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_Cancer In Organ Transplant Recipients_
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Hör upp du sorgset kvidande,
se här din svåra roll:
att inse världens lidande
med glädjen i behåll.

– Tage Danielsson

I dedicate this thesis to my beloved friend Martha Ehlin 1976–2016 and all other transplanted patients and those on the waiting list.
Abstract

Tens of thousands of transplantations are performed around the world each year. Organ transplant recipients (OTR) are obliged to receive life-long medical treatment with immunosuppressive drugs to ensure graft function. However, such medications entail an increased risk of developing a broad spectrum of malignancies, especially skin cancer. This thesis aims to study cancer in OTRs from different aspects such as cancer incidence, survival, risk factors and prevention. Also, differentiation of squamous cell carcinoma (SCC) among OTRs.

Study I: The aim of this study was to investigate the degree of differentiation of SCC in OTRs compared to immunocompetent individuals. The degree of differentiation refers to how cancer cells look and function compared to normal cells. Data from the Swedish Cancer Registry (SCR) were cross-checked with data from the Transplant Registry (TR). Only patients with a diagnosis (SCC, Basosquamous Carcinoma and/or SCC in situ) from the Department of Dermatology, SUH (Sahlgrenska University Hospital), between 2002–2010 were included. The control group consisted of those who were diagnosed with the same diagnosis at the same time period at SUH as OTRs. No significant differences were observed in the degree of tumour differentiation in SCCs appearing in OTRs compared to those in the control group (p=0.4). In conclusion: SCCs in OTRs do not seem to be more aggressive than in the general population.

Study II: The aim of this study was to investigate whether specialized OTR clinics with dermatological follow-up, as has been suggested, provide additional benefit. In this descriptive study, in total, 696 OTRs and non-organ transplant patients (non-TPs) completed a sun exposure questionnaire between 2011 and 2015. The control group, the non-TPs, were recruited among outpatients at the Department of Dermatology, SUH. We also compared OTRs with dermatological follow-up to OTRs with no follow-up. Fewer OTRs than non-TPs had experienced ≥1 sunburn in the past year (20% vs 46% p<.0001). There were more frequent users of sunscreen among OTRs with follow-up than among other OTRs (63% vs 44%, p=0.006). More OTRs with follow-up used ≥1 sun protection measure (covering clothes etc.) than other OTRs (54% vs 34%, p=0.016). Thus, OTRs reported less sun exposure compared to non-TPs, consolidating the positive effect of sun protection advice following transplantation. Today, post-transplant sun protection advice is standard.

Study III: The aim of this study was to investigate cancer incidence and survival in 664 patients who underwent heart transplantation (HTx) at SUH between 1985–2017. Data was retrieved from the SCR and the Cause of Death Registry. We found in total 231 malignancies in 138 patients. Of all patients, 19% had experienced malignancy after almost seven years after HTx. We found an overall risk of cancer to be over 6.2-fold higher than the general population and 2.9-fold higher when excluding non-melanoma skin cancer (NMSC).

Study IV: The aim of this study was to investigate cancer incidence and survival in 614 patients who underwent lung transplantation (LTx) at SUH between 1990–2016. Data was retrieved from the SCR and the Cause of Death Registry. We found 159 malignancies in 111 patients which corresponds to 18% of the total study population. We found an overall risk of cancer to be 5.6-fold higher than the general population and 2.8-fold higher when excluding NMSC.
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Organtransplantation är en etablerad behandlingsmetod i Sverige som har gett tio-
tusentals människor möjligheten att leva ett längre och friskare liv. Donationsviljan
har ökat i Sverige det senaste decenniet vilket har bidragit till en positiv utveckling
avseende antalet organdonationer. Även insatser på regeringsnivå i form av lagför-
änderingar och organisation av sjukvården har gjorts för att främja donations- och
transplantationsverksamheten i landet. För att kroppen inte ska stöta bort ett nytt
organ måste transplanterade patienter stå på livslång behandling som dämpar det
egna immunförsvaret. En vanlig och allvarlig biverkan av medicinerna är en ökad risk
att drabbas av cancer, framför allt hudcancer. Detta beror på den immundämpande
effekten i kombination med exponering för solljus.

Det övergripande syftet med denna avhandling är att titta på cancer hos organtrans-
planterade patienter ur olika perspektiv såsom förekomst av cancer efter hjärt- eller
lungtransplantation, överlevnad hos de patienterna som drabbas av cancer efter hjärt-
eller lungtransplantation jämfört med den svenska normalbefolkningen. Vi har även
undersökt om graden av aggressivitet bland hudtumörer hos organtransplanterade
skiljer sig åt jämfört med hudtumörer hos icke-transplanterade patienter. Slutligen
har vi studerat solvanor och solskyddsbeteende hos transplanterade och icke-trans-
planterade patienter med olika risk att drabbas av hudcancer och olika förväntad nivå
kring kunskap om risker med solexponering.

Följande delarbeten ingår:

**Delarbete I** är en retrospektiv kohortstudie av skillnaden i differentieringsgrad av
hudtumörer mellan organtransplanterade och icke-organtransplanterade patienter.
Data inhämtades från Regionalt Cancercentrum Väst. Resultatet visade att organtrans-
planterade patienter hade i medeltal fyra gånger så många skivepitelcancertumörer
jämfört med de icke-transplanterade patienterna men det fanns ingen signifikant
skillnad i differentieringsgrad.

Det övergripande syftet med denna avhandling är att titta på cancer hos organtransplanterade patienter ur olika perspektiv såsom förekomst av cancer efter hjärt- eller lungtransplantation, överlevnad hos de patienterna som drabbas av cancer efter hjärt- eller lungtransplantation jämfört med den svenska normalbefolkningen. Vi har även undersökt om graden av aggressivitet bland hudtumörer hos organtransplanterade skiljer sig åt jämfört med hudtumörer hos icke-transplanterade patienter. Slutligen har vi studerat solvanor och solskyddsbeteende hos transplanterade och icke-transplanterade patienter med olika risk att drabbas av hudcancer och olika förväntad nivå kring kunskap om risker med solexponering.

**Delarbete II** består av en enkätstudie med patienter från Hudkliniken, SU. I studien har patienterna svarat på frågor om solvanor och solskyddsbeteende. De transplanterade patienterna rapporterade mindre solexponering och bättre solskyddsvanor jämfört med icke-transplanterade patienter vilket indikerar en positiv effekt av den information som de transplanterade patienterna getts på Hudkliniken.


**Delarbete IV** har vi tittat på cancerförekomst och överlevnad hos patienter som genomgått lungtransplantation på SU mellan 1990 och 2016, jämfört med en genomsnittlig svensk. De patienterna som hade lungtransplanterats utvecklade sammanlagt 159 tumörer under en uppföljningstid på 5.1 år. Vid jämförelse med en svensk genomsnitts population hade de lungtransplanterade patienterna en 5.6 gånger högre risk att drabbas av cancer och en 2.8 gånger högre risk om man tar bort hudcancertumörerna.
This thesis is based on the following studies, which are referred to in the text by their Roman numerals.


List of Papers

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Abbreviations

ATG Anti-thymocyte globulin
BCC Basal cell carcinoma
BOS Bronchiolitis obliterans syndrome
CAV Cardiac allograft vasculopathy
CLAD Chronic lung allograft dysfunction
CNI Calcineurin inhibitor
CS Corticosteroids
CsA Cyclosporine A
HLA Human leucocyte antigen
HTx Heart transplant
ISHLT The International Society for Heart and Lung Transplantation
LTx Lung transplant
MHC Major histocompatibility complex
MM Malignant melanoma
MMF Mycophenolate mofetil
mTOR Mammalian target of rapamycin
NMSC Non-melanoma skin cancer
Non-TPs Non-organ transplant patients
OTR Organ transplant recipient
RAS Restrictive allograft syndrome
SCC Squamous cell carcinoma
SCR Swedish Cancer Registry
SUH Sahlgrenska University Hospital
Tac Tacrolimus
TR Transplant Registry
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A brief history of organ transplantation

Organ transplantation is the best treatment for well-selected patients with end-stage organ failure. To replace diseased organs by transplantation of tissue or organ is a well-known and old method. There are examples of organ transplantation in ancient Greek, Chinese, Roman and Indian mythology of bone, skin extremities and even heart transplantation. Since then, tens of thousands of transplantations are performed worldwide each year and have given patients the opportunity to long-term survival and quality of life. However, many years have been spent on experimental studies and clinical trials to reach this level of success for organ transplant recipients (OTRs). Dr Jean Hamburger performed the first successful solid organ transplantation in Paris on Christmas Eve in 1952 when a mother gave one of her kidneys to her son (1). The boy died three weeks after the transplantation. Two years later, Joseph Murray at Brigham Hospital in Boston, also performed a kidney transplantation from a living donor with successful long-term outcome. Thanks to Hamburgers previous attempt, the transplantation team used a kidney given by a monozygotic twin.

It is now known that this innovation was successful because the brothers had identical human leukocyte antigen (HLA) types, and thus, allograft recognition in the recipient as non-self was not possible. Ronald Herrick donated one of his kidneys to his identical twin brother Richard who lived for eight years. The cause of death was cardiovascular disease. However, no evidence of rejection was ever seen postoperatively (2).

One decade later (1964), the first patient in Sweden underwent kidney transplantation at the Serafimer Hospital in Stockholm. Almost 60 years later, 24,770 organs have been transplanted in Sweden (as of March 31, 2021), with the majority of organs being kidneys (68%). The first successful lung transplantation (LTx) was carried out by James D Hardy and his team at the University Hospital Jackson, Mississippi, in 1963. Unfortunately, the 58-year recipient died 18 days after LTx. According to the autopsy, the cause of death was acute renal failure. However, the lungs showed no signs of rejection (3). The first clinical liver transplantation was carried out the same year (4). Three years later, the first successful pancreas transplantation was performed in the USA in an attempt to treat a type-1 diabetes patient (5). In Cape Town, South Africa, in 1967, the first heart transplantation (HTx) ever was carried out (6). The patient, a 54-year old man who suffered from ischemic cardiomyopathy, died 18 days postoperatively of pneumonia and acute rejection. The second patient who underwent HTx, only one month later, lived several years.
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A brief history of organ transplantation

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1. There is a shortage of organs in Sweden and many more patients awaiting transplantation than there are organ donors. There is a possibility for anyone with a Swedish identification number to register their preferences for donating organs and tissue in the Swedish National Donor Register. At the moment of writing, 820 patients are on the waiting list for an organ in Sweden.

2. Once the patient is declared dead and there is a positive donation will, a surgical team from the recipient’s hospital travel to the donor hospital, recover the organs and transport them to the waiting recipients.

3. Time is essential for the success of the transplantation. Prolonged ischemic times is a risk factor for adverse graft function. Each organ is preserved using special solutions and packed on ice. Once the transport team arrives at the recipient’s hospital with the organ the transplantation starts.
**Immune system and response to transplantation**

A reason for the successful kidney transplantation in 1954 was that the recipient and the donor were identical twins with almost identical immune expressions. Consequently, there was no need for immunosuppression agents to decrease the activity of the immune system. Therefore, a prerequisite for successful organ transplantation is the acceptance of the donor tissue by the host’s immune system. However, when the immune expression between donor and recipient is different, the immune system of the OTR will activate the immune system to attack, referred to as the rejection process.

The human immune system consists of two lines of defense: the innate and the adaptive, also called the acquired immune system. The innate system is an old defense line of attack selected during evolution. The cells and molecules of the innate immune system respond to foreign structures within seconds to hours. Prolonged infection or insult, such as an organ transplant will also activate the adaptive immune system, which takes several days to become efficient as it requires cell division of lymphocytes, also called white blood cells. Lymphocytes consist of different subtypes where B- and T-cells are key players in the rejection process. Lymphocytes recognize specific antigens expressed by pathogens or a transplant and are responsible for the immunological memory, the immediate and efficient response to re-infection or re-exposure of the antigen.

Lymphocytes are produced by the bone marrow where B-cells mature, whereas T-cells migrate and mature in the thymus; hence the name T-cells and B-cells. T- cells have the ability to recognize foreign antigens that are displayed on the surfaces of the body’s cells. Therefore, T-cells can detect the presence of an intracellular pathogen because infected cells display peptide fragments derived from the pathogen’s proteins. These foreign peptides are transferred to the cell surface by specialized host-cell glycoproteins, the major histocompatibility complex (MHC)(7). Activated B-cells called plasma cells produce antibodies that contribute to immunity in a number of ways. Firstly, they bind to their specific targets to induce phagocytosis by neutrophils and macrophages, a process called opsonization. Further, the antibodies activate the complement system, which contains a broad spectrum of proteins and, when activated, result in lysis of pathogens, recruitment of immune cells and opsonization(8).

**Human leucocyte antigen**

The human variant of MHC is called HLA. The genes are expressed on almost all nucleated cells and are the significant molecules responsible for graft rejection. There are three main groups of HLA; HLA-A, HLA-B and HLA-D. There are also many different specific HLA proteins within each of these three groups(9). All humans have two sets of HLA antigens, named haplotypes. Half are inherited from the mother, and the other half from the father. Furthermore, there is a 25% chance for siblings of
inheriting all of the same HLA (same 2 haplotypes), but there is also a risk of 25% of not inheriting any of the same HLA (none of the same haplotypes) and there is a 50% chance of sharing 1 haplotype with your siblings. Furthermore, there is a 1 in 4 chance of being an identical match with siblings. Monoyctotic twins therefore share the same haplotypes. The closer match between the donor and the patient’s HLA markers you can achieve the more successful the transplant outcome will be(10). As soon as the graft from the donor has been transplanted, the recipients B- and T-cells will recognize the donor’s HLA-antigens.

To make sure that the T-cells won’t attack the body’s own cells and tissue, there is a selection process in the thymus. Those thymocytes that are capable of strongly binding with self-antigens are being removed, in contrast to those lymphocytes with low affinity to their HLA-antigens being developed in the thymus and therefore kept.

**Immunosuppression**

By manipulating the recipient’s immune system by immunosuppression, graft rejection is delayed and the time of graft survival increases. The level of immunosuppression therapy is initially high to alleviate the immune response to the allograft but is slowly decreased over time as the risk of acute rejection decreases. Preferably, kidney transplanted patients with a graft from an HLA-identical donor require lower dosages of immunosuppressive treatment(11). Heart and lung transplant recipients require higher doses of immunosuppressive agents to prevent organ rejection, as compared to recipients of abdominal organs(12, 13). The immunosuppression regime depends on graft type, gender, age, and different local routines, recommendations and preferences. The goal of treatment with immunosuppression is to maintain organ function at the expense of minimal adverse effects. Consequently, there is a difficult balance between the risk of infections and the risk of rejection. Transplantation tolerance is still the “Holy Grail” for transplant immunologists, physicians and surgeons.

At the beginning of the transplantation era, corticosteroids (CS) were used to prevent graft rejection, often in combination with azathioprine, which was discovered in 1959(14). Due to the excessive immunosuppression, the prolonged use of CS resulted in a high mortality rate, although the initial effects were beneficial. However, the breakthrough of transplantation did not come until the first calcineurin inhibitor (CNI), came into clinical use in the early 1980s(15). The first CNI was named cyclosporin A (CsA) and discovered in Norway in 1969. However, the immunosuppressive effects were revealed three years later. Early studies, in connection with the introduction of CNI, demonstrated that acute rejection was reduced by 50%(14, 16). The 1-year survival for liver transplant patients increased from approximately 20% before 1985 to 66% in 1989, demonstrated with data from the European Transplant Registry(17).
However, there has been more difficult to achieve long-term improvements in graft survival with CNIs. CsA was followed by Tacrolimus (Tac) some 20 years later. Calcineurin is a protein phosphatase that stimulates T-cell growth and differentiation that inhibit by CsA and Tac. More than 40 years later, CNIs remain the standard treatment even in other OTRs and for treatment of other autoimmune diseases.

Induction therapy
The use of induction therapy after transplantation has been extensively discussed and it is still an ongoing debate. The International Society for Heart and Lung Transplantation (ISHLT) has reported that 60% of all transplant centers use T-cell antibody induction for lung transplant recipients(18). Induction therapy after solid organ transplantation is characterized by a more intensive initial treatment in order to reduce the risk of an immune response of T-cells to the transplanted organ, prevent an early acute rejection, and delay the introduction of CNI(19).

The induction therapy regime varies between transplant centers. For example, all patients who underwent heart and lung transplantation at SUH were treated with induction therapy(20). The anti-thymocyte agent used primarily was anti-thymocyte globulin (ATG), as this is a well-established treatment.

Cyclosporine
The immunosuppression treatment is based on a CNI that interacts with intracellular proteins and blocks cytokines important for activation of mainly T-cells and B-cells. CsA has dramatically improved the survival rate of patients and grafts after organ transplantation(21).

CsA acts by binding to molecules of the cyclophilin family, with a high affinity for calcineurin, which is the key protein phosphatase for the activation of T-cells. An earlier study has shown that CsA has been shown to inhibit DNA repair(22). Compared to other treatments, CsA has been shown to increase the risk of developing SCC. A low dose of CsA had a lower incidence of SCC compared to routine therapy according to a five-year randomized study(23). The medication has several other side effects besides cancer, such as vasoconstriction of the afferent and efferent glomerular arterioles and therefore, reductions in renal blood flow and glomerular filtration rate leading to nephrotoxicity. However, the exact mechanisms underlying nephrotoxicity are still not fully understood. Additionally, hypertension, hyperkalemia, hyperglycemia and an increased risk of opportunistic infections (viral, bacterial and fungal) are also well-known side-effects.
**Tacrolimus**

Tacrolimus was introduced in the field of transplantation in the beginning of the 1990s and in Sweden during the early 2000s. The mechanism for Tac is similar to CsA of activating T-cell suppression via inhibition of calcineurin(24). More than 90% of kidney transplant recipients receive Tac, instead of CsA, as their anticalcineurin treatment(25, 26). Several studies have shown a better graft survival, a lower risk of rejection and fewer side effects with Tac compared to CsA(27, 28). However, Tac has several side effects, where nephrotoxicity is the Achilles’ heel. The mechanisms behind the side effect are not completely understood. However, the main mechanisms are changes in the glomerular and tubular function. Diabetes (because of glucose intolerance), nephrotoxicity, cardiovascular diseases, hypertension are other known side effects.

**Inhibitors of the mammalian target of rapamycin (mTOR inhibitors)**

Almost 50 years ago, a Canadian expedition collected a set of the soil sample on Easter Island. They collected the samples in an attempt to understand why the inhabitants never caught tetanus, despite walking around barefoot. They had limited success at finding tetanus spores as it was found in only one of 67 samples. However, a member of the expedition gave the soil samples to some scientists he knew who were interested in medicinal compounds made by bacteria. As a result, the research group discovered a compound in one of the samples with remarkable antifungal, immunosuppressive, but also having antitumour properties(29). Mammalian target of rapamycin (mTOR) is a protein kinase regulating cell growth, survival, metabolism, and immunity(30). It mainly functions in its immunosuppressive capacity by inhibiting activation of T-cells and proliferation of regulatory T-cells. It also diminishes B-cell proliferation and differentiation to antibody-secreting cells. Renal dysfunction is a well-known complication after HTx, and affects more than half of all patients(31) with a risk of end-stage renal failure in approximately one in ten recipients(32). Everolimus and sirolimus, different mTOR inhibitors, are used both as substitutes for CNI to reduce nephrotoxicity or combined with a CNI to produce synergistic effects and reduce the dosage of CNI. A study has demonstrated a significant improvement in renal function (maintained for at least five years) when introducing everolimus with reduced CNI(33). Further, both sirolimus and everolimus have shown a reduction in incidence and decrease in cardiac allograft vasculopathy (CAV) progression(34).

**Corticosteroids**

The treatment have been used since the beginning of the transplantation era(35). Almost all patients receive CS in conjunction with organ transplantation in induction therapy and maintenance therapy. The patients receive larger doses of CS in
the beginning after transplantation in order to prevent rejection. These nonspecific anti-inflammatory agents affect the immune system in various ways, among others; reduced macrophage activation inhibition of the cytokine gene transcription in order to prevent T-cell activation and has played a key role in the history of immunosuppression. The treatment is widely used in cancer therapy(36). The downside is the many side effects of CS, for example: type 2 diabetes, leukocytosis, gastrointestinal hemorrhage, osteoporosis, hypertension and adrenal insufficiency.

**Mycophenolate Mofetil**

The treatment has been administrated in Sweden since the late 1990s. The main mechanism of MMF is inhibition of T- and B-cell proliferation. MMF is widely used in transplant recipients. A randomized controlled trial in the late 1990s demonstrated that MMF was associated with significantly lower mortality rates and decreased need for antirejection treatment in patients after their first HTx when compared with azathioprine(37). The primary immunosuppressive treatment in heart transplant recipients at SUH consisted of CsA and azathioprine but was then replaced with Tac and MMF during the 2000s. However, there are several side effects such as bone marrow depression, increased risk of infections and abdominal pain.

**Immunosuppressive medication and skin cancer**

Assessing the risk of post-transplant cancer and its association with immunosuppressive drugs is a challenge. Patients often need multiple immunosuppression drugs and changed regimes over time, which makes the identification of a specific drug and its contribution to cancer difficult. A Swedish case-control study demonstrated that patients who had received a high accumulated dose of azathioprine had an 8.8-fold increased risk of developing SCC compared to patients never treated with Azathioprine(38). A similar result was also shown in other studies(39, 40). Earlier studies have reported that CsA, Tac and CS also may be associated with a higher risk of cancer(41).

**Lung transplantation**

The first lung transplantation in Sweden took place in 1990. LTx has experienced improvements in mortality and morbidity over the latest 30 years. The most significant progress has been made in short-term survival. The one-year survival rate in the early cohorts of lung transplant recipients was reported to be 45%(42). More than two decades later, the one-year survival has risen to 83% for a bilateral lung transplant, which is the most common procedure according to data from the ISHLT(43).
However, despite the decrease in early mortality, the long-term survival rate after LTx has remained suboptimal also during the last two decades(44). The five-year survival has increased from 46% in 1990 to 57% in 2015. The median survival after lung transplantation is 6.5 years, according to the last ISHLT registry report(45). Although lung transplant recipients have experienced improved survival, they still limb behind that after patients who underwent other solid organ transplantations(46).

Complications and limitations to survival after LTx

The lungs are vital organs and are also extremely vulnerable to environmental factors through their contact with air inhaled, in the form of airborne and potentially infective agents, which can threaten their function. However, there are several barriers to defend against infectious agents in immunocompetent patients with healthy airways. However, in lung transplant patients those functions are reduced.

Infections

Infection is a common complication after LTx and the second cause of death within the first 30 days after LTx (19.2%). However, it is the first cause of mortality (37.3%) between 30 days and one year after LTx. After one year has passed, the mortality rate decreases modestly after LTx(47). Pneumonia is the most common form of infection after lung transplantation. However, there are several types of different infections which are also affected by the time since LTx. Early after LTx infections are often related to germs presented in the donor or recipient but also related to catheter infections and surgical site infections. The infections are dominated by community-acquired pathogens(48).

Chronic lung allograft dysfunction

Chronic lung allograft dysfunction (CLAD) is another important reason for graft loss one year after LTx(18). The latest consensus statement from the Council of the ISHLT defines CLAD as “a persistent and irreversible decline in forced expiratory volume in one second (FEV1) of at least 20% compared to the mean of the two best postoperative values at least three weeks apart”(49). It is essential to exclude other potential diagnoses before concluding that CLAD is the correct one.

CLAD has been proposed as an umbrella term with two subgroups: (i) bronchiolitis obliterans syndrome (BOS); (ii) and restrictive allograft syndrome (RAS). BOS is characterized by obstructive physiology with airway obstruction which causes difficulties to expel air from the lungs. The condition is usually caused by airway inflammation. The chest radiographic findings can be normal or if abnormal, non-specific
findings are also compatible with BOS. Unlike RAS, which shows a restrictive physiology with reduced distensibility of the lungs, a reduced total lung capacity and persistent chest imaging. RAS also has a significantly poorer outcome than BOS(1,6,8).

Chronic obstructive pulmonary disease alpha-1-antitrypsin deficiency, cystic fibrosis, pulmonary fibrosis and others were the most common diagnoses currently leading to LTx.

**Rejections**

Allograft failure is the leading cause of death, accounting for more than 40% of deaths the first year after LTx(45, 46). Acute rejection occurs in approximately 50% of the lung transplant recipients during the first year after LTx(45). The reason for this phenomenon is called alloimmunity on the first hand, driven by T-cells and their ability to recognize foreign HLA-molecules as described earlier.

Even if the patients are immunosuppressed after LTx the innate immune system in the lung is very active. Therefore, the patients are likely to develop a rejection especially in conjunction with an infection.

**Heart transplantation**

Almost 55 years have passed since the first HTx from human to human took place in South Africa. The 55-year-old patient survived only 18 days and died from sepsis. Four years earlier, the American surgeon James Hardy transplanted a heart from a chimpanzee into a 36-year-old man(51). The initial signs looked promising, but the heart’s size from the ape was not powerful enough.

For selected patients, HTx is considered the gold standard treatment. However, there are several complications associated with the surgery.

The year after Barnard’s transplantation in South Africa in 1967, there were 120 heart transplants performed globally. Despite the euphoria after the first transplantation, the 1-year survival rate of only 20% was not encouraging.
The development of the endomyocardial biopsy in the middle of 1970 was a milestone in order to monitor rejection and improve postoperative survival (52). Since the majority of the patients are asymptomatic when a rejection occurs, they may go undetected, at least until organ function is compromised. Rejections may be detected earlier with an endomyocardial biopsy and it is therefore of significant value if it detects an ongoing rejection microscopically. The method is still the gold standard in order to diagnose rejection (53). The appearance of CsA by Borel at the end of the 1970s, together with the endomyocardial biopsies, allowed better control of rejections and a breakthrough of HTx.

Complications and limitations to survival after HTx

Infections, rejection and CAV have been shown to be the most common complications shortly after HTx (Figure 1).
**Infections**

Infections are a common side effect following HTx, with a cumulative incidence of 85% after five years(54). The majority of the infections involved the urinary tract, the respiratory system and the skin(55). The most common infections have reported being herpes simplex virus, Epstein-Barr virus, varicella zoster virus, tuberculosis, and pneumonia(48 56). The risk of infection is greatest in the first six-month post-HTx and a leading cause of death during the first year (57). Both recipients and donors are screened before HTx for some infections, among others: HIV (human immunodeficiency virus), hepatitis B and C viruses and varicella zoster virus.

**Rejections**

Classically, there are three types of rejection; hyperacute rejection, acute cellular rejection and antibody-mediated rejection(58).

Hyperacute rejection, which manifests within minutes after transplant, is uncommon nowadays because of both antibody screening of donor and recipient before transplantation and blood type matching.

Acute cellular rejection is the most frequent type and is characterized by the presence of inflammatory cells in the myocardium. Although a rejection might begin, already one week after HTx, the risk of acute rejection is highest in the first three months.

Antibody-mediated rejection is characterized by the presence of antibodies (mainly anti-HLA) against the vascular endothelium of the graft, and within this context, is associated with worse clinical progress. The risk of developing antibody-mediated rejection is highest the first six months after HTx but continues also long-term(59).

**Cardiac allograft vasculopathy**

CAV is characterized by intimal hyperplasia and persistent perivascular inflammation in the coronaries, with fast progression, of the transplanted heart. Earlier studies have reported CAV as one of the most important limiting factors in long-term survival, with an incidence of between 8% and 30% at 5 years, and 50% in 10 years(57). The most common reason for re-transplantation the first year after HTx is CAV(60).

**Cancer**

Cancer encompasses a complex collection of diseases in different organs, which can be defined as an uncontrolled growth of abnormal cells that can spread or metastasize to other organs in a multistep process. The mechanisms that lead to the onset
of cancer contain both environmental (e.g. tobacco smoke, ultraviolet radiation) and genetic factors. In the year 2000, Hanahan and Weinberg stated that most cancers share six hallmarks in an effort to explain cancer biology. These hallmarks consist of biological capabilities acquired during the process of developing a tumour(61, 62).

1. Self-sufficiency in growth signals indicates that cancer cells do not need stimulation from external signals, compared to normal cells.
2. Insensitivity to anti-growth signals. Tumour suppressor genes act to prevent cell growth and division. However, they can no longer perform their function in cancer cells.
3. Evading apoptosis means that cells are normally programmed to die in the event they become damaged. However, cancer cells can bypass this process.
4. Limitless replicative potential. Normal cells have a limited number of divisions. Cancer cells, on the other hand, are capable of indefinite growth and division.
5. Sustained angiogenesis is the development of new blood vessels. A tumour cell needs adequate blood supply as nutrition to continue to grow. The cells have the ability to send out signals that encourage the growth of new blood vessels surrounding the tumour. This mechanism also promotes metastasis.
6. Activating invasion and metastasis is a process where the cells detach from the primary tumour and spread to surrounding tissue by lymphatic vessels or the bloodstream.

Classification of cancer
Different classifications systems are used in order to diagnose, assess the prognosis and determine appropriate therapy for cancer patients. The TNM classification system is one such classification, which was developed by the World Health Organization (WHO) and the Union for International Cancer Control(63).

The TNM classification defines tumour size (T), lymph node metastasis (N) and absence or presence of distant metastasis (M). Histopathological analysis determines the cellular origin of cancer cells, differentiation grade, proliferation rate and the presence of specific tumour markers. Gene expression analysis can also be used in further classification of cancer subtypes.

Cancer after solid organ transplantation
At the end of 1960, the first report of an increased risk of malignancies in OTRs was published. Since then, cancer is a well-known side-effect after organ transplantation.
The risk of malignancy in OTRs has reported as being increased by 2- to 4-fold compared with the general population(64, 65). Skin cancer is reported to be the most common type of cancer, especially in combination with exposure to ultraviolet (UV) radiation. Further, non-Hodgkin lymphoma, lung cancer and kidney cancer have shown to be common after organ transplantation(66, 67). Many cancer types for which incidence is substantially elevated in OTRs are caused by viruses such as Kaposi Sarcoma, and Epstein-Barr virus(68).

The risk of early post-transplantation lymphoproliferative disorders has also become more common since there is a rising proportion of pediatric patients who undergo organ transplantation(69, 70). Breast cancer and prostate cancer which, are the most prevalent cancer types in the general population, seem not or only marginally increased in OTRs(64-66, 71).

**Cancer after LTx**

Lung cancer has reported being the second most common malignancy after solid organ transplantation (67). The development of lung cancer after LTx is associated with different factors such as: higher age of both donor and recipient; previous smoking habits of donors and recipients; type of immunosuppression; and type of LTx (single or bilateral)(70, 72). The fact that the 5-year survival rate after LTx has increased from 46% in 1990 to 57% in 2015 also affect the prevalence of cancer(18, 43).

**Cancer after HTx**

The risk of malignancy after heart transplantation is increased by 2- to 4-fold compared with the general population(65, 73). The most frequent cancers after HTx have been reported to be non-melanoma skin cancer (NMSC), lung cancer and lymphomas(74). Further, thoracic transplant recipients have an even higher risk of developing cancer compared with other solid organ transplant patients due to the higher doses of immunosuppressive agents needed to prevent organ rejection(12, 13, 75).

**Skin cancer**

Skin cancer, includes malignant melanoma (MM) and NMSC. There are several types of NMSC. The main forms are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and several rare skin cancers such as Merkel cell carcinoma.

There are many risk factors for developing skin cancer. Cumulative and excessive exposure to ultraviolet radiation is the most important.
Skin cancer is also a large and growing problem among non-transplanted patients (non-TPs) in the general population. In the last ten years, the Swedish melanoma incidence has increased by just over 5% yearly (6.2% for women and 5.0% for men, respectively)(167).

It is predicted that MM and SCC incidence will continue to escalate. In the year 2040, it is estimated that four to five times as many melanomas will be diagnosed in Sweden compared to today and the SCC incidence is predicted to increase at least as much(76).

**Types of skin cancer**

Basal cell carcinoma (BCC) is by far the most common type of cancer in Sweden. More than 60 000 tumours are histopathologically confirmed annually(77). The tumours are usually detected in middle-aged and elderly individuals. The median age is 73 years at diagnosis of BCC in Sweden(78). BCC usually develops on sun-exposed areas, especially the face, head, and neck(79). BCC tends to grow slowly invading only surrounding tissues, and rarely spreads to other parts of the body. Hence mortality due to BCC is very low.

**Squamous cell carcinoma**

In Sweden, SCC is the second most common type of cancer both in men and women(78). SCC is one of the types of cancer that increase the most. The highest incidence rates have been observed both in men and women over 85 years of age(80). UV radiation is the most important risk factor for the development of SCC(81). Fair skin is also seen as a risk factor(82).

These tumours usually arise in chronically UV-exposed areas, for instance the head and neck and the dorsum of the hands. The risk of metastasis increases in SCCs located on the ear and lip(83, 84). The 10-year relative survival was 91.4% for women and 88.5% for men in Sweden(78).

**Malignant melanoma**

Malignant melanoma is ranked as the fifth most common type of cancer among both men and women in Sweden (melanoma in situ not included)(78). Recently, the median age for melanoma reported to be 66 years for women and 70 years for men(85). MM is the most serious of the main types of skin cancer. It is associated with accumulated episodes of UV exposure resulting in sunburns. The reason is the higher potential for lymphatic and hematogenous spreading and therefore a higher mortality risk. The outcome depends on the stage of the disease at the time of diagnosis. The relative survival is 95% for women and 90.5% for men. Exposure to UV light is the major risk factor for development of MM. The following other risk factors are listed in a
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Caroline Stenman

Introduction
descending order of importance: strong family history of MM, a large number of nevi or large nevi, personal history of MM and freckles, and fair complexion(71, 86–88, 89). In men MM appears slightly more often on the torso, while in women such lesions are more often found on their lower extremities.

Skin cancer after solid organ transplantation
The incidence of skin cancer in OTRs after transplantation accounts for 24% – 69% and is proportional to the cumulative level of immunosuppression(12, 64, 65, 90). The variations in cancer incidence may depend on reporting only the first of multiple tumours when registration, which leads to underestimation of the true incidence. In order to report correct numbers of cancer tumours, the International Rules for Multiple Primary Cancers (IARC, ICD-0 Third Edition) has been developed(91). The rules are for reporting data on cancer incidence and survival data, so that cancer risk and outcome can be compared between different populations.

NMSC, in particular SCC and BCC, are the most common malignancies seen in OTRs(92-94). The risk of developing SCC among OTRs is 20 to 200 times higher compared to the general background populations, depending on age, organ type and time after transplantation(12, 95, 96). The cumulative incidence of SCC 10 and 20 years after transplantation have reported being ~7% and 20%, respectively in Sweden(65). The corresponding numbers in a study from Australia were greatly elevated, 52% and 82%, which may be due to the additional impact of sun exposure in this setting. The risk of developing BCC and MM has been found to be approximately 7–10 and 2–3 times higher in OTRs, respectively(97-99). In addition, OTRs have an increased risk of distant metastases and mortality from SCC(92, 100, 101).

Differentiation grade
The human body consists of over 200 different cells types with specialized functions, stemming from the pluripotent embryonic stem cells(102). The cell differentiation grade defines the maturity of the cancer cell, i.e. how specialized the cancer cell is. The development of a tumour is seen as a multistep process including proliferation and mutilations. That may explain the fact that the majority of all cancers develop late in life. Cancer can result from abnormal proliferation of any of the different kinds of cells in the body, so there are more than a hundred distinct types of cancer, which can vary substantially in their behavior and response to treatment.
Figure 2. Degree of differentiation

Well-differentiated SCC

Look more like normal cells with a large central keratin plug. Recognizable squamous epithelium, intercellular bridges apparent. Tend to grow slowly, low metastatic potential.

Moderately differentiated SCC

Broad trabecular pattern with several mitoses and apoptotic bodies.

Poorly differentiated SCC

The cell has lost most of its squamous epithelial characteristics and architecture. No or minimal keratinization.

www.dermnetnz.org/topics/squamous-cell-carcinoma-pathology/

Degree of differentiation in SCC

SCC tumours are often divided into three categories: well-differentiated, moderately differentiated, and poorly differentiated. The category depends on the resemblance of the tissue of origin (Figure 2).

Grading the differentiation of SCCs is considered to be a rather subjective assessment. One classification states that $>75\%$ of the cells are differentiated in well-differentiated tumours, 25%–75% in moderately differentiated tumours, and <25% in poorly differentiated tumours(103).
Prevention

In the middle of the 1800s, pale skin was considered an indicator of high social status in Sweden. Sunbathing started in the early 1900s as a part of a “heliotherapy”, originated with the work of Rollier (1927) who advocated that certain diseases such as tuberculosis improved following sun exposure. Therefore, tanned skin came to be associated with good health and paleness with poor health. Additionally, as a consequence of the Industrial Revolution, more people from the lower classes shifted from outdoor work to indoor work. Tanned skin had now become a sign of higher status as it was associated with not having to work.

Popularity of the suntan may also be traced to the iconic French designer Coco Chanel who was photographed on a yacht on the Côte d’Azur in 1923 with a deep tan (104). The first warnings about the correlation between sun exposure and skin cancer came in the beginning of the 1940s and has continued since. Among Swedes, tanned skin is still considered socially desirable and attractive. Two large international studies demonstrated this (105, 106). Computer-generated photos of people, with varying levels of suntan were presented to the participants. Swedes had the highest preferred level of tan.

 SCC originates from keratinocytes, epithelial cells of the epidermis.
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Computer-generated photos of people with different levels of tanning. Participants from Sweden had the highest preferred level of tan of all participating countries, choosing the photo in the bottom left corner in general. Reprinted from Branstrom et. al. Melanoma risk factors, perceived threat and intentional tanning: an international online survey. Eur J Cancer Prev. 2010 May; 19(3): 216–226.

The consequences of a low degree of sun-protection behaviours are presented in a report from the Public Health Agency of Sweden in 2019. Almost 45% of the participants had been sunburnt during the past year. Among those who were 18–29 years old, 65% had been sunburnt once during the year, and 17% had been sunburnt three times or more (107). Therefore, it is a true challenge to promote sun protection behaviors and increase skin cancer awareness. Skin cancer can be prevented by avoiding sun exposure. Prevention and early detection are an effective way to decrease the burden of the disease. Australia and New Zealand have the highest rates of MM incidence in the world.

Altogether, countries in Europe are recording increased rates of MM closing in on the rate in Australia. Furthermore, Sweden, Denmark and Norway have the highest incidence in Europe with a rate of 26.2–33.1 per 100 000 for females and 22.4–29.0 for males (170).

As shown by more than 30 years of experience from Australia, primary prevention and early detection campaigns, have been beneficial in helping to slow, and in the young even reverse the trend for increasing incidence and morbidity. Substantial
inroads have been made in Australia to reduce the attractiveness of tanned skin and encourage individuals to adopt sun protection practices such as staying indoors during peak UV times and wearing sunscreen and protective clothing when in the sun.(108). One good example is the launching of the National SunSmart Schools program in 1998. Nowadays, the program is offered to all primary schools in Australia. In order to receive SunSmart status the schools are obliged to teach sun protection behavior, reschedule activities in direct sun during peak UV periods of the year etc.(109). On the other hand, there is an ongoing debate whether there is an overdiagnosis behind the increase in MM cases. Welch et al points to several trends that may have led to more MM diagnoses such as more screening skin examinations, falling clinical thresholds to biopsy suspected lesions, and also among pathologists to label those lesions as skin cancer(110). Additionally, despite the increase in MM diagnoses, the rate of mortality from skin cancer has remained stable.

**Background to population and health care registries**

In comparison with many other countries, Sweden has a long tradition of collecting epidemiological data, with more than 100 national health care quality registers. These registries cover certain areas of the healthcare system in order to develop and ensure the quality of care but also for clinical research and public quality reporting. This thesis (study I, III and IV), were made possible owing to those high-quality data registries. The registries contain personal data, diagnosis and treatment outcome that allows researchers to link data from different registers to a specific individual. Furthermore, they consist of long-term data with the possibility to a long follow-up to examine exposure that will lead to complications and adverse events many decades later.

Since more then 70 years, all Swedish citizens are assigned a unique ten-digit number at birth. The first 8 digits associated to the date of birth(111). This last number is essential to cross-link data from patient charts to national health care registries in order to collect data from different sources over time.

**The Swedish Cancer Registry**

The SCR is the oldest health registry in Sweden (established 1958), which contains data on all cancers diagnosed among the Swedish population. Since the start of the registry, it has been mandatory by law for pathologists and clinicians to report cancer diagnoses to the SCR. Therefore, the registry has a very high coverage rate with missing data reported to be less than 2%(112). All malignancies and precancerous lesions (atypia/dysplasia, cancer in situ, epithelial and melanocytic) and some benign tumours are reported to the SCR. The registry contains data on the patient (personal identity number, age, gender and place of residence), medical aspects (tumour location,
type of cancer according to the ICD-10 classification (International Classification of Disease 10th revision), TNM stage, date of diagnosis, reporting hospital/pathology department) and follow-up data (date of death, cause of death and date of emigration). The SCR was used for studies I, III and IV.

**The Swedish Cause of Death Registry**
This registry, which stems from 1961, registers the cause of death, including cancer, for all deceased citizens registered in Sweden who died during one calendar year. The Swedish Cause of Death Registry contains data on approximately 98% of all deaths. The process for identifying the cause of death may be complex for physicians in order to separate conditions that directly led to the death from other conditions that did not. Consequently, the quality of the registry may vary, because of the variations in the accuracy of the attending physicians. All cancer diagnoses in this report were verified according to the international version of the disease classification ICD-10. The Swedish Cause of Death Registry was used for studies I–IV.

**The local transplant registry**
The Transplant Registry (TR) at the Transplant Institute at SUH has collected data from all transplant recipients from 1965 regarding all patients who underwent transplantation at SUH. The TR was used in studies I, III, IV.

**The Swedish Population Registry**
The registry was originally administered by the church since the early 17th century but nowadays by the Swedish Tax Agency. Today, the registry consists of complete data about population changes, such as the number of births, deaths, immigration, and emigration and is managed by the government. The Swedish Population Registry was used in studies III and IV.

**The International Rules for Multiple Primary Cancers**
There are several primary cancer coding rules to count incident tumour cases. Cancer registries in the U.S. and Canada use, for example, SEER (Surveillance, Epidemiology and End Results Program) multiple primary rules. In studies III and IV, the International Rules for Multiple Primary Cancers (IARC/IACR, ICD-0 Third Edition) was applied. Compared to SEER rules, IARC/IACR recognizes fewer multiple primary cancers(113). That may explain the differences in the number of tumours in our studies compared to others(73). The International Rules for Multiple Primary Cancers (IARC, ICD-0 Third Edition) were applied in our work to ensure correct numbers of cancer tumours reported(91). These rules enable comparison of cancer risk and outcome between different populations.
Aims

The overall aim of this thesis was to investigate different aspects of cancer in OTRs compared to those of non-TPs.

The objectives of each study were as follows:

1. To investigate the degree of differentiation of SCCs in OTRs compared with non-TPs.
2. To compare the sun exposure and sun protection behaviour in OTRs to non-TPs. Further to compare sun exposure and sun protection behaviour in OTRs with dermatological follow-up to OTRs with no such follow-up.
3. To examine the incidence of post-transplant cancer and the survival rate among HTx recipients at SUH. In addition, to investigate if a history of treated cancer before HTx affected post-transplant cancer incidence and survival.
4. To examine the incidence of post-transplant cancer and the survival rate among lung transplant patients diagnosed with cancer at SUH. Also, to evaluate if a history of treated cancer before LTx affected post-transplant cancer incidence and survival.
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Patients and Methods

The study participants in this thesis consist of OTRs and non-TPs. Non-TPs are referred to as non-OTRs in studies I, III and IV.

The participants in study I consist of 965 patients in total. Patients were allocated into two groups, OTRs (n=82) and non-TPs (883). All patients in the cohort were diagnosed with SCC tumours at the Department of Dermatology, SUH between 2002 and 2015.

Study II consists of 969 adult patients divided into 5 groups. The first 3 groups comprised OTRs who underwent transplantation at SUH between 1976 and 2014. The first group of OTRs had no dermatological follow-up visits, the second group had recently been referred for follow-up at the specialized OTR clinic and the third group had been followed there for a longer period. The remaining groups consisted of non-TPs referred for suspicion of a malignant skin tumour or for a non-tumour related skin disease, at the Department of Dermatology, between September 2011 and September 2015.

In the first two studies, we investigated different aspects of skin cancer between OTRs and non-TPs, namely degrees of differentiation of SCCs and comparing sun exposure and sun protection behaviour by means of a questionnaire.

Study III consists of 664 patients aged >18 years after exclusion of heart transplant patients treated with re-transplantation (n=21) and patients followed abroad (n=23) who underwent HTx at SUH between 1985 and 2017.

Finally, study IV comprised 614 lung transplant recipients, transplanted between 1990 and 2016 at SUH, were included in study. Those who underwent re-transplantation (n=52) and those who were not Swedish citizens (n=19) were excluded.

The aim of these final two studies was to report the incidence of cancer before and after LTx and HTx but also, long-term outcomes.

The Gothenburg Regional Ethical Review Board approved the studies (EPN no. 019-09 and 146-11) and they were conducted in accordance with the Declaration of Helsinki I–IV.

Histopathological reports and ICD-codes (Study I)

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Board of Health and Welfare and linked with data from the TR of the Transplant Institute at SUH in order to find OTRs with an ICD code for SCC in situ and/or SCC. The International Statistical Classification of Diseases (ICD-10) codes C44.0S-C44.9S (SCC), D04.0-D04.9 (SCC in situ), and Z08.9B (follow-up visit for SCC) were used to identify patients. Tumours, which occurred before transplantation were excluded. A total of 82 patients with 515 tumours, who were diagnosed with SCC tumours at the Department of Dermatology, SUH from 2002 (the year the electronic chart system was introduced) until May 31, 2015, were included in the study. The control group comprised non-TPs diagnosed with SCC and/or SCC in situ at the Department of Dermatology, SUH from 2002 to May 31, 2015. In total of 883 patients with 1,247 tumours were included in the control group. The histopathological report for each tumour was collected from the local electronic chart system at SUH. All of the tumours were divided into six groups which contained SCC in situ, well-differentiated SCC, moderately differentiated SCC, poorly differentiated SCC, and “SCC, other” (including cases of invasive or microinvasive SCC without a specified degree of differentiation, SCC and basosquamous carcinoma). In some cases, the same tumour had multiple histopathological reports. If the first report was from a punch biopsy and the next report was from when the tumour was excised in toto, the lowest differentiation level was chosen. The same tumour is represented only once in the material.

**Specialized OTR clinic (Study II)**

The OTRs, in this questionnaire-based study, were identified through the TR at SUH’s Transplant Institute. The non-TPs were not randomized but recruited among randomly selected patients referred to the outpatient clinic at the Department of Dermatology, between September 2011 and September 2015. The information about the study, together with the questionnaire was randomly sent to the patients. The non-TPs were not known to be under immunosuppression. The study participants were allocated into five groups, stratified by their status as OTRs or non-TPs, as well as by whether or not they had attended the specialized OTR clinic. We did not stratify the patients by type of transplant. In order to estimate the minimum sample size required for the study, a statistical power calculation was performed. Group 1 consisted of OTRs transplanted during 2010–2014, who had not attended follow-up at the specialized OTR clinic, due to residing outside of the SUH catchment area. Group 2 consisted of OTRs transplanted during 1992–2014 with a new referral but no previous follow-up at the specialized OTR clinic. Group 3 comprised OTRs transplanted between 1976 and 2011 with a history of follow-up at the specialized OTR clinic. Based on risk factors for skin cancer, the frequency of follow-up in the specialized OTR clinic was individually determined. Importantly, all OTRs (groups 1, 2 and 3) had received both written and verbal information about sun protection from the Transplant Institute following the transplantation, but differed with regards to follow-ups in the specialized
Patients in groups 4 and 5 consisted of non-TPs referred to the outpatient clinic at the Department of Dermatology for a suspicion of skin cancer and for assessment of a non-cancerous skin disease, respectively. Participants in the study were selected amongst patients who had attended the Department of Dermatology. They were approached at the time of their visit to the hospital. Once a sufficient number had been recruited, as indicated by the power calculation, recruitment ceased. All those who agreed to participate completed the questionnaire. All patients gave their written informed consent to participate in the study.

The questionnaire (Study II)

All study participants completed a detailed questionnaire, the Sun Exposure and Protection Index (SEPI), either in writing or online. The SEPI (www.sepiscore.com) has previously been validated in several languages and in populations with low as well as high ambient UV radiation(115). The questionnaire consisted of five parts. The first part included background questions on educational level, smoking, type of organ transplant, immunosuppressive medications (if applicable), phenotypic characteristics (skin type, hair colour and eye colour) as well as family and personal history of skin cancer. The second part consisted of questions on sun exposure and sun protection. In the third part, questions addressed readiness to change sun protection behaviour, based on the Transtheoretical Model of Behaviour Change(116). This model has been extensively used in studies on sun exposure risk behaviour, as well as in studies on smoking cessation(117). In the fourth part, attitudes towards sun bathing were measured on a five-point Likert scale(118). A Likert scale is used to capture attitudes and opinions with a greater degree of nuance. In the fifth part, all participants reported on skin cancer awareness and OTRs reported on post-transplant skin checks by a dermatologist.

Cancer reporting after thoracic transplantation (Studies III and IV)

Digital and scanned medical records from the transplantation unit were reviewed for all the heart and lung transplant patients. Also, data was used from the National Board of Health and Welfare. Study participants from the SCR were crosschecked with those of the TR with the aim of finding patients with a cancer diagnosis. All cancer diagnoses were histopathologically verified. The ICD-10 was used to classify all incident cancers during the years of follow-up for this study. In order to report correct numbers of cancer tumours the International Rules for Multiple Primary Cancers (IARC, ICD-0 Third Edition) was used.
We did not investigate whether the patients have had BCC, since it is not reported in the SCR, but also since the BCC carcinoma type tends to grow slowly and metastases rarely occur\(^\text{(119)}\). Therefore, the NMSCs in these studies did not include BCCs. At our centre, cancer diagnosis has been a contraindication for listing for LTx and HTx with a few exceptions. We have followed ISHLT recommendations, and those with a cancer-free interval of at least five years, have been eligible for waitlisting\(^\text{(120)}\). All of the cancer diagnoses were histopathologically verified.

**Statistical methods**

Some statistical methods, which were used in more than one study in the thesis, are listed below. A p-value of \(<0.05\) was considered statistically significant (study I, II, III and IV). Data are presented as means and standard deviations, medians and interquartile ranges, or numbers and percentages as appropriate. All analyses were conducted using R version 3.0.3 software (The R Foundation for Statistical Computing, Vienna, Austria). Also, the the Fisher exact test and Wilcoxon rank sum test was used to compare proportions and for two-samples test (Studies I and II).

Relative survival was calculated using the Ederer II method (Studies I, III and IV) \(^\text{(121)}\). The Mantel-Haenszel test was used when stratifying (Studies I and II).

Mortality data for the general population in Sweden were used to estimate expected survival rates for the study populations. The data contained the probability of death for single-year age groups and gender in one-year calendar periods (Studies I, III and IV).

**Relative survival (Study I)**

In this retrospective cohort study, the relative survival was calculated by the strs macro developed by Paul Dickman, Enzo Coviello, and Michael Hills in the Stata statistical software, version 13.1. Survival time was calculated from date of diagnosis to date of death or to December 31, 2016.

**Kruskal-Wallis and Manel-Haanszel test (Study II)**

In this questionnaire-based study Kruskal-Wallis test was used for comparing three or more samples. When stratifying for a factor, the Mantel-Haanszel test was used. In general, ranked questionnaire responses were given a score, i.e., a numerical value, when comparing groups, for example: ‘Never’\(^\text{=1}\), ‘Rarely’\(^\text{=2}\), ‘Sometimes’\(^\text{=3}\), ‘Often’\(^\text{=4}\) and ‘Always’\(^\text{=5}\). Incomplete questionnaires were included in the study. However, missing values for specific questionnaire items were excluded from any statistical tests. When comparing groups, stratification with respect to sex and age
group (≤50 years, 51–65 years and >65 years) was performed unless otherwise specified. Groups were combined when estimates for a variable under investigation did not differ significantly after stratifying for sex and age group. For example, OTRs with no follow-up and OTRs with a new referral were combined when the results were similar. We named this combination ‘other OTRs’.

**Kaplan-Meier and Cox proportional hazards regression model (Study III and IV)**

The Kaplan-Meier method was used to estimate the overall survival over time. The comparisons between groups were performed with the log rank test(121). When analyzing cumulative incidence of cancer the competing risk methods with death as a competing event was used(122). In order to identify cancer incidence for different cancer types, person-years were calculated from date of the transplantation to the first of the following events: diagnosis of the cancer site; death; or end of surveillance period, i.e. December 31, 2018. The standardized incidence ratio (SIR) was used to evaluate the cancer incidence with a 95% confidence interval. It is an estimate of the occurrence of cancer in a population relative to what might be expected. It’s calculated by the ratio of the observed number of cancers, during the observation time and the expected number of cases by using incidence rates from the Swedish population stratified for 5-year age groups (0–4, 5–9, … 80–84, 85–years), gender and calendar year. In case where the observed number of cancer cases was equal to the expected number, the SIR is 1. The NORDCAN project was used in order to identify incidence rates for different cancer sites.

Furthermore, the coding of cancer followed definitions according to International rules for multiple primary cancers(91). In order to analyze the development of post-transplant malignancy, univariable and multivariable risk factor analyses, by Cox proportional hazards regression model was used. The following parameters were tested by univariable analyses: age (per 10 years), sex, BMI (<20; 20–30; >30), smoking (never; cessation >6 months before listing; cessation <6 months before listing), donor age (per 10 years), CMV (cytomegalovirus) seropositive vs. seronegative donor, CMV seropositive vs. seronegative recipient, CMV mismatch (R-/D+).

The following parameters were tested only in patients after HTx: diabetes mellitus, hypertension, TIA/stroke, previous cardiac surgery, ventricular assist device (VAD), ischemic time (<3 ; 3-4; >4 hours), total induction dose with T-cell antibody (<200; 200–800; >800 mg) and proliferation inhibitors (azathioprine vs. MMF). Recipient blood group and diagnosis group were only tested in lung transplant patients. Parameters with significant risk factors from the univariable analysis, with and without NMSC, were further tested in a multivariable analysis. Statistical analyses were carried out with Stata/IC 16.1.
Results

4.5 times more SCCs among OTRs compared to non-TPs (Study I)

Between 2002 and 2015, the OTRs were diagnosed with 515 tumours and the non-TPs with 1,247 tumours. The median and mean ages at diagnosis among OTRs were 61 years and 59 years, respectively. In the non-TPs the median and mean ages at diagnosis were 79 and 81 years respectively.

Of those OTRs, 36 (44%) were women and 46 (56%) were men. Corresponding numbers among the immunocompetent patients, 405 (46%) were women and 478 (54%) were men.

In the group comprised of OTRs, we found a total of 515 tumours with an average of 6.3 tumours per patient. The average follow-up time was 13.5 years, which corresponds to 0.47 tumours/year.

Of those 515 tumours, 198 were SCC in situ and 258 were SCC with a known degree of differentiation.

Among those, 22 (8.5%) were poorly differentiated, 57 (22.1%) were moderately differentiated, and 179 (69.4%) were well-differentiated.

The corresponding number of tumours in the non-TPs group was 1,247, an average of 1.4 tumours/patient and 0.10 tumours/year. Among these tumours, 86 were SCC in situ and 1,019 were SCC with a known degree of differentiation: 127 (12.5%) were poorly differentiated, 305 (29.9%) were moderately differentiated, and 587 (57.6%) were well-differentiated.
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When comparing the distribution of the level of differentiation of the SCCs (Figure 3) with available data while also stratifying with respect to age group between the OTRs and non-TPs, no significant difference was seen (p=0.4, Mantel-Haenszel test). As an incidental finding, an association was seen between the distribution of the level of differentiation of SCCs and age groups below and above the median age at diagnosis in both groups. OTRs who were above the median age of 62 years had significantly fewer well-differentiated SCCs (61%, CI 52–70) than younger OTRs (76%, CI 69–83) (p=0.03, Fisher’s exact test).

Another incidental finding was tumour site which differed significantly between the OTRs and the non-TPs when stratifying for age group (p<0.0001). The group consisted of OTRs who were above the median age of 62 years had significantly fewer well-differentiated SCCs (61%, CI 52–70) than younger OTRs (76%, CI 69–83) (p=0.03, Fisher’s exact test).

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Less sun exposure and better sun protection behaviour (Study II)
The median age for all, 696, study participants was 57 years. There were significant age differences between the groups when controlling for sex (p<0.0001), with younger patients in group 5 (median 45 years) and older patients in groups 3 and 4 (median 65 and 64 years, respectively). There were 362 women (52%) (Figure 4).

Study participants most commonly reported to have blue eyes (65%), ash blond hair (48%) and to be of skin type II (28%) or III (57%). There was no significant difference in the distribution of skin type between the groups (p=0.09). The distribution of organs transplanted among the OTRs was: kidney (55%), heart (20%), liver (18%), lung (9%) and pancreas (1%). The total percentages exceeded 100% due to a few participants receiving multiple organs and/or receiving several transplants. The majority of the OTRs used more than one type of immunosuppressive medication and the most commonly used drugs included prednisolone (79%), MMF (73%), Tac (61%) and CsA (34%). The proportion of participants reporting a history of skin cancer was unevenly distributed across the five groups (Table 1).
Table 1. Characteristics of organ transplant recipients (OTRs) and non-transplant recipients (non-TPs) in a questionnaire-based study of N=696 patients in a dermatology outpatient clinic in Sweden.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OTRs n (%)</th>
<th>Non-TPs n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OTRs with no follow-up</td>
<td>OTRs with a new referral</td>
</tr>
<tr>
<td><strong>Type of transplant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>69 (53)</td>
<td>26 (42)</td>
</tr>
<tr>
<td>Liver</td>
<td>34 (26)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Heart</td>
<td>15 (11)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Lung</td>
<td>16 (12)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>What immunosuppressive medication are you on right now?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>94 (72)</td>
<td>53 (85)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>36 (27)</td>
<td>19 (31)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 (2)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>85 (65)</td>
<td>40 (65)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>110 (84)</td>
<td>42 (68)</td>
</tr>
<tr>
<td>Mycophenolate sodium</td>
<td>3 (2)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>12 (9)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other or no answer</td>
<td>7 (5)</td>
<td>5 (8)</td>
</tr>
<tr>
<td><strong>Skin phototype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin phototype I</td>
<td>1 (1)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Skin phototype II</td>
<td>36 (27)</td>
<td>16 (26)</td>
</tr>
<tr>
<td>Skin phototype III</td>
<td>63 (48)</td>
<td>36 (58)</td>
</tr>
<tr>
<td>Skin phototype IV</td>
<td>25 (19)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Skin phototype V</td>
<td>3 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Skin phototype VI</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other or no answer</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Have you yourself had any of these diseases?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>123 (94)</td>
<td>58 (94)</td>
</tr>
<tr>
<td>BCC</td>
<td>4 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>SCC</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MM</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Yes, but do not remember which type</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

BCC – basal cell carcinoma, MM – malignant melanoma, OTRs – organ transplant recipients, non-TPs – non-transplant patients, SCC – squamous cell carcinoma

† Due to rounding, percentages may not add to 100%.

‡ Total percentages may exceed 100% due to a few participants receiving multiple organs, and/or undergoing repeat transplantation, and/or being treated with several immunosuppressive drugs, and/or having a personal history of multiple skin tumours.
The median time from transplantation to study inclusion differed between the OTR groups. Groups 1 and 2 were recruited to the study shortly post-transplant, after a median time of 1.2 and 2.0 years, respectively. In those two groups combined, 15% (95% confidence interval [CI] 10–20) confirmed to have had a post-transplant skin check by a dermatologist. In contrast, group 3 had a median time from transplantation of 16.7 years and all participants in this group had a history of follow-up with skin checks at the specialized OTR clinic with a shorter time from transplantation (groups 1 and 2 combined: 5%, [95% CI: 2–9]) (p<0.0001). The corresponding proportion for non-TPs was 39% (95% CI: 33–46) in group 4 and 3% (95% CI: 1–7) in group 5 (Table 2).

Table 2. Background demographic variables for the N=696 study participants, divided into groups of organ transplant recipients (OTRs) and non-transplant patients (non-TPs).

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>OTRs</th>
<th>Non-TPs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OTRs with no follow-up</td>
<td>OTRs with a new referral</td>
</tr>
<tr>
<td>Number of patients</td>
<td>131</td>
<td>62</td>
</tr>
<tr>
<td>Proportion male</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>Proportion female</td>
<td>39%</td>
<td>39%</td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Transplantation time period</td>
<td>2010-2014</td>
<td>1992-2014</td>
</tr>
<tr>
<td>Median time from transplantation to study inclusion (yrs)</td>
<td>1.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

OTRs – organ transplant recipients, non-TPs – non-transplant patients

**Sun exposure in OTRs compared to non-TPs**

More non-TPs than OTRs had experienced ≥1 sunburn in the past year, 46% (95% CI: 41–51) vs. 20% (95% CI:15–25)(p<0.0001). Also, more non-TPs than OTRs had spent ≥1 hour/day in the summer sun, 69% (95% CI: 64–73) vs. 41% (95% CI: 35–47) (p<0.0001). Among OTRs, 29% (95% CI: 24–34) stated that they never sunbathed with the intention to tan during the summer in Sweden, while the corresponding number for non-TPs was 11% (95% CI: 8–15) (p<0.0001). More OTRs (32%, 95% CI: 27–38) than non-TPs (15%, 95% CI: 12–19) reported that it was “not important at all” to get tanned during the summer (p<0.0001). Among OTRs in group 3, 89% reported to use sunscreen.
Benefit of dermatological follow-up in a specialized OTR clinic

We found more ‘often’ or ‘always’ users of sunscreen among OTRs with follow-up than among other OTRs, 63% (95% CI: 52–73) vs. 44% (95% CI: 37–51)(p=0.006). The group of OTRs with a follow-up used at least one sun protection measure (for example, covering clothes) than other OTRs, 54% (95% CI: 43–65) vs. 34% (95% CI: 27–41)(p=0.016).

With respect to skin cancer awareness, 96% of the patients in group 3 stated that they had received advice about the increased risk when taking immunosuppressive medications, compared to 87% and 91% in groups 1 and 2, respectively (p=0.18). In group 3, 72% (95% CI: 61–81) of the participants perceived the risk of developing skin cancer to be rather high or very high. This proportion was significantly higher than the 37% (95% CI: 32–42) in groups 1, 2 and 4 combined (p<0.0001) (Table 3).

Table 3. Sun exposure and sun protection behaviour in organ transplant recipients (OTRs) and non-transplant patients (non-TPs) in a questionnaire-based study of N=696 patients in a dermatology outpatient clinic in Sweden.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OTRs n (%)†</th>
<th>Non-TPs n (%)†</th>
<th>Non-TPs referred for a non-tumoural skin disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OTRs with no follow-up</td>
<td>OTRs with a new referral</td>
<td>OTRs with follow-up</td>
</tr>
<tr>
<td>How often do you sunbathe with the intention to tan during the summer in Sweden?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>29 (22)</td>
<td>21 (34)</td>
<td>31 (35)</td>
</tr>
<tr>
<td>Rarely</td>
<td>51 (39)</td>
<td>17 (27)</td>
<td>27 (30)</td>
</tr>
<tr>
<td>Sometimes in sunny weather</td>
<td>42 (32)</td>
<td>16 (26)</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Often in sunny weather</td>
<td>9 (7)</td>
<td>5 (8)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Almost daily in sunny weather</td>
<td>0 (0)</td>
<td>3 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>No answer</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Do you usually use a sunscreen when sunbathing?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>25 (19)</td>
<td>11 (18)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Rarely</td>
<td>15 (11)</td>
<td>6 (10)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>37 (28)</td>
<td>14 (23)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Often</td>
<td>18 (14)</td>
<td>13 (21)</td>
<td>24 (27)</td>
</tr>
<tr>
<td>Always</td>
<td>36 (27)</td>
<td>18 (29)</td>
<td>32 (36)</td>
</tr>
<tr>
<td>No answer</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

OTRs – organ transplant recipients,
non-TPs – non-transplant patients

†Due to rounding, percentages may not add to 100%.
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<table>
<thead>
<tr>
<th></th>
<th>n (%): OTRs</th>
<th>n (%): Non-TPs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Covering clothes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>8 (6)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Seldom</td>
<td>17 (13)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>37 (28)</td>
<td>19 (31)</td>
</tr>
<tr>
<td>Often</td>
<td>40 (31)</td>
<td>16 (26)</td>
</tr>
<tr>
<td>Always</td>
<td>16 (12)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>No answer</td>
<td>13 (10)</td>
<td>4 (6)</td>
</tr>
<tr>
<td><strong>Sun hat, cap or similar:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17 (13)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Seldom</td>
<td>8 (6)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>29 (22)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Often</td>
<td>40 (31)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Always</td>
<td>26 (20)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>No answer</td>
<td>11 (8)</td>
<td>7 (11)</td>
</tr>
<tr>
<td><strong>Staying in the shade:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Seldom</td>
<td>7 (5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>36 (27)</td>
<td>16 (26)</td>
</tr>
<tr>
<td>Often</td>
<td>59 (45)</td>
<td>29 (47)</td>
</tr>
<tr>
<td>Always</td>
<td>24 (18)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>No answer</td>
<td>5 (4)</td>
<td>5 (8)</td>
</tr>
<tr>
<td><strong>How many times have you been sunburnt (redness and smarting pain) during the past year?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>108 (82)</td>
<td>42 (68)</td>
</tr>
<tr>
<td>1-2 times</td>
<td>20 (15)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>3-5 times</td>
<td>3 (2)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>6-10 times</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>&gt;10 times</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No answer</td>
<td>5 (4)</td>
<td>5 (8)</td>
</tr>
<tr>
<td><strong>How long do you usually stay in the sun between 11 am and 3 pm, during a typical day-off in the summer (June-Aug)?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 min</td>
<td>33 (25)</td>
<td>14 (23)</td>
</tr>
<tr>
<td>30 min -1 h</td>
<td>38 (29)</td>
<td>18 (29)</td>
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<td>1-2 h</td>
<td>33 (25)</td>
<td>18 (29)</td>
</tr>
<tr>
<td>2-3 h</td>
<td>19 (15)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>&gt; 3 h</td>
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<td>4 (6)</td>
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<td>1 (2)</td>
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<tr>
<td><strong>How extensive do you consider the risk for you to develop skin cancer?</strong></td>
<td></td>
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</tr>
<tr>
<td>Very high</td>
<td>8 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Rather high</td>
<td>29 (22)</td>
<td>22 (35)</td>
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<tr>
<td>Not very high</td>
<td>71 (54)</td>
<td>25 (40)</td>
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<tr>
<td>Very low</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
<td><strong>How important is it for you to get tanned during the summer?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td>3 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
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<td>22 (17)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Not very important</td>
<td>69 (53)</td>
<td>31 (50)</td>
</tr>
<tr>
<td>Not important at all</td>
<td>36 (27)</td>
<td>20 (32)</td>
</tr>
<tr>
<td>No answer</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>There is an increased risk for skin cancer when taking immunosuppressive medication. Have you received information about this?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>119 (91)</td>
<td>54 (87)</td>
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<td>3 (5)</td>
</tr>
<tr>
<td>Don't know</td>
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<td>5 (8)</td>
</tr>
<tr>
<td>No answer</td>
<td>2 (2)</td>
<td>0 (0)</td>
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When in the sun without intention to tan, how often do you use any of the following ways to protect from the sun?

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<th></th>
<th>n (%): OTRs</th>
<th>n (%): Non-TPs</th>
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<tr>
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<tr>
<td>Sometimes</td>
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<td>13 (21)</td>
</tr>
<tr>
<td>Often</td>
<td>40 (31)</td>
<td>15 (24)</td>
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<tr>
<td>Always</td>
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<td>10 (16)</td>
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<td>7 (11)</td>
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<tr>
<td>Staying in the shade:</td>
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<tr>
<td>Seldom</td>
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<tr>
<td>Sometimes</td>
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</tr>
<tr>
<td>Often</td>
<td>59 (45)</td>
<td>29 (47)</td>
</tr>
<tr>
<td>Always</td>
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<td>9 (15)</td>
</tr>
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<td>5 (8)</td>
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</tr>
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<td>&gt; 3 h</td>
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<td>4 (6)</td>
</tr>
<tr>
<td>No answer</td>
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<tr>
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<tr>
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<tr>
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</tr>
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</table>
No significant differences in cumulative incidence of cancer between different time periods but better overall survival after HTx (Study III)

Of the total 664 patients in the study, 494 (74%) were men and 170 (24%) were women. The study population had a mean age of 48 years. The median follow-up time was 7.7 years.

Cancer incidence after HTx

In the follow-up we found in total 231 de novo cancers which were diagnosed in 138 HTx patients. This corresponds to 19.6% of the total study population. In a cohort from the general population matched by age, sex and time period, 37.5 cancers would have been expected to be detected. This resulted in an SIR of 6.2 (95%CI 5.4–7.0) for all cancers and an SIR of 2.9 (95%CI: 2.4–3.5) after exclusion of NMSC.

The overall risk of de novo malignancy between 1 and 5 years after HTx was 8%. The incidence of cancer for the total cohort at 1, 5, 10, 15 and 20 years was 2.4% (95%CI 1.5–3.9), 7.0% (95%CI 5.2–9.3), 19% (95%CI 15.8–23), 26% (95%CI 22–31) and 33% (95%CI 28–38), respectively. Cumulative incidence of cancer after HTx, when apportioned into three prespecified time periods showed no difference over time. However, during these same time periods there was a significant decrease in overall cumulative mortality (Figures 5a and 5b).

Cancer types and standardized incidence ratio (SIR) after HTx

The most common type of cancer in this cohort was NMSC (55% of all cancers). The second most common cancer was non-Hodgins lymphoma (11.7% of all cancers) followed by lung cancer (4.3% of all cancers). Among patients who developed lung cancer (8 men and 2 women), 80% had a history of smoking. Among these patients, 50% had stopped smoking < 6 months before HTx and 50% had stopped smoking > 6 months before HTx. More than one third of the cohort, 44 patients (32%) had multiple types of tumours; 18 patients had 2 tumours, 6 patients had 3 tumours, 3 patients had 4 tumours and 5 patients had 5 tumours. Two patients developed 7 tumours each. One had 5 NMSC, one lip tumour and one salivary gland tumour, and the other had 5 NMSC, 1 anal cancer and 1 salivary gland tumour.

We found the excess risk of all cancers (SIR) for the total cohort was 6.2 and similar between men and women (6.39 and SIR 5.18, respectively). The overall incidences of cancers in our cohort were higher than expected for: NMSC (SIR 82.6, 95%CI 69.4–98.3); non-Hodgkin lymphoma (SIR 24.8, 95%CI 17–36.1); MM (SIR 9.42, 95%CI 4.24–21.0); multiple myeloma (SIR 9.08, 95%CI 3.41–24.2); stomach (SIR 7.86, 95%CI 3.27–18.9); lung (SIR 3.68, 95%CI 1.98–6.84); and kidney (SIR 3.20, 95%CI 1.03–9.92). Of those patients who developed post-HTx cancer (n=138), 29 died from their malignancy: non-Hodgkin lymphoma (n=13), lung cancer (n=8), NMSC (n=5) and stomach (n=3) (Table 4).

Improved survival between time periods after HTx

Mortality for the whole patient cohort within 30 days and 1-year was 51/664 (8%) and 78/664 (12%), respectively. Overall survival was for the whole cohort at 1, 5, 10, 15 and 20 years was: 88% (95%CI 86%–90%); 80% (95%CI 76%–83%); 67% (95%CI 63%–71%); 53% (95CI 48–58%) and 37% (95%CI 32%–43%), respectively. Overall survival for HTx patients increased significantly over time (p<0.001). Five-year overall survival for those who underwent HTx between 1985 and 2000 was: 70% (95%CI: 64%–75%); between 2001 and 2010 81% (95%CI: 75%–86%); and between 2011 and 2018 92% (95%CI: 85%–96%).
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**Risk factors for developing cancer after HTx**

Independent predictors of cancer development included smoking cessation <6 months before listing. (HR 3.46, 95% CI 1.69–7.07, p<0.001); hypertension (HR 2.16, 95% CI 1.10–4.26, p<0.026); ischemic time (reference: <3 hours) 3–4 hours (HR 1.93 (95% CI 1.09–3.40, p=0.024); ischemic time >4 hours (HR 1.92, 95% CI 0.87–4.24, p=0.11); and treatment with azathioprine (reference: MMF) (HR 1.69, 95% CI 0.99–2.90, p<0.055). CMV mismatch was not significantly associated with cancer (HR 0.79, 95% CI 0.39–1.62, p=0.53).

Risk factors in the multivariable model predicting NMSC only were: age per 10 years (HR 2.90, 95% CI 1.85–4.55, p<0.001); hypertension (HR 1.87, 95% CI 0.91–3.84, p=0.091), seronegative CMV-donor (HR 2.14, 95% CI 1.11–4.14, p=0.024), and treatment with Azathioprine (HR 2.53, 95% CI 1.20–5.36, p<0.015) (Table 5).
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Table 4. Observed and expected cancer risks following HTx.*

<table>
<thead>
<tr>
<th>Site (ICDO-10)</th>
<th>Observed number</th>
<th>Expected number</th>
<th>Person years</th>
<th>SIR (95% CI)</th>
</tr>
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<tr>
<td>All sites</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>231</td>
<td>37.5</td>
<td>5668</td>
<td>6.16 (5.42-7.01)</td>
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<tr>
<td>Males</td>
<td>195</td>
<td>30.5</td>
<td>4175</td>
<td>6.39 (5.55-7.35)</td>
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<tr>
<td>Females</td>
<td>36</td>
<td>6.95</td>
<td>1493</td>
<td>5.18 (3.74-7.18)</td>
</tr>
<tr>
<td>All sites (except NMSC)</td>
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<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>104</td>
<td>35.9</td>
<td>5668</td>
<td>2.89 (2.39-3.51)</td>
</tr>
<tr>
<td>Males</td>
<td>85</td>
<td>29.2</td>
<td>4175</td>
<td>2.91 (2.35-3.60)</td>
</tr>
<tr>
<td>Females</td>
<td>19</td>
<td>6.73</td>
<td>1493</td>
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</tr>
<tr>
<td>Lip (C00)</td>
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<tr>
<td>Total</td>
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<td>7.86 (3.27-18.9)</td>
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<tr>
<td>Lung (C33, C34)</td>
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<tr>
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<td>9.43 (4.24-21.0)</td>
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<tr>
<td>Males</td>
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<td>0.56</td>
<td>4175</td>
<td>7.13 (2.68-19.0)</td>
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<tr>
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<td>Skin, NMSC (C44)</td>
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<tr>
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<td>1.54</td>
<td>5668</td>
<td>82.6 (69.4-98.3)</td>
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<tr>
<td>Males</td>
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<td>1.31</td>
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<tr>
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<tr>
<td>Males</td>
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<td>0.82</td>
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<tr>
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<td>5668</td>
<td>24.8 (17.0-36.1)</td>
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<tr>
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<tr>
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<tr>
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<td>0.44</td>
<td>5628</td>
<td>9.08 (3.41-24.2)</td>
</tr>
<tr>
<td>Males</td>
<td>4</td>
<td>0.38</td>
<td>4135</td>
<td>10.6 (3.99-28.3)</td>
</tr>
<tr>
<td>Females</td>
<td>0</td>
<td>0.06</td>
<td>1493</td>
<td>-</td>
</tr>
</tbody>
</table>

* Observed and expected number of cancers, person years in follow-up and Standardized Mortality Ratio (SIR) per site after heart transplantation. NMSC = nonmelanoma skin cancer (not including basal cell carcinoma).
### Table 4. Uni- and multivariable Cox proportional hazard regression for developing cancer.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of persons with cancer/N</th>
<th>Cox proportional hazard regression</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, never</td>
<td>23/355</td>
<td>1.0 (ref.)</td>
<td></td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>No, stopped &gt;6 mo. before HTx</td>
<td>27/227</td>
<td>1.84 (1.05-3.21)</td>
<td>0.032</td>
<td>1.70 (0.96-3.02)</td>
</tr>
<tr>
<td>No, stopped &lt; 6 mo. before HTx</td>
<td>12/57</td>
<td>3.12 (1.55-6.27)</td>
<td>0.001</td>
<td>3.46 (1.69-7.07)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>51/565</td>
<td>1.0 (ref.)</td>
<td></td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Yes</td>
<td>11/74</td>
<td>1.92 (1.00-3.68)</td>
<td>0.050</td>
<td>2.16 (1.10-4.26)</td>
</tr>
<tr>
<td>Ischemic time (hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>23/285</td>
<td>1.0 (ref.)</td>
<td></td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>3-4</td>
<td>30/274</td>
<td>1.44 (0.84-2.48)</td>
<td>0.19</td>
<td>1.93 (1.09-3.40)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>10/97</td>
<td>1.59 (0.75-3.34)</td>
<td>0.22</td>
<td>1.92 (0.87-4.24)</td>
</tr>
<tr>
<td>Proliferation inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF</td>
<td>23/355</td>
<td>1.0 (ref.)</td>
<td></td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>40/288</td>
<td>1.68 (1.00-2.83)</td>
<td>0.050</td>
<td>1.69 (0.99-2.90)</td>
</tr>
</tbody>
</table>

### Table 5. Uni- and multivariable Cox proportional hazard regression for developing cancer.*

*Time to first cancer analyzed. Twenty years of follow-up.

**HTx** = heart transplantation, **CMV** = cytomegalo virus, **MMF** = mycophenolate mofetil.

---

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A history of malignancy before HTx showed no worse outcome than others
A total 4% of patients (n=26) had a history of malignancy >5 years before HTx listing. The median age at their first tumour was 34 years (IQR; 11.3–52.2 years). The most common cancers were: acute lymphoblastic leukemia, lymphosarcoma, and Hodgkin lymphoma.

There were no significant differences in overall survival between those with and without cancer before HTx Furthermore, there was no significant difference in post HTx relative survival between patients who were cancer-free before and after HTx (Figure 6).

Figure 6. Relative survival after HTx

The curves shows the relative survival, accounting for the expected survival among patients as if they had the same death risk as people with the same age and sex in the Swedish population.

Pretransplant malignancy relative survival compared to those without.
No significant differences in cumulative incidence of cancer between different time periods after LTx (Study IV)

Of those 614 patients included in the study, 266 were men (43%) and 348 (57%) were women with a mean age of 50.0 years. The median follow-up time was 5.1 years.

Cancer incidence after LTx

A total of 159 de novo cancers were diagnosed in 111 LTx patients (48 men and 63 women) during follow-up, which corresponds to 18% of the total study population. In comparison to the general population matched by age, sex, and time period, 28.6 cancers would have been detected. This resulted in an SIR of 5.56 (95%CI 4.76–6.50) for all cancers after LTx, and 2.76 (95%CI: 2.21–3.46) after excluding NMSC. The incidence of cancer for the total cohort at 1, 5, 15 and 20 years were 2.7% at 1 year; 10.6% at 5 years; 17.9% at 10 years; 22.5% at 15 years; and 23.6% at 20 years respectively.

The cumulative incidence of de novo malignancy after LTx showed no significant difference between time eras (p=0.37) (Figures 7a and 7b).

Figure 7a. Cumulative incidence of cancer as first event

Figure 7b. Cumulative incidence of death as first event

Cumulative incidence of competing risks cancer (panel a) and death (panel b), and related to time period after lung transplantation. Both outcomes cancer and death need to be assessed together since they are competing outcomes.
Cancer types and standardized incidence ratio (SIR) for cancer after LTx

The most common type of cancer after LTx was NMSC (52.2% of all cancers), lung cancer (11.9% of all cancers), and non-Hodgkin Lymphoma (11.3% of all cancers). Of those 19 lung cancers that we found after LTx, the majority (n=13) were developed in the transplanted lung, four in the native lung and two were unknown.

The excess risk of all cancers for the total population was 5.6 and similar between men and women (SIR 4.90 and SIR 6.17, respectively).

The overall incidences of cancer in the cohort was higher than expected for: NMSC (SIR 76.5 (95%CI 61.7–94.8); non-Hodgkin Lymphoma (SIR 23.5, 95%CI 14.8–37.2); lung cancer (SIR 8.89, 95%CI 5.67–13.9); and MM (SIR 3.24, 95%CI 0.35–7.78) (Table 6).

Table 6. Observed and expected cancer risks following LTx.*

<table>
<thead>
<tr>
<th>Site (ICDO-10)</th>
<th>Observer number</th>
<th>Expected number</th>
<th>Person years</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>159</td>
<td>28.6</td>
<td>3903</td>
<td>5.56 (4.7-6.50)</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>28.6</td>
<td>3903</td>
<td>5.56 (4.7-6.50)</td>
</tr>
<tr>
<td>Males</td>
<td>67</td>
<td>13.7</td>
<td>1722</td>
<td>4.90 (3.8-6.23)</td>
</tr>
<tr>
<td>Females</td>
<td>92</td>
<td>14.9</td>
<td>2181</td>
<td>6.17 (5.03-7.57)</td>
</tr>
<tr>
<td>All sites (excluding NMSC)</td>
<td>76</td>
<td>27.5</td>
<td>3903</td>
<td>2.76 (2.21-3.46)</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>27.5</td>
<td>3903</td>
<td>2.76 (2.21-3.46)</td>
</tr>
<tr>
<td>Males</td>
<td>28</td>
<td>13.1</td>
<td>1722</td>
<td>2.14 (1.48-3.10)</td>
</tr>
<tr>
<td>Females</td>
<td>19</td>
<td>14.4</td>
<td>2181</td>
<td>3.34 (2.51-4.43)</td>
</tr>
<tr>
<td>Lung (C33, C34)</td>
<td>19</td>
<td>2.14</td>
<td>3903</td>
<td>8.89 (5.67-13.9)</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>2.14</td>
<td>3903</td>
<td>8.89 (5.67-13.9)</td>
</tr>
<tr>
<td>Males</td>
<td>6</td>
<td>0.90</td>
<td>1722</td>
<td>6.64 (2.98-14.8)</td>
</tr>
<tr>
<td>Females</td>
<td>13</td>
<td>1.23</td>
<td>2181</td>
<td>10.5 (6.12-18.1)</td>
</tr>
<tr>
<td>Malignant melanoma (C43)</td>
<td>5</td>
<td>1.54</td>
<td>3903</td>
<td>3.24 (0.35-7.78)</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>1.54</td>
<td>3903</td>
<td>3.24 (0.35-7.78)</td>
</tr>
<tr>
<td>Males</td>
<td>2</td>
<td>0.71</td>
<td>1722</td>
<td>2.82 (0.70-11.3)</td>
</tr>
<tr>
<td>Females</td>
<td>3</td>
<td>0.83</td>
<td>2181</td>
<td>3.60 (1.16-11.1)</td>
</tr>
<tr>
<td>Skin, exkl. malignant melanoma (C44)</td>
<td>83</td>
<td>1.09</td>
<td>3903</td>
<td>76.5 (61.7-94.8)</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>1.09</td>
<td>3903</td>
<td>76.5 (61.7-94.8)</td>
</tr>
<tr>
<td>Males</td>
<td>39</td>
<td>0.58</td>
<td>1722</td>
<td>68.6 (50.1-93.9)</td>
</tr>
<tr>
<td>Females</td>
<td>44</td>
<td>0.52</td>
<td>2181</td>
<td>85.1 (63.3-114)</td>
</tr>
<tr>
<td>Prostate (C61)</td>
<td>8</td>
<td>5.12</td>
<td>1696</td>
<td>1.56 (0.78-3.13)</td>
</tr>
<tr>
<td>Males</td>
<td>8</td>
<td>5.12</td>
<td>1696</td>
<td>1.56 (0.78-3.13)</td>
</tr>
<tr>
<td>Females</td>
<td>18</td>
<td>0.77</td>
<td>3903</td>
<td>23.5 (14.8-37.2)</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (C81-C85)</td>
<td>4</td>
<td>0.40</td>
<td>1722</td>
<td>10.0 (3.76-26.7)</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>0.77</td>
<td>3903</td>
<td>23.5 (14.8-37.2)</td>
</tr>
<tr>
<td>Males</td>
<td>4</td>
<td>0.40</td>
<td>1722</td>
<td>10.0 (3.76-26.7)</td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
<td>0.17</td>
<td>2180</td>
<td>38.1 (22.5-64.3)</td>
</tr>
</tbody>
</table>

* Observed and expected number of cancers, person years in follow-up and Standardized Mortality Ratio (SIR) per site after lung transplantation.

NMSC = nonmelanoma skin cancer (not including basal cancer)
No difference in survival between time periods after LTx

Mortality for the whole patient cohort within 30 days and 1-year was 36/614 (6%) and 107/614 (17%), respectively. Overall survival for the whole cohort at 1, 5, and 10 years was: 82% (95%CI 79%–85%); 61% (95%CI 57%–65%); and 43% (95%CI 38%–47%), respectively. The 5-year overall survival for those who underwent LTx: was 59% (95%CI: 51%–66%) between 1990 and 2000; 65% (95%CI: 59%–71%) between 2001 and 2010; and 57% (95%CI: 49%–64%) between 2011 and 2016. There was no significant difference in overall survival over time (p=0.52). However, risk profile has dramatically changed over time as illustrated by recipient age above 60 were higher than 40% in the last time period compared to (p<0.001).

There was no significant difference in overall mortality (p=0.39) between the three time periods.

Our study’s cumulative incidence of death was 16.4% at 1 year, 33.3% at 5 years, 46.8% at 10 years and 56.1% at 15 years post-transplantation. Corresponding numbers for the cumulative incidence of cancer were: 2.7% at 1 year; 10.6 % at 5 years; 17.9% at 10 years; 22.5% at 15 years; and 23.6% at 20 years.

Risk factors for developing cancer after LTx

When investigating significant risk factors in the multivariable model predicting NMSC only, we found: age per 10 years (HR 2.23, (95%CI 1.51–3.42), p<0.001) and recipient blood group A (HR 2.36, (95%CI 1.01–5.53), p<0.001) (Table 7).

Univariable analyses between baseline factors and cancer (omitting NMSC) were performed However, we were not able to identify any significant predictors of cancer by univariable analyses in our population, and therefore no multivariable analysis was performed.
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There was no significant difference in overall mortality (p=0.39) between the three time periods.

Our study’s cumulative incidence of death was 16.4% at 1 year, 33.3% at 5 years, 46.8% at 10 years and 56.1% at 15 years post-transplantation. Corresponding numbers for the cumulative incidence of cancer were: 2.7% at 1 year; 10.6 % at 5 years; 17.9% at 10 years; 22.5% at 15 years; and 23.6% at 20 years.

### Risk factors for developing cancer after LTx

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Univariable analyses between baseline factors and cancer (omitting NMSC) were performed. However, we were not able to identify any significant predictors of cancer by univariable analyses in our population, and therefore no multivariable analysis was performed.

### Table 7. Uni- and multivariable Cox proportional hazard regression for developing NMSC after LTx.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of persons with cancer/N</th>
<th>Cox proportional hazard regression</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td><strong>Age at LTx, per 10 years</strong></td>
<td>36/614</td>
<td></td>
<td>2.25 (1.51-3.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16/266</td>
<td></td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Female</td>
<td>20/348</td>
<td></td>
<td>0.98 (0.50-1.88)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>13/196</td>
<td></td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>20-30</td>
<td>22/363</td>
<td>1.06 (0.54-2.12)</td>
<td>0.86</td>
<td>0.42 (0.05-3.12)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1/50</td>
<td>0.42 (0.05-3.12)</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ended &gt;6 mon before LTx</td>
<td>9/206</td>
<td>1.0 (ref.)</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>No, ended &lt;6 mon before LTx</td>
<td>27/391</td>
<td>1.67 (0.78-3.55)</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Diagnosis group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>15/177</td>
<td>1.0 (ref.)</td>
<td></td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Alfa1 deficiency</td>
<td>9/104</td>
<td>0.96 (0.42-2.19)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td>0/69</td>
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<td>-</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1/53</td>
<td>0.21 (0.03-1.56)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>9/139</td>
<td>0.96 (0.42-2.19)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2/72</td>
<td>0.94 (0.40-2.22)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td><strong>Donor age, per 10 years</strong></td>
<td>36/614</td>
<td>0.34 (0.08-1.50)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient blood group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7/221</td>
<td>1.0 (ref.)</td>
<td></td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>A</td>
<td>22/294</td>
<td>2.46 (1.05-5.76)</td>
<td>0.038</td>
<td>2.36 (1.01-5.53)</td>
</tr>
<tr>
<td>AB</td>
<td>2/28</td>
<td>2.45 (0.51-11.8)</td>
<td>0.18</td>
<td>2.96 (0.61-14.3)</td>
</tr>
<tr>
<td>B</td>
<td>5/71</td>
<td>1.95 (0.62-6.16)</td>
<td>0.72</td>
<td>1.73 (0.55-5.46)</td>
</tr>
<tr>
<td><strong>CMV mismatch</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24/408</td>
<td>1.0 (ref.)</td>
<td></td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Yes</td>
<td>8/80</td>
<td>1.92 (0.86-4.28)</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

* Time from date of lung transplantation (LTx) to first cancer analyzed. Twenty years follow-up.

LTx = lung transplantation, NMSC = non-melanoma skin cancer, BMI = body mass index, CMV= Cytomegalo virus, COPD = Chronic obstructive pulmonary disease.

---

### Results

Table 7. Uni- and multivariable Cox proportional hazard regression for developing NMSC after LTx.*

* Time from date of lung transplantation (LTx) to first cancer analyzed. Twenty years follow-up.
A history of malignancy before LTx did not result in worse outcome

We found 26 (4%) malignancies in 26 patients that had occurred 9.1 years (IQR 2.3–18.3) before LTx. Three of these were actually lung cancers detected at LTx. The median age at their first tumour before LTx was 42 years (IQR 33–53 years), and at LTx the recipient median age was 53 years (IQR 44–59). The most common cancers were: lung, breast, prostate, lymphosarcoma and reticulosarcoma. There was no significant difference in overall survival between those with and without a history of cancer before LTx (p=0.56) Furthermore, there was no significant difference (p=0.57) in post-LTx relative survival between cancer-free patients versus those who had experienced cancer before LTx (Figure 8).

Figure 8. Relative survival after LTx

Relative survival in OTRs with and without pretransplant malignancy.
A history of malignancy before LTx did not result in worse outcome. We found 26 (4%) malignancies in 26 patients that had occurred 9.1 years (IQR 2.3–18.3) before LTx. Three of these were actually lung cancers detected at LTx. The median age at their first tumour before LTx was 42 years (IQR 33–53 years), and at LTx the recipient median age was 53 years (IQR 44–59). The most common cancers were: lung, breast, prostate, lymphosarcoma and reticulosarcoma. There was no significant difference in overall survival between those with and without a history of cancer before LTx (p=0.56). Furthermore, there was no significant difference (p=0.57) in post-LTx relative survival between cancer-free patients versus those who had experienced cancer before LTx (Figure 8).

Relative survival in OTRs with and without pretransplant malignancy.

\[ P = 0.57 \]

Cumulative probability

Time since lung transplantation (years)

Cancer−free before LTx (n=588)

Cancer before LTx (n=26)

Relative survival after LTx

Figure 8. Relative survival after LTx
No difference in the degree of tumour differentiation between OTRs and non-TPs (Study I)

To our knowledge, there are only two studies, which have compared the degree of differentiation of SCCs among OTRs and non-TPs, and showed no significant difference (123, 124). In this retrospective cohort study, almost 79% (69.45) of the SCC tumours among OTRs were well-differentiated, which is consistent with the results from Lindelöf et al., (68.3%) (125). There was no difference in the degree of tumour differentiation between OTRs and non-TPs. Further, we observed a higher frequency of poorly differentiated SCC in both OTRs and non-TPs in patients above the median age. The OTRs acquire their tumours at a much younger age than non-TPs, also shown in an article by Harwood et al., which may explain the fact that OTRs have a relatively small proportion of poorly and moderately differentiated tumours (123).

Among the OTRs we found an average of 6.3 tumours/patient with an average follow-up time of 15.5 years, which corresponds to 0.47 tumours/year. In the non-TPs group the corresponding number was 1.4 tumours/patient and 0.10 tumours/year. The difference in results is probably due to the immunosuppression medication but also the fact that those OTRs who were referred to the Dermatology Department for dermatological assessment of any type of skin condition have closer follow-up visits.

We found, as compared to other studies, (126, 127) that SCC in situ was significantly more common in OTRs.

A Swedish study from 2000 showed that 172 OTRs had 325 (NMSCs) with an average follow-up time of 9.2 years. The number of NMSCs per patient/year was 0.20 (128). Compared to a study from the United Kingdom, 257 OTRs had 622 NMSCs (including SCC in situ and basal cell carcinomas). The follow-up time for these patients was 8 years and the number of NMSCs per patient and year was 0.30 (126). When comparing to our study, the number of tumours per patient and year was lower in these two studies. That may be explained by the fact that the study period was more recent but also that the incidence of SCC in Sweden has increased during the past decade (129).

Furthermore, our cohort had also been immunosuppressed for a longer period of time (13.5 years vs 9.2 years) and the knowledge about the higher risk of SCC in OTRs has increased the last years. Consequently, there is a much more organized system for follow-up of those patients, which might have resulted in more diagnosed cases per patient.
Discussion & Methodological Considerations

No difference in the degree of tumour differentiation between OTRs and non-TPs (Study I)

To our knowledge, there are only two studies, which have compared the degree of differentiation of SCCs among OTRs and non-TPs, and showed no significant difference(123, 124). In this retrospective cohort study, almost 79% (69.45) of the SCC tumours among OTRs were well-differentiated, which is consistent with the results from Lindelöf et al., (68.3%)(125). There was no difference in the degree of tumour differentiation between OTRs and non-TPs. Further, we observed a higher frequency of poorly differentiated SCC in both OTRs and non-TPs in patients above the median age. The OTRs acquire their tumours at a much younger age then non-TPs, also shown in an article by Harwood et al., which may explain the fact that OTRs have a relatively small proportion of poorly and moderately differentiated tumours(123). Among the OTRs we found an average of 6.3 tumours/patient with an average follow-up time of 15.5 years, which corresponds to 0.47 tumours/year. In the non-TPs group the corresponding number was 1.4 tumours/patient and 0.10 tumours/year. The difference in results is probably due to the immunosuppression medication but also the fact that those OTRs who were referred to the Dermatology Department for dermatological assessment of any type of skin condition have closer follow-up visits. We found, as compared to other studies, (126, 127) that SCC in situ was significantly more common in OTRs.

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Surprisingly, non-TPs had a significantly higher proportion of tumours in the head and neck area compared with OTRs. The significance also remained when comparing the anatomic location of the tumours between the groups for SCCs and SCC in situ lesions separately.

Since 1994, OTRs received both oral and written information at SUH after they underwent organ transplantation, about their increased risk of developing skin cancer. We believe that OTRs therefore may use sunscreen on the chronically exposed facial skin more frequently than non-TPs. The fact that UV radiation is not the only risk factor for SCCs in OTRs, could be another explanation. Among OTRs, 80% of SCCs are associated with HPV infection, in contrast to only 40% among immunocompetent individuals(130).

There was no significant difference between OTRs and non-TPs in relative survival. However, the comparison is difficult to make due to the large difference in mean age between the groups.

Limitations
There are some limitations in this study. There was an unknown degree of differentiation in 11% of the invasive SCCs, among both OTRs and non-TPs. We were also confined to the use of the electronic chart system, implemented at our hospital in 2002. Because there is no national central medical record, we were not able to follow-up with patients who may have been diagnosed with SCC at other clinics. Finally, other factors that may also contribute to the aggressiveness of SCCs in OTRs and non-TPs (eg, tumour depth) were not analyzed.

Specialized OTR clinics should be more broadly implemented (Study II)
Before data was collected, a power calculation based on a similar study by Falk et al.,(114) was made. The total amount of patients was divided into five groups. The patients in Group 1 consisted of OTRs with no follow-up. The information about the study, together with the questionnaire was randomly sent to the patients. All patients who underwent consultation at the Department of Dermatology were asked to participate in the study. Recruitment stopped once a sufficient number of patients had been recruited according to the power calculation. Of those patients who gave their approval for participation were given the questionnaire at the hospital with the possibility to ask questions according to the questionnaire directly. However, for the assessment of sun exposure and sun protection behaviour, we used the established Sun Exposure and Protection Index(115). This questionnaire has been validated in several languages and in populations with low as well as high ambient UV radiation.

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To better suit the purpose of this study we modified the questionnaire, adding items related to organ transplantation. The patients in group 3, comprised OTRs who had a history of follow-up in the specialized OTR clinic, which was established in 2008.

We found that OTRs at SUH reported lower sun exposure compared to non-TPs, most likely attributed to the sun protection advice that OTRs are routinely provided with. Also, we showed that OTRs who attended a specialized OTR clinic with dermatological surveillance used more sunscreen and other sun protection measures compared to OTRs that did not. To prevent skin cancer, avoidance of excessive UV exposure is key. In OTRs, who are at very high risk of skin cancer, this is even more critical. In our study, OTRs repeatedly reported lower levels of sun exposure compared to non-TPs. For example, one fifth of OTRs had experienced ≥1 sunburn during the past year, as opposed to nearly half of non-TPs. Comparably to our results among non-TPs, another recent Swedish study among the general population reported that 45% of participants had experienced a sunburn during the past year (107), and a study from the United States showed a sunburn prevalence of 34% in 2005(131). Furthermore, OTRs spent less time in the summer sun than non-TPs. In our study, only 41% of OTRs spent ≥1 hour in the sun, which can be compared to 70% of OTRs in a study by Firooz et al., (132). We believe, that the lower level of sun exposure among OTRs likely is a result of educational intervention.

Although the sun safety advice provided to all OTRs in our study appears to have been relatively successful, with twice as many OTRs as non-TPs reporting that they never sunbathed with the intention to tan, the sun protection message has to be continually reinforced in both groups. In regards to sunscreen use, Green et al., has shown this to be efficient in SCC prevention in OTRs(133). In the present study, 9 out of 10 OTRs under dermatological surveillance reported to use sunscreen, which is comparable to 95% in a study by Ismail et al., (134). Both our study and the study by Ismail et al. reported higher use of sunscreen in OTRs who attended dermatological follow-ups than in OTRs who did not. Other studies, that did not separate OTRs based on dermatological follow-ups, have shown the use of sunscreen to range from 34–74%(135-138). Further, more than half of the OTRs under surveillance in our study reported always using at least one sun protection measure (covering clothes etc), which was higher than for OTRs who were not under surveillance. This is another indication that the repeated personal doctor consultations in the specialized OTR clinic is effective. Among non-TPs who were referred for assessment of a non-cancerous skin disease the use of at least one sun protection measure was as low as 17%.

When surveyed, almost all OTRs under surveillance (96%) stated that they had received advice about the increased risk for skin cancer when taking immunosuppressive medications. In the previously mentioned study by Ismail et al., 71% of OTRs
under surveillance responded positively to a similar question\(\text{(134)}\). The risk of skin cancer strongly increases 5 years after the onset of chronic immunosuppressive therapy\(\text{(128)}\). Among OTRs under surveillance, the high proportion \((64\%)\) of previous skin cancer may offer an additional explanation to why this group showed improved compliance with sun protection as compared to OTRs who were not under surveillance \((5\%\) with previous skin cancers in groups 1 and 2 combined). However, there was another group of participants with a high proportion of previous skin cancers: 39\% of non-TPs referred for a suspicion of skin cancer had a previous history of skin cancer. Expectedly, sun safety should have been considered important also among participants in this group. Nevertheless, these patients reported lower use of sunscreen and other sun protection measures than did OTRs under surveillance.

**Limitations**

Potential limitations include the unevenly sized groups, the varying time since transplantation and the varying length of follow-up in the specialized OTR clinic. To account for the uneven distribution of age and sex over the five groups, we applied stratification to the statistical analysis. Due to relatively low numbers of thoracic organ recipients, we were unable to perform any sensitivity analysis focusing specifically on these high-risk patients. Our results indicated lower sun exposure in OTRs than in non-TPs, which we believe to be a result of the sun protection advice provided to OTRs. But we cannot exclude that this is partially explained by poorer overall health status following transplantation, preventing OTRs from spending time outdoors. A further limitation was that, out of convenience, non-TPs were recruited from dermatology outpatients and not from the general population, which may have caused selection bias. We have no information regarding the numbers of non-responders, consequently we are not certain about the representativeness of the selected sample. The patients in these groups completed the questionnaire without the possibility of assistance from a doctor. If a question was read improperly, it could have had an impact on the data set. Also, we had no information about whether the non-TPs had received sun protection advice on an individual basis. However, we tried to mitigate any selection bias by separating the non-TPs into groups at high or low risk of skin cancer at inclusion. Our hypothesis was confirmed by the finding that a personal history of skin cancer was much more common among non-TPs referred for a skin tumour than in non-TPs referred for a non-tumoural skin disease. Lastly, there is a risk that the patients did not remember specific details (recall bias), which is a problem in studies that use self-reported data.
Time to revise and individualize the relapse-free period before transplantation? (Study III and IV)

Our study showed that the excess risk of cancer in patients, who underwent HTx was 6.2-fold and 2.9-fold compared to the general population, after exclusion of NMSC. The median follow-up time was 5.1 years. Corresponding numbers for patients following LTx were 5.56-fold and 2.76-fold respectively with a median follow-time of 7.7 years. Consequently, there was a lower excess risk for lung transplant patient to develop cancer compared to the those who underwent HTx, which we believe is of no significance.

Cancer after LTx and Htx

The most common cancers after HTx were NMSC (SIR 82.6), lip cancer (SIR 72.6), non-Hodgkin lymphoma (SIR 24.8) and MM (SIR 9.42). Among lung transplant patients corresponding numbers were NMSC (SIR 76.5), non-Hodgkin lymphoma (SIR 23.5), lung cancer (SIR 8.89) and MM (SIR 3.24).

It is well known that OTRs have a disproportionately high incidence of NMSC compared to immunocompetent patients and the tumours also develop at a younger age, behave more aggressively and often develop at multiple sites, compared to the general population(139).

It is also acknowledged that the incidence of NMSC increases with the duration and degree of immunosuppression(140). Among HTx the SIR for NMSC of 82.6 was more than four times higher as compared to a previous study by Collett et al., (SIR 18.5)(64). The authors didn't give any information pertaining to skin type (eg Fitzpatrick classification). However, given that the main skin type population of Sweden and the United Kingdom can be regarded as comparable (skin type 1 or 2 according to the Fitzpatrick scale (I–VI)), we feel that it is safe to assume that the studies hold validity in both regions. However, Collett et al., reported that their results might have been underestimated, since lesions might have been removed without a histological examination.

A possible explanation for the high incidence of NMSC among HTx compared to other studies might be related to the increasing incidence of NMSC in the general population in Sweden(78). Additionally, the use of Azathioprine (instead of MMF) was identified as a predictor of NMSC in the multivariable analysis(141). Azathioprine constituted the primary immunosuppressive treatment but was replaced with MMF during the mid 2000s. This is supported by the fact that previous studies have suggested that there is an association between Azathioprine and NMSC(38, 40). Additionally, the mean interval for the development of the first SCC in OTRs, with the age at transplantation between 18–40 years has reported to be 13 years, after
transplantation(142). But also the fact that the cumulative incidence of cancer, among HTx in our study, at 15 and 20 years was 26% and 33% respectively.

Among our cohort of lung transplant recipients, NMSC had a of SIR 76.5 and almost 55% of the tumours (127 of 231) were NMSC. Corresponding numbers from a Spanish study by Crespo Leiro et al.,(74). and a Belgian study by Vaan Keer et al.(143) were 51% (324 of 490) and 22% (58 of 263) respectively. Those two studies didn’t compare the cancer incidence to the general population, why SIR could not be calculated.

We identified NMSC as the most common cancer, with 83 cancers in a total cohort of 614 patients (13.5%) after LTx. Rashtag et al., identified skin tumours in approximately 28% (47/166 patients) after a median follow-up of 3 years. Berastegui et al., found 39 cases of NMSC in their cohort of 1,100 patients (3.5%) after a follow-up of 3 years. However, the data from these studies were not obtained from a national population registry or cancer registry, as in our study, but from individual hospital databases, which might result in missing cancer diagnoses during follow-up.

All patients who undergo transplantation at SUH after 1994 receive written and oral information about sun protection behaviour, use of sun protection and sunscreen and the increased risk of developing skin cancer. Also, all lung and heart transplant patients at SUH have been referred to a skin exam at least once at the Department of Dermatology at SUH.

Based on the result of an earlier study, at minimum, an annual consultation with a dermatologist is recommended for transplanted patients(144). Since 2008 there is a specialized OTR clinic at the Department of Dermatology, SUH. Based on risk factors for skin cancer, the frequency of follow-up is individually determined.

As mentioned, an excess risk of lip cancer was seen after HTx in our study (SIR 72.6). Comparable studies by Collet et al., and Jääma-Holmberg et al.,(145) reported a SIR of 60 and of 47.4 respectively. The incidence of lip cancer was not significant increased among the lung transplant recipients in our study and comprised only 2 of 159 tumours. The reason remains unclear, but may be related to the fact that lip cancer is a NMSC, and therefore may have been incorrectly classified as skin cancer in the SCR. Earlier studies have shown an association between smoking and lip cancer(146 147). The fact that two patients who underwent HTx and were diagnosed with lip cancer (7 lip cancers among 4 persons) had a history of smoking may partially explain the results. Among those patients that had undergone a HTx, in the studies by Collet et al., and et Jääma-Holmberg et al., the smoking history was unknown. Sun exposure is also a well-established risk factor for the development of lip cancer(148, 149). Among the 7 patients with a lip cancer, 5 (71%) also had a NMSC.
The excess risk of lung cancer was almost 2.5 times higher among lung transplant patients (SIR 8.89) compared to heart transplant patients (SIR 3.68). However, the overall SIR for lung cancer after HTx was higher than observed in other comparable studies (2.0-2.79)(64, 73, 150-152).

In our study, we observed a total of 19 lung cancers in 19 patients (3.1%) after LTx. In comparison, a French study by Chatron et al., found a total of 19 lung cancers in 463 patients after LTx (4.10%) with a median follow-up time of 21.5 months(153). Out of 633 lung transplant patients Pérez-Callejo et al., found that lung cancer was detected in 23 of them (3.63%), with a median follow-time of 3.5 years(154). Magruder et al., reported a higher SIR (6.49) among their lung transplant patients(155). Corresponding results in a large study from the USA by Engels et al. resulted in an SIR of 6.13(66).

Of the LTx patients in our cohort, 65% had a smoking history. The corresponding number for HTx patients was 41%. The main indication for LTx in this cohort was chronic obstructive pulmonary disease, which is usually caused by cigarette smoking. A previous study has demonstrated that both smoking history and older age increase the risk of lung cancer after LTx(156). Previous smoking was only identified as a predictor of cancer for heart transplant recipients, in the univariable and multivariable analysis (smoking cessation <6 months before HTx listing). That might be associated with the fact that the majority of the lung transplant patients, in this study, received double lungs (62%) and 38% had a single lung transplant. Those patients who received a single lung have been reported to be at a higher risk for lung cancer (compared to those who underwent double lung transplantation). The native lung may have been exposed to risk factors for cancer, smoking, which has been claimed as a possible explanation(66, 154, 155, 157-159). We have no information about donors smoking history.

The SIR for prostate cancer among HTx (1.13) was lower than expected. Similar results were found in a meta-analysis including six independent studies, with over 21 000 heart transplant patients(160). Why immunosuppression does not increase the risk for prostate cancer remains largely unknown, but this may in part be explained by the fact that these patients are intensively screened prior to HTx, and the possibility that many of them don’t survive until the age when prostate cancer is most likely to occur i.e. >70 years old(78). But also, the fact that the follow-up time is too short. These findings support that patients with low-grade prostate cancer could be accepted for HTx without the often applied five-year cancer-free waiting period. According to a review article by Mistiaen et al., patients with localized prostate cancer before transplantation had no increased risk of reduced survival after HTx(161). Presently, there is no consensus regarding the optimal time interval between cancer treatment and HTx(162, 163). A relapse-free period of ≥ five years is a common criterion, which
has also been applied at our center. However, when post-HTx mortality is constantly getting lower while as cancer treatment is continuously improving it might be time to revise and individualize these criteria.

Cancer before LTx and HTx

We found 26 (4%) malignancies that had occurred more than 5 years before both LTx and HTx. Among lung transplant patients, the most common cancers were: lung, breast, prostate, lymphosarcoma and reticulosarcoma and among heart transplant patients there were acute lymphoblastic leukemia, lymphosarcoma, and Hodgkin lymphoma. There were no significant differences in overall survival between those with and without cancer before HTx and LTx. Furthermore, there was no significant difference in post-LTx and post-HTx relative survival between cancer-free patients versus those who had experienced cancer before LTx and HTx.

Limitations

As the SCR only includes histopathologically verified cancers, those cancers diagnosed at a late stage might have occurred and consequently tumours were not histopathologically verified which can be seen as a limitation. We have no knowledge of whether or not patients have had viral infections (such as human papillomavirus virus, Epstein-Barr virus etc) contributing to the development of cancer. The current study did not investigate whether the patients had BCC before or after LTx, since this cancer form has been considered rather benign and, therefore, not reported in the SCR. The growth rate of BCC is slow, and this cancer rarely metastasizes(119). However, post-transplant lymphoproliferative disease (PTLD), a well-known complication after LTx(164). It is not recorded as a specific entity in the SCR, why the exact number of patients with PTLD cannot be reported. Instead, such cases are presented as lymphomas.

Future Perspectives

OTRs are a growing group of patients. The number of transplanted organs has almost doubled in Sweden from 450 each year in the beginning of the 21st century to 800 in 2016(165).

The numbers of children who undergo organ transplantation are also increasing(69). Further, it is acknowledged that the incidence of cancer post-transplantation increases with the intensity and duration of immunosuppression. These young individuals have a great risk of developing cancer during their life.
Malignancies after transplantation, particularly skin cancer will probably increase. Skin cancer is the most common malignancy after transplantation, especially in combination with exposure to UV radiation. In Sweden, as in most countries with predominantly fair-skinned populations, increasing incidence rates of skin cancer have been observed in the last decades. Additionally, many Swedes enjoy getting a suntan. Further, calculations suggest that four to five times as many MMs will be diagnosed in Sweden in the next 20 years.

Immunosuppression medications also play a key role in the risk of developing cancer after transplantation. Many of the side effects following immunosuppression might be solved with safer and more effective immunosuppression. Unfortunately, the development of new treatments has slowed markedly. According to Stegall et al., (166) there are several barriers according to different actors on the transplantation arena. Firstly, there is a general misconception that the status of organ transplantation is acceptable and cannot be improved. Due to the high cost of trials versus the risk of not showing sufficient result, compared to the standard care, it may appear unattractive for the biopharmaceutical industry to develop new treatments. Further, there is a lack of data with detailed information regarding specific transplant conditions such as subclinical inflammation, de novo donor-specific, antibodies etc. Even if the transplantations have increased in Sweden and worldwide, nevertheless, the number of available organs does not match the number of patients on the waiting list. Patients therefore die before transplantation. In the future, de- and recellularization of organs and 3D bioprinting technologies may be the solution according to Atala et al., (168). Three-dimensional bioprinting is a process were cells and other biocompatible materials, also known as bioinks, are used to print living structures layer by layer already shown by Simons-son et al., in cartilage tissue with pluripotent stem cells in Nanocellulose/Alginate bioink(169).

Beside the development of new treatments, there is also a great challenge to promote sun protection behavior. Earlier studies have shown that specialist OTR dermatology clinics have been shown to be significantly more effective in providing information about risk factors for skin cancer(134). In our study, OTRs reported less sun exposure compared to non-TPs, consolidating the positive effect of sun protection advice following transplantation. While follow-up by dermatologists resulted in improved sun protection behaviour, we suggest that specialised OTR clinics should be more broadly implemented.
Conclusion

For a well-selected group of patients, with end-organ failure, organ transplantation is the best life-saving treatment. The immunosuppressive agents, which are essential to prevent graft rejection, have several side-effects. One of them, the increased risk of developing cancer. In this thesis, we have investigated the incidence of cancer after heart and lung transplantation, the degree of differentiation of SCC in OTRs compared to immunocompetent individuals. We also compared the sun exposure and sun protection behaviour in OTRs to non-TPs. Future cancer research post-transplantation ought to be focused on strategies of optimal allocation and matching of organs so as to minimise the need for the potentially damaging but necessary immunosuppression. Furthermore, a focus on investigating the optimal use of current as well as potential novel medications should also be a consideration.
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Foremost, I would like to thank my main supervisor and professor Göran Dellgren, for believing in me and for giving me this opportunity, for that I will always be grateful. You have been generous with your time (24/7), your knowledge and always being positive and encouraging. Without you and your generosity, I would not have been where I am today. Your very high standard has pushed me to achieve what I thought not possible. Thank you!

Furthermore, I would like to thank my co-supervisor Jesper Magnusson, for always being enthusiastic, positive and boosting my confidence. I really appreciate all those conversations we have had, not only about science but also about life. Also, thank you for being my linguistically inquisitive interlocutor! Andreas Wallinder, my co-supervisor. Thank you for giving me absolutely brilliant feedback on our studies. Your guidance and overall insights have made this an inspiring experience for me. You have had a great impact on me and my professional development; thank you!

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A special thanks to co-author Magdalena Claeson for the big effort you put in to study II. I am also truly grateful for the constructive feedback from Kristian Karason, regarding study III and IV.

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