ultrasound imaging into the regular follow-up of renal transplant recipients, particularly during the first year post-transplant when cancer risk is highest (Dahle, 2022; Scott, 2023).

**2. Risk-Stratified Immunosuppressive Regimens**

Adjust immunosuppressive therapies based on individual risk factors such as genetic predisposition, iodine status, and baseline thyroid pathology. mTOR inhibitors may be preferred where oncogenic risk is high (Leandro-García, 2023; Parlakpinar, 2021).

**3. Enhance Patient Education and Informed Consent**

Educate patients about the potential oncogenic effects of immunosuppressants, warning signs of thyroid dysfunction, and the importance of compliance with follow-up and screening protocols (Myint, 2022; Domínguez-Gil, 2022).

**4. Encourage Prospective and Mechanistic Research**

Support large-scale prospective cohort studies and case-control studies to explore dose–response relationships, mechanistic pathways (e.g., immune suppression, oxidative stress), and variations across ethnic and geographic populations (Masone, 2021; Von Itzstein, 2022; Ferrari, 2020).

**5. Use of Biomarkers and Advanced Imaging**

Investigate the utility of novel biomarkers and imaging modalities for the early detection of thyroid abnormalities in immunosuppressed individuals (Cuomo, 2022; Koehler et al., 2021).

**6. Promote Multidisciplinary Care**

Foster collaboration between nephrologists, endocrinologists, oncologists, and transplant surgeons to develop integrated care plans, especially for patients with pre-existing thyroid abnormalities or those receiving high-risk immunosuppressants (Karwacka, 2021; Neto, 2024).

**7. Develop Personalised Monitoring Protocols**

Establish long-term monitoring systems tailored to patient-specific immunosuppressive exposure, cancer history, and comorbid conditions to detect and manage malignancies early (Braaten, 2020; Olsen, 2022).

**8. Evaluate Immunosuppressive Reduction Strategies Cautiously**

Recognise that abrupt or non-standard reductions in immunosuppressants may not lower cancer risk and could increase the chance of graft rejection. Decisions must be made on a case-by-case basis, balancing benefits and risks (Verheijden, 2023).

**9. Standardise Screening for High-Risk Cancers**

Beyond thyroid cancer, ensure high-risk patients are regularly screened for HPV-related, nasopharyngeal, and skin cancers, particularly in regions with elevated endemic risk (Boucai, 2024; Peled, 2020).

**10. Strengthen Global Research Collaborations**

Facilitate international studies to improve generalisability, compare drug effects across populations, and build a global evidence base for thyroid cancer prevention in transplant settings (Javed, 2024; Wunderlich, 2024).

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