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CANCER AFTER SOLID ORGAN TRANSPLANTATION – INCIDENCE, RISK FACTORS, AND SURVIVAL

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Cancer after solid organ transplantation – incidence, risk factors, and survival

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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POPULAR SCIENCE SUMMARY OF THE THESIS

Organ transplantation is a remarkable means of treating advanced organ disease, such as kidney, liver, or heart failure. In almost all cases, transplantation of an organ from one person to another demands treating the recipient with immunosuppressive medication, in order to counteract rejection of the transplanted organ. However, immunosuppressive treatment has been linked to increased risk of developing many types of cancer. The relative risk of cancer among organ transplant recipients, compared to that of the general population, has previously been estimated to be two to four times increased, but the absolute risk – i.e. the actual risk that a patient will develop some kind of cancer – has not been as thoroughly investigated. Also, whether cancers developing in transplant recipients are more dangerous, and if cancer treatment is different from that in non-transplanted cancer patients, is still largely unclear.

Over time, both immunosuppressive treatment regimens and surgical management have changed for the better, resulting in a substantial improvement of overall survival after solid organ transplantation. However, several previous landmark studies on cancer after organ transplantation are gaining age. We were therefore interested in studying how the relative and absolute risks among Nordic organ transplant recipients have evolved during the modern treatment era, and how cancer patients with and without previous transplantation in their medical history compare, with regards to cancer characteristics, treatment, and outcomes.

In the first study of this thesis, almost 13,000 Danish, Finnish, Norwegian and Swedish kidney transplant recipients were followed from their transplantation until diagnosis of cancer. Compared with the general population, relative and absolute cancer risks were increased both overall and for a wide range of cancers, most notably non-melanoma skin cancer. While infection-related cancers, such as post-transplant lymphoma, and nose, mouth, and lip cancer were associated with the highest relative risks, the absolute risks were generally higher for non-infection-related cancers common also in the general population, such as malignant melanoma, lung cancer, and colon cancer.

The second study involved all Swedish cancer patients diagnosed with cancer during 1992 through 2013. Over two thousand patients with an organ transplantation prior to their cancer diagnosis, and close to a million cancer patients without such medical history, were included. The study showed that a history of transplantation at cancer diagnosis was associated with a 35% increased rate of cancer-specific death, i.e. that the cancer prognosis was worse among patients with a previous transplantation, compared with cancer patients without such history. The rate of cancer-specific death spanned from 40% to 200% increased for transplanted patients with colorectal, head/neck, breast, and urinary tract cancer, as well as malignant melanoma and lymphoma, while no increased death rates were found for other cancer forms, such as lung and prostate cancer. Overall, transplantation was also associated with a two-fold increased rate of death due to any cause among cancer patients.

The third study aimed to establish differences in cancer characteristics and treatment among colorectal cancer patients with and without a previous solid organ transplantation in their

medical history. In a cohort of almost 80,000 Swedish patients with colorectal cancer, 99 transplanted patients were identified and compared with 491 non-transplanted patients, matched to be similar to the transplanted ones regarding age at diagnosis, sex, year of diagnosis, and cancer location (i.e. colon or rectum), to account for confounding effects. The analyses showed that organ transplant recipients were less likely to be treated with surgery and associated oncological treatments, such as chemo- and radiotherapy, and had higher rates of death due to both cancer and other causes, compared with non-transplanted colorectal cancer patients.

In conclusion, Nordic kidney transplant recipients were at higher risk of developing cancer compared with the general population, and Swedish organ transplant recipients had worse outcomes once diagnosed with cancer, than comparable cancer patients without transplantation history. Also, having gone through a previous transplantation impacted both the treatment administered and survival among colorectal cancer patients. This thesis thus puts further emphasis on the need for effective cancer management protocols for organ transplant recipients, in order to provide the best possible treatment for an already vulnerable patient group.

ABSTRACT

Background: Solid organ transplant recipients (OTRs) are at increased risk of cancer compared with the general population, mainly due to post-transplant immunosuppressive treatment. Furthermore, once diagnosed with cancer, OTRs might experience worse cancer-specific and overall survival than non-transplanted cancer patients. Colorectal cancer (CRC), one of the most commonly occurring cancers in the general population, has often been associated with an even higher incidence after organ transplantation. Its relatively high post-transplantation frequency enables epidemiological research with comparatively high statistical power on e.g. differences in cancer characteristics and treatment associated with transplantation. The aims of the present thesis were to estimate relative and absolute (including excess) risks of a wide range of cancers among Nordic kidney transplant recipients (KTRs), compared with the general population (Study I); to investigate differences in cancer-specific survival among OTRs with cancer, compared with non-transplanted cancer patients, for different types of cancer (Study II); and to establish the influence of organ transplantation on various cancer characteristics, as well as on cancer treatment and outcomes, among Swedish CRC patients (Study III).

Materials and methods: In Study I, Nordic national patient, cancer, cause of death, kidney, and transplantation registers were used to identify all recipients of a kidney transplant during 1995 through 2011, as well as corresponding patient and donor characteristics possibly associated with cancer risk. Standardized incidence ratios (SIR), cumulative incidence in the presence of competing events, and absolute excess risks of cancer were calculated. Risk factors for cancer were studied using Cox regression. In Study II, the Swedish national cancer register was used to identify all Swedish cancer patients with a first cancer diagnosis during 1992 through 2013. Data on patient, cancer, and cause of death characteristics were obtained through linkage with the national cancer and cause of death registers. Cox regression was used to estimate hazard ratios for cancer-specific and all-cause death, comparing cancer patients with a history of solid organ transplantation to those without. In Study III, the Swedish register linkage database CRCBaSe was used to identify all Swedish CRC patients with a history of solid organ transplantation prior to first CRC. Five non-transplanted CRC patients were matched to each OTR. Logistic and multinomial regression was used to evaluate the impact of transplantation on cancer characteristics and treatment, and Cox regression was used to estimate rates of cancer-specific and all-cause death depending on previous organ transplantation.

Results: Among 12,984 Nordic KTRs included in Study I, increased incidence rates (compared with the general population) were found for a wide range of cancers, especially infection-related cancer types such as non-melanoma skin cancer (NMSC), lip, oral and nasal cancers, male and female external genital cancer, and non-Hodgkin lymphoma. However, excluding NMSC, absolute risks were generally higher for non-infection-related cancers (which were often associated with moderately increased rates), such as lung and kidney cancer. Accounting for the competing event of death, the five-year cumulative incidence of

cancer was 8%. In Study II, the rate of cancer-specific death was 1.35-fold increased among 2,143 cancer patients with a history of organ transplantation, compared with 946,089 non-transplanted cancer patients. Specifically, lymphoma, malignant melanoma, and urothelial, breast, head/neck, and colorectal cancers were associated with increased cancer-specific death rates among OTRs, compared with non-OTRs. Study III included 99 OTRs and 491 matched non-OTR comparators with CRC. Transplantation history was associated with lower odds of receiving treatment with abdominal surgery, neoadjuvant radiation for rectal cancer, and adjuvant therapy for colon cancer. Cancer-specific and overall survival, as well as disease-free survival, was lower among the OTRs than among the non-OTRs.

Conclusions: Nordic KTRs are at increased risk of developing a wide range of cancers post-transplant, both in relative and absolute terms. Once diagnosed with cancer, OTRs with cancer had worse cancer-specific prognosis, both overall and for several specific cancer types, than non-transplanted cancer patients. Among CRC patients, previous transplantation was associated with differences in both treatment and outcomes. These findings should be considered when evaluating Nordic post-transplant cancer screening protocols, and support holding multidisciplinary team conferences, including organ transplant specialists, for post-transplantation cancer care.

LIST OF SCIENTIFIC PAPERS

I. Benoni H, Eloranta S, Dahle DO, Svensson MHS, Nordin A, Carstens J, Mjøen G, Helanterä I, Hellström V, Enblad G, Pukkala E, Sørensen SS, Lempinen M, Smedby KE.
Relative and absolute cancer risks among Nordic kidney transplant recipients – a population-based study.
Transplant International. 2020 Dec; 33(12): 1700-1710.

II. Benoni H, Eloranta S, Ekbom A, Wilczek H, Smedby KE.
Survival among solid organ transplant recipients diagnosed with cancer compared to nontransplanted cancer patients – a nationwide study.
International Journal of Cancer. 2020 Feb; 146(3): 682-691.

III. Benoni H, Nordenvall C, Hellström V, Weibull CE, Martling A, Smedby KE, Eloranta S.
Colorectal cancer patients with a history of solid organ transplantation receive less intense cancer treatment than non-transplant recipients.
Manuscript.

Other relevant publications:

- Benoni H, Smedby KE, Eloranta S.
Author's reply to: A note on competing risks in analyses of cancer-specific mortality.
International Journal of Cancer. 2019 Sep; 145(6): 1706-1707.

CONTENTS

LIST OF ABBREVIATIONS

AER	Absolute excess risk
AIDS	Acquired immunodeficiency syndrome
CCI	Charlson comorbidity index
CRC	Colorectal cancer
GI	Gastrointestinal
HL	Hodgkin lymphoma
HPV	Human papilloma virus
HR	Hazard ratio
ICD-7/8/9/10	International Classification of Diseases, Injuries, and Death Causes, version 7/8/9/10
IPITTR	Israel Penn International Transplant Tumor Registry
KTR	Kidney transplant recipient
MDT	Multidisciplinary team meeting
mTOR	Mammalian target of rapamycin
NCR	(Swedish) National cancer register
NHL	Non-Hodgkin lymphoma
NMSC	Non-melanoma skin cancer
OR	Odds ratio
OTR	(Solid) organ transplant recipient
PIN	Personal identity number
PSC	Primary sclerosing cholangitis
SCC	Squamous cell cancer
SCDR	Swedish cause of death register
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
SPR	Swedish patient register
TNM	Tumor-node-metastasis
UC	Ulcerative colitis

1 INTRODUCTION

1.1 SOLID ORGAN TRANSPLANTATION

Solid organ transplantation includes a range of surgical procedures performed to replace an organ that has ceased working properly with a functioning one. In this context, terms such as *end-stage organ failure* are commonly used. Although many people live with varying degrees of organ failure of different kinds, there is a paucity of transplantable organs, and organ transplantation thus becomes a plausible option only when a failing organ merely retains a rudimentary function or fails completely. For example, in Sweden at the end of 2019, more than 4,000 patients with end-stage kidney failure were treated with dialysis, and over 6,000 were living with kidney transplants.[1] Furthermore, an all-time high of 467 kidney transplantations had been registered during the year. On the other side, over 1,100 patients with renal failure entered renal replacement therapy (i.e. dialysis or transplantation) during 2019, and 911 died (out of which 744 on dialysis and 167 with working kidney transplants), mainly due to cardiovascular disease. This implies that 1) kidney transplantation is an effective means of treating end-stage kidney failure, 2) kidney transplantation is a treatment form associated with relatively high mortality, but 3) dialysis is associated with considerably lower survival, making transplantation an excellent treatment form for a condition with poor prognosis. While there are alternative treatments also for other variants of organ failure, such as mechanic pumps replacing failing hearts, organ transplantation is a far superior option, as other means of treatment are often unsustainable for long-term use.

The first kidney transplantation (between identical twins) with significant graft survival was performed in 1954, representing a medical revolution and marking the start of a new era.[2] The patient, Richard Herrick, lived for eight more years before succumbing to cardiac disease, and the surgeon, Joseph E Murray, kept breaking ground in the field of transplantation surgery, for which he was awarded the Nobel prize in 1990.[3] However, developing transplantation of organs between people who are not identical twins has not been trivial, due to the excellent ability of the immune system to find and attack foreign substances and tissues, including transplanted organs.

During the early years of organ transplantation the main obstacle was thus understanding the importance of suppressing the immune reactions.[4] Initial immunosuppressive treatments included total body irradiation, a procedure associated both with severe and potentially lethal acute side effects, as well as with delayed ones, such as cancer development.[5] However, extensive research during the latter half of the 20th century has provided knowledge both about the constitution of the immune system, and about more suitable treatments to suppress those parts of it that cause rejection of transplanted organs. This has enabled performing progressively more successful organ transplantations between ordinary, non-identical people since the late 1950's.[4] Nowadays, in Sweden, approximately 450 kidneys (out of which 25-30% come from living donors), 170 livers, 60 hearts, 60 pairs of lungs, and 15 pancreases are transplanted every year.[6] Modern solid organ transplantation has also evolved to include other

organs, such as bowel and pancreatic islet cells, as well as hand, face, and uterus, which are, however, transplanted significantly less commonly.[7-9] Even more sensationally, advances in xenotransplantation (i.e. transplantation between species) recently resulted in a porcine heart transplantation performed on David Bennett, Sr., a patient with terminal heart failure.[10] With a patient survival of only two months, this procedure truly evokes questions of both ethical and scientific nature.

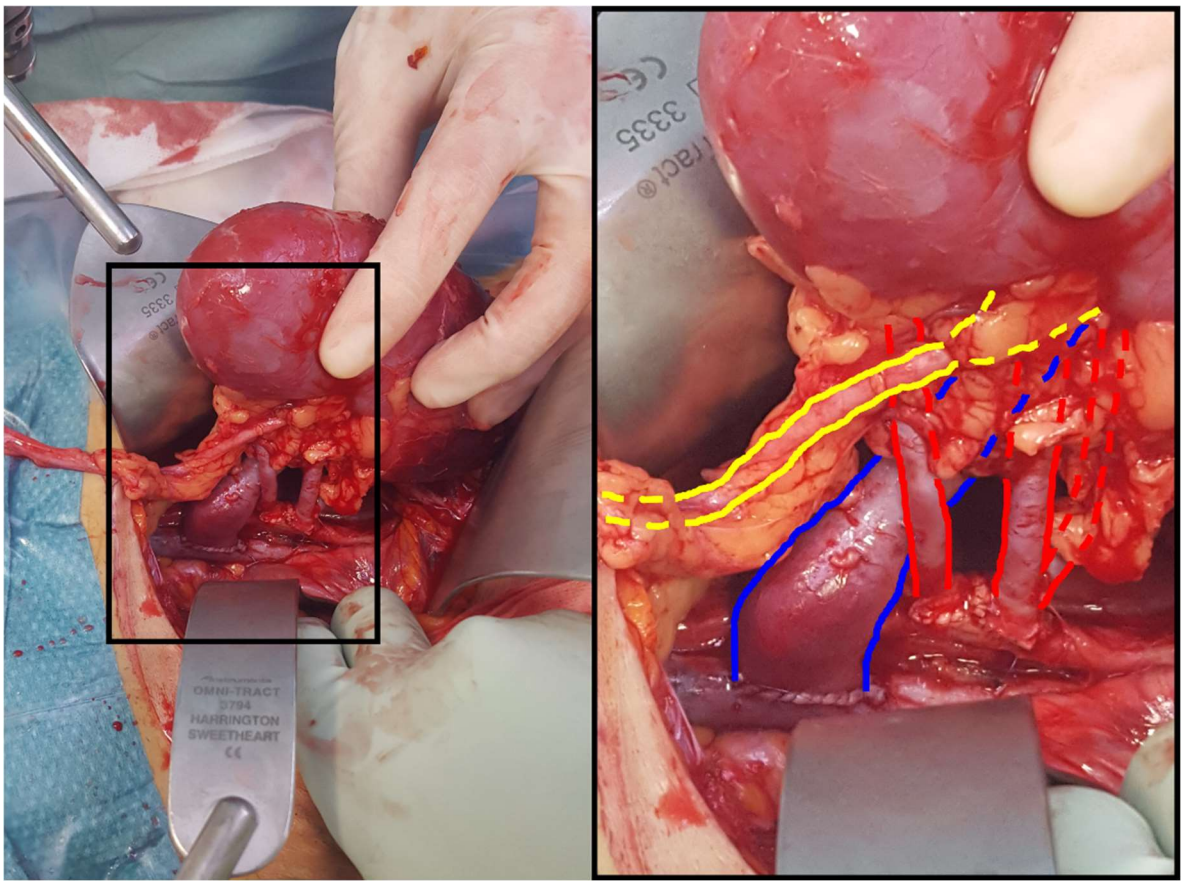

Figure 1. Kidney transplantation. Here, the donor renal arteries (one main artery with an early branch, and a caudal polar artery, outlined in red) and vein (outlined in blue) have been sutured onto the recipient external iliac artery and vein. The donor ureter (outlined in yellow) will now be sutured onto the recipient urinary bladder, after which the abdominal wall is closed and the operation is complete. Photograph taken by the author and used with the patient's permission.

1.2 CANCER AFTER TRANSPLANTATION

Over time, surgical techniques, post-transplant immunosuppressive treatments, and the comorbidity associated with the transplant procedures have all improved. In 1999, Wolfe et al demonstrated that kidney transplantation is a very effective measure for improving survival among patients with end-stage kidney disease, after the risks associated with the immediate post-operative period have passed.[11] However, as early as in the 1960's and 1970's an unusually large amount of cancers occurring after transplantation were reported.[12] Further research subsequently revealed a 2-4 times increased risk of cancer, with squamous cell skin cancer (SCC) being the most commonly occurring cancer type, among solid organ transplant recipients (OTRs).[13-17]

Several explanations have been proposed and investigated to understand the reasons for the increased cancer risk among OTRs. Compared to non-transplanted persons, OTRs are different in a number of ways. For example, they…

… use immunosuppressive treatment.
… suffer from end-stage organ failure.
… have a different spectrum of comorbidity (for some of which, e.g. autoimmune diseases, immunosuppressive treatment is indicated, thereby modifying the total load of immunosuppression pre- and possibly post-transplantation).
… see health care professionals regularly, and could thus be subject to increased cancer vigilance.
… might be more meticulously screened for cancer, both pre- and post-transplant.
… might adhere to post-transplantation as well as routine cancer screening recommendations to a lower extent than the general population (e.g. due to other frequent health care visits associated with their transplant-related and other comorbidity).

Furthermore, post-transplant cancer management is complicated by comorbidity and the presence of the organ transplant itself.

1.3 CANCER DURING END-STAGE ORGAN FAILURE AND DIALYSIS

Several diseases associated with end-stage organ failure and subsequent transplantation are also associated with increased cancer risk. This is the case with, for example, liver cirrhosis and hepatocellular carcinoma, one of several indications for liver transplantation; inflammatory bowel disease, associated with both colorectal cancer (CRC) and primary sclerosing cholangitis (PSC), which in turn can be another cause for liver transplantation; and with cystic fibrosis, associated with both digestive tract cancer and lung transplantation.[18-20] Furthermore, moderate chronic kidney disease, albuminuria, and dialysis have all been associated with increased cancer incidence.[21]

Knowledge about cancer occurring during dialysis is of special interest to health care professionals working with presumptive kidney transplant recipients (KTRs), as such knowledge helps physicians inform patients about how cancer incidence during dialysis compares with that after kidney transplantation, the most commonly performed type of solid organ transplantation. Several population-based studies on cancer during dialysis have shown either similar or slightly increased risks of cancer overall among patients with kidney failure before and during dialysis, compared to the general population.[22-29] Markedly increased risks have been found for mainly kidney and urinary tract cancer, i.e. cancers occurring in or near the failing kidney, and multiple myeloma. This association with organ-specific cancer is valid also for other types of organ failure (e.g. hepatocellular carcinoma after liver cirrhosis). Most other frequently occurring cancer types have been reported to be more moderately (up to two times) increased among dialysis patients compared with the general population, except

thyroid cancer, which various studies have found to be significantly more common during dialysis.

Various reasons for increased cancer risk during end-stage renal failure and dialysis have been proposed, some of which are listed below:[21,30]

- Cancer and kidney disease share many risk factors, such as male sex, smoking, obesity, and malnutrition (among hemodialysis patients).
- Several genetic conditions associated with kidney disease are also associated with cancer.
- Inflammatory and immune disorders, infections, and acute kidney injury can trigger local inflammation, possibly leading to cancer development.
- Treatment (for example with chemotherapeutic agents, such as cyclophosphamide) for either kidney disease or cancer could trigger development of the other.
- Carcinogenic agents are retained and accumulated to a larger degree in patients with kidney disease than in healthy people, especially in predialytic patients.
- The expression and inducibility of genes important to immune response is altered in dialysis patients.
- Long-term hemodialysis has been shown to impair DNA repair processes.

1.4 CANCER DURING IMMUNOSUPPRESSION

OTRs need continuous immunosuppressive treatment to counter rejection of the organ transplant. As there is a clear relationship between graft function and (ongoing) immunosuppressive treatment, several studies have been able to investigate the association between immunosuppressive medication and cancer incidence (not least since graft failure could arguably be seen as a proxy for halted or heavily reduced immunosuppressive treatment).

Induction therapy at the time of transplantation surgery (i.e. administering an additional, heavily immunosuppressive agent, such as anti-thymocyte globulins, or interleukin-2 receptor antibodies) has been associated with higher risk of developing post-transplant lymphoma.[31,32] Increasing time on and dosage of maintenance immunosuppressive therapy, that is, the every-day medication OTRs need to take to counter graft rejection, has been shown to increase cancer risk.[32-34] Furthermore, some specific immunosuppressants (e.g. azathioprine and calcineurin inhibitors) have been associated with increased risks of certain types of cancer.[32,33] On the other hand, switching treatment type to mTOR (mammalian target of rapamycin) inhibitors seems to have beneficial effects on some cancers such as non-melanoma skin cancers (NMSC) and Kaposi's sarcoma.[35,36] Treatment with mTOR inhibitors should, in theory, exert an antitumoral (cytostatic) effect on a wide range of cancer types. This, combined with their role as immunosuppressants, could have made them ideal for cancer treatment among OTRs. However, in practice, treatment with mTOR inhibitors has a limited antitumoral effect on many cancer types, and is associated with an increased frequency of side-effects among OTRs.[37] Return to dialysis after kidney graft failure has been

associated with decreased risk of cancers associated with infection and/or immunosuppression, but not of cancers associated with end-stage renal failure and dialysis, implying that heavily reducing or discontinuing immunosuppressive treatment decreases the risk of the former cancer types.[38] A cornerstone of cancer treatment among OTRs is thus to reduce the level of maintenance immunosuppressive treatment to a minimum, while keeping enough to avoid transplant rejection.[38,39]

Immunosuppression also occurs as a consequence of certain diseases. A meta-analysis comparing cancer incidence among OTRs with that of patients with acquired immunodeficiency syndrome (AIDS) showed remarkable similarities in the distribution of de novo cancers.[40] This indicates that the immune system, in this aspect the T-cell component thereof, has an important role protecting against cancer development. Both patient groups are at increased risk of developing several infection-related cancers, e.g. cervical, vulvar, and anal cancer (associated with human papilloma virus [HPV]), non-Hodgkin and Hodgkin lymphoma (associated with e.g. Epstein-Barr virus, as well as with other infections), and stomach cancer (associated with Helicobacter Pylori). On the contrary, no consistently increased risks of breast and prostate cancer have been found for neither OTRs nor AIDS patients. For the former but not the latter, increased risks were seen for colorectal, bladder, and thyroid cancer, whereas AIDS patients but not OTRs were at increased risk of brain and testicular cancer. Taken together with the aforementioned studies on cancer during immunosuppressive treatment, a compelling argument can be made that immunosuppression seems to be a substantive reason for cancer development and behavior among OTRs.

The considerably increased incidence of both cutaneous melanoma and, especially, non-melanoma skin cancer among OTRs has been linked to both ultraviolet radiation and subtypes of HPV, where the former induces skin changes leading to an immunosuppressed environment where HPV can flourish.[41] These hospitable conditions are then further enhanced by immunosuppressive treatment due to transplantation. Because of this, OTRs are advised to apply strict protective measures against skin sun exposure. Naturally, the risk of cancer development is also dependent on skin type and color, as well as the climate.

1.5 POST-TRANSPLANT CANCER SCREENING

While a more thorough account of the current knowledge on post-transplant cancer screening follows (see *6.3.1 Cancer screening*), a recent review of guidelines indicated that there is broad support for screening among OTRs for cancers that are already screened for in the general population, such as breast and cervical cancer in most countries with cancer screening programs, and lung and colorectal cancer in some countries.[42] The cost-effectiveness of screening has, for several additional cancer types, been questioned due to the lower overall life expectancy among OTRs. In other words, transplantation has been associated with such high rates of overall mortality that, even in a setting with increased cancer incidence, OTRs die from other causes to a larger extent than the general population before developing cancer, which limits the benefits of screening (see also *4.3.2.2 Statistical analyses* for discussion on competing risks).

1.6 POST-TRANSPLANT CANCER TREATMENT

Post-transplant cancer treatment is complicated by the comorbidity associated with organ transplantation. On the one hand, the often severe concomitant health issues arising in combination with (and due to) end-stage organ failure can be quite improved by transplantation. However, persistent underlying comorbidity, and additional comorbidities caused by immunosuppressive treatment (e.g. diabetes and kidney damage), can pose a problem when deciding on suitable oncological treatment for the post-transplant cancer patient – not to mention consideration of the organ transplant itself, which could be damaged by the cancer treatment.

The latter half of the 20th century saw a growing arsenal of chemotherapeutic agents for cancer treatment discovered and developed, and during the 21st century several new lines of treatment, such as monoclonal antibodies and checkpoint inhibitors, have been introduced. However, few studies have investigated the effects of such treatment in OTRs, quite possibly due to well-known side effects such as nephrotoxicity. While some smaller studies report successful and safe administration of some chemotherapeutic agents in OTRs for e.g. lymphoma treatment, and monoclonal antibodies such as rituximab regularly being used in preparation of blood group (AB0) incompatible living donor kidney transplantation, there have also been reports of fulminant, acute rejection after administering immune checkpoint inhibitors for e.g. malignant melanoma.[36] On the other hand, recent case reports and studies report successful administration of specific checkpoint inhibitors, such as nivolumab, to KTRs with cancer, with variable cancer response but without occurrence of untreatable rejections leading to graft loss.[43,44] Accordingly, adjuvant and neoadjuvant oncological treatment for post-transplant cancer requires careful consideration and is challenging to study scientifically, not least due to the comparatively few OTRs found within each group of patients with specific cancer types (except NMSC).

A recent overview of oncological drug safety for post-transplant cancer treatment concluded that few (if any) drugs are absolutely contraindicated, but a risk-benefit evaluation for each patient is imperative.[45] Reducing maintenance immunosuppression means balancing between treating the cancer optimally, and the risk of rejection and possible subsequent return to organ failure. Furthermore, OTR cancer patients may differ considerably in their wishes for subsequent management (e.g. maximizing their chances of living for as long as possible, or minimizing the risk of returning to dialysis for the remainder of their lives), which further complicates the already difficult clinical decision-making.

1.7 THE PURPOSE OF THIS THESIS

Despite the aforementioned accumulated knowledge produced during the last decades, much is still left to discover. How do regional differences in post-transplant cancer incidence and prognosis affect pre- and post-transplant cancer management and screening needs? Compared with previous research performed during a different era of immunosuppressive treatment, how have cancer risks among Nordic KTRs evolved over time? Once diagnosed with cancer,

how do OTRs fare compared with non-transplanted cancer patients? And, given the widely different spectra of comorbidity, how are post-transplant cancer patients treated as compared with cancer patients in the general population? This thesis seeks to provide some answers to these questions.

2 LITERATURE REVIEW

2.1 CANCER INCIDENCE AMONG KIDNEY TRANSPLANT RECIPIENTS

After a growing number of case reports of post-transplant cancer were published in the late 1960's, formal studies during the 1970's pointed towards an increased incidence of some cancers among KTRs, mainly lymphoma and SCC.[46,47] Several subsequent studies have found 2-4 times increased risks among KTRs of cancer overall, still with the highest relative and absolute risks associated with SCC, either by itself or included in the larger group of NMSC. Furthermore, lymphoma forms part of a spectrum of benign and malignant disorders collectively termed post-transplantation lymphoproliferative disease.[48]

Many register-based studies of cancer risks, however, have not included SCC/NMSC, as these cancer types are often not included in cancer registers. The Nordic cancer registers have historically been unique in their national and population-based scope, and reporting is mandatory by law, resulting in virtually complete coverage of all diagnosed primary cancers, including NMSC (but slightly differing in their treatment of basal-cell cancer, which historically has sometimes been included in the NMSC group and sometimes not).[49] These registers have accordingly provided excellent material for epidemiological studies, explaining why several of the nationwide and population-based previous studies on post-transplant cancer incidence have been conducted in the Nordic countries.[13-16,28,50] The standardized incidence ratio (SIR) has typically been the main measure used, i.e. the number of observed cancer cases among KTRs divided by the number of cases that would be expected if the KTRs had had the same cancer incidence rates as the comparator population, while accounting for important confounders such as age at and year of cancer diagnosis, country, and sex.

2.1.1 Nordic studies

In an early Nordic population-based study from 1994, Kyllönen et al reported that among all Finnish KTRs until 1991, 94 cancers were diagnosed among 2,090 patients, resulting in an absolute cancer risk (including NMSC, but in the absence of competing events, thereby probably overestimating the real-world absolute risk) of 14% at 15 years after transplantation.[13] The SIR of any cancer, compared to the general population, was 2.7. Cancers with increased rates were those of the skin (SIR 20), thyroid (11), kidney (7), colon (5), bladder (4) and female genital organs (3), as well as non-Hodgkin lymphoma (NHL) (6).

With an update in 2000, the same author noted 230 malignancies among 2,890 KTRs, with an overall SIR of 3.3 and significantly increased rates for cancers of the skin (SIR 39), lip (23), small bowel (12), pleura (8.4), thyroid (8.1), kidney (8.0), lymph nodes (4.8), colon (3.9), and urinary tract (3.2).[15] The absolute risk of cancer (again including NMSC and in the absence of competing events) was approximately 4% and 9% at 5 and 10 years after transplantation, respectively.

Birkeland et al made the first (published) effort to compare Nordic KTRs regarding development of post-transplantation cancer, and published a report in 1995 showing a 4.5 times higher rate of any cancer compared to the general population among 5,692 KTRs.[14] Cancers with significantly increased rates among both sexes were NHL (SIR 10 among males/11 among females) and NMSC (29/18), and cancers of the lip (14/117), colon (3.2/3.9), larynx (3.8/15), lung (1.8/4.9), kidney/ureter (4.6/19), bladder (3.1/17), and thyroid (16/5.1) cancer, as well as vulvar/vaginal cancer (31) and Hodgkin lymphoma (HL) (11) among women, and prostate (2.1), testis (3.9), rectum (4.5), and brain (3.0) cancer among men.

Among 5,931 Swedish OTRs during 1970-1997, out of whom 5,004 (84%) were KTRs, Adami et al (in 2003) found an SIR of 4.0 of any cancer compared to the general population, and increased rates for lip (SIR 53), oral cavity (5.5), esophageal (3.2), stomach (2.3), colon (2.3), rectal (1.9), lung (1.7), mediastinal (43 [n=1]), cervix in situ (1.3), vulvar and vaginal (21), kidney (4.9), thyroid (3.8), and bladder (2.3) cancer, and for malignant melanoma (1.8), NMSC (56), NHL (6.0), and multiple myeloma (2.7).[16] Specifically for KTRs, the authors reported increased rates for cancers of the lip (SIR 55), colon (2.4), and kidney (5.2), and for NMSC (58), NHL (3.8), as well as for any cancer (3.9). The absolute risk of cancer was 6% and 14% over 5 and 10 years, respectively, including NMSC but in the absence of competing events.

Following up on the study by Adami et al, Krynitz et al in 2013 demonstrated an overall SIR of 6.5 of any cancer post transplantation among 7,952 KTRs in Sweden during 1970-2008, and an SIR of 2.3 of any non-NMSC cancer.[50] Increased incidence rates were seen for cancers of the lip (SIR 46), oral cavity (5.2), stomach (1.8), colon (2.3), anus (6.3), liver (2.7), pancreas (2.2), nose and middle ear (5.9), lung (1.7), cervix (2.4) (and cervical intraepithelial neoplasia III [3.0]), ovaries (1.9), vulva and vagina (14), penis (4.5), kidney (6.2), bladder (2.0), thyroid (4.1), and of other types (1.9), and for SCC (52), malignant melanoma (2.3), Merkel cell carcinoma (52), Kaposi's sarcoma (40), appendageal carcinoma (43), NHL (4.8), and HL (3.2).

In 2017, Hortlund et al published a study on cancer after solid organ transplantation (and during dialysis), including 19,214 Swedish and Danish OTRs, among which 13,855 (72%) KTRs.[28] Increased incidence rates of post-kidney transplantation cancer were presented for any cancer ($SIR_{Swedish}$ 3.6/SIR_{Danish} 3.2), any cancer but NMSC (2.2/2.3), and for kidney (6.5/6.9), lip (43/12), non-melanoma skin (49/50), and thyroid (5.6/4.7) cancer. Swedish KTRs were at increased risk of HL ($SIR_{Swedish}$ 2.4), and Danish KTRs of NHL (SIR_{Danish} 6.1). For all OTRs, increased rates were seen for the overwhelming majority of cancers, except those of the eye, brain and CNS, hypopharynx, pleura, corpus uteri, prostate, and testis among both Swedish and Danish OTRs; cancers of the esophagus, gallbladder, small intestine, breast, and uterus other than corpus among Swedish OTRs; and leukemia, HL, and cancers of the bone, larynx, pancreas, ovaries, and penis among Danish OTRs. Notably, Danish but not Swedish female OTRs were at increased risk of breast cancer (SIR_{Danish} 1.3).

2.1.2 Oceanian, North American, and British studies

In 2006, Vajdic et al presented SIRs > 1 (exact estimates not presented) for cancer overall as well as cancers of the lip, oral cavity, esophagus, stomach, colon, anus, liver, gallbladder, lung and bronchus, connective and soft tissue, vulva, cervix, penis, eye, and thyroid, and also for melanoma, Kaposi sarcoma, lymphoma, leukemia, and unspecified cancer, when comparing post-transplantation cancer incidence among 10,180 Australian KTRs to that of the general population.[24]

Villeneuve et al published a study in 2007 on cancer risks among 11,155 Canadian KTRs during 1981-1998, and found a 2.5 times increased rate of cancer incidence among KTRs relative to the Canadian population.[17] SIRs > 1 were seen for lip (SIR 31), head/neck (3.1), stomach (2.1), colorectal (1.4), gallbladder (4.1), lung (2.1), breast (1.3), vulva (5.5), connective tissue (4.8), bladder (2.0), kidney (7.3), and thyroid (5.0) cancer, malignant melanoma (1.9), NHL (8.8), HL (3.6), multiple myeloma (3.9) and leukemia (2.3). NMSC was not included. An analysis of cumulative incidence of cancer (excluding NMSC), in the presence of competing risks of death or diagnosis of another cancer, yielded an absolute risk of approximately 12% after 17 years of follow-up (4% after 5 years, and 8% after 10 years).

Also in 2007, Webster et al found a significantly higher cumulative incidence of cancer for all age groups among 15,183 KTRs in Australia and New Zealand from 1963 through 2004, with the highest excess risk among transplant recipients under 35 years of age, compared to the general population.[51] The analyses were performed in the absence of competing events.

Among 25,104 KTRs (including 764 combined kidney and pancreas transplant recipients) from 1980 through 2007, Collett et al in 2010 found an overall SIR of 2.4 of any cancer excluding NMSC compared to the general population, as well as significantly increased rates (SIRs within parentheses) of NMSC (17), malignant melanoma (2.6), Kaposi's sarcoma (17), and of lip (66), oral cavity (4.2), esophagus (1.8), stomach (2.0), colorectal (1.8), anal (10), liver (2.4), lung (1.4), cervix (2.3), kidney (7.9), bladder (2.4), and thyroid (7.0) cancer, and in HL (7.4), NHL (13), multiple myeloma (3.3), and other specific sites (2.8).[52] The five- and ten-year absolute risks of any cancer excluding NMSC were approximately 4 and 9 percent, presumably not considering competing risks.

A 2011 study by Engels et al on post-transplantation cancer risk covering 175,732 OTRs nationwide in the USA during 1987-2008, including 58% KTRs, yielded an SIR of 2.1 of developing any cancer (excluding SCC) compared to the general population.[53] Significantly elevated rates (SIRs within parentheses) among virus associated cancers were found in NHL (7.5), HL (3.6), and Kaposi's sarcoma (61), and liver (12), stomach (1.7), oropharynx (2.0), anal (5.8), vulva (7.6), unspecified (14), and penile cancer (4.1). Additionally, almost all non-virus associated post-transplant cancers were associated with increased incidence, except for prostate, breast, uterine corpus, ovarian, and brain cancer, as well as mesothelioma and some types of leukemia. The overall absolute excess risk (AER) was 719 per 100,000 person-years,

with the highest risks found for NHL (AER 168), and for liver (110), lung (85) and kidney (76) cancer. Most cancer type-specific results were not stratified by type of transplantation.

Using the same database but focusing on absolute instead of relative cancer risks, a follow-up report by the same research group noted 8,520 de novo post-transplant cancers among 164,156 OTRs (among which 102,106 (62%) KTRs). The five-year absolute risk of first cancer (excluding NMSC) was 4.2% among patients with transplantations during the period 1987-1999, and 4.4% during 2000-2008, accounting for the competing risks of death, re-transplantation, or graft failure.[54]

2.1.3 Asian studies

In a Taiwanese study by Li et al published in 2012, 4,716 KTRs developed 320 incident cancers corresponding to an overall SIR of 3.8 compared to the general population.[55] Significantly elevated rates were noted for colon (SIR 2.0), liver (5.1), lung (4.8), bladder (43), kidney (44), and thyroid (2.4) cancer, and for lymphoma (4.8).

In another Asian study from 2012, Cheung et al gathered data on 4,674 KTRs in Hong Kong from 1972 and onwards, and found an SIR of 2.9 of any cancer, compared to the general population.[56] Specific cancers with increased incidence rates (SIRs within parentheses) included NHL (16), malignant melanoma (9.1), and NMSC (7.4), as well as liver (2.5), colorectal (1.8), lung (1.7), breast (1.7), cervical (7.2), kidney (13), bladder (8.2), thyroid (4.4), stomach (2.9), and ovarian cancer (3.3). Interestingly, the incidence of NMSC was markedly lower in these studies compared to non-Asian ones, and there is no mention of any different definition of NMSC. However, this phenomenon might partly be explained by differences in e.g. climate, sun exposure habits, and skin complexion and type.

Three recent Korean population-based studies have investigated relative risks of post-transplant cancer. First, Heo et al in 2018 found an overall SIR of 3.5 for cancer among 1343 KTRs, with surgery performed 2010 through 2014, compared to the general population.[57] The mean KTR follow-up time was just over two years. Increased rates were seen for thyroid (SIR 4.6), kidney (16), liver (2.7), skin (7.6), and brain (13) cancer, and for leukemia (27), myleoma (24), NHL (29), and Kaposi's sarcoma (447). Furthermore, SIRs > 1 were also found among women for breast (3.9) and cervical (6.1) cancer. Skin cancer SIRs were comparable to those of the aforementioned Asian studies.

Second, in a study from 2020 including 9,915 KTRs transplanted between 2003 and 2016, Jeong et al demonstrated a 3.9 times increased rate of post-transplant cancer overall.[58] Most cancers presented were associated with increased rates, with the highest SIRs seen for kidney (SIR 25), bladder (20) and urethral (44) cancer.

Third, in 2021 Kim et al found SIRs > 1 for prostate (SIR 5.2) and female breast cancer (1.3) among 14,842 Korean KTRs with transplant surgery performed from 2002 through 2017.[59] The SIR for any cancer was 2.5, with increased rates seen for virtually all presented cancer types (excluding myeloid leukemia and cancers of the gallbladder and rectum among men,

and lung cancer among both men and women). Cancers with the highest SIRs were Kaposi's sarcoma (SIR 185/341 among men/women), NHL (12.2/13.2), and kidney cancer (11.3/11.7), with SIR 7.7 for NMSC.

2.1.4 Summary

In summary, previous research shows convincing evidence worldwide of increased risks of NMSC, NHL, and liver, stomach, thyroid, cervical, kidney, lung, colon and colorectal, and bladder and urinary tract cancer after kidney transplantation (Table 1). In Western countries, the relative risk of NMSC is higher and that of kidney cancer lower than in Asian countries, and lip, vulvar, penile, and oropharyngeal and mouth cancer risks are consistently increased, as are the risks of HL and melanoma. On the contrary, in Asian countries, the relative risks of kidney, bladder and urinary tract cancer are overall higher, and increased risks have been seen for pancreatic, breast, and prostate cancer, as opposed to in Western countries.

However, there is far less knowledge of the absolute risk of cancer among Nordic KTRs, both due to conflicting previous results, and to NMSC being omitted in most previous studies on overall cancer risk. Additional studies that quantify absolute risks in a real-world setting (accounting for the competing risk of death) would be a valuable contribution to inform patients and clinicians of the impact of cancer after transplantation, and could help guide which cancers to screen for.

Table 1. Standardized incidence ratios of cancer among kidney transplant recipients, compared to the general population, overall and by cancer type, according to selected previous research reports.

Report	Kyllönen 1994	Birkeland 1995	Kyllönen 2000	Adami 2003	Vajdic 2006	Villeneuve 2007	Collett 2010	Engels 2011[1]	Li 2012	Cheung 2012	Krynitz 2013	Hortlund 2017[2]	Hortlund 2017[3]	Heo 2018	Jeong 2020	Kim 2021
Cancer type																
Infection-related																
NMSC	20	29/18	39	58	-	-	17	14[4]	O	7.4	52	49	50	7.6	5.7	7.9/6.5
Lip	-	14/117	23	55	X	31	66	17	O	-	46	43	12	-	-	-
Vulva, vagina	3	31	O	-	X	5.5	-	7.6, 3.0	-	-	14	-	-	-	-	-
NHL	6	10/11	4.8	3.8	X	8.8	13	7.5	4.8	16	4.8	-	6.1	29	7.9	12/13
Penis, male genitals	-	-	O	-	X	-	-	4.1	-	-	4.5	-	-	-	-	-
Nose, nasopharynx	-	-	-	-	X	3.1[5]	-	O	-	-	5.9	-	-	-	5.4	-
HL	-	O/11	O	-	X	3.6	7.4	3.6	-	-	3.2	2.4	-	-	O	-
Mouth, oropharynx	-	O	O	-	X	3.1[5]	4.2	2.6, 2.0	O	O	5.2	-	-	-	8.3	-
Liver	-	O	-	-	X	O	2.4	12	5.1	2.5	2.7	-	-	2.7	2.5	3.2/9.4
Cervix	-	8.6	O	-	X	O	2.3	O	O	7.2	2.4	-	-	17	5.0	3.0
Stomach	-	O	O	O	X	2.1	2.0	1.7	O	2.9	1.8	-	-	O	2.3	1.4/2.5
Larynx	-	3.8/15	-	-	O	O	-	1.6	O	-	O	-	-	-	-	-
Esophagus	-	O	O	-	X	O	1.8	1.6	O	O	O	-	-	-	O	-
Eye	-	-	-	-	X	-	-	2.8	-	-	-	-	-	-	-	-
Anus	-	-	-	-	X	-	10	5.8	O	-	6.3	-	-	-	-	-
Non-infection-related																
Kidney	7	4.6/19	8.0	5.2	-	7.3	7.9	4.7	44	13	6.2	6.5	6.9	16	21	11/12
Thyroid	11	16/5.1	8.1	-	X	5.0	7.0	3.0	2.4	4.4	4.1	5.6	4.7	4.6	3.6	3.1/2.6
Melanoma of skin	-	O	O	-	X	1.9	2.6	2.4	O	9.1	2.3	-	-	-	O	-
Lung	-	1.8/4.9	O	-	X	2.1	1.4	2.0	4.8	1.7	1.7	-	-	O	2.7	O
Unknown	-	O	-	-	X	-	-	14	O	-	-	-	-	-	-	-
Gallbladder	-	O	O	-	X	4.1	-	2.0	O	-	-	-	-	-	O	O
Multiple myeloma	-	O	O	-	-	3.9	3.3	-	-	-	O	-	-	24	-	-
Pleura	-	-	8.4	-	-	-	-	-	-	-	-	-	-	-	-	-
Colon	5	3.2/3.9	3.9	2.4	X	1.4[6]	1.8[6]	1.2[6]	2.0	1.8[6]	2.3	-	-	O	3.6[6]	1.8/3.6
Small intestine		-	12	-	O	-	-	2.4	-	-	-	-	-	-	-	-
Bladder, urinary tract	4	3.1/17	3.2	-	-	2.0	2.4	1.5	43	8.2	2.0	-	-	O	7.6	3.7/20
Connective/soft tissues[7]	-	O	-	-	X	4.8	-	X	-	-	O	-	-	-	-	-
Pancreas	-	O	O	-	O	O	O	1.5	O	O	2.2	-	-	O	3.1	3.6/4.4
Uterus	-	O	O	-	O	O	O	O	O	O	O	-	-	O	5.7	-
Testis	-	3.9	O	-	O	-	-	2.0	-	-	O	-	-	-	-	-
Leukemia	-	O	-	-	X	2.3	O	X	O	O	O	-	-	27	4.3	O
Rectum	-	4.5/O	-	O	O	1.4[6]	1.8[6]	1.2[6]	O	1.8[6]	O	-	-	O	3.6[6]	O/3.0
Brain	-	3.0/O	O	-	O	O	-	O	-	-	O	-	-	13	O	-
Prostate	-	2.1	O	-	O	O	O	0.9	O	O	O	-	-	O	6.9	5.2
Breast (female)	-	O	O	-	O	1.3	O	0.9	O	1.7	O	-	-	3.9	3.6	1.3
Ovary	-	O	O	-	O	O	O	O	O	3.3	1.9	-	-	O	5.9	5.1
All sites	2.7	4.5	3.3	3.9	-	-	-	-	3.8	2.9	6.5	3.6	3.2	3.5	3.9	2.5
All sites except NMSC	-	3.1	-	-	X	2.5	2.4	2.1	-	2.8	2.3	2.2	2.3	-	-	-

Note: Some cancer classifications have been altered for comparability. #/# denotes male/female. - denotes no estimate. [1] Estimates for OTRs, not only KTRs. [2] Swedish patients. [3] Danish patients. [4] Nonepithelial only. [5] Head/neck cancer. [6] Colorectal cancer. [7] Including bone. NMSC, non-melanoma skin cancer. (N)HL, (Non-)Hodgkin lymphoma. O, no significant difference. X, significantly increased.

2.2 CANCER-SPECIFIC SURVIVAL AMONG SOLID ORGAN TRANSPLANT RECIPIENTS

While increased post-transplant cancer incidence became apparent early in the history of successful organ transplantation, cancer-specific survival (see *4.3.3.2 Statistical analyses* and *6.2.2 Study II*) among OTRs had not been as well-studied, until several population-based research reports surfaced in the beginning of the 21st century.

2.2.1 Cancer survival studies

Studies of cancer survival after previous exposure to transplantation have been comparatively few. In 2005, Pond et al reported a five-year Kaplan-Meier estimate of 89% for cancer-specific survival among 23 thyroid cancer patients out of 10,689 KTRs in Australia and New Zealand, albeit with only two cancer-related deaths.[60]

In a study from 2009 by Miao et al, outcomes among 635 post-transplant cancer patients in the US reported to the Israel Penn International Transplant Tumor Registry (IPITTR), with malignant melanoma or non-small cell lung, colon, breast, prostate, bladder, or renal cell cancer, were compared to those of the general population.[61] For all cancer types, transplantation was associated with an increased rate of cancer-specific death, ranging from approximately 1.5 times for lung cancer; 2 times for melanoma, renal cell cancer, and breast cancer; 2.5-3 times for colon and bladder cancer; and 5 times for prostate cancer. While this study was one of the earlier ones investigating post-transplant cancer mortality, it was not population-based (as reporting to the register was voluntary, implying some selection of OTRs being reported to the IPITTR).

In 2015, Sigel et al found similar lung cancer-specific survival among 597 OTRs aged 65 years or more compared to non-OTRs in the US, adjusting for the competing event of death due to other causes.[62] However, their research question was different, as this study measured the actual outcomes of cancer- and non-cancer-specific deaths, while most other studies presented here have tried to measure the impact of transplantation on cancer-specific survival (see *4.3.1 Statistical concepts common to all three studies*). Nevertheless, the results imply that net cancer-specific survival was indeed worse among OTRs, as the rates of cancer-specific death were similar among OTRs and non-OTRs, given that OTRs have considerably higher rates of non-cancer death.

Two more recent US studies published in 2019 used the same data source as Engels et al and Hall et al (see *2.1.2 Oceanian, North American, and British studies*). First, D'Arcy et al noted increased cancer-specific death rates among 11,416 OTRs for diffuse large B-cell lymphoma (Hazard Ratio [HR] 1.3) and melanoma (2.6), and for bladder (1.9), breast (1.9), oral cavity (1.2), colorectal (1.8), stomach (1.5), pancreatic (1.5), lung (1.4), and kidney (1.2) cancer.[63] Second, Noone et al found a cancer-attributable mortality rate of 516/100,000 person years among OTRs.[64]

In a Scottish KTR cohort from 2020, Murray et al found, while accounting for the competing risk of death from other causes, both a 3.9 times increased sub-distribution hazard rate of cancer-specific death for NMSC (but not for colorectal, lung, breast, prostate, or renal cancer, or NHL), and increased mortality rates for cancer-specific death overall (SMR [standardized mortality ratio] 1.4, excluding NMSC) and due to NHL (1.8) and NMSC (3.7).[65] Like in the aforementioned study by Sigel et al, this approach using competing risks analysis provides a real-world estimate of the risk of dying from a specific cancer, and answers the question of whether a cancer patient is likely to die from cancer or from something else. However, for

investigating whether cancers arising among OTRs are different from those in the general population, i.e. if they are associated with properties or circumstances making them more (or less) dangerous, the net (or marginal) survival is a more appropriate measure.[66] Even if the cancer in question is associated with a higher rate of cancer-specific death among OTRs, making it more dangerous than to non-OTRs, this association is likely to be underestimated in a competing risks analysis, as OTRs are at comparably higher risk of dying from something else than cancer (in large part due to their often substantial comorbidity).

Finally, two other recent studies investigated prostate cancer outcomes among KTRs. In 2020, Bratt et al found no increased rate of prostate cancer-specific death among Swedish KTRs, and later the same year, Liauw et al presented similar results using data from the US, albeit with adjustment for competing risks.[67,68] The studies concluded that patients on active surveillance for low-grade prostate cancer can be accepted for transplantation without previous radical treatment, and that active surveillance is a viable management option for low-grade prostate cancers after transplantation.

2.2.2 Cancer SMR studies

The SMR, or standardized mortality ratio, is a measure of the number of deaths in a population compared to the number that would be expected if the death rate was the same as in a reference population, adjusted for confounding factors such as age and sex. However, if the incidence rates of cancer differ between the groups, the death rates of cancer will naturally differ as well. Therefore, successful interpretation of SMRs demand that incidence rate differences are clear. Optimally, a study reporting SMRs would also report SIRs, to offer a sense of how much of an impact the incidence ratio has on the mortality ratio.

Kiberd et al published a study in 2009, investigating differences in cancer-specific deaths (expressed as SMRs) among 164,078 US KTRs compared to the general population, finding no increase in cancer-specific death among KTRs.[69] However, out of all classified non-cancer deaths, 44% were deaths with unknown cause and thus assumed not to be cancer-related, which is obviously a strong assumption and arguably a critical weakness of the study.

In their 2012 study on KTR cancer risk and mortality in Hong Kong, Cheung et al found significantly increased mortality rates for any cancer (SMR 2.3) as well as colorectal (2.2), lung (1.5), breast (1.9), cervical (2.8), ovarian (7.3), uterine (5.5), kidney (4.4), bladder (4.7), and stomach (3.5) cancer, and for melanoma (6.3), leukemia (2.8), and NHL (18).[56] However, as SIRs were similarly increased for almost all of the same cancer forms, whether SMRs > 1 really do reflect worse cancer survival for these cancers is not clear.

Also reporting SMRs, Na et al (2013) found increased cancer-specific mortality among 4,644 Australian liver, heart and lung transplant recipients with any cancer (SMR 2.8), as well as for non-melanoma skin (50), connective and soft tissue (5.6), liver (3.2), lung (1.7), and unknown (6.1) cancer, as well as NHL (17) and melanoma (6.9).[70]

Acuna et al published a study in 2016 in which they found an SMR (for death due to any cancer type) of 1.9 among 11,061 Canadian OTRs compared with the general population, and SMRs > 1 for non-melanoma skin (SMR 30), bone/soft tissue (3.1), stomach (2.3), oral cavity (2.1), colorectal (1.8), lung (1.6), and unknown (3.6) cancer, as well as for NHL (8.1), melanoma (3.4), and leukemia (2.5).[71]

In 2018, Jackson-Spence et al instead found significantly decreased SMRs among English KTRs for a wide range of cancers including overall (SMR 0.75), and increased mortality rates only for laryngeal (SMR 1.9) and ovarian (1.5) cancer, and melanoma (2.3).[72] However, the mortality analyses were confined to KTRs with cancer compared with individuals in the general population diagnosed with cancer, in order to account for the incidence differences among the groups. Even though the methods are thus different to those of other post-transplant cancer mortality studies, the results contradict several published reports, which the authors themselves note; also, the results would expectedly be similar to those found in post-transplant cancer survival studies, which they are not. Some explanations, such as increased cancer vigilance among KTRs, are listed as possible causes. Death due to competing events, another possible explanation, was actually lower among KTRs than the general population comparators and is thus another counterintuitive finding.

Those results were, however, contrasted by those of three studies published in 2019. First, a study by Au et al found SMRs > 1 for de novo (i.e. the first occurrence of) cancer of the majority of types presented (except for testicular, bone, brain, thyroid, breast and prostate cancer, as well as multiple myeloma) among Australian KTRs.[73] The SMR for any de novo cancer was 2.6.

Second, Jäämaa-Holmberg et al found an SMR of 3.1 for any cancer among Finnish heart transplant recipients compared to the general population.[74]

Third, Rosales et al reported elevated SMRs for any cancer (SMR 2.3), and for non-melanoma skin (51), oral cavity (17), unspecified (14), kidney (11), soft tissue (6.5), colorectal (3.8), CNS/eye (3.5), lung (2.7), cervical (2.6), anal (2.5) and liver (2.3) cancer, and lymphoma (31), leukemia (8.4), and melanoma (5.2).[75]

Furthermore, in their 2020 report on Korean cancer incidence and outcomes among KTRs, Jeong et al found an overall SMR of 1.4 for cancer-specific death, with SMRs > 1 also for NHL (SMR 5.5), Kaposi sarcoma (5.6), and colorectal (2.7), kidney (5.8), nasopharyngeal (3.7), ovarian (4.0), cervical (2.3), breast (1.8), and non-melanoma skin (7.0) cancer.[58]

In 2022, Friman et al found an overall SMR of 2.5 for cancer-specific death due to any cancer in a Finnish OTR cohort, with transplantation surgery performed from 1987 through 2016, compared with the general population.[76] For specific cancers, increased mortality rates were found for mouth/pharyngeal (SMR 2.5), liver (6.1), pancreatic (2.2), colorectal (1.6), lung (1.9), kidney (4.8), bladder and urinary tract (2.3), ill-defined and unknown (2.0), and non-melanoma skin (35 for SCC, 66 for Merkel cell carcinoma, and 43 for other types) cancer.

NHL (SMR 14), malignant melanoma (2.6) and unspecified hematological disease (6.3) were also associated with SMRs>1 of cancer-specific death.

2.2.3 Summary

In conclusion, several studies present SMRs > 1 for cancers with increased incidence rates, e.g. lymphoma, and skin, colorectal and lung cancer (often with striking similarities in the magnitudes of the SIRs and SMRs of respective cancer) (Table 2). However, incidence rates of prostate and breast cancer, the most common cancers in the general population, have mostly not been increased among OTRs, and standardized mortality rates are similarly not increased for OTR prostate cancer patients, while there is conflicting evidence of worse breast cancer-specific outcomes among OTRs. Colon cancer (sometimes represented together with rectal cancer as CRC), also among the most commonly occurring cancers in the general population, has been associated with increased standardized rates of both incidence and mortality among OTRs (Tables 1 and 2). Furthermore, although these studies indicate an increased mortality rate from post-transplant cancer, overall and for specific types, compared with that in the general population, increased incidence rates partly explain these differences.

Studies using cancer-specific death as a measure of the impact of transplantation on cancer prognosis, such as the one by D'Arcy et al (i.e. net survival), have found increased rates of cancer-specific death for e.g. lymphoma, melanoma, and urothelial, breast and colorectal cancer in OTRs, as compared to patients without a history of organ transplantation. Some studies have adjusted for stage at diagnosis (which would possibly be more advanced due to e.g. immunosuppression, or less advanced due to increased vigilance among OTRs), finding no impact on the results; however, stage is unlikely to be a confounder in the relationship between transplantation and death due to post-transplant cancer (since stage is classified at diagnosis of post-transplant cancer, which accordingly happens after the transplantation), but could instead be viewed as a mediator (i.e. an event that occurs in the causal pathway and thus could in part explain differences in survival). As this research subject has not been thoroughly investigated, it was therefore reasonable to look further into if, and why, some cancers are associated with worse cancer-specific survival among Swedish OTRs.

Table 2. Standardized mortality ratios and hazard ratios for cancer-specific mortality among solid organ transplant recipients compared to the general population, overall and by cancer type, according to selected previous research reports.

Measure	Standardized mortality ratio										Hazard ratio	
Report	Cheung 2012	Na 2013	Acuna 2016	Jackson-Spence 2018	Au 2019	Jäämaa-Holmberg 2019	Rosales 2019	Jeong 2020	Murray 2020	Friman 2022	Miao 2009	D'Arcy 2019
Cancer type												
Infection-related												
NMSC	-	50	30	-	-	-	51	7.0	3.7	35[1]	-	-
NHL	18	17	8.1	O	10	-	31[2]	5.5	1.8	14	-	1.3[3]
Nose, nasopharynx	O	-	-	-	3.1[4]	-	-	3.7	-	-	-	-
HL	-	-	-	-	5.1	-	-	O	-	O	-	-
Mouth, oropharynx	O	O	2.1	O	3.1[4]	-	17	-	-	2.5	-	1.2
Liver	O	3.2	O	O	-	-	2.3	O	-	6.1	-	0.8
Cervix	2.8	-	-	0.4	-	-	2.6	2.3	-	-	-	-
Stomach	3.5	-	2.3	0.8	-	-	-	O	-	O	-	1.5
Larynx	-	-	-	1.9	-	-	-	-	-	-	-	O
Esophagus	O	O	O	0.9	-	-	-	O	-	-	-	-
Anal	-	-	-	-	-	-	2.5	-	-	-	-	-
Non-infection-related												
Kidney	4.4	-	O	0.4	6.1	-	11	5.8	O	4.8	2	1.2
Thyroid	-	-	-	-	O	-	-	O	-	-	-	-
Melanoma of skin	6.3	6.9	3.4	2.3	5.1	-	5.2	-	-	2.6	2	2.6
Lung	1.5	1.7	1.6	0.9	1.5	-	2.7	O	O	1.9	1.5	1.4
Unknown	-	6.1	3.6	-	2.2	-	-	-	-	2.0	-	-
Multiple myeloma	-	-	-	0.8	O	-	O	-	-	O	-	O
Colorectal	2.2	O[5]	1.8	0.6	2.3	-	3.8	2.7	O	1.6	2.5[5]	1.8
Bladder, urinary tract	4.7	-	O	0.8	3.4	-	-	O	-	2.3	3	1.9
Connective/soft tissues[6]	-	5.6	3.1	-	O	-	6.5	-	-	O	-	-
Pancreas	O	O	O	0.7	-	-	-	O	-	2.2	-	1.5
Uterus	5.5	-	-	-	-	-	-	-	-	-	-	-
Testis	-	-	-	-	O	-	-	-	-	-	-	-
Leukemia	2.8	-	2.5	0.9	1.9	-	8.4	O	-	O	-	-
Brain/CNS	-	O	-	0.6	O	-	3.5[7]	O	-	O	-	-
Prostate	O	O	O	0.6	0.6	-	O	O	O	O	5	O
Breast (female)	1.9	-	O	-	O	-	O	1.8	O	O	2	1.9
Ovary	7.3	-	-	1.5	-	-	-	4.0	-	-	-	-
All sites	2.3	2.8	1.9	-	-	3.1	-	1.4	-	2.5	-	-
All sites except NMSC	-	-	-	0.8	2.6	-	2.3	-	1.4	2.5	-	-

Note: Some cancer classifications have been altered for comparability. - denotes no estimate. [1] Squamous cell cancer only. [2] Including Hodgkin lymphoma. [3] Diffuse large B-cell lymphoma only. [4] Head/neck cancer. [5] Colon cancer only. [6] Including bone. [7] Including eye. NMSC, non-melanoma skin cancer. (N)HL, (Non-)Hodgkin lymphoma. O, no significant difference. CNS, central nervous system.

2.3 POST-TRANSPLANT COLORECTAL CANCER: RISK FACTORS, TREATMENT, AND OUTCOMES

Lymphoma and skin cancer are among the most commonly studied post-transplant malignancies, but for other specific cancer types, research (especially on specific risk factors and treatment) is scarce. CRC is the third most frequently diagnosed cancer (after breast and lung cancer) worldwide, and the second most common cause of cancer-specific death (after lung cancer).[77] As shown in the previous sections on cancer risk and survival among kidney and other OTRs, CRC incidence is estimated to be 1.2- to 3.6-fold increased among KTRs, with SMRs of similar magnitude, ranging from 1.6 to 3.8 (Table 1, Table 2), compared with the general population. However, the few existing studies estimating CRC-specific survival among OTRs have indicated an approximately 2-fold increased rate of cancer-specific death (Table 2). The relatively large incidence of post-transplant CRC thus indicates not only a need, but also feasibility, for performing research on cancer characteristics and treatment factors, and their association with prognosis, among CRC patients with a previous solid organ transplantation, compared with CRC patients without such history. However, early reports on post-transplant CRC among predominantly kidney and liver transplant recipients were either case reports, case series, or single institution reports, encompassing only few CRC cases among OTRs and are therefore not included in the following short review.

Papaconstantinou et al were among the first to present any larger epidemiological study on post-transplant cancer outcomes in 2004.[78] Among 150 OTRs with CRC in the IPITTR, the authors demonstrated lower five-year overall survival among post-transplant CRC patients (44%), compared to CRC patients in the general population (62%). Significant differences in survival were found among patients with local and regionally metastasized disease, but not among patients with distant metastases. No measure of cancer-specific survival was presented. This report was not population-based (as reporting to the IPITTR was voluntary), indicating that CRC incidence was underestimated. Furthermore, as the control population was identified from the Surveillance Epidemiology and End Results database, covering only 14% (but shown to be representative) of the US population, regional differences could have influenced the results.

Kim et al in 2011 published a Korean study encompassing 17 KTRs and 170 matched (on closest date of surgery) non-KTR comparators with CRC, finding similar stage at diagnosis, histologic type, and number of dissected lymph nodes (arguably a measure of the extent of surgery performed).[79] KTRs were more likely to be diagnosed with right-sided colon cancer. Adjuvant treatment was less frequently administered to KTRs than non-KTRs, and chemotherapy was preferentially given orally to the former group, as opposed to intravenously to the latter. Overall five-year survival was 40% for KTRs, and 68% for the comparators. Cancer-specific survival was not presented.

A descriptive study (with no control group) on post-transplant CRC from 2014 by Merchea et al identified 20 CRC patients out of 3,946 OTRs, of whom 18 were surgically treated, and of those, 5 out of 7 with positive lymph node metastases were selected for adjuvant

chemotherapy.[80] 70% of tumors were right-sided. Five-year overall survival was 69%. The same author in 2019 identified 63 OTRs diagnosed with de novo post-transplant CRC during 1987 through 2016.[81] Excluding cancers in the transverse colon and rectosigmoid, 61% of remaining cancers were right-sided colon cancers, 24% left-sided, and 15% rectal cancers. The five-year overall survival was 43%, but cancer-specific survival was not reported, nor was administration of adjuvant therapy. Again, no control group was presented for comparison.

CRC occurring among liver transplant recipients deserves extra consideration, as liver transplantation is sometimes performed as a treatment for PSC, a disease associated with ulcerative colitis (UC), which in turn is strongly associated with colon cancer.[18,82] Also, CRC metastases can be an indication for liver resection or hepatectomy, with subsequent liver transplantation.[83] Therefore, increased incidence of CRC among liver transplant recipients is associated with underlying disease. Also, immunosuppression plausibly predisposes for both post-transplant liver cancer (as seen in post-transplant cancer incidence studies), and liver metastases from CRC and other cancers (as indicated by post-transplant cancer mortality studies).

One multicenter study by Rompianesi et al published in 2019, encompassing 8,115 liver transplant recipients with surgery performed during 1990 through 2010, in 6 out of 7 liver transplantation-performing hospitals in the UK, found a five-year overall survival of 48% among the 52 CRC patients found, and a cancer-specific cumulative incidence of death of 17%, accounting for the competing risk of non-cancer death.[84] Interestingly, the sub-cohort of 25 patients without prior diagnosis of UC or PSC had comparatively lower five-year overall survival of 37%, and a five-year cumulative incidence of 32% for cancer-specific death (in the presence of competing events), almost twice that reported in the overall cohort (17%). This could reflect a possibly more aggressive screening for CRC among the UC/PSC patients due to the well-known increased risk, finding cancers at an earlier stage; or it could be due to non-UC/PSC patients developing more dangerous cancers or receiving suboptimal cancer treatment; or it could perhaps be explained by different distributions of confounders, such as non-UC patients possibly being older than UC patients at CRC diagnosis.

In 2021, a Korean study by Kim et al included 33 post-transplant CRC patients, propensity-score matched (accounting for sex, age, tumor location, T and N stage, and differentiation) to 132 non-transplanted comparators with CRC, who had undergone cancer surgery.[85] The authors found no differences in the five-year overall survival between the groups, and no differences in adjuvant treatment administered were found, which might explain the similarity in survival to some extent. On the other hand, as differences in biological properties of the cancer (such as tumor location, stage and grade) as well as different cancer treatment plausibly influence cancer survival, including such variables in the matching algorithm could eliminate pertinent associations in the causal pathway between exposure (organ transplantation) and the outcome (death).

2.3.1 Summary

In summary, there is a paucity of research on CRC outcomes among OTRs compared with non-OTR CRC patients. Most studies are either small, case-reports/-series, or do not include a control group. Furthermore, overall (but not cancer-specific) survival is usually reported, which is already expected to be lower among OTRs due to their more extensive comorbidity and in which cancer outcomes are masked in the long list of potential non-cancer outcomes. As OTRs are at risk of receiving suboptimal cancer treatment, research investigating transplantation-associated differences in cancer prognosis, characteristics, and treatment is therefore much needed, as such knowledge would be vital to improving post-transplant cancer prognosis.

3 RESEARCH AIMS

Study I

To provide estimates of

- the relative and absolute excess risks of post-transplant cancer,
- the cumulative incidence in the presence of competing events,
- and risk factors for cancer,

in a Nordic kidney transplant cohort from the modern (1995-2014) treatment era. The results will be presented overall and for specific cancer types.

Study II

To estimate cancer-specific and overall survival for Swedish OTRs with cancer compared with non-transplanted cancer patients, overall and for a wide range of cancers.

Study III

To investigate differences in cancer characteristics and treatment among Swedish CRC patients, as well as survival, comparing cancer patients with a previous solid organ transplantation to those without such medical history.

4 MATERIALS AND METHODS

4.1 MAIN DATA SOURCES

4.1.1 The Swedish Patient Register (SPR)

The SPR was initiated by the Swedish National Board of Health and Welfare in 1964, and while initially only covering 16% of patients in somatic care, the subsequent initiation of mandatory reporting has resulted in complete inpatient care coverage since 1987.[86] All transplantation-performing Swedish hospitals are covered by the register since 1972. From 2001 and onwards, outpatient specialized care clinic visits are included. The register contains information on personal data (e.g. personal identity number [PIN], sex, and age), geographical data (e.g. county council and relevant hospital), administrative data (e.g. dates of admission and discharge) and medical data (e.g. main and secondary diagnoses by International Classification of Diseases, Injuries, and Death Causes version 7 to 10 [ICD-7 to ICD-10] codes, and procedure codes [for identifying surgical and other procedures]). This enables selecting and matching patients on e.g. a surgical procedure performed, such as an organ transplantation, and several associated variables (date, performing hospital, etc.).

4.1.2 The Swedish National Cancer Register (NCR)

The NCR is the most recently (1958) established Nordic cancer register. Reporting is mandatory by law, resulting in an estimated 96% coverage. The underreporting is attributed to the fact that cancers from cause of death certificate notifications are not included (in contrast to the other Nordic cancer registers).[49] In 2009, Barlow et al selected patients with a hospital discharge code for cancer, but with no corresponding cancer diagnosis in the NCR, and reviewed a sample of medical records, finding that an additional 3.7% of incident cancers should have been reported to NCR in addition to all cancers recorded in 1998.[87] Cancers without histological diagnosis, and with comparatively high probability of distant metastases (i.e. palliative stage) at diagnosis, like pancreatic, lung, and esophageal cancers, are more likely of underreporting, especially when occurring in older patients. Despite this, the coverage is excellent for most cancer types. Only de novo cancers are registered. All registered cancers are classified according to ICD-7, as well as the ICD version (ICD-9 from 1987, and ICD-10 from 1993) that was used during the time of diagnosis; also, oncology codes (ICD-O/2 and 3) are available from their respective years of introduction, as are other cancer classification codes.

The NCR contains similar personal data as the SPR, as well as cancer data (date and basis of diagnosis, site, histological type, stage [since 2004], reporting hospital and pathology department, and tissue identification number), and follow-up data (death date and cause, and dates of migration).[88]

4.1.3 The Swedish Cause of Death Register (SCDR)

Although existing in previous versions since as early as 1749, the modern SCDR was established in 1961 and covers all deaths that occur in Sweden.[89] The register uses the ICD classification since 1951, in order to enable international comparisons of cause of death statistics. Upon completing a mandatory cause of death certificate (including the main and contributing causes of death, as well as any other pertinent diseases), the responsible physician is required to submit the certificate within three weeks to the SCDR, where one death cause is selected, according to an algorithm, as the principal underlying cause of death (which might thus differ from the one selected by the reporting physician). The coverage used to be virtually complete, but has declined since the latter half of the 20th century; in 2017, approximately 0,9% of cause of death certificates had not been submitted for the year 2015.[89]

With each subsequent update, the ICD has contained increasingly detailed instructions on how to classify certain death causes. Taking cancer as an example, there is an obvious ambiguity in whether to classify some deaths as due to cancer or to some other underlying condition, but the current practice at least minimizes the risk of different classification in different countries. Another way to put it is that the validity of the method can in some cases be questioned, but the reliability should hopefully be satisfactory. At least two studies have shown that malignancy was correctly coded as the cause of death in SCDR for approximately 90% of cancer deaths, compared with medical records or case summaries.[90,91]

PIN, sex, attained age, place/region and date of death, grounds for death cause classification (autopsy or clinical examination), death cause ICD codes, and association to any surgical procedure, are examples of variables in the SCDR.

4.2 ADDITIONAL DATA SOURCES

4.2.1 NORDCAN

NORDCAN, a free-to use database maintained by the Association of Nordic Cancer Registries, contains incidence and prevalence data on over 50 cancer types, covering all of the Nordic countries from 1960 and onwards.[92] Incidence rates are limited to the first cancer occurrence of each type, and are available overall as well as stratified by country, sex, age in five-year intervals, and year of cancer diagnosis.

4.2.2 ScandiaTransplant

ScandiaTransplant is the official organ exchange organization of the Nordic countries and Estonia, founded in 1969 and jointly owned by the participating transplantation-performing hospitals, in order to facilitate organ allocation and exchange.[93] Solid organ (i.e. including kidney, liver, heart, lung, pancreas, pancreatic islet cells, and bowel) transplantation procedures and associated organ, recipient, and donor characteristics are registered, as are all patients on the waiting lists for transplantation. The ScandiaTransplant register thus contains data on e.g. donor and recipient detailed tissue type, recipient immunization to human tissues, donor vital status (living/dead) at transplantation, donor and recipient viral infections (such as

cytomegalovirus and Epstein-Barr virus), blood group (AB0 and Rhesus), and several other characteristics.

4.2.3 The Danish, Finnish, and Norwegian Cancer and Cause of Death Registers

Established in 1942, the Danish Cancer Register is the oldest of the Nordic national cancer registers, followed by the Finnish and Norwegian cancer registers, founded in 1952. Overall, the other Nordic cancer registers are similar and comparable to the NCR.[49] Also, like the SCDR, the other Nordic national cause of death registers similarly use the ICD coding classification for death causes, and the variables registered overlap to a large extent.[94-96]

4.2.4 The Swedish Renal Registry

The Swedish Renal Registry is a national quality register for renal replacement therapy (e.g. dialysis and kidney transplantation) maintained by the Swedish Society of Nephrology and the Swedish Transplantation Society, and contains data on dialysis, kidney transplantation, and rejections as well as other adverse events among Swedish KTRs.[97]

4.2.5 The Danish National Patient Registry

The Danish National Patient Registry was established in 1977 and has complete nationwide coverage since 1978.[98] The register contains data on in- and outpatient clinic visits and is for practical purposes similar to the SPR.

4.2.6 Norwegian and Finnish transplantation and kidney disease quality registers

Register linkage data from the Norwegian End-Stage Renal Disease and Transplant Registry, and transplantation clinic quality registers in Oslo and Helsinki, were used to determine patient and transplant characteristics, as well as death dates and causes of death, among Norwegian and Finnish KTRs.[99]

4.2.7 CRCBaSe

CRCBaSe is a recently established Swedish CRC register linkage research database, including data from the Swedish colon and rectal cancer registers, SPR, SCR, and SCDR, as well as several other nationwide registers.[100] It contains data on almost 80,000 colorectal cancer patients, and the purpose of the register is to facilitate epidemiological research on CRC. Colon and rectal cancer data include date of and age at diagnosis, cancer stage (I-IV), TNM (tumor-node-metastasis) stage, whether a surgical procedure was performed and, if so, what type (endoscopic polypectomy, abdominal surgery, or palliative stenting or stoma), pathological characteristics (tumor grade, frequency of dissected lymph nodes and of metastases therein), planned adjuvant treatment and which types, and relapses.

4.3 STUDY DESIGN AND STATISTICAL METHODS

All three studies are variants of register-based, retrospective cohort studies, comparing an exposed population to an unexposed, for different outcomes. All confidence intervals were estimated at the 95% confidence level, and all presented p-values for hypothesis tests were two-sided and considered significant if less than 5%.

4.3.1 Statistical concepts common to all three studies

4.3.1.1 Survival analysis

In research, a common approach is to compare two (or more) groups and compare the frequencies with which some event, or outcome, occurs. In some situations, the time at risk for the outcome varies between individuals. For example, individuals may be included at different points in time, and events may occur (e.g. death) that end their follow-up in the study. In this setting it is therefore important to consider both if the event of interest occurred and the time until the event occurred, thus giving survival analysis outcomes two dimensions. Survival analysis is thus comparing event rates, or hazard rates (the number of events per time unit). The study groups are typically compared in relative terms, i.e. using hazard ratios (HR), which provide a measure of whether members of one group tend to experience the event at higher/lower intensity than members of the other group(s).

The hazard rate is the instantaneous speed at which an event happens, given that the subject has survived until that time, and is comparable to the derivative of a mathematical function, or "the slope of the curve". In the context of the survivor function, the rate can be obtained by taking minus the derivative of the logarithm of the Kaplan-Meier function.

4.3.1.2 Cox regression

Cox regression was introduced by Sir David Cox in 1972, and can be used to estimate the impact of several variables on the HR, given that proportional hazards apply.[101] The condition of proportional hazards means that the ratio of one hazard (e.g. among the exposed) to another (e.g. among the unexposed) is a constant factor over time on the hazard scale (or a difference on the log hazard scale). That is, a certain set of variables exert a constant effect on the hazard rates over the whole time period of interest.

The hazard function, representing the hazard rate over time, can then be expressed as a baseline hazard function $h_0(t)$, multiplied by the exponentiated sum of various independent variables ($\mathbf{X}$, or X_1 to X_n), each multiplied by some variable-specific parameter (β_1 to β_n):[102]

$$h(t|\boldsymbol{X}) = h_0(t) * e^{(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n)}$$

If we take X_1 to be the exposure (true or false, i.e. 1 or 0), and X_2 to X_n to be other explanatory variables (e.g. confounding factors) that we want to adjust for, we can thus write the HR as:

$$HR = \frac{h_0(t) * e^{(\beta_1 * 1 + \beta_2 X_2 + \cdots + \beta_n X_n)}}{h_0(t) * e^{(\beta_1 * 0 + \beta_2 X_2 + \cdots + \beta_n X_n)}} = \frac{h_0(t) * e^{\beta_1 * 1} * e^{\beta_2 X_2} * \ldots * e^{\beta_n X_n}}{h_0(t) * e^{\beta_1 * 0} * e^{\beta_2 X_2} * \ldots * e^{\beta_n X_n}} = \frac{e^{\beta_1 * 1}}{e^{\beta_1 * 0}} = e^{\beta_1}$$

So, given that all other explanatory variables are kept constant, the HR (comparing exposed to unexposed) is e^{β_1}. Equivalently, persons that are exposed will, on average, experience an event at a similar rate (HR = 1), higher rate (HR > 1), or lower rate (HR < 1), than unexposed persons. It follows that the baseline hazard function $h_0(t)$ represents the hazard rate when all explanatory variables are 0 (at their reference level), as $e^0 = 1$.

Like other regression methods, Cox regression optimizes a likelihood function to produce a model, that includes the specified covariates, that fits as closely as possible with the data observed. However, while Cox regression makes no assumptions for the distribution of survival times (such as normality), the proportional hazards assumption has to be satisfied. There are several ways to assess this, e.g.:[103]

1) Plotting the cumulative survivor functions S(t) for each exposure level (e.g. Kaplan-Meier curves), and the corresponding hazard functions, checking visually that the hazards seem to be proportional over time.
2) Plotting the log cumulative hazard functions ("log-log plot"), which is equivalent with plotting ln(-ln[S(t)]) versus time. If proportional hazards apply, the resulting curves will be roughly parallell.
3) Testing whether the Shoenfeld residuals are independent of time, e.g. using the Grambsch-Therneau test.[104]
4) Fitting interaction terms between covariates and time bands that represent follow-up, and formally testing if the covariate effect is modified by time.

Non-proportional hazards can, however, be handled by further developing the model, for example, by:

1) Stratifiying the analysis on the variable causing non-proportional hazards.[105] This allows for separate baseline functions ($h_0[t]$) for each stratum.
2) Restricting the time of interest.
3) Introducing interaction terms between covariates and covariates representing time (see point 4 just above).

4.3.1.3 Net (marginal) survival

Overall (sometimes referred to as all-cause) survival is commonly estimated in clinical studies, and is a measure of the rate of occurrence of death due to any cause. However, sometimes you might want to estimate the *net* or *marginal* survival, i.e. the effect of an exposure on the survival probability associated with a specific disease, in a hypothetical world where that disease is the only thing that can kill you.[66] Accordingly, net survival is used to study the biological processes and mechanisms, or etiology, associated with a certain outcome. In such analyses, competing events disrupt our experiment, and net survival is thus a construct to eliminate those interfering events. However, this approach has no "real"

interpretation for the actual prognosis of a certain patient group, for which instead survival models incorporating competing events are appropriate (see *4.3.3.2 Statistical analysis*). For example, survival analysis in the presence of competing events can be useful to decide whether it is reasonable to screen for some disease, e.g. cancer; if the patients usually die from other causes before being diagnosed with (or dying from) a particular form of cancer, it might not be cost-effective to screen for that cancer type.

4.3.1.4 The 30-day criterion

The common exposure in all three studies is organ transplantation (i.e. kidney transplantation in study I, and kidney, liver, pancreas, heart, heart-lung, lung, and/or bowel transplantation in studies II and III). The primary outcomes are cancer incidence (study I), cancer-specific and all-cause death (studies II and III), and cancer characteristics and treatment factors associated with transplantation (study III). Accordingly, post-transplantation cancer is the common ground.

It cannot be excluded that a cancer diagnosis very early after transplantation *could* represent an unusual case of de novo cancer developing extremely quickly as a result of the transplantation and associated procedures. However, given that cancer development often takes several months or years, such early cancer diagnoses are more likely representative of established, pre-transplant cancers, that are either unveiled in the early post-operative course, or the indication for transplantation (e.g. liver transplantation). In the latter case, pathological examination of the removed organ might serve as the definitive base of a registered cancer diagnosis (and associated date). It is also conceivable, but uncommon, that a donor-derived cancer (i.e. an occult, undiagnosed donor cancer, accompanying the transplanted organ into the recipient) would be diagnosed and registered within 30 days post-transplant. Furthermore, previous studies on the association between immunosuppression and cancer risk have found that cancer incidence increases with time on immunosuppressive treatment, and 30 days represent a very short time in this context.[32-34]

Based on these arguments, several previous studies on post-transplant cancer incidence have excluded cancers diagnosed within 30 days of the transplantation date (while others have used 3 or 6 months post-transplant as cut-offs).[16,17,50,52] That line of thinking was also adopted for the three studies presented here, and cancers diagnosed before or within 30 days of transplantation were therefore not included in the analyses for that specific cancer type. However, in the case of occurrence of several cancers diagnosed pre- and post-transplant in the same patient, a pre-transplant cancer of type X excluded any such post-transplant cancer from analysis (Figure 2). While cancer Y diagnosed within 30 days of transplantation was thus also excluded, cancer Z diagnosed after transplantation was included on the condition that no such cancers were registered pre-transplant (Figure 2).

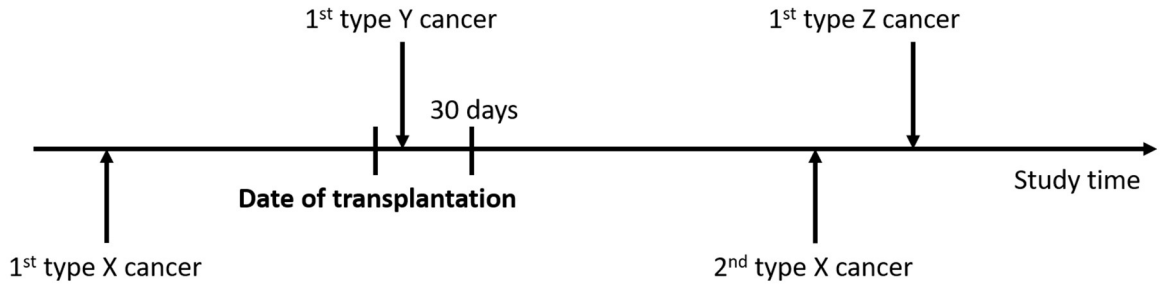

Figure 2. The 30-day criterion. The horizontal line represents time for a single patient in the study. The 2nd type X cancer is not included in the analysis, because such a cancer occurred pre-transplantation; neither is the type Y cancer, because it occurred within 30 days of transplantation. Consequently, only the type Z cancer is included for this patient.

4.3.2 Study I

4.3.2.1 Study population

All Swedish, Danish, Norwegian and Finnish KTRs, with a first kidney transplantation performed during 1995 through 2011, were selected using inpatient, kidney, or transplant surgery registers. National cancer and cause of death register data were linked to the dataset, and dates of graft loss and dialysis were added using renal disease and transplantation registers. Additional transplantation-related characteristics were added using ScandiaTransplant register data. The patients entered the study at the date of kidney transplantation, and were followed until the earliest of either 1) date of first cancer diagnosis of the specific type under study, 2) date of death, or 3) end of follow-up (Dec 31st, 2011 for Sweden and Denmark, 2013 for Finland, and 2014 for Norway).

4.3.2.2 Statistical analyses

Standardized incidence ratio

When comparing incidence rates among an exposed and unexposed population, different distributions of confounding factors can have substantial impact on the results. To make the exposed population more comparable to the unexposed, *standardization* can be used as a means of confounding control by stratifying the data according to a set of confounders. Here, in accordance with several previous studies, indirect standardization was used to produce standardized incidence ratios (SIR), interpreted in our study as relative risks.

$$SIR = \frac{Observed\ number\ of\ events}{Expected\ number\ of\ events}$$

Patient follow-up time was stratified by country, sex, calendar year, and age group in five-year intervals. For each such stratum, the sum of follow-up time (in the form of person-years) was multiplied with the cancer rates in the general population (retrieved from NORDCAN), producing estimates of the number of cancers that would be expected among the KTRs if they would have had the same cancer incidence rates as the unexposed background population. The SIRs were then produced by dividing the observed number of cancers by the

expected number of cancers. For the overall SIRs, the observed counts for the individual cancer types were summed up and divided by the sum of the expected counts.

Absolute excess risk

The AER is a measure of how many extra cancers are found in the exposed population, compared to the unexposed, if following both populations for some amount of time (often expressed as thousands of person-years). AERs per 100,000 person-years were calculated by dividing the difference of the observed number and the expected number of cancers by the number of person-years of follow-up, and multiplying the result by 100,000. Confidence intervals for the AERs were calculated by first using an exact method (assuming a Poisson distribution of observed cancer counts) for establishing upper and lower confidence limits for the numbers of observed cancers, and then using the AER formula, replacing the observed count with the upper and lower confidence limits, respectively.[106]

$$AER = \frac{Observed\ number\ of\ events - expected\ number\ of\ events}{Follow\text{-}up\ time}$$

Risk factors for cancer

A Cox regression model, including (and mutually adjusting for) sex, age at and calendar period of transplantation, donor vital status, ongoing dialysis (as a time-varying exposure) representing graft non-function, underlying kidney disease, and pre-transplant cancer diagnosis, was fitted. The model was stratified by country, to allow the baseline hazard to vary between countries. As age at transplantation was categorized into broad groups, we also performed a sensitivity analysis modelling age as a continuous variable using a restricted cubic spline with four degrees of freedom (with knots at the 20^{th}, 40^{th}, 60^{th}, and 80^{th} percentile of the age distribution).

Cumulative incidence, adjusting for competing events

Cumulative incidence is a measure of the cumulative probability of an event (such as cancer diagnosis) occurring over time, and is thus often presented as a reversed (upside down) survivor function. A competing event is an event that precludes the event of interest from happening (or, strictly, alters the probability of the occurrence of the event of interest) – for example, death is a competing event when investigating cumulative incidence of cancer, since if you die first, you can't be diagnosed with cancer later. Under the independence assumption, standard Kaplan-Meier analysis estimates net survival. This typically overestimates the probability of the event if there are competing events. Since KTRs have a comparatively high risk of death due to any cause, estimating the survivor function of cancer in the absence of competing events will inflate the cancer risk.

Cumulative incidence of cancer in the presence of the competing event of death was used as a measure of absolute risk of cancer in the present study. We decided against adjusting for other competing events, such as graft loss, re-transplantation, or diagnosis of a different

cancer type, which have been included in previous analyses.[17,54] These studies, however, do not clearly explain why the aforementioned events, other than death, would preclude (or alter the probability of) development of post-transplant cancer; however, a plausible reason could be that any one of them would probably modify the level of immunosuppressive treatment administered to the patient thereafter.

In the present study, cumulative incidence was estimated in two steps. First, by fitting a Cox regression, modeling the main event (cancer) and competing event (death) separately. Then, using predictions of survival and rates from the models, the cumulative incidence of cancer (i.e. the probabilities of cancer as a function of follow-up) was estimated along with confidence intervals produced using bootstrapping.[102] The unadjusted cumulative incidence of any cancer, as well as of infection- and non-infection-related cancer stratified by age and sex, and time trends of cumulative cancer incidence stratified by age and sex, were estimated. Like previous studies, we also presented age- and sex-stratified cumulative incidence for common cancers such as NHL, NMSC, and colorectal, lung, prostate, breast, and kidney cancer.[54]

4.3.3 Study II

4.3.3.1 Study population

All Swedish cancers diagnosed during 1992 through 2013 were identified using the NCR. The exposure, i.e. medical history of solid organ transplantation, was determined by linkage to the SPR, using surgical procedure codes. The first post-transplant cancer of every type was included for analysis; however, cancers diagnosed within 30 days of transplantation were considered non-transplant associated, and not included in the analyses (for that cancer type). Diagnoses of myeloproliferative diseases, as well as of other neoplasms of uncertain or unknown behavior of lymphoid, hematopoietic and related tissue (ICD-10 code D47) were excluded. Cancers were classified into 19 groups according to ICD-10 (if available) or ICD-7 code based on anatomical location. Hypothesizing that larger doses of immunosuppressive treatment would influence the cancer risk, exposure to transplantation was analyzed both overall (yes/no) as well as by type of transplanted organ (Figure 3).

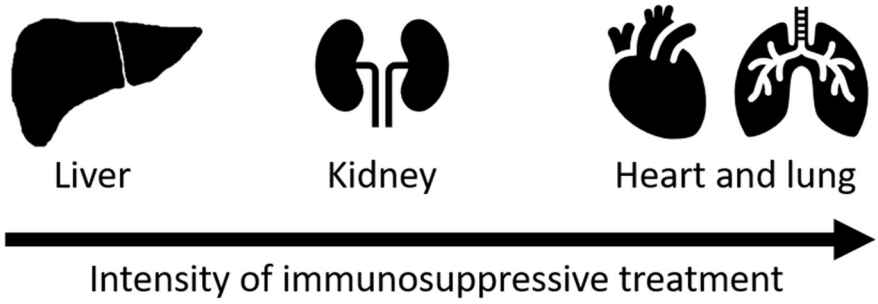

Figure 3. Presumed intensity of immunosuppressive treatment by type of organ transplant, with the lowest intensity administered to patients with liver transplants, and the highest to patients with heart and/or lung transplants (as well as pancreas transplants).

The death cause ICD-10 and ICD-7 codes were established by linking the dataset to the SCDR. However, as death causes were coded according to ICD-9 for part of the study period (1992 through 1996), ICD-9 codes for deaths occurring in that period were reclassified according to the corresponding ICD-7 codes. Cancer-specific death was established if the death cause ICD-code corresponded to the same cancer group as the cancer ICD-code. ICD-10 codes were used if they were available in both NCR and SCDR, which was the case for the majority of study persons; otherwise, ICD-7 codes were used. Furthermore, if a study person had been diagnosed with only one cancer before dying, and the cause of death ICD code corresponded to death from cancer of any type (including unspecified), then that death cause was classified as cancer-specific, and the discrepancy assumed to be due to misclassification or coding errors, in accordance with an algorithm proposed by Howlader et al.[107]

Cancer-specific and all-cause death were the primary and secondary outcomes, respectively. Follow-up started at date of cancer diagnosis, and ended at the earliest of date of death or December 31st, 2013.

4.3.3.2 Statistical analyses

Cox regression models, including the variables previous solid organ transplantation (yes/no), age at and calendar year of cancer diagnosis, and sex, were used to estimate HRs for cancer-specific and all-cause death, comparing OTRs to non-OTRs. The models were stratified by cancer subtype according to ICD-7, to allow separate baseline hazard functions for each subtype (e.g. esophageal and stomach cancers both belonging to the Upper gastrointestinal [GI] cancer group). Furthermore, unadjusted cancer-specific mortality (all cancers combined and by cancer group) were also estimated as a measure of the corresponding average rate over the follow-up time. Cancer groups for which a significant association between previous solid organ transplantation and cancer-specific death was observed, as well as lung cancer and NMSC, were further divided into subgroups for separate analysis, to investigate whether some specific cancer types in that group were driving the association.

International Federation of Gynecology and Obstetrics (for gynecological cancers) and T stage were included in the Cox regression models for the subgroup of cancers diagnosed 2004 and onwards (before which stage was not included in the NCR). N- and M-stage were missing to a large extent and therefore not included. Wald tests were used to evaluate effect modification by transplantation type, where liver transplantation implied low level immunosuppression, kidney transplantation medium level, and heart/lung transplantation high level, for the respective cancer type. A sensitivity analysis, where the exposure (previous solid organ transplantation) was reclassified to be time-varying, was also conducted. In this analysis, a recipient of an organ associated with lower level immunosuppression (e.g. liver), who later additionally went through a transplantation implying higher level immunosuppression (e.g. kidney), accordingly changed exposure level. The proportional hazards assumption was tested with the Grambsch-Therneau test on the Schoenfeld residuals.[104]

4.3.4 Study III

4.3.4.1 Study population

As previously described, CRCBaSe contains virtually all Swedish patients diagnosed with colon (2007-2016) or rectal (1995-2016) cancer. First, the CRC patients were linked to the SPR data. Medical history of solid organ transplantation, and the dates of first, second, and third transplantation, were established using surgery codes. No OTR went through more than three transplantations. OTRs with CRC before (or within 30 days of) first transplantation were excluded. Five non-OTR comparators were matched to each OTR, on cancer location (colon/rectum), year of diagnosis, age±1 year at diagnosis, and sex. Cause of death, CRC characteristics, and CCI (Charlson comorbidity index) data were further linked to the cohort, as were NCR data (to determine the total number of cancers of any type diagnosed for each patient). Only the first CRC occurring in each patient was included for analyses.

4.3.4.2 Statistical analyses

Logistic and multinomial regression

In study III, logistic regression was used to estimate the effect of transplantation on a number of cancer characteristics, including the occurrence of patient case discussion at a pre-operative MDT (multidisciplinary team meeting) (yes/no), whether any abdominal surgery was performed (yes/no), if the surgical result was assessed as curative (yes/no) and/or radical (yes/no) by the surgeon, colon (left-/right-sided, the latter including the transverse colon) and rectal (0-5 or 6-15 centimeters from the anal verge) cancer location, tumor grade (low- or high-grade), neoadjuvant and adjuvant chemo- and/or radiotherapy (yes/no), number of lymph nodes dissected, whether surgery was performed emergently or planned, and local and/or distant relapse.

Multinomial regression was used for outcomes with more than two levels, such as cancer stage (I/II, III, or IV). While logistic regression compares the odds of a binary outcome occurring in e.g. one (exposed) group compared to another (unexposed), multinomial logistic regression compares how the probability of being in one level of the outcome, compared with the base level, changes when you move from one exposure level (e.g. being an OTR) to another (e.g. not being an OTR). This makes the interpretation a little more complicated, but it is nevertheless a useful measure for estimating the association between exposures and categorical outcomes. When the outcome is binary, multinomial regression equals logistic regression.

CCI score distribution was presented but not included in analyses, due to the complicated associations between organ transplantation and concomitant diseases both pre- and post-transplant.

Survival analysis

The Kaplan-Meier estimator was used to present five- and ten-year estimates and graphs of cancer-specific (net) and overall survival among OTRs and non-OTRs, among all patients as well as among those receiving curative abdominal surgery (as assessed by the surgeon), with cause of death information available until December 31st, 2017. Furthermore, five- and ten-year disease-free survival (until all-cause death, relapse, or administrative censoring) was contrasted to overall survival with additional follow-up until June 4th, 2022, among patients treated with curative abdominal surgery. The time scale, and start of patient time at risk, was time from diagnosis, except for analyses on patients treated with curative abdominal surgery, where the time scale (and time at risk) was time from surgery. Cox regression models, adjusted for the matching variables (see above), were used to estimate HRs for cancer-specific and all-cause death, comparing OTRs with non-OTRs, among all patients and among patients receiving presumed curative surgery.

4.4 ETHICAL CONSIDERATIONS

The studies in this thesis focus on cancer among patients with serious concomitant disease, i.e. end-stage organ failure and organ transplantation, both of which are conditions that can severely impact quality of life and require regular contact with healthcare providers. Therefore, any research concerning such patients will most likely involve very personal and sensitive information, and such research must therefore be carefully motivated and scrutinized to make sure that the benefits outweigh the risks.

As described, the data sources for this project were both domestic and Nordic national inpatient, cancer, and death cause registers, national and regional kidney and transplantation registers, and the ScandiaTransplant register. Normally, research using personal data requires every study person's informed consent, to ensure that anyone not willing to participate is able to opt out. However, collecting informed consent from thousands of patients is not plausible. Therefore, other measures need to be taken to ensure the personal integrity of the study persons.

For these studies, this meant that all PINs (which have been used for linking patients between data registers) were removed from the data before analyses began; linking was, to as large an extent as possible, performed by the register holders, so that only pseudonymized data were handled by the researchers; data were stored on a secure server at the Clinical Epidemiology Division, Karolinska Institutet; only the researchers directly involved in analyses had access to data; and all results were presented on an aggregated level, so that no individual data or results could be tracked back to any particular study person.

An important question is what value this research has to the people it is supposed to benefit. Cancer incidence and survival is important to evaluate as such results constitute the basis for screening practices and general cancer vigilance. If some cancer types are associated with increased risk or decreased survival in a patient group, this is important information for the patient as well as the physicians involved in the care. Also, if cancer patients in a particular

patient group are treated differently compared to the general population, causes for this should be investigated as they might sometimes be unjustified, e.g. due to uncalled-for concerns of the organ transplant as compared with the overall benefit of the patient, or lack of knowledge or experience among healthcare professionals. As previous studies have indicated some cause for concern about post-transplant cancer treatment, further research is highly needed to verify this and, if possible, provide solutions in order to ensure optimal and equal healthcare for OTRs with cancer, compared with that given to other cancer patients.[108]

5 RESULTS

5.1 STUDY I

Demographics and crude cancer incidence

In total, 12,984 KTRs, out of whom 4,723 Swedish, 3,156 Norwegian, 2,629 Finnish, and 2,476 Danish, were included. Sixty-four percent were male. The median age at transplantation was 50 years. Thirty-nine percent went through their first transplantation in 2006-2011, 35% in 2000-2005, and 26% in 1995-1999.

Overall, 2,215 cancers were diagnosed in 1,845 KTRs, among which NMSC was the most common (34% of all cancer cases). Other common cancers diagnosed were lung (7.6%), prostate (7.0%), kidney (5.5%), and colon (3.9%), as well as NHL (6.6%) and malignant melanoma (3.9%). The crude cancer incidence rate was 2,243 per 100,000 person-years.

Risk factors for cancer

Male sex, age exceeding 60 years at transplantation, and pre-transplant cancer diagnosis were strong risk factors of post-transplant cancer; additionally, a first transplantation procedure during 2000 through 2005 was indicative of lower risk of cancer than during 1995 through 1999. Post-transplantation time on dialysis, donor vital status, and underlying kidney disease was not associated with cancer risk.

Standardized incidence ratios

Increased risks were noted for a wide range of cancer types (Figure 4). The SIR for any cancer was 3.3 (2.2 if excluding NMSC), for infection-related cancers 11, and for non-infection-related cancers 2.0. Specific infection-related cancers with increased incidence rates were NMSC (SIR 36), NHL (7.6), HL (2.7) and lip (27), vulvar and vaginal (8.8), penile (6.2), nasal (3.9), oral cavity (2.3), liver (2.3), cervical (2.2), and stomach (1.8) cancer. SIRs > 1 were seen for the non-infection-related kidney (7.7), thyroid (4.2), other specified (3.1), lung (2.9), unknown and ill-defined (2.7), gallbladder (2.6), colon (2.2), bladder and urinary tract (2.1), pancreatic (1.9), and uterine (1.9) cancer, as well as for malignant melanoma (3.0) and multiple myeloma (2.5).

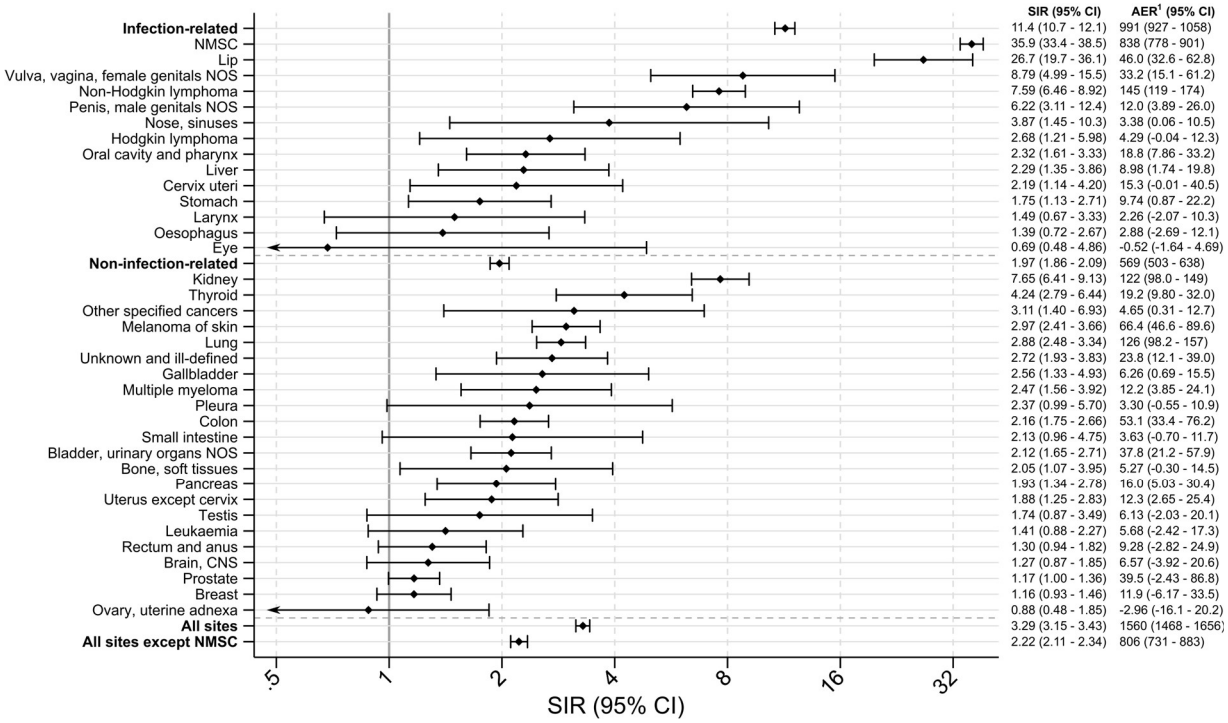

Figure 4. Standardized incidence ratios (SIR) and absolute excess risk (AER), with 95% confidence intervals (CI), of infection- and non-infection-related cancers among Nordic kidney transplant recipients. [1] Absolute excess risk per 100,000 person-years. NMSC, non-melanoma skin cancer. NOS, not otherwise specified. CNS, central nervous system.

Absolute excess risks

Most of the cancers with SIRs > 1 also showed absolute excess rates > 0 per 100,000 person-years (Figure 4). The AER was 1,560 (including NMSC) and 806 (excluding NMSC) per 100,000 person-years for any cancer. With an AER of 838 per 100,000 person-years, NMSC thus represented a large part of the total AER. Other cancers with AERs over 100/100,000 person-years were NHL (145), as well as lung (126) and kidney (122) cancer.

Cumulative incidence

The five- and ten-year cumulative incidence of cancer was 8% and 17%, translating to a 5-year absolute risk of 1 in 12 KTRs developing any cancer, and 1 in 6 over 10 years. The cumulative incidence was heavily influenced by sex, age at transplantation, and cancer association with infection (Figures 5 and 6). However, excluding NMSC from the analyses showed that although the relative risk among KTRs was markedly higher for infection- than non-infection-related cancers, the absolute risks of developing non-infection-related cancer was several times greater (Figure 6). The absolute risk of cancer as first event increased among men, but not (significantly) among women, over calendar time; however, the competing risk of death as first event declined, more so among women (data not shown).

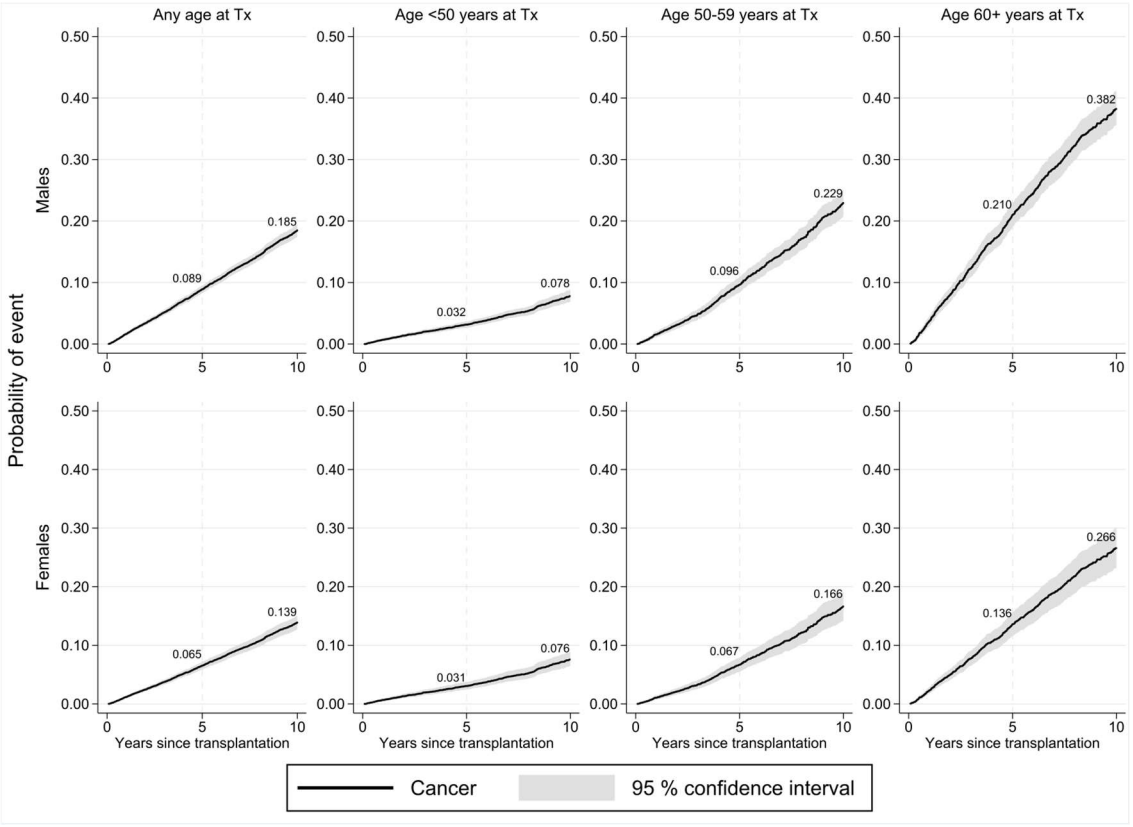

Figure 5. Cumulative incidence of cancer, in the presence of the competing risk of death, among Nordic kidney transplant recipients, by sex and age at transplantation. Tx, transplantation.

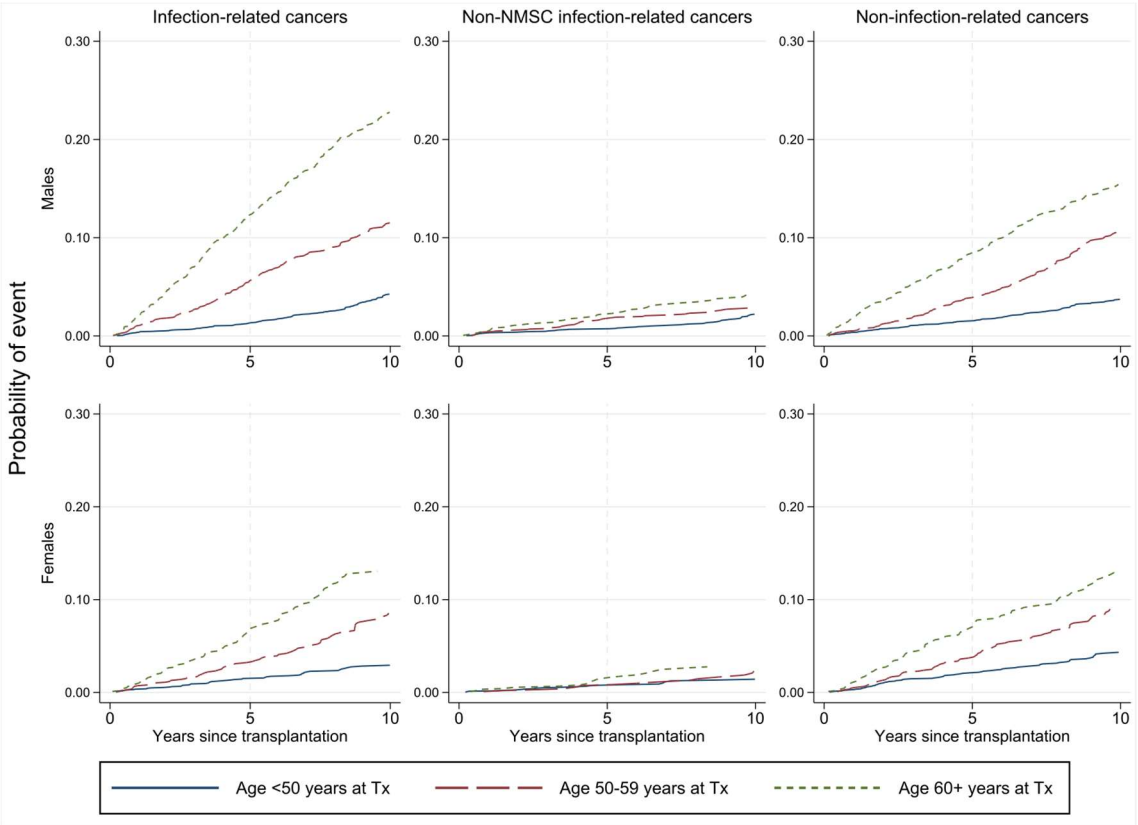

Figure 6. Cumulative incidence of cancer, in the presence of the competing risk of death, among Nordic kidney transplant recipients, by sex and cancer relation to infection. NMSC, non-melanoma skin cancer. Tx, transplantation.

5.2 STUDY II

Demographics and cancer incidence

Among 948,232 patients with 1,029,452 cancers, 2,143 OTRs with 2,589 cancers were identified. OTRs with cancer were more likely male (65% vs 52%), and younger at cancer diagnosis (median 61 vs 69 years), than non-OTR cancer patients. Excluding *other or unknown* cancer (constituting 10% of cancers diagnosed among both OTRs and non-OTRs), the three most common cancer types were NMSC (41%), lymphoma (7.9%), and lung cancer (5.1%) among OTRs, and prostate (17%), breast (13%), and colorectal (11%) cancer among non-OTRs.

Cancer survival

Overall, 1,205 OTRs (56%) died during follow-up, of whom 540 (45%) due to cancer. Of all 2,589 cancers, 540 (21%) thus resulted in cancer-specific death. Cox regression analysis showed a 1.35-fold rate of cancer-specific death due to any cancer, and higher rates of cancer-specific death due to lymphoma (HR 3.1), malignant melanoma (2.8), and urothelial (2.6), breast (2.1), head/neck (1.6), and colorectal (1.4) cancer (Figure 7). The rates of cancer-specific death were increased for any cancer, as well as for lymphoma and malignant melanoma, for all transplant types (liver, kidney, or heart/lung/pancreas) compared to those observed in non-OTRs. However, pancreatic cancer was the only form where type of transplanted organ significantly modified the rate ratio of cancer-specific death. Adjusting for T-stage and including transplantation as a time-varying exposure (as a proxy for altered burden of immunosuppressive treatment) did not change the results. Overall, OTRs had a two-fold increased rate of all-cause death compared with non-OTRs.

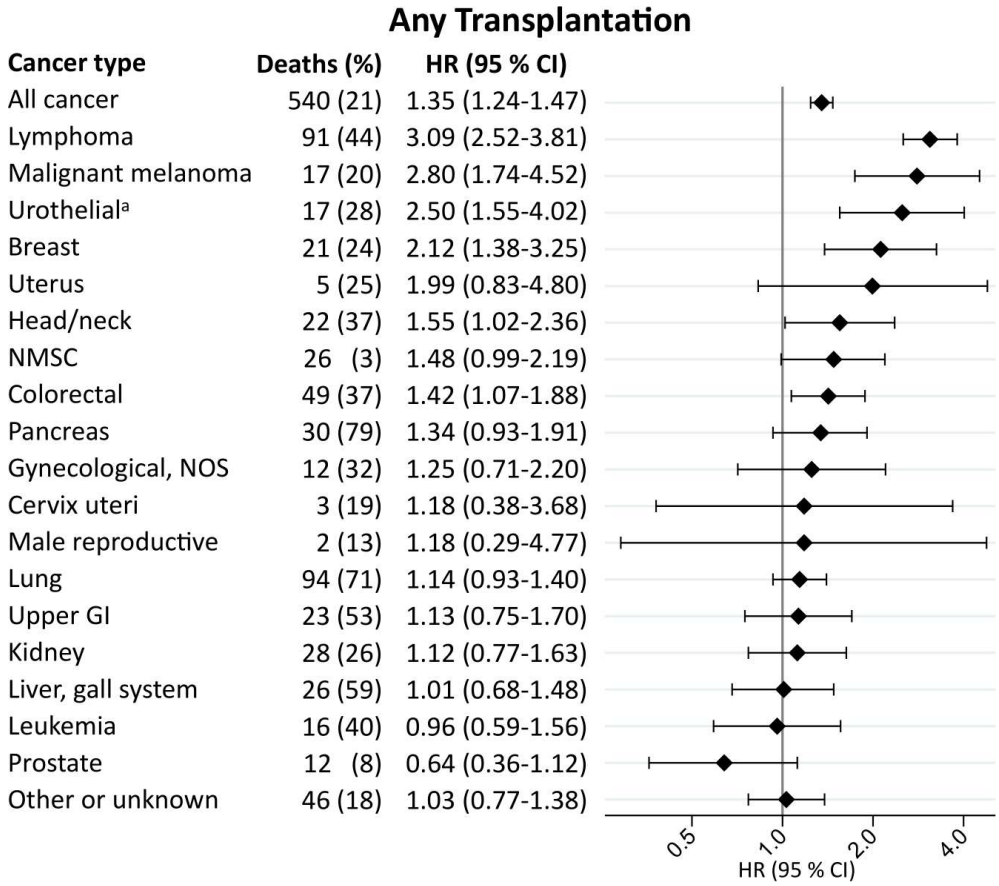

Figure 7. Numbers of and hazard ratios (HR), with 95% confidence intervals (CI), for cancer-specific deaths among Swedish solid organ transplant recipients with cancer, compared with non-transplanted cancer patients. NMSC, non-melanoma skin cancer. NOS, not otherwise specified. GI, gastrointestinal.

5.3 STUDY III

Demographics

A total of 590 CRC patients, among whom 99 OTRs (74 with colon cancer and 25 with rectal cancer) and 491 non-OTRs (368 with colon cancer and 123 with rectal cancer) were included. Two OTRs had only three eligible non-OTR comparators, but the remaining 97 had five. The majority of patients were male (61%) and/or at least 60 years old (82%) at CRC diagnosis. Among OTRs, the most common organ transplant type was kidney (77%), followed by liver (16%), heart and/or lung (4%), and combined pancreas and kidney (3%). Most OTRs (88%) had gone through only one organ transplantation procedure before first CRC diagnosis.

Cancer characteristics

Comparing OTRs and non-OTRs with CRC, stage at diagnosis was overall similar, as were the odds of case discussion at pre- and post-operative MDTs. However, OTRs were less likely to be treated with abdominal surgery (OR 0.40), while the success of surgery (i.e. curative and/or radical), as assessed by the surgeon, was similar among OTRs and non-OTRs. Among colon cancer patients treated with curative abdominal surgery, OTRs went through less extensive lymph node dissection (OR 2.99 of 0-14 versus 15-78 lymph nodes examined) during surgery, and had lower odds of treatment with adjuvant chemotherapy (OR 0.28), than non-OTRs. While no difference in colon cancer location was found in this sub-cohort, OTRs

were however more likely of diagnosis with right-sided instead of left-sided colon cancer than non-OTRs (OR 2.27) when all colon cancer patients were included. Among rectal cancer patients treated with curative abdominal surgery, OTRs had lower odds of treatment with neoadjuvant radiotherapy (OR 0.23), as well as less extensive lymph node dissection (OR 9.62 of 0-9 vs 10-54 lymph nodes examined). Previous transplantation did not modify the odds of high (vs low) tumor grade, or undergoing emergent (vs planned) surgery. No differences between OTRs and non-OTRs were found for adjuvant treatment for rectal cancer; however, those data were not systematically recorded before 2007 for that cancer type. While colon cancer relapse frequencies were similar among OTRs and non-OTRs, transplantation history was associated with 4 times increased odds of rectal cancer relapse (OR 4.21), of which most occurrences were classified as distant rather than local. The majority (65%) of non-OTRs had CCI 0 at CRC diagnosis, while all OTRs had CCI > 0. 32% of OTRs had been diagnosed with a previous cancer (most commonly NMSC), as opposed to 10% of the non-OTRs, before contracting CRC.

Survival

Of the 71 (72%) OTRs and 200 (41%) non-OTRs that died of any cause during follow-up until December 31st, 2017, 38 OTR (54%) and 134 non-OTR (67%) deaths were classified as cancer-specific. OTRs had worse five- and ten-year survival than their matched non-OTR comparators, except for cancer-specific survival among patients with curative surgery (Table 3, Figure 8). Extending the follow-up until June 4th, 2022, the five- and ten-year disease-free survival was notably worse among the OTRs than the non-OTRs, with ten-year disease-free survival of 14% among the OTRs, and 55% among the non-OTRs (Table 3, Figure 9).

Table 3. Net survival proportions among Swedish colorectal cancer patients, stratified by medical history of solid organ transplantation.

	Cancer-specific survival		**Overall survival**		**Disease-free survival[1]**	
	Five-year	Ten-year	Five-year	Ten-year	Five-year	Ten-year
All patients						
OTRs	57%	38%	35%	8%	-	-
Non-OTRs	68%	67%	57%	52%	-	-
p-value	*<0.001*	*<0.001*	*<0.001*	*<0.001*	-	-
Patients treated with curative surgery						
OTRs	79%	79%	50%	17%	46%	14%
Non-OTRs	83%	82%	71%	65%	69%	55%
p-value	*0.23*	*0.25*	*<0.001*	*<0.001*	*<0.001*	*<0.001*

[1] Follow-up from date of surgery until date of death, relapse, or June 4th, 2022. OTRs, organ transplant recipients.

Similar to the Kaplan-Meier analyses, Cox regression, adjusted for the matching variables, showed a 2-fold increased rate of cancer-specific death, and a 2.5-fold increased rate of all-cause death, associated with previous organ transplantation. Among patients treated with curative surgery, a 3.1-fold increased rate of all-cause death was found, but no long-term (past the first 3 years) difference regarding cancer-specific death. The proportional hazards assumption was satisfied for all analyses.

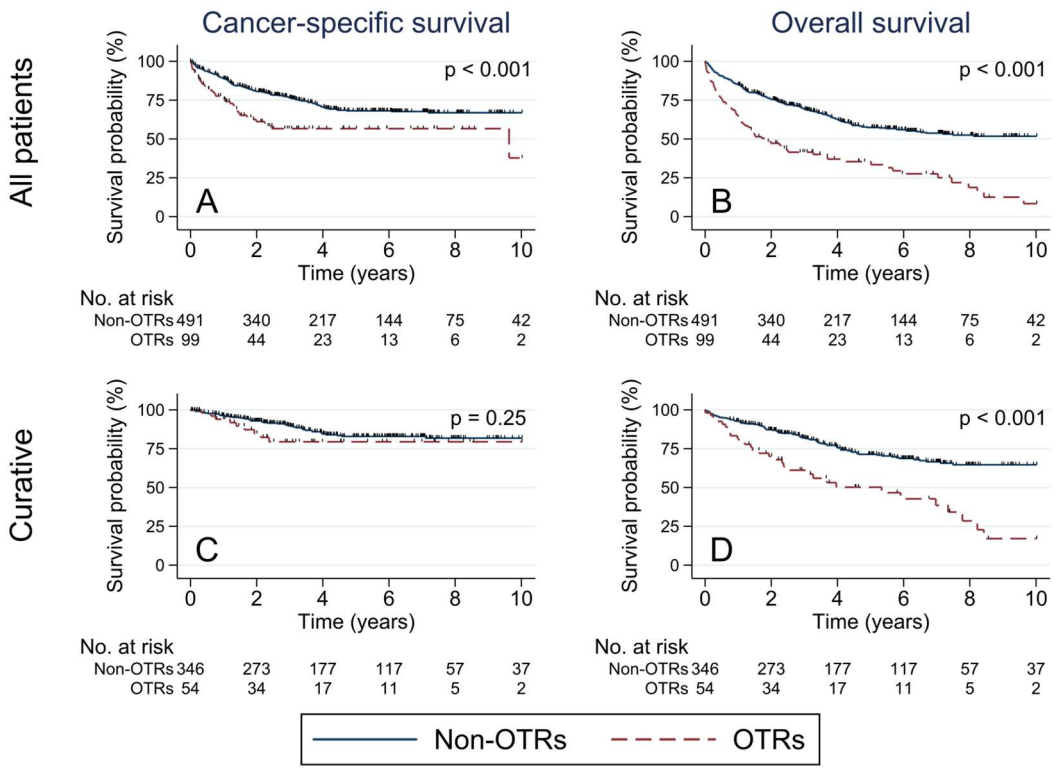

Figure 8. Cancer-specific and overall survival among Swedish colorectal cancer patients, contrasting organ transplant recipients (OTRs) to non-OTRs. The upper row (A and B) shows survival for all patients, and the lower row (C and D) shows survival for patients treated with curative surgery (as assessed by the surgeon). No, number. OTR, organ transplant recipient.

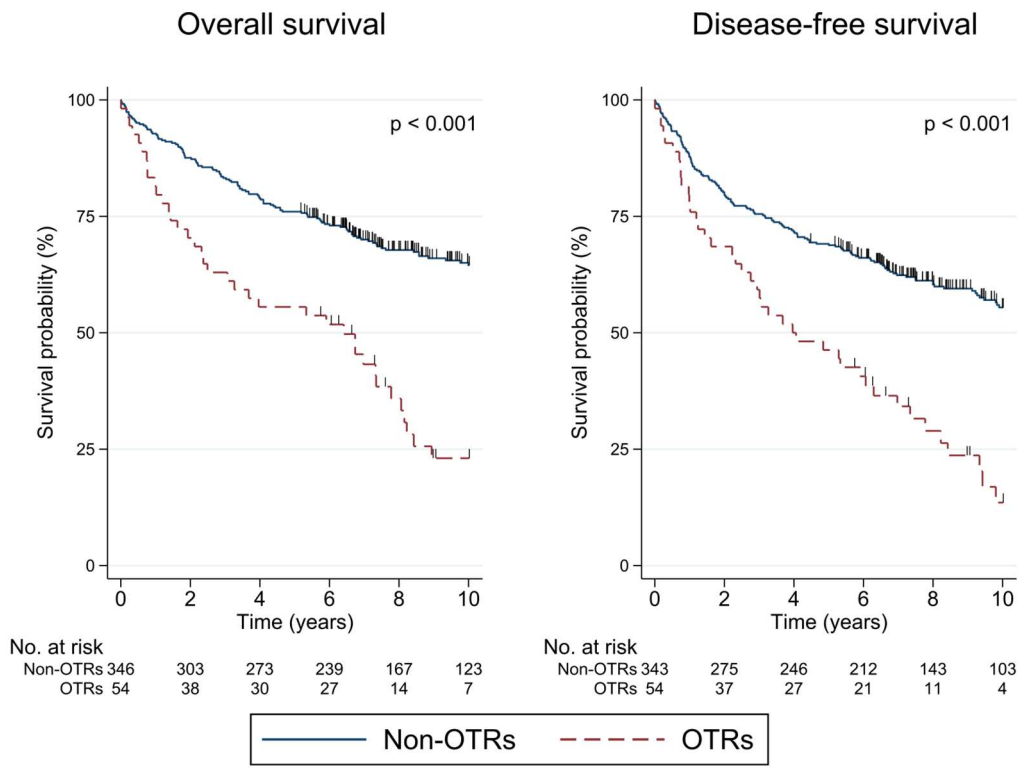

Figure 9. Overall and disease-free survival among Swedish colorectal cancer patients with follow-up until June 4th, 2022, contrasting organ transplant recipients (OTRs) to non-OTRs. Note: Three non-OTRs had known (operable) metastases (2 liver, 1 *other* [non-lung, non-liver]) at start of follow-up and were therefore excluded from the analysis of disease-free survival. No, number. OTR, organ transplant recipient.

6 DISCUSSION

6.1 MAIN FINDINGS

- Nordic KTRs were at increased risk of developing a wide range of cancers. On the relative scale (SIRs), the excess risk was greatest for infection-related cancers. However, on the absolute scale (cumulative incidence and AERs), non-infection-related cancers were associated with the largest risks. The five- and ten-year cumulative incidence of any cancer was 8% and 17%, respectively. The excess number of cancers seen among OTRs, compared with the general population, was 1,560 per 100,000 person-years.
- Compared with non-transplanted cancer patients, Swedish OTRs with cancer had higher cancer-specific mortality for a range of cancers, including lymphoma, malignant melanoma, and urothelial (i.e. urinary tract), breast, head/neck, and colorectal cancer. Furthermore, the rate of all-cause death was two-fold increased among OTRs. No association with (TNM) T-stage was found in a subset of patients with available staging information, and type of transplantation did not modify cancer outcomes.
- Swedish CRC patients with a previous solid organ transplantation had a 2-fold increased rate of cancer-specific death, and were less likely to receive treatment with abdominal surgery, as well as neoadjuvant (rectal cancer) and adjuvant (colon cancer) treatment, than their non-transplanted comparators.

6.2 COMPARISON WITH PREVIOUS REPORTS

6.2.1 Study I

Comparable previous studies have demonstrated SIRs ranging from 2.5 to 6.5 of any cancer including NMSC, and 2.1 to 2.5 of any cancer excluding NMSC (Table 4).[13-17,24,50,52,53,55-59] The SIRs found in the present study of 3.3 including and 2.2 excluding NMSC thus harmonize well with previous results. For specific cancers, there seems to be solid evidence for the increased risks seen in the present study for NMSC, NHL, and liver, stomach, kidney, thyroid, lung, colorectal, and bladder and urinary tract cancers. Interestingly, Asian studies have tended to find higher SIRs for kidney, bladder and urinary tract cancer, in contrast to Western studies, which have usually presented higher SIRs for skin cancers such as NMSC and malignant melanoma, as well as lip and external genital cancers (Table 1). This might be due to different susceptibility to development of cancers associated with end-stage organ failure (i.e. kidney and urinary tract cancer), and differences in skin type, social and sexual behavior patterns, and sun exposure habits. However, indirect standardization (such as using SIRs) is often inappropriate for comparing incidence rates between different populations (e.g. those of different countries), as the strata-specific ratios of rates in the groups under study and in the reference populations can differ considerably, thus explaining the SIR disparities.[109] Furthermore, the definition of NMSC sometimes includes actinic keratosis and SSC in situ as precursors to invasive SCC, as well as basal cell cancer, which can complicate comparisons.

Table 4. Comparison of the results of Study I and Study II with previous reports of increased cancer incidence and rates of cancer-specific death among KTRs (Study I) and OTRs (Study II) compared with the general population.

	Cancer incidence			**Cancer-specific mortality/survival**		
Cancer type	SIRs in previous studies (n=16)	Studies with SIR>1	Study I SIR	SMRs in previous studies (n=10)	Studies with SMR>1	Study II HR
Infection-related						
NMSC	5.7 to 52	14 of 16	36	3.7 to 51	6 of 6	O
Lip	17 to 66	10 of 11	27	-	-	-
Vulva, vagina	3 to 31	6 of 7	8.8	-	-	-
NHL	4.8 to 29	15 of 16	7.6	1.8 to 31	8 of 9	3.1[1]
Penis, male genitals	4.1 to 6.0	3 of 4	6.2	-	-	-
Nose, nasopharynx	5.4 to 5.9	4 of 5	3.9	3.1 to 3.7	2 of 3	1.6[2]
HL	3.2 to 11	6/1[3] of 9	2.7	5.1	1 of 3	-
Mouth, oropharynx	2.0 to 8.3	6 of 10	2.3	2.1 to 17	4 of 7	1.6[2]
Liver	2.4 to 12	9 of 11	2.3	2.3 to 6.1	3 of 7	O
Cervix	1.3 to 6.1	8 of 12	2.2	0.4 to 2.8	3 of 4	O
Stomach	1.7 to 2.9	8 of 12	1.8	0.8 to 3.5	2 of 5	-
Larynx	1.6 to 15	2 of 6	O	1.9	1 of 1	-
Esophagus	1.6 to 3.2	3 of 10	O	0.9	0 of 5	-
Eye	2.8	2 of 2	O	3.5	1 of 1	-
Anus	5.8 to 10	4 of 5	O	2.5	1 of 1	-
Non-infection-related						
Kidney	4.6 to 44	14 of 15	7.7	0.4 to 11	5 of 8	O
Thyroid	2.4 to 11	15 of 15	4.2	-	0 of 2	-
Melanoma of skin	1.8 to 9.1	6 of 10	3.0	2.3 to 6.9	7 of 7	2.8
Lung	1.4 to 4.8	9 of 12	2.9	0.9 to 2.7	6 of 9	O
Unknown	14	2 of 4	2.7	2.0 to 6.1	4 of 4	O
Gallbladder	2.0 to 4.1	3 of 8	2.6	-	-	O
Multiple myeloma	2.7 to 24	3 of 6	2.5	0.8	0 of 4	-
Pleura	8.4	1 of 1	O	-	-	-
Colon	1.2 to 5	12 of 13	2.2	0.6 to 3.8[4]	6 of 9[4]	1.4[4]
Small intestine	2.4 to 12	2 of 3	O	-	-	-
Bladder, urinary tract	1.5 to 43	11 of 12	2.1	0.8 to 4.7	3 of 6	2.6
Connective/soft tissues[5]	4.8	3 of 5	2.1	3.1 to 6.5	3 of 5	-
Pancreas	1.5 to 3.3	4 of 12	1.9	0.7 to 2.2	1 of 6	O
Uterus	5.7	1 of 11	1.9	5.5	1 of 1	O
Testis	2.0 to 3.9	2 of 5	O	-	0 of 1	-
Leukemia	2.3 to 27	5 of 11	O	0.9 to 8.4	4 of 7	O
Rectum	1.2 to 4.5	5/2[3] of 11	O	-	-	1.4[4]
Brain	3.0 to 13	1/1[3] of 8	O	3.5	1 of 6	-
Prostate	2.1 to 6.9	3 of 12	O	0.6	0 of 9	O
Breast (female)	1.3 to 3.9	5 of 12	O	1.8 to 1.9	2 of 7	2.1
Ovary	1.9 to 5.9	4 of 12	O	1.5 to 7.3	3 of 3	-
All sites	2.5 to 6.5	11 of 11	3.3	1.4 to 3.1	6 of 6	1.4
All sites except NMSC	2.1 to 2.5	9 of 9	2.2	0.8 to 2.6	4 of 5	-

Note: Some cancer classifications have been altered for comparability. [1] Including Hodgkin lymphoma. [2] Head/neck cancer. [3] Increased for both sexes/for one sex only. [4] Colorectal cancer. [5] Including bone. SIR, standardized incidence ratio. SMR, standardized mortality ratio. NMSC, non-melanoma skin cancer. (N)HL, (Non-)Hodgkin lymphoma. O, no significant difference.

Also, several of the Asian studies mentioned demonstrated significantly increased incidence rates for breast and prostate cancer, i.e. cancer types that have typically not been associated with increased post-transplant incidence in the Western world (including in the present study). The geographical differences in cancer incidence patterns could thus indicate that different cancer vigilance and screening protocols might be advised in different parts of the world.

While the SIR has been the standard measurement of post-transplant cancer rates among KTRs compared with the general population, cumulative incidence and absolute excess risk have not as commonly been presented. Our findings of an 8% and 17% cumulative incidence of any cancer (5% and 10% excluding NMSC) over five and ten years, respectively, are slightly higher than those previously shown.[15-17,52,54] The 6% and 14% five- and ten-year absolute risk found by Adami et al, including NMSC but not accounting for competing events, is the one closest to the present study, while most other reports have shown a cumulative incidence of approximately 4% over five years and 9% over ten years, regardless of NMSC and competing events (Table 5). The overall excess risk was 1,560 (including NMSC) and 806 (excluding NMSC) additional cases per 100,000 person-years in Study I, arguably similar to the non-NMSC AER of 719 reported by Engels et al (Table 5).[53]

Table 5. Cumulative incidence and absolute excess risk (compared to the general population) of post-transplant cancer among kidney transplant recipients, according to selected previous research reports.

Report	Kyllönen 2000	Adami 2003[1]	Villeneuve 2007	Collett 2010	Hall 2013	Engels 2011[1]	Study I	
Cumulative incidence								
Five-year	4%	6%	4%	4%	4%	-	8%	5%
Ten-year	9%	14%	8%	9%	-	-	17%	10%
Including NMSC?	Yes	Yes	No	No	No	-	Yes	No
Competing events	No	No	Death Other cancer	No	Death Graft loss Re-Tx	-	Death	
Absolute excess risk per 100.000 person-years						719	1,560	806
Including NMSC?						No	Yes	No

[1] All organ transplant recipients (not only kidney). NMSC, non-melanoma skin cancer. Re-Tx, re-transplantation.

The differences in cumulative incidence and AER can partly be explained by different distributions of cancer incidence and competing events among KTRs, inclusion of NMSC and geographical differences of NMSC incidence, inclusion and distribution of competing events (with presumably lower incidence of competing events in later time periods, due to better post-transplant non-cancer outcomes), and different background rates in the general population. The AER shown by Engels et al pertains to OTRs overall, not only KTRs.

Using NORDCAN as reference material

In Study I, as well as in several other similar studies, the grouping of cancers can pose some difficulty. In most materials, the possibilities of subdividing cancer types are limited due to statistical power; rather, grouping of similar cancers (or worse, adjacent cancer sites) is commonly performed to increase power. One such example is that of colorectal cancer, which might or might not include anal cancer (which is often of substantially different origin, i.e. squamous cell cancer instead of adenocarcinoma). In NORDCAN, anal cancer (a virus-related cancer) is included in the rectal cancer (a non-virus-related cancer) group; and both might be included in the colorectal cancer category in other studies. Anal cancer has previously been associated with highly increased risk among OTRs, which is plausible due to its relation to viral infections (Table 4).[40] The increased incidence associated with colorectal cancer might in some cases thus be partly explained by anal cancer. Interestingly, though, Study I found no increased relative or absolute excess risk of rectal (including anal) cancer among KTRs.

6.2.2 Study II

NMSC, NHL, and kidney, melanoma, lung, and colorectal cancer are consistently associated with cancer-specific SMRs > 1 in previous studies, but also with increased incidence rates, often of comparable magnitude. Whether the increased mortality rates seen are explained in total or partly by increased incidence is not clear. As an alternative to estimating cancer-specific mortality, a few studies (including Study II) have instead measured cancer-specific survival, in order to explain the impact of transplantation on cancer prognosis.[61,63] Study II demonstrated increased rates of cancer-specific death among OTRs with cancer, compared with non-OTR cancer patients, for lymphoma, melanoma, and cancers of the urinary tract, breast, head/neck, and colorectum. Of those, breast cancer is especially interesting, as it is usually associated with similar post-transplant incidence compared with that in the general population. This implies that breast cancers, once developed, could be more dangerous in the post-transplant setting (e.g. due to differences in biological characteristics, cancer treatment, or other factors). Another interesting comparison relates to urinary tract cancer (also known as urothelial cancer, i.e. bladder, ureter, and urethra), a form with widely recognized increased incidence, but less evidence of increased mortality, among OTRs (Table 4). The increased incidence has been attributed to underlying urinary tract disease, including cancer, before kidney transplantation. However, in combination with reported standardized mortality rates in some populations similar to the background rates, these cancer forms have not appeared to be as dangerous post-transplant. Nevertheless, Study II found a 2.6 times increased rate of cancer-specific death among OTRs, compared with non-transplanted urothelial cancer patients.

The post-transplant cancer survival study by D'Arcy et al from 2019 displays several similarities to Study II, in both design and results (Table 2).[63] Rates of cancer-specific death due to lymphoma, melanoma, and bladder, breast, head/neck (including mouth and oropharynx), and colorectal cancer were increased in both studies when comparing OTRs to

non-OTRs, often with HRs of comparable magnitude. In addition, D'Arcy et al found HR estimates >1 of cancer-specific death for stomach, lung, and kidney cancer, all of which had estimates close to 1.0 in Study II, and pancreas cancer, for which no significantly increased rate of cancer death among OTRs could be confirmed in Study II. Also, while no increased rate of death due to NMSC was found, the subtype SCC was indeed significantly associated with a 1.6-fold increased rate of cancer-specific death in Study II.

In the 2009 study by Miao et al, cancer-specific death rate increases for breast and bladder cancer were similar, but slightly lower for melanoma, compared with those in Study II; also, a five times increased rate of prostate cancer-specific death was found, which has not been confirmed (but rather contradicted) by subsequent analyses.[68]

The 1.35 times increased rate of cancer-specific death among OTRs compared with non-OTRs, presented in Study II, deserves a mention. Clinically, this measure is a bit difficult to explain, as it does not apply to any one cancer patient. Basically, it says that "if you are an organ transplant recipient, and you are diagnosed with some type of cancer, your cancer-specific death rate (that is, your rate of death due to cancer, in the hypothetical world where cancer is the only thing that can kill you) is 35% increased, compared with that of a patient with a similar type of cancer but no history of organ transplantation." Its meaning can be interpreted as purely of epidemiological interest.

6.2.3 Study III

One of the main findings of Study III was that OTRs with colon cancer were less probable of being planned for adjuvant treatment than the non-OTRs. This was also the case in the 2011 study by Kim JY et al, but not in the 2021 study by Kim M et al. Neither study found any differences in tumor grade or stage at diagnosis among OTRs compared with non-OTRs; however, the latter only included stage I-III, and (TNM) T- and N-stage, as the study base was CRC patients receiving surgery. Also, neither study reported data on neoadjuvant treatment, which was significantly less commonly administered to rectal cancer OTRs, compared with non-OTRs, in Study III.

Several studies (including the present one, when including all colon cancer patients in the analysis) have shown that OTRs are more often diagnosed with right-sided colon cancer, as opposed to left-sided in the general population.[79,110] Right-sided colon cancers have been associated with worse prognosis and different clinicopathological characteristics compared with left-sided, with more aggressive behavior and advanced stage at diagnosis, suggestive of two different diseases.[111,112] Furthermore, right-sided tumors may be less susceptible to treatment with chemotherapy, but respond better to immune therapy (which might be contraindicated in OTRs due to increased risk of rejection).[113-115]

Based on the present and previous findings, the worse cancer-specific CRC survival seen among OTRs could accordingly be influenced by differences in treatment (in turn associated with different comorbidity) and colon cancer location (in turn associated with different

biological aggressiveness and susceptibility to treatment), rather than tumor grade or stage at diagnosis, compared with that among non-OTRs.

6.3 IMPLICATIONS

6.3.1 Cancer screening

Although often suggested in the literature, expanded cancer screening among OTRs is controversial, and both original studies and reviews addressing cancer screening question the cost-effectiveness among OTRs due to the abundant comorbidity and competing causes of death. Wong et al have published several research reports and reviews on cancer screening before and after kidney transplantation, both overall and for specific cancer types, finding very small survival gains associated with breast cancer screening among women on dialysis, while fecal occult blood testing may be favorable among KTRs. Furthermore, annual cytology tests for cervical cancer were found to be cost-effective (compared with no screening), in contrast to routinely screening for renal cancers, except perhaps among patients with increased risk.[35,116-120] Screening recommendations also depend on any associations between immunosuppression and cancer incidence and survival; for example, for prostate cancer, frequently associated with similar incidence and survival among OTRs compared with the general population, no further screening measures are recommended.[68,121]

A recent overview of post-transplantation screening recommendations by Acuna et al showed that current guidelines advise using the same screening protocols as those used for the general population, with the addition of regular dermal check-ups due to the increased risk and rate of death associated with post-transplant skin cancer.[42] (The last part is crucial, as modern treatment for e.g. advanced malignant melanoma includes treatment with checkpoint inhibitors, such as programmed cell death protein 1 inhibitors, which have been associated with fulminant graft rejection. Finding these tumors at an early stage could therefore substantially improve outcomes.) However, regarding cancers not routinely screened for in the general population, recommendations in current guidelines varied significantly.[42]

Decisions on screening recommendations should not only incorporate relative risks, but also absolute risks, survival, and how cancer stage impacts treatment. First, relatively common cancers among OTRs may not pose a significant clinical impact (e.g. infection-related cancers, excluding NMSC, constituted a lower absolute risk in study I, than non-infection-related), implicating that absolute risks should also be considered. Second, common cancers with no or moderately increased relative risk, but with significantly worse cancer-specific survival (such as breast cancer, colorectal cancer, and malignant melanoma in study II), should be considered for additional screening to diagnose such cancers at an earlier stage. As lower stage cancer is often treated with surgery only, i.e. without chemotherapy or other types of neo-/adjuvant treatment, interactions with immunosuppressive drugs and detrimental effects on the organ transplant associated with such treatment could be avoided.

Screening modality and patient preferences must also be considered. Some patients (and patient groups) will be disinterested in additional health care visits, while others will embrace

them with open arms. A chest X-ray will presumably be more tolerable to most than a colonoscopy, but even a stool sample might be intolerable to some. Two previous studies showed that only 10-20% of female KTRs went through cervical cancer screening at the recommended rate of once per year, and approximately one third of KTRs never attended screening at all over a median follow-up of 10-12 years, compared with 23-29% screening uptake in the general population.[122,123] This implies that a personalized screening plan, originating in current screening recommendations but possibly modified in order to suit the patient, should be discussed with each patient in order to maximize compliance. Accordingly, while screening is a complex machinery with several conflicting concepts, the present thesis will hopefully provide some additional epidemiological evidence to consider for future screening guidelines.

6.3.2 Post-transplant cancer management

The worse outcomes, possibly in part due to higher biologic aggressiveness for some cancers (e.g. skin cancer), associated with post-transplant cancer calls for swift and effective management after diagnosis.[124] However, this is an area where current knowledge is limited. Chemotherapy is associated with a spectrum of significant side-effects, including nephrotoxicity. Nevertheless, several reports have demonstrated that some chemotherapeutic agents, such as cisplatin, were well-tolerated among recipients of both kidneys and other organs.[125-127] On the other hand, the notion that chemotherapy might partly act as a substitute for immunosuppressive treatment (i.e. counteracting rejection) when reducing the latter has been contradicted by at least one case series.[128]

In the case of KTRs, administration of adjuvant therapy is dependent both on the level of comorbidity, and in many cases also on a working kidney transplant. KTRs could presumably be treated with e.g. adjuvant chemotherapy to a larger extent, given that a working kidney transplant tolerates chemotherapy and other treatment similarly to native kidneys. However, as some types of oncological treatment are also immunosuppressive, maintenance transplantation-related immunosuppressants might have to be reduced in order to avoid excess immunosuppression, lest severe and possibly fatal complications occur (e.g. due to infections).

Hellström et al showed in 2016 that organizing an additional MDT for KTRs with cancer resulted in altered immunosuppressive treatment for 71% of patients, including the addition or switch to mTOR inhibitors for 63% of patients.[108] Furthermore, the planned regimens for adjuvant chemo- and radiotherapy were changed in 52% of patients with solid or hematological malignancies, resulting in an 82% adherence rate to national treatment guidelines for those cancers. While this study was one-armed and thus not included a control group, the results are nevertheless interesting and call for further research on multidisciplinary decisions on post-transplant cancer management. However, the design of such a study could pose a challenge, both due to the heterogeneity of the post-transplant cancer spectrum, and – not least – due to the ethical considerations possibly involved (e.g. randomizing patients to cancer treatment without prior evaluation at an MDT, something

believed to be beneficial to the patient). Moreover, a meta-analysis from 2015 on how comorbidity affects MDT decisions showed that for patients with comorbidity, MDT treatment decisions are less likely to 1) be made at all, 2) harmonize with clinical guidelines, and 3) be coherent with the actual treatment later administered to the patient.[129] This implicates that patients with some key but relatively uncommon comorbidity, such as organ transplantation, could benefit from being represented at the MDT by an expert representative (e.g. on relevant organ transplantation management).

Consequently, it is plausible that OTRs sometimes receive lighter neoadjuvant and adjuvant therapy than non-OTRs of comparable age and sex, partly due to differences in comorbidity, but also due to drug toxicity and interactions. The question whether such differences are common and justified in the organ transplantation setting remains unanswered. Further research, evaluating differences in cancer treatment by transplantation history, is thus needed. Also, formal studies on optimal neo-/adjuvant therapy protocols for OTRs, taking the aforementioned characteristics into account, would provide valuable insight on how to treat post-transplant cancer.

6.4 METHODOLOGICAL ASPECTS

6.4.1 The causal implications of noted associations

All three studies included in this thesis are observational studies, which limits the possibilities for causal inference. (Meta-analyses of) randomized controlled trials (RCT) are considered the gold standard for increasing the medical knowledge base, and if perfectly designed and executed, RCTs can demonstrate real, causal relationships, and within the concept of evidence-based medicine.[130] However, in many cases RCTs are not feasible, for example due to ethical issues (e.g. when the exposure is smoking, randomizing participants to smoke would be unethical as there is a plethora of evidence for the harmful effects of smoking), economical limitations, or other difficulties. Observational studies are then an alternative to investigate relationships where exposure is not randomized.

The conclusions of any single observational study are bound to be influenced by more or less unmeasured confounding, i.e. factors other than the exposure of interest that influence the probabilities of both exposure and outcome. Therefore, reproducing such studies becomes more important. However, study design choices tend to accompany future research studies, underlining the importance of sound methodology. A large amount of studies producing similar results and conclusions could actually by harmful to medical knowledge by reinforcing “truths” built on originally faulty concepts, which have then been propagated using similar study designs.

6.4.2 Comparison groups for studies on post-transplant cancer

The general population

Many previous post-transplant cancer incidence studies have used the general population, or some representation thereof, as the comparison group. In study I, primary cancer rates in the general population were used. This method slightly underestimates the relative risk of cancer among KTRs, as these patients also contribute to the background rates when they develop a post-transplant primary cancer. However, given the very limited prevalence of OTRs in the general population, these errors are presumably very small. Another factor to consider is that OTRs are meticulously screened for cancer pre-transplant, a process that can include abdominal and thoracic x-ray procedures, endoscopy, and other invasive and noninvasive procedures. Because of this, OTRs constitute a very selected group of patients by being almost by definition cancer-free at transplantation. Given this process, cancer incidence would reasonably be lower among OTRs than in the general population, as most cancers found in the pre-transplant investigation would preclude the patient from transplantation. A previous medical history of cancer can be a weak or very strong contraindication, and zero, two or five years are commonly recommended thresholds for relapse-free waiting time before kidney transplantation, depending on the cancer type and spread.[131]

Patients with several years of end-stage renal failure in their medical history behind them can seem biologically significantly older than their healthy peers at similar chronological age. For this reason, matching KTRs (or OTRs) to comparators by chronological age, as done in study III, can be questioned. While this is standard and comparatively easy, an alternative would perhaps be to match younger KTRs to older comparators based on comorbidity scores and remaining life expectancy, as has been suggested in the cancer setting.[132]

Patients on dialysis

Some studies on cancer after kidney transplantation have used patients on dialysis as the comparison population. This is appropriate when the research question is related to the treatment effect of moving from dialysis to kidney transplantation, i.e. to be able to inform a dialysis patient about the changes in cancer risk and survival associated with kidney transplantation. However, dialysis patients are, like OTRs, heavily burdened with comorbid conditions, some of which will improve after transplantation (i.e. reversible effects of kidney failure), and some that might be introduced, or worsen (e.g. diabetes induced or accelerated by some immunosuppressive agents, such as tacrolimus).[133] As previously shown, those conditions (if not dialysis itself) might alter the spectrum of cancer risk, compared with that in the general population. Furthermore, like OTRs, dialysis patients experience increased observation by healthcare professionals, which presumably also influences cancer incidence rates.

The question is: what is the research question?

Other comparison groups, such as AIDS patients or other immunosuppressed patients, are also plausible. As with the question of whether to account for competing events in survival analysis, which comparison group to choose depends on the research question. Is it about comparing OTRs to healthy and/or "normal" people, or about how the risks associated with dialysis evolve when you go through a kidney transplantation, or about comparing the cancer risk and characteristics associated with different immunosuppressed states? Is it about whether cancers among transplant recipients are associated with factors making them more dangerous than to other people, or about the actual survival probability of transplant recipients due to cancer or to other diseases? There is an analysis for almost everything, as long as you understand what question you are asking.

6.4.3 Multiple comparisons

The more hypothesis tests you conduct, the higher the probability that you will find significant differences between the groups under study which are actually due to chance (Figure 10). However, the question of when and how to handle multiple testing statistically is not trivial. An extreme approach is to never adjust for multiple testing, as it risks missing important research findings.[134] Recent papers have suggested using a Bayesian approach to determine which groups of analyses are suitable for multiple testing adjustment methods, due to the otherwise obvious difficulties associated with choosing the appropriate testing bounds – should you adjust for other tests within or outside the stratum, all other tests in your study, or all other tests in other similar studies?[135,136] Furthermore, in studies with a large number of comparisons, such as study I described herein with approximately 50 primary analyses, the easy-to-use Bonferroni correction (i.e. dividing the p-values with the number of analyses conducted) would require p-values to be $< 0.05/50 = 0.001$ to be considered significant, which would undoubtedly invalidate some potentially important findings.

While statistics is a powerful tool, it only supplies you with a result depending on whatever input you provide. Deciding on the appropriate significance level is a minor problem compared to obtaining unbiased data, choosing the right analysis methods, interpreting the results, and using those interpretations to modify or supplement existing knowledge. Observational studies with multiple comparisons are common in epidemiology, but the credibility of such studies could be improved by deciding and describing beforehand what it is you set out to do, as well as pre-registering your observational studies (e.g. at www.clinicaltrials.gov). Furthermore, this type of research demands that follow-up studies be conducted, in order to confirm any previous findings. For example, as the albeit non-comprehensive summary above shows (Table 4), several cancer forms have indeed been consistently associated with increased risks and worse survival among transplant recipients compared with both the general population and other comparison groups. This illustrates the need to reproduce and challenge previous research, and publish the findings even if only confirmatory results are found.

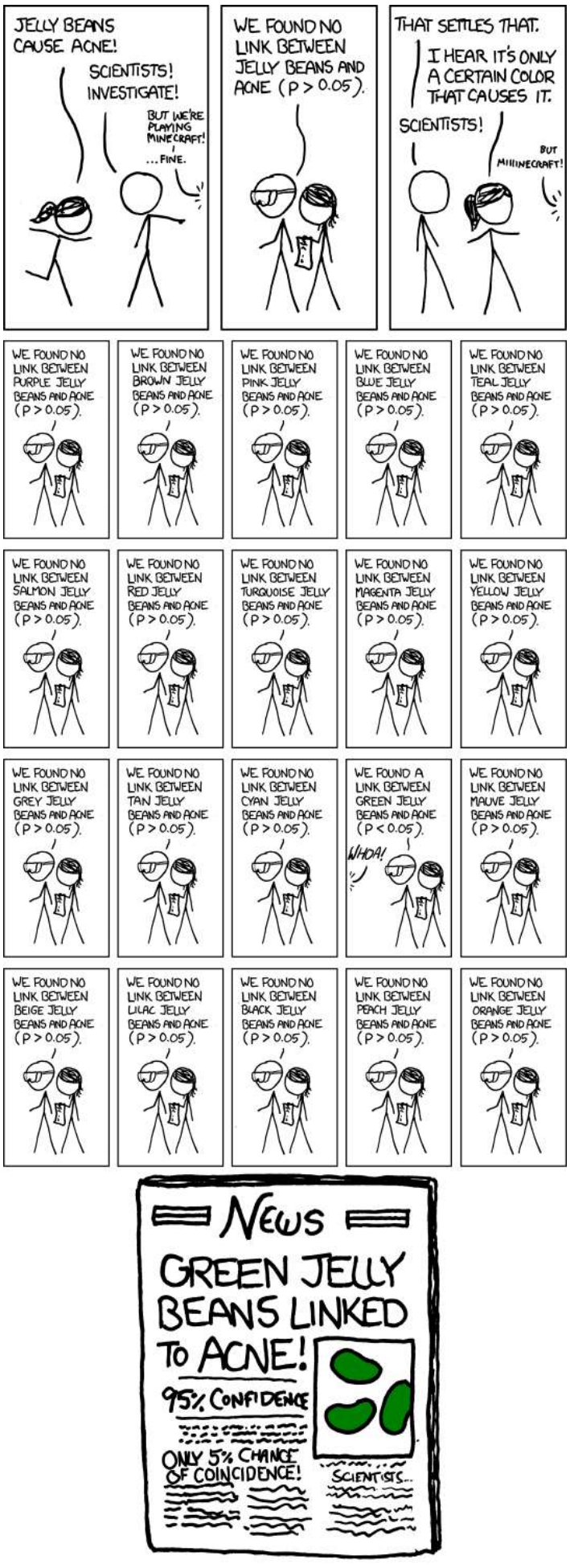

Figure 10. *Significance.* URL: https://xkcd.com/882/ Published under a Creative Commons Attribution-NonCommercial 2.5 License (https://xkcd.com/license.html).

7 CONCLUSIONS

- Nordic KTRs were at increased relative and absolute risks of developing post-transplant cancer compared to the general population.
- Swedish OTRs with cancer had higher rates of cancer-specific death, overall and for a number of specific cancers, compared with non-transplanted cancer patients.
- Swedish CRC patients with a medical history of solid organ transplantation had lower odds of receiving surgical, neoadjuvant, and adjuvant treatment, and worse cancer-specific and overall survival, compared with matched non-transplanted CRC patients.

These findings should be considered when developing post-transplant cancer management strategies, as regards both potential cancer screening and treatment. Due to the complexity of these concepts, solid advice on changes in their implementation is difficult to give based on this thesis. However, the results presented herein clearly underline the need for potential organ transplant candidates to be made aware of how transplantation affects cancer risk and outcomes, in order to ensure that they both adhere to screening practices, and report usual as well as unusual new symptoms so that de novo cancers are diagnosed at an early stage. For the same reason, health care personnel need to take such symptoms seriously and act swiftly to investigate any signs of post-transplant cancer. Once diagnosed, cancers among OTRs should be evaluated from a transplant perspective in addition to a surgical/oncological one. Cancer MDT discussions should accordingly incorporate the views of transplant specialists in order to provide OTRs with the best cancer care possible.

8 POINTS OF PERSPECTIVE

Even though post-transplant cancer incidence epidemiology has been thoroughly investigated, there is still a lack of research on cancer survival and associated determinants among OTRs. Future research efforts could be directed towards:

- Understanding reasons for the worse cancer prognosis seen among OTRs, not only at an epidemiological but also at a biological level
- Expanding cancer treatment studies to include OTRs, to clarify which patients are at higher risk of side-effects and adverse events, and ensure optimal treatment protocols
- Further evaluating MDTs for post-transplant cancer, given the plausible survival gains associated with such meetings
- Improving screening protocols among OTRs as well as the general population, such as developing methods that are less invasive and/or uncomfortable, especially among patients with increased cancer risk (e.g. OTRs) as more frequent screening may be indicated among such groups
- Developing methods and interfaces for helping patients partake to a larger extent in their own healthcare, which might increase patient compliance with given recommendations and treatments
- Establishing tolerance among OTRs, to be able to eventually attenuate or even discontinue immunosuppressive treatment, which would presumably both decrease cancer incidence and simplify oncological therapy, given less complicating drug-drug interactions

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