**University of Alberta**

# Incidence and Risk Factors for Non-Melanoma Skin Cancer Post Renal Transplant

by

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## Dedication

I dedicate my thesis to my loving husband Chris and children, Joshua and Nicole who collectively made many sacrifices, in order to see me through to completion of my program. In addition, they supported and gave me encouragement when I needed it and showed patience and understanding during challenging times throughout this long process. Also, to my mother, June Riauka whose endless support throughout my whole education I will never forget. And to my late father, Stanley Riauka, who would have been so very proud of my accomplishments.

**Abstract**

Non-melanoma skin cancer (NMSC) remains a problem post renal transplant. The purpose of this study was to determine incidence, time to development, and risk factors for NMSC post renal transplant. A retrospective cohort design was used to examine the relationship between demographic, clinical, and transplant variables, sun exposure history, and NMSC in the Northern Alberta Renal Program (NARP). A NARP database was cross-referenced with the Alberta Cancer Registry from 1990-2003. Data were analyzed by Chi-square, Cox Proportional Hazard analysis, and logistic regression. This cohort (n=926) had a 9.7% incidence of NMSC lesions post renal transplant. Time to development of a first NMSC lesion was 4.03 years. Predictors were older age, male, post transplant warts, and time lived in Northern Alberta. No predictors were identified for Squamous Cell Carcinoma, Basal Cell Carcinoma, or multiple lesions. This study identified a high-risk cohort who requires education, surveillance, and early treatment.

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## Table of Contents

## List of Tables

## List of Figures

# CHAPTER ONE

## Introduction

Organ transplantation is one of the marvels of modern medicine, adding years of life to patients suffering from various diseases. Generally for patients suffering from end-stage renal disease, renal transplantation is the treatment of choice. In 2003, the United Network of Organ Sharing (UNOS) recorded over 25 000 solid organ transplants performed in the United States (Traywick & O'Reilly, 2005), with 60% of all organ transplants for end stage renal disease (Durando & Reichel, 2005). This treatment spares patients from being 'hooked up to machines' for hours each week, and allows a more normal diet and lifestyle. Numerous advances have been made in the field of renal transplantation in recent years. These advances include improved immunosuppressive therapy, as well as better surgical techniques, resulting in longer graft and patient survival. In addition, more surgeries are being performed due to increased awareness of organ donation. As a result of these advances, renal graft survival now approaches 90% at one year post transplant and 70% at five years post transplant for deceased donor transplants, and approaches 95% at one year post transplant and 85% at five years post transplant for living donor transplants (United States Renal Data System-Annual Report, 2005). Despite these advances, a number of long-term problems remain, specifically, non-melanoma skin cancer (NMSC), of which squamous cell carcinoma (SCC) is the most common post organ transplant malignancy (Euvrard, Kanitakis, Pouteil-Noble, Dureau et al., 1995).

In a review of 7316 organ transplant patients, Penn (1994) reported skin cancer accounts for approximately 37% of all cancers in organ transplant recipients, with a

tendency to be more aggressive in the transplanted patient. Sheil, Disney, Mathew, and Amiss (1993) further reported 7% recurrence and metastasis rate of SCC in renal transplant patients. Incidence rates of NMSC are between 22-50% post organ transplants depending on where the patient resides (Jemec & Holm, 2003). In comparison to the general population, Bordea, Wojnarowska. Millard, Doll, Welsh, and Morris (2004) found renal transplant patients developed NMSC 15-20 years sooner. Lindelof, Sigurgeirsson, Gabel, and Stern (2000) reported the risk of developing NMSC is approximately 100 times greater by 5 years after organ transplant than in the general population. As well, Ramsey, Fryer, Hawley, Smith, Nicol, and Harden (2003) noted this risk could increase depending on the age of the recipient at the time of transplant and the duration of immunosuppressive therapy. The time to diagnosis of SCC post renal transplant could be between 3-13 years depending on age at time of transplant (Webb, Compton, Andrews, & Koffman, 1997). Euvrard, Kanitakis, Pouteil-Noble, Dureau et al. (1995) found the mean interval of time from renal transplant and the appearance of SCC was 8.6 $\pm$ 6 years. Gupta, Cardella, and Haberman (1986) found the mean time to development of NMSC of Caucasian renal transplant patients was 5.3 years (range 24-181 months). As survival time of the renal transplant patient increases due to better immunosuppressive therapy and post-transplant care, so will the incidence of skin cancer (Naldi et al., 2000). National differences do occur and reflect both the composition of the population at risk and environmental factors. Hartevelt, Bouwes Bavinck, Kootte, Vermeer, and Vandenbroucke (1990) reported rates of non-melanoma skin cancer are 10% at 10 years, and 40% at 20 years post renal transplant in the Netherlands. Bouwes Bavinck, Hardie et al. (1996) in Australia, noted that they could be as high as 45% at 11

years and 70% at 20 years. Furthermore, skin cancer is also responsible for a mortality rate of 5-8% in organ transplant recipients (Stockfleth, Ulrich, Meyer, & Christophers, 2002). Penn (2000) reported 5% of transplant patients died of skin cancer, of which 60% were from SCC, 30% from malignant melanoma, 8% from Merkel cell tumors, and 2% from Basal Cell Carcinoma (BCC), thus highlighting the aggressive nature of SCC. With little research done on the incidence of NMSC in Northern Alberta, coupled with the impact of newer immunosuppressive therapy, lifestyle, and sun exposure in this region, it is important to examine the proportion of renal transplant patients who develop NMSC and identify associated risk factors.

## Purpose of the Study

The purpose of this study was to identify the incidence of non-melanoma skin cancer post renal transplant and to examine the associated risk factors for developing non-melanoma skin cancer. The research questions addressed were:

1. What is the incidence of non-melanoma skin cancer in post renal transplant patients in Northern Alberta?
2. What is the length of time to primary non-melanoma skin cancer lesion in post renal transplant patients in Northern Alberta?
3. What are the risk factors for non-melanoma skin cancer in post renal transplant patients in Northern Alberta?

## Significance of the Study

As more renal transplant patients are living longer, a higher incidence of skin cancer may result. In order to decrease the morbidity and mortality of these patients, there needs to be a clearer understanding of why some patients develop skin cancer and why

some do not. Once risks are identified, patient education, both pre and post transplant can be provided, along with development of a surveillance program to modify therapy as needed.

# CHAPTER TWO

## Literature Review

Upon review of the literature, there are a number of factors involved in the development of non-melanoma skin cancer (NMSC) in renal transplant patients. The primary factors identified were sun exposure, lifestyle, genetic influences, human papilloma virus (HPV), and immunosuppressive therapy.

### Risk Factors for Non-Melanoma Skin Cancer

#### Sun Exposure History

Sun exposure is important in the development of skin cancer as it directly causes DNA damage to the skin and induces further immunosuppression in an immunocompromised patient (Bouwes Bavinck, Boer et al., 1993; Boyle, MacKee, Briggs, Junor, & Aitchison, 1984; Parrish, 1983). Sun exposure is thought to be one of the most influential risk factors for the development of skin cancer (Dreno, 2003). In the general population, Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) are the most common skin cancers among Caucasians in Europe, North America, and Australia (BC Cancer Agency, 2004), with a BCC: SCC ratio of 5:1 (Penn, 1994). However, in the immunosuppressed population, BCC is about 6 times more frequent than in the general population and SCC is about 27 times more frequent, causing a reversal of the BCC: SCC ratio (Dreno, Mansat, Legous, & Litoux, 1998). Some studies cite BCC as 10 times and SCC as high as 250 times more frequent in the transplant population as in the general population (Hartevelt, Bouwes Bavinck, Koote, Vermeer, & Vandenbroucke, 1990). The risk appears to increase linearly for BCC and exponentially for SCC (Webb et al., 1997). In the general population, studies have suggested that BCC may be a result of

early exposure to sunlight, with emphasis on childhood sunburn, whereas SCC may be more associated with total lifetime exposure (BC Cancer Agency, 2004). It is also suggested that the last 10 years of exposure to sunlight may be significant in the development of SCC (BC Cancer Agency, 2004). Bouwes Bavinck, Boer et al. (1993) found in renal transplant patients, exposure to sunlight before the age of 30 rather than exposure after 30 years of age, contributed to increased risk of developing skin cancer later in life.

The effects of sunlight on renal transplant patients appear to accelerate the development of NMSC in sun-exposed areas, along with their immunosuppressive therapy (Moloney, DeFreitas, Conlon, & Murphy, 2005). Skin cancer in organ transplant patients occurs mostly in sun-exposed areas such as the head, arms, hands, and lower legs, with 80% SCC and 60% BCC occurring on sun-exposed areas of skin, with the highest prevalence on the face and the backs of the hands and BCC lesions also being found on the trunk of the body (26%) (Naldi et al., 2000). Dreno (2003) reported NMSC occur in an extra-cephalic location for patients less than 40 years of age and in a cephalic location for patients greater than 40 years of age. Skin cancer being found mostly in these sun-exposed areas demonstrates a positive correlation between sun exposure and the development of these lesions (Dreno et el., 1998).

Sun Exposure and Geographic Location

Geographical location and its relationship to sun exposure seem to have a definite impact on rates of skin cancer in renal transplant patients. As stated earlier, renal transplant patients living in Australia have almost double the incidence of skin cancer at 20 years post transplant as compared to patients living in the Netherlands (Hartevelt et al.,

1990; Bouwes Bavinck, Hardie et al., 1996), and in comparison to patients in Japan where very little skin cancer is reported (Kishikawa et al., 1998). A study in Oregon, a little closer to Northern Alberta, reported an incidence of 35% for skin cancer 10 years post heart transplant (Lampros, Cobanoglu, Parker, Ratkovec, Norman, & Hershberger, 1998). It is known that proximity to the equator, higher altitudes and thinning ozone layer increase the risk of developing skin cancer in the general population due to more intense sun exposure. People who move closer to the equator develop higher rates of skin cancer than their native countrymen; however lower rates than the residents of their new country (Hu, Fangchao, Collado-Meza, & Kirsner, 2004). Webb et al. (1997) described that time after renal transplant and decreasing latitude as important risk factors in the development of skin cancer. Ulrich, Schmook, Sachse, Wolfram, and Stockfleth (2004) described a significant relationship between altitude and the incidence of NMSC in organ transplantation; increasing altitude increased the incidence of NMSC. Thinning ozone layer also allows more ultraviolet radiation to reach the earth potentiating the problem of skin cancer (Rhodes, 1995). Bordea et al. (2004) reported an increased incidence of skin cancer in temperate climates. Ramsey, Fryer, Reece, Smith, and Harden (2000) identified that people who live in a more temperate climate have a higher incidence of SCC than originally thought due to more frequent holidays in a hot climate.

Sun Exposure and Lifestyle

When looking at geographic location as a risk factor for skin cancer, one must consider how climate affects the lifestyle of that region. Robinson, Rigel, and Amonette (1997) reported that in the general population, with most exposure between 10:00 am and 4:00 pm, "greater duration of weekend exposure was significantly associated with higher

skin cancer, being white, being male, living in areas of the country with lower daily sunshine levels, and working indoors" (pg.182). As well, "a greater duration of weekday outdoor exposure was significantly associated with a lower education, being male, living in areas of the country with a lower daily sunshine level and working outdoors" (pg.182). Rhodes (1994) suggested that most people use sunscreen to prevent sunburn but stay in the sun longer leading to more ultraviolet exposure. Dreno (2003) agrees that prolonged time in the sun should be avoided, even with sunscreen, to decrease the chance of skin cancer. One study found that 91% of renal transplant patients knew the dangers of UVR exposure, and 77% of patients knew they were more likely to develop skin cancer; however, 31% were not changing their lifestyle to decrease UVR exposure (Butt & Roberts, 1997). Another study by Seukeran, Newstead, and Cunliffe (1998) found only 30% of the responders knew why they needed to take extra protection against the sun post renal transplant, and that only 18% made any attempt to avoid mid-day sun, with a minority wearing protective clothing.

Smoking

Tobacco smoking has also been implicated on the development of skin cancer in renal transplant patients. In animal studies tobacco smoke has been found to directly or indirectly act as a skin carcinogen (Wynder & Hoffman, 1968). Tobacco smoke has also been found to suppress the immune system therefore decreasing immune surveillance (Johnson, Houchens, Kluwe, Craig, & Fisher, 1990; Wewers et al., 1998). De Hertog et al. (2001) found, in the general population a significant association between tobacco smoking and SCC, with a higher risk for current smokers than for former smokers. The number of cigarettes smoked and development of SCC was observed, as well as, noted

cigar smokers were observed to have less risk of SCC in comparison to cigarette and pipe smokers (De Hertog et al., 2001). Ramsey et al. (2003) reported there was a greater risk of SCC than BCC for renal transplant patients with a history of smoking, in contrast to lifelong smokers, but did not find that an increase in the amount of smoking nor was current smoking associated with more risk. However, in renal transplant patients the effects of smoking may be overridden by other more important risk factors (Bordea et al., 2004).

Ethnicity

In the general population, certain physical characteristic such as fair skin as well as light colored eyes and hair increase the risk of SCC (Ramsey et al., 2003). Espana, Martinez-Gonzalez, Garcia-Granero, Sanchez-Carpintero, Rabago, & Herreros (2000) noted that heart transplant patients with skin type I/II (burns in sun) have a higher risk of skin cancer than those with skin type III/IV (tans in sun). Glover et al. (1993) also found renal transplant recipients with skin types I and II had higher rates of SCC. Moosa (2005) found that the most prominent difference between Caucasian and non-Caucasian renal transplant patients was the incidence of skin cancer, where Caucasians had cancers of the skin, non-Caucasians had Kaposi sarcoma and no reports of skin cancer. To further illustrate how important ethnicity is in the development of skin cancer, Caucasian renal transplant patients who reside in Australia have the highest rates of non-melanoma skin cancer in the world (Penn, 1994; Bouwes Bavinck, Hardie et al., 1996).

Gender

Gender has been described as a risk factor for NMSC. Godar, Wengraitis, Schreffler, and Sliney (2001) found that men in the general population over the age of 40

years had the highest exposure to UV light. Men, more than women, used less sunscreen, less protective clothing, less shade, and had an attitude that a tan looked healthier (Robinson & Rigel, 2004). Euvrard, Kanitakasis, Pouteil-Noble et al. (1995) and Jemec and Holm (2003) and Liddington et al. (1989) concurred that male gender is significant risk factor for skin cancer. Bordea et al. (2004) found males have a higher risk of skin cancer attributed to higher levels of sun exposure, with female risk almost half that of male risk. Harden, Fryer, Reece, Smith, and Ramsey (2001) and Jemec and Holm (2003) described the high risk individual as male, older, and having an outdoor occupation, long duration of immunosuppressive therapy, and positive smoking history. However, there have been other studies in renal transplant patients and gender was not a significant risk factor for NMSC (Jensen et al., 1999).

Age

Age at time of renal transplant has a large impact on the development of skin cancer. Bordea et al. (2004) found the risk of skin cancer increased by 7% for each additional year of age at transplantation. Therefore, as long as recipient age and duration of immunosuppressive therapy increases, so will NMSC (Bayes et al., 1999). Webb et al. (1997) described median time after transplant and diagnosis of skin cancer being 13 years for those who received renal transplants between 18-40 years of age, but only 3 years for those who received transplants after the age of 60 ($p>0.001$). As stated earlier, SCC is the result of cumulative sun exposure, therefore as a patients' age increases so will the risk of SCC (Berg & Otley, 2002; Gilchrest, Eller, Gellar, & Yaar, 2001). Liddington et al. (1989) agreed the duration of immunosuppressive therapy is an important risk factor for skin cancer but found this was irrespective of the patients' age at time of transplant. With

the immunosuppressive medications available today that significantly decrease the risk of rejection, more elderly are being transplanted. Thus, the history of sun exposure is longer, increasing the risk of SCC (Berg & Otley, 2002). As well, immunosuppressive therapy is directly carcinogenic, contributing to more skin cancer (Hojo et al., 1999; Kelly, Meikle, & Sheil, 1987; Servilla, Burnham, & Daynes, 1987). This is also impacted by the fact that renal transplant patients develop skin cancers 15-20 years earlier than the general population (Bordea et al., 2004).

Genetic Influence

Human Leukocyte Antigens (HLA) has an impact on the development of skin cancer. Bock, Bliss, Matas, Arthur, and Little (2004) described theoretical reasons for this impact: some HLA types may be more associated with higher rate of rejection, some HLA types may have higher rates of acquiring oncogenic viruses, some HLA types may be linked to skin pigmentation. Bouwes Bavinck, Kootte,Van der Woude et al. (1991) and Czarnecki et al. (1992) stated that renal transplant patients whom possess HLA B-27, and DR-7, have an increased risk of developing skin cancer. It was also noted that there was a slight relative increase in SCC and keratotic skin lesions for patients positive for HLA A-3 (Bouwes Bavinck, Kootte,Van der Woude et al., 1991) They also stated that the presence of HLA A-11 decreases the chance of skin cancer, but this effect may be regional. Australian researchers found patients with HLA A-11 had skin cancer (Bouves Bavinck, Vermeer et al., 1991; Czarnecki et al., 1992). Others also disagree with HLA-11 as being protective against skin cancer (Bock et al., 2004). As well, the HLA matching between donor and recipient has an impact on the development of skin cancer, since a poorly matched recipient theoretically will require more immunosuppressive medication

to decrease risk of rejection (Ulrich et al., 2004). When donor and recipient do not match on the HLA B locus, there is an increase in SCC for the recipient (Bouwes Bavinck, Vermeer, Van der Woude et al., 1991). However, mismatches on HLA A and DR do not seem to matter (Bouwes Bavinck, Vermeer, Van der Woude et al., 1991). Glover, Bodmer et al. (1993) and Jensen et al. (1999) disagree with the importance of HLA and risk of SCC post renal transplant. Bordea et al. (2004) also found no association between HLA mismatch of the donor and recipient and risk of skin cancer. Each mismatch of HLA antigens between donor and recipient has an incremental decrease in survival by 1.6 years (Ulrich et al., 2004). Ulrich et al. (2004) stated that most studies report that the importance of HLA for skin cancer to be small and in select geographic locations and larger studies are needed to establish a relationship between HLA antigens and skin cancer development after renal transplants.

Human Papilloma Virus

The role of Human Papilloma Virus (HPV) and the development of skin cancer post renal transplant remains controversial. Warts are a well-known problem post transplant especially to uncovered areas like the face, hands, and forearms, and can increase with duration of immunosuppressive therapy (Dreno et al., 1998). The pathophysiology by which HPV may play a role in carcinogenesis have yet to be determined, but one possible explanation is that the virus has a promoter effect acting in conjunction with specific tumor initiators or other promoters of which UVR is the most influential (Harwood et al., 2000). Harwood et al. (2000) detected HPV DNA in 37/44 (84.1%) of SCC, 18/24 (75%) of BCC, and 15/17 (88.2%) of pre-malignant skin lesions from the immunosuppressed group, in contrast to the immunocompetent group which had

6/22 (27.2%) of SCC, 11/30 (36.7%) of BCC and 6/11 (54.4%) pre-malignant lesions. De Jong-Teiben et al. (2000) found epidermodysplasia-verruciformis associated subgroup of HPV (EV-HPV DNA) in biopsies of premalignant lesions and NMSC of renal transplant patients. De Jong-Teiben et al. (2000) also found a higher prevalence of EV-HPV DNA in SCC and skin lesions in sun-exposed areas suggesting EV-HPV benefits from UVR and immunosuppressive therapy. Shamanin et al. (1996) found the presence of HPV DNA in a large percentage of specimens of NMSC in immunosuppressed (64%) and immunocompetent (32%) patients, rendering HPV as a possible factor in etiology of NMSC. Glover et al. (1993) found viral warts and SCC co-localize in sun-exposed sites and also found UVR to be an important variable in the development of warts and cancer. Boxman et al. (1997) and Shamanin et al. (1996) suggested that immunosuppressive therapy and /or UVR due to immune suppression may lead to (re) activation of latent HPV infection.

Alternatively, HPV may be simply a coincidental cutaneous passenger for HPV, having been detected in nonimmunosuppressed skin (Harwood et al., 2000). In one study, 45 out of 49 (92%) hair samples from immunosuppressed patients were found to harbor EV-HPV DNA versus 10 out of 22 (45%) in immunocompetent patients (Boxman et al., 1997). Another study found HPV DNA in 8 out of 42 (19%) skin samples from immunocompetent patients (Weissenborn et al., 1999). Euvrard et al. (2003) also found that organ transplant patients who have long lasting warts do not progress into skin cancer.

Immunosuppressive Therapy

Immunosuppressive medications induce skin cancer by directly being carcinogenic to cells and by decreasing immune surveillance of abnormally dividing cells (Hojo et al., 1999; Otley, Coldiron, Stasko, & Goldman, 2001; Servilla, Burnham, & Daynes, 1987). Immunosuppressive medications are necessary to prevent rejection (Otley et al., 2001). However, immunosuppressive medications have many side effects including promoting the development of skin cancer (Otley et al., 2001; Dreno, 2003). To decrease or eliminate these undesired effects, immunosuppression should only target elements of the immune response specific to the renal transplant, but this is not possible at this time (Otley et al., 2001). As a result, renal transplant patients are generally on multiple (maintenance) immunosuppressive medications (Durando & Reichel, 2005). The longer they are on immunosuppressive medications, the greater their risk of skin cancer (Liddington et al., 1989).

Immunosuppressive medications are divided into induction and maintenance therapies. Induction medications are antibody-based preparations used in the early transplant period to decrease the risk of acute rejection (Durando & Reichel, 2005). Bordea et al. (2004) found using induction therapy (Anti-lymphocyte globulin, methylprednisolone) at the time of transplant did not increase patients' risk of skin cancer. Jensen et al. (1999) found no increase in skin cancer with the use of OKT3 or Anti-thymocyte globulin. Maintenance medications are used in combination with each other because each targets certain aspects of the immune response with the goal of using the lowest possible dose to decrease side-effects without increasing the risk of rejection

(Moloney et al., 2005). Maintenance immunosuppressive therapies can be divided in Pre-cyclosporin, Cyclosporin, and Post-Cyclosporin eras.

*Pre-Cyclosporin Era.* The Pre-cyclosporin era (1954-1962) consisted of identical twin donations and the use of prednisone (Durando & Reichel, 2005), along with whole body irradiation, splenectomy, thymectomy, and thoracic duct drainage (Moloney et al., 2005)). Renal transplantation then progressed to non-twin related donation with some cadaveric transplants with use of prednisone and azathioprine as immunosuppressive therapy (1962-1983) (Durando & Reichel, 2005). Historically, " the increase in skin cancer post transplant was explained as a defect in surveillance of the skin which normally destroys potentially malignant cells, a proliferation of oncogenic viruses, and the carcinogenic effect of the immunosuppressive medications" (Westburg & Stoen, 1973, pg.895*).* It was discovered that Azathioprine had tumor promoting qualities as well as increasing the photosensitivity of the skin, all which contributed to an increase in the risk of skin cancer in immunosuppressed patients (Hemmans & Moore, 1986). Lennard, Thomas, Harrington, and Maddocks (1985) found that patients on Azathioprine and Prednisone who developed skin cancer had an increased concentration of the Azathioprine metabolite (6-thioguanine nucleotide) in their red blood cells and concluded that this increased concentration was the cause of the development of actinic keratosis and malignant skin lesions, which supported Azathioprine as a possible cause in skin cancer. Penn (1996) found patients on Azathioprine had a higher percentage of skin cancers (40.6%) versus Cyclosporin and Azathioprine therapy (34.2%) versus Cyclosporin (25.1%). As well, Kelly et al. (1987) described an animal model comparing Prednisone, Cyclosporin, and Azathioprine. It was found that Prednisone failed to intensify

carcinogenesis; Cyclosporin decreased the time to tumor development and Azathioprine had the greatest increase in cancer development. However, Bouwes Bavinck, and Hardie et al. (1996) disagree that Azathioprine is solely responsible for the increased incidence of cancer due to metabolites.

*Cyclosporin Era.* There was a defining moment in renal transplantation when Cyclosporin was developed. Cyclosporin era was marked with the discovery of Cyclosporin in 1976 and its use (1983-1990s) improved graft and patient survival (Durando & Reichel, 2005). It was a much stronger immunosuppressive medication than previously used (Azathioprine and Prednisone) which allowed more renal patients to be transplanted due to better immunosuppression, resulting in decreased risk of rejection (Durando & Reichel, 2005). In addition to its immunosuppressive qualities, it was found that Cyclosporin advanced the acceleration of cancer at a cellular level, independent of its effect on host's immune cells (Hojo et al., 1999).

Studies are inconclusive as to whether Cyclosporin or Azathioprine is more responsible for the development of skin cancer (Berg & Otley, 2002). The addition of Cyclosporin to Azathioprine therapy seemed to be associated with an increase risk of SCC (Hiesse et al., 1997; Jensen et al., 1999). Bordea et al. (2004) stated that comparing the two therapies (Azathioprine and Cyclosporin) is difficult, as patients taking Azathioprine also received high-dose then low dose steroids, whereas patients taking Cyclosporin received low dose Azathioprine and low dose Prednisone. In contrast, Blohme and Larko (1992) reported there was no difference in the incidence of skin cancer between Cyclosporin and Azathioprine therapy on a five-year retrospective review of

patients, but acknowledged there has not been enough experience with the effects of Cyclosporin therapy.

Authors disagree about the impact of immunosuppressive therapy on the development of skin cancer. This is complicated by the fact that most data on skin cancer post renal transplant are from the Cyclosporin era. Some studies found that the increase in skin cancer post transplant is a result of overall immunosuppression from multiple drug therapy and not just none agent (Bouwes Bavinck et al., 1996; Durando & Reichell, 2005; Glover et al., 1997; Jensen et al., 1999). Jensen et al. (1999) found triple therapy (Cyclosporin, Prednisone, Azathioprine) to be 3 times more risk for SCC than double therapy. However, it has been suggested that patients on double therapy (Prednisone, Azathioprine) may have benefited from better HLA matching, shorter pretransplant wait times, and longer follow-up than patients on triple therapy (Hiesse, et al., 1995 as cited in Durando & Reichell).

The amount of time on immunosuppressive therapy may be directly related to risk of skin cancer (Bordea et al., 2004). Bordea et al. (2004) reported that for patients on immunosuppressive therapy for greater than 10 years there was a 10 times increase in skin cancer compared to patients on immunosuppressive therapy for five years or less. As well skin lesions occurred earlier in patients on Cyclosporin therapy compared to Azathioprine treated patients (Hiesse et al., 1997). Another study showed a decrease in the incidence of skin cancer for patients on low dose Cyclosporin compared to standard dose Cyclosporin therapy (Dantal et al, 1998). Otley et al. (2001) also found that a discontinuation of immunosuppressive medications was associated with a deceleration of skin cancers and viral warts. Trembley, Fernandes, Habbab, Edwards, Loertscher, and

Meterissian (2002) found, when comparing patients from the pre-Cyclosporin era to the Cyclosporin era, that there was an increased incidence of skin cancer in the Cyclosporin group (5.8% vs. 10.2%, p=.04). There was a further increase in skin cancer if the patients were 45 years and older and on Cyclosporin versus pre-Cyclosporin (14.3% vs. 5.3%, p=.03). This finding was important as more elderly are currently being transplanted and are on Cyclosporin.

*Post-Cyclosporin Era.* Since 1990, a number of new immunosuppressive medications have been discovered, with their use further improving graft and patient survival (Durando & Reichel, 2005). Tacrolimus, Mycophenolate mofetil, and Rapamycin are new medications designed to provide more selective immunosuppression, but studies of these newer immunosuppressive medications are few. It is thought that increased specificity of the medications will result in fewer undesirable effects (Otley et al., 2001). Moloney, Kelly, Kay, Conlon, and Murphy (2004) suggested that newer immunosuppressive agents might be less carcinogenic than standard immunosuppressive regime. It has been suggested that Tacrolimus and Rapamycin are associated with less cancers and that Cyclosporin is directly carcinogenic. (Durando & Reichel, 2005). However there is a dearth of information on the effects of Tacrolimus and the development of skin cancer.

Mycophenolate mofetil with the active component Mycophenolic acid (MPA) is currently being used since 1995 for the prevention of acute rejection in organ transplantation (Danovitch, 2005). In the 1960s MPA emerged as a potential anti-cancer drug in animal studies (Carter et al., 1969). More recently, Mycophenolate mofetil was also noted to possess anti-tumoral properties, particularly in colon and prostate carcinoma

(Engl et al., 2005). Yet, the effects of Mycophenolate mofetil needs to be examined as to how influential it is in the development of skin cancer (Euvrard, Ulrich, & Lefrancois, 2004; Moloney et al., 2005).

There have been animal studies showing that Rapamycin has the ability to inhibit the growth of malignant cells (Luan, Hojo, Maluccio, Yamaji, & Suthanthiran, 2002). As well, Luan et al. (2002) found that Rapamycin decreased the incidence of skin cancer even when administered with Cyclosporin. Rapamycin has strong anti-tumor activity in vitro and in vivo (Campistol, Gutierrez-Dalmau, & Torregrosa, 2004). Results from multicenter human trials have indicated that after 2 years: patients on Rapamycin and Cyclosporin had a lower incidence of skin cancer than placebo; patients receiving Rapamycin as maintenance therapy instead of Cyclosporin had no incidence of malignancies; patients that were weaned off Cyclosporin and remained on Rapamycin had lower incidence of skin cancer (Mathew, Kreis, & Friend, 2004). Mathew et al. (2004) suggested that Rapamycin maybe advantageous in decreasing the incidence of skin cancer even when given with Cyclosporin. Kahan et al. (2005) concurs that receiving Rapamycin-Cyclosporin+/-Prednisone lowers the incidence of skin cancer versus conventional triple therapy (Cyclosporin-Azathioprine/Mycophenolate mofetil-Prednisone). Kreis et al. (2004) found patients on Sirolimus-Cyclosporin-Prednisone therapy versus Sirolimus-Prednisone therapy had 6.5% versus 3.7% incidence at 36 months post transplant. Patients could possibly benefit from a switch in medication after the occurrence of the first skin tumors (Euvrard et al., 2004).

With so many more immunosuppressive medications available to renal transplant programs, transplant physicians have begun to personalize immunosuppressive

medications in order to decrease the side effects. Kaufman, Shapiro, Lusey, Cherikh, Bustami, and Dyke (2004) stated that transplant programs continue to utilize Prednisone as part of the backbone of immunosuppressive therapy in 96% of patients. However, the usage of Cyclosporin has decreased from 96% to 39% during the period of 1992-2002, while Tacrolimus therapy has increase from 2% to 64%. Since Mycophenolate mofetil and Rapamycin have been introduced, Mycophenolate mofetil use has increased to 80% and Rapamycin use has increase to 21%, and continues to increase, with the use of Azathioprine decreasing from 87% to 6%. As well, Kaufman et al. (2004) noted that induction therapy increased in use from 9% to 65% between 1992-2002. Because of these changes, it is difficult to assess the effects of immunosuppressive medications on skin cancer due to different study methods, use of combinations therapy, and introduction of different immunosuppressive medications at different times (Moloney et al., 2005). As well, most studies to date have been retrospective in examining the effects of Cyclosporin and Azathioprine on the development of skin cancer (Berg & Otley, 2002). The factors that do not seem to increase the rates of skin cancer are type of donor, anti-rejection therapy with Anti-Thymocyte Globulin (ATG) or OKT3 (Harden et al., 2001; Jensen et al., 1999; Ramsey et al., 2000), duration of dialysis (Webb et al., 1997), and gender of recipient (Jensen et al., 1999).

In summary, factors that influence NMSC risk are multiple and interacting. Geographic location and lifestyle are important factors when determining sun risk. With most studies having been conducted outside of Alberta, it is important to know the risk for skin cancer in this area, where the environment and lifestyle differs from those previously studied. Also, most studies evaluate the "old" immunosuppressive medications

and do not represent the impact of personalizing "new" immunosuppressive medications. Furthermore, most previous studies of immunosuppressive therapy did not control for age, therefore, it is difficult to determine if the increase was due to the immunosuppressive therapy. As well, with more high-risk patients transplanted; ie., elderly, it will be useful to know how new immunosuppressive medications impact the development of non-melanoma skin cancer. With a larger choice of agents for immunosuppressive therapy available, better patient and graft survival, the number of patients presenting with NMSC may increase (Bordea et al., 2004).

# CHAPTER THREE

## Methods

### Design

A retrospective cohort design was used to examine the incidence and the relationship between demographic characteristics, clinical variables, renal transplant variables, sun exposure history and the development of non-melanoma skin cancer (NMSC) in renal transplant patients in the Northern Alberta Renal Program (NARP).

### Sample

The sample included all patients, over the age of 16 years, registered in NARP with a renal transplant since 1990, due to incomplete records prior to 1990. Patients were excluded if: pediatric patients; enrolled in a clinical trial for do not know what medication they are on; renal transplant patients transferred into the NARP program from another program; and/or if received a kidney and an extra-renal organ transplant.

### Definition of Terms

*Renal transplant* is receiving a kidney from a living-related (LRD), living-unrelated (LURD), or deceased donor donation (DDT). Number of renal transplants received and cause of transplant failure, were also documented.

*Immunosuppressive therapy* is medications taken to prevent rejection of the transplanted organ by decreasing the body's immune response to foreign entities. This included induction medications as well as maintenance medications. Induction medications include: IL-2, ALG, or OKT3. Maintenance medications include: Cyclosporin, Prednisone, Azathioprine, Cellcept (Mycophenolate mofetil), Tacrolimus,

and Rapamycin (Sirolimus). Immunosuppressive medications were recorded based on what patients were on as of month one of their renal transplant for the majority of time.

*Non-melanoma skin cancer* is the presence of Basal Cell Carcinoma and/or Squamous cell carcinoma as documented (biopsy proven). Squamous Cell Carcinoma (SCC) is described as a type of non-melanoma skin cancer that may be more related to total lifetime sun exposure; Bowens Disease is SCC in situ and will be treated as SCC; Basal Cell Carcinoma (BCC) is a type of non-melanoma skin cancer (BC Cancer Agency, 2004). Type of lesion, number of lesion(s), location of lesion(s), and when the lesion(s) was diagnosed were recorded.

*Genetic influences* are HLA typing. Both recipient and donor HLA antigens were recorded as the genetic mismatch between recipient and donor. As well, genetic influence of HLA antigens known to increase skin cancer risk was documented as the presence or absence of HLA antigens.

*Human Papilloma Virus (HPV)* is a virus that may increase risk of skin cancer, especially in the development of SCC (Dreno, 2003), and was documented from the health record as present or absent.

*Demographic variables* are age, ethnicity, and gender. Age was documented in number of years. Ethnicity was documented as Caucasian, Afro-American, Aboriginal, Indoasian, East Indian, Middle Eastern, or other.

*Clinical variables* are cause of renal failure. These were classified as Glomerulonephritis (GN), Diabetes Mellitus (DM), Hypertension (HTN), and other.

*Sun exposure* is ultraviolet radiation. Sun exposure history was assessed by a self-report questionnaire adapted from Moloney et al. (2005) (Appendix B). The Sun

Exposure Questionnaire addressed the patients' occupation, recreation, eye colour, hair colour, skin type as described by Fitzpatrick skin types (Type 1: Always burns/Never tans, Type II: Always burns/Sometimes tans, Type III: Always tans/Sometimes burns, Type IV: Always tans/Never burns, Type V: Never burns/Brown skin, Type VI: Never burns/Black skin), history of sunburn, artificial UVR exposure which includes the use of tanning salons and their tanning equipment, use of sun screen pre and post renal transplant, history of precancerous lesions, warts, and/ or skin cancer, family history of skin cancer, number of years lived in Northern Alberta recorded as a percentage of years lived in Northern Alberta over years lived, and history of smoking.

## Data Collection Procedure

Age, gender, ethnicity, cause of renal failure, number of renal transplants, cause of transplant failure, cause of death of recipient (where applicable), type of renal donation, type and duration of immunosuppressive therapy (including induction and maintenance medications), HLA antigens of both recipient and donor were retrieved from Dr. Gourishankar's Alberta Heritage Foundation for Medical Research (AHFMR) data base (Appendix A). HPV status was not obtained as it was not found upon review of health records. History of skin cancer (type, location, number of lesions, when lesions occurred and treatment) and presence of skin cancer post renal transplant (type, location, number of lesions, when lesions occurred) were documented from the health record and cross-referenced with the Alberta Cancer Registry (Appendix A). The Sun Exposure Questionnaire (Appendix B) was completed during patients' regularly scheduled post transplant clinic visits and by telephone if patients did not show for their clinic appointment or for patients with a failed transplant who do not have transplant clinic

appointments (Appendix C), to obtain occupation, recreation habits, eye colour, hair colour, skin type (Fitzpatrick Skin Types 1, 2, 3, 4, 5, and 6), history of sun burn, sun screen use, history of precancerous lesions, warts, and/or skin cancer pre and post renal transplant, family history of skin cancer, number of years lived in Northern Alberta recorded as percentage of years lived in Northern Alberta over years lived, and history of smoking.

## Data Analysis

Data were coded and entered into the Statistical Package for the Social Sciences (SPSS) software package version 15. Descriptive statistics were used to describe characteristics of the cohort and all variables of the study. Chi-square analysis was performed to examine differences between cohorts with and without non-melanoma skin cancer, between those with SCC and BCC, and between those that had greater than six and those that had less than six NMSC lesions. Cox Proportional Hazard analysis was used to examine the time to development of first NMSC post renal transplant. Predictors of NMSC post renal transplant were examined using logistic regression analysis. Significance level was $p < 0.05$.

## Ethical Considerations

Approval to access to patient health records in NARP was obtained from the Director of NARP; access to Dr. Gourishankar's AHFMR database was obtained from Dr. Gourishankar; and access to the Alberta Cancer Registry was obtained from the Alberta Cancer Board. Ethical approval for this study was obtained from the Health Research Ethics Board, University of Alberta. There were no identified direct risks or benefits for patients participating in this study, however information obtained would

potentially contribute to the understanding of the development of skin cancer in renal transplant patients living in Northern Alberta. Subjects could refuse to complete the Sun Exposure Questionnaire (Appendix C). Confidentiality of the patients was maintained and no names appeared on the Data Collection Tool (Appendix A) or Sun Exposure Questionnaire (Appendix B). Code numbers were used to identify all data. All data are stored in a locked and secured cabinet for a period of seven years.

# CHAPTER FOUR

## Findings

The purpose of this study was to identify the incidence of non-melanoma skin cancer post renal transplant and to examine the associated risk factors for developing non-melanoma skin cancer (NMSC). A retrospective cohort design was used to examine the relationship between demographic characteristics, clinical variables, renal transplant variables, sun exposure variables and the development of NMSC in renal transplant patients in the Northern Alberta Renal Program (NARP). Data were analyzed using descriptive statistics, Chi-Square analysis, Cox Proportional Hazard analysis, and logistic regression analysis.

### Characteristics of Subjects

All renal transplant patients in the NARP were retrieved from Dr. Gourishankar's Alberta Heritage Foundation for Medical Research (AHFMR) database, which totaled 1242 patients from January 1, 1990 to December 31, 2005. Excluded were pediatric patients, extra-renal organ transplant patients, patients enrolled in other clinical trials, and a small cohort of patients that were transplanted at the University of Alberta Hospital but subsequently followed at another institution (Figure 1). The remaining patients were cross-referenced for the development of NMSC with the Alberta Cancer Registry, which included information from January 1, 1990 to December 31, 2004. Information from the Alberta Cancer Registry for the time period January 1 to December 31, 2005 was not available at the time of this study. Therefore, patients from 2004 and 2005 in Dr. Gourishankar's AHFMR database were not included to allow at least one-year follow-up on all patients. This exclusion left 926 patients from the time period of January 1, 1990 to

December 31, 2003. Of these 926 patients, 199 patients had died, and 59 patients were lost to follow up.

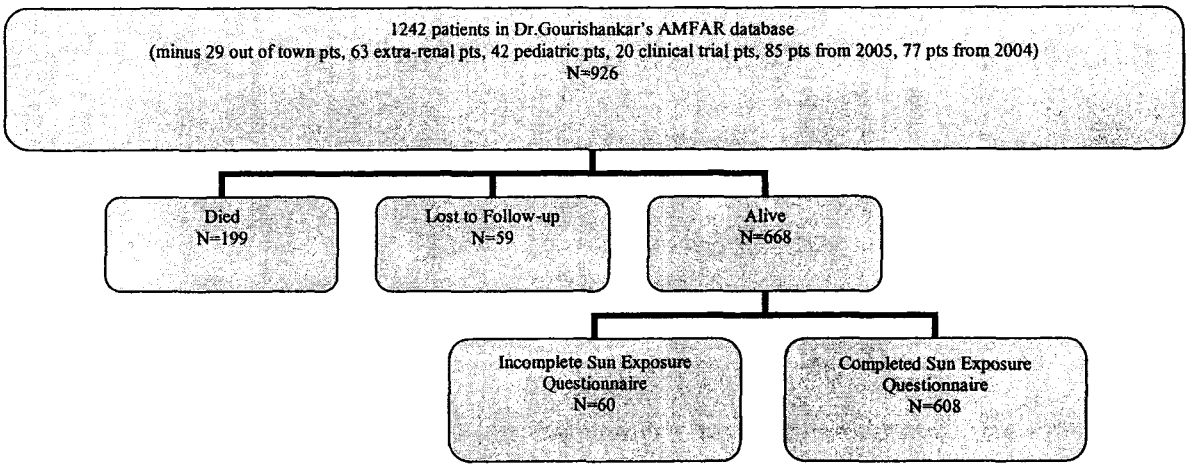


Figure1. Study Cohort

The study cohort consisted of 585 males (63.2%) and 341 females (36.8%). The age ranged from 17 to 75 years, with a mean of 44.71 years (SD=13.55), or median of 45 years. The majority were Caucasian (n=736, 79.5%). The main cause of renal failure was Glomerulonephritis (n=386, 41.7%). Graft failure was predominately due to death of the renal transplant patient (n=109, 34.9%), followed by chronic rejection (n=78, 25%). The cohort was mainly patients having a first renal transplant (n=786, 84.9%), largely from deceased donors (n=606, 65.4%). The average length of graft survival was 5.52 years (SD=3.83 years), or median of 4.82 years (Table 1). The mismatch between recipient and donor was mostly 3 antigen mismatch or greater (n=697, 75.3%) (Table 2).

Immunosuppressive therapy was analyzed using intention to treat looking at month one of the patient's regimen (Table 3). Most patients did not receive induction

Table 1

Demographics of Study Cohort

| Variable | Frequency (%) | |
|---|---|---|
| Gender | | |
| Female | 341 | (36.8%) |
| Male | 585 | (63.2%) |
| Age | | |
| Less than 45 years old | 456 | (49.2%) |
| Equal or greater than 45 years old | 470 | (50.8%) |
| Ethnicity | | |
| Caucasian | 736 | (79.5%) |
| Afro-American | 19 | ( 2.1%) |
| Aboriginal | 58 | ( 6.3%) |
| Indoasian | 72 | ( 7.8%) |
| East Indian | 33 | ( 3.6%) |
| Middle Eastern | 7 | ( 0.8%) |
| Other | 1 | ( 0.1%) |
| Original Renal Disease | | |
| Glomerulonephritis | 386 | (41.7%) |
| Hypertension | 21 | ( 2.3%) |
| Diabetes Mellitus | 167 | (18.0%) |
| Other | 242 | (26.1%) |
| Unknown | 110 | (11.9%) |
| Cause of Death | | |
| Cardiac | 48 | (24.1%) |
| Infection | 42 | (21.1%) |
| Malignancy | 36 | (18.1%) |
| Other | 42 | (21.1%) |
| Unknown | 31 | (15.6%) |
| Cause of Transplant Failure | | |
| Acute Rejection | 29 | ( 9.3%) |
| Chronic Rejection | 78 | (25.0%) |
| Malignancy | 5 | ( 1.6%) |
| Death | 109 | (34.9%) |
| Non-Function | 12 | ( 3.8%) |
| Recurrent Disease | 30 | ( 9.6%) |
| Technical Problems | 16 | ( 5.1%) |
| Other | 22 | ( 7.1%) |
| Unknown | 11 | ( 3.5%) |
| Number of Renal Transplants | | |
| First Transplant | 786 | (84.9%) |
| Second Transplant | 115 | (12.4%) |
| Third Transplant | 22 | ( 2.4%) |
| Fourth Transplant | 3 | ( 0.3%) |
| Type of Donation | | |
| Deceased Donor | 606 | (65.4%) |
| Live Donor | 320 | (34.6%) |
| Transplant Year | | |
| 1990-1994 | 292 | (31.5%) |
| 1995-1999 | 333 | (36.0%) |
| 2000-2003 | 301 | (32.5%) |
| Graft Survival | | |
| Less than 1759 days (4.92 years) | 463 | (50.0%) |
| Equal or greater than 1759 days (4.92 years) | 463 | (50.0%) |

Table 2

Human Leukocyte Antigen (HLA) Mismatch Between Recipient and Donor

| Variable | Frequency (%) | |
|---|---|---|
| HLA A Antigen Mismatch | | |
| No mismatch | 205 | (22.4%) |
| One mismatch | 456 | (49.8%) |
| Two mismatch | 254 | (27.8%) |
| HLA B Antigen Mismatch | | |
| No mismatch | 123 | (13.4%) |
| One mismatch | 393 | (43.0%) |
| Two mismatch | 399 | (43.6%) |
| HLA AB Antigen Mismatch | | |
| No mismatch | 83 | ( 9.1%) |
| One mismatch | 115 | (12.6%) |
| Two mismatch | 283 | (30.9%) |
| Three mismatch | 263 | (28.7%) |
| Four mismatch | 171 | (18.7%) |
| HLA DR Antigen Mismatch | | |
| No mismatch | 166 | (18.4%) |
| One mismatch | 443 | (49.2%) |
| Two mismatch | 292 | (32.4%) |
| Total Antigen Mismatch | | |
| Zero mismatch | 71 | ( 7.8%) |
| One mismatch | 44 | ( 4.9%) |
| Two mismatch | 93 | (10.3%) |
| Three mismatch | 223 | (24.6%) |
| Four mismatch | 206 | (22.8%) |
| Five mismatch | 185 | (20.4%) |
| Six mismatch | 83 | ( 9.2%) |
| HLA A11 Antigen | | |
| Yes | 130 | (14.1%) |
| No | 789 | (85.9%) |
| HLA B27 Antigen | | |
| Yes | 71 | ( 7.8%) |
| No | 839 | (92.2%) |
| HLA DR7 Antigen | | |
| Yes | 170 | (18.7%) |
| No | 741 | (81.3%) |

therapy (n=598, 64.6%). Of the 926 patients, most were started on maintenance therapy of Prednisone (95.3%), Mycophenolate mofetil (57.7%), and Cyclosporin (68.2%). The standard immunosuppressive protocol consisted of Cyclosporin (target trough levels were 100-125 ug/l after the first year), Azathioprine (1-2 mg/kg/day), and Prednisone (0.5

mg/kg/day at time of transplant and tapered down to a maintenance dose of 2.5 mg/day at the end of the first transplant year). Mycophenolate mofetil (MMF) became available in 1995, and patients were converted from Azathioprine to MMF at a dose of 1 gram twice daily. Tacrolimus was available in 1998 and became the first line calcineurin inhibitor for patients, with target trough levels between 5-7 ug/l after the first transplant year. Sirolimus became available in approximately 2000, and a minority of patients were converted, with target trough levels of 5-15 ug/l after the first transplant year. The mean cumulative dose of immunosuppressive medications (days of immunosuppressive therapy) was 5.64 years (SD=3.88), or median of 4.98 years.

Table 3

Study Cohort Immunosuppressive Medications

| Variable | Frequency (%) | |
|---|---|---|
| Induction Medications | | |
| None | 598 | (64.6%) |
| Polyclonal Antibody | 144 | (15.6%) |
| Interleukin 2 (IL-2) | 117 | (12.6%) |
| Monoclonal Antibody (OKT3) | 66 | ( 7.1%) |
| Unknown | 1 | ( 0.1%) |
| Maintenance Medications at Month 1 | | |
| Prednisone | 795 | (95.3%) |
| Azathioprine | 284 | (34.1%) |
| Cyclosporin | 569 | (68.2%) |
| Mycophenolate Mofetil (MMF) | 481 | (57.7%) |
| Tacrolimus | 254 | (30.5%) |
| Sirolimus | 21 | ( 2.5%) |
| Cumulative Duration of Immunosuppressive Therapy | | |
| Less than 1818.5 days | 464 | (50.1%) |
| Equal or greater than 1818.5 days | 462 | (49.9%) |

## Sun Exposure History

Of the 668 out of 926 patients that were alive, 608 completed the Sun Exposure Questionnaire (Appendix B), for a response rate of 91.02%. The remaining 60 patients did not complete due to translation difficulties, refusal to complete, not wanting to talk

about skin cancer, or not returning the questionnaire. Eye color of respondents was split between blue (n=233, 38.3%), brown (n= 247, 40.6%), and other (n=128, 21.0%); the

Table 4

Sun Exposure History – Study Cohort Personal Characteristics

| Variable | Frequency (%) | |
|---|---|---|
| PERSONAL CHARACTERISTICS | | |
| Eye color | | |
| Blue | 233 | (38.3%) |
| Brown | 247 | (40.6%) |
| Green | 50 | ( 8.2%) |
| Hazel | 78 | (12.8%) |
| Hair Color | | |
| Blonde | 128 | (21.1%) |
| Red | 18 | ( 3.0%) |
| Brown | 349 | (57.5%) |
| Black | 112 | (18.5%) |
| Skin Type | | |
| Always burns/never tans | 31 | ( 5.1%) |
| Always burns/sometimes tans | 107 | (17.6%) |
| Always tans/sometimes burns | 275 | (45.2%) |
| Always tans/never burns | 133 | (21.9%) |
| Never burns/brown skin | 56 | ( 9.2%) |
| Never burns/black skin | 6 | ( 1.0%) |
| Pretransplant Warts | | |
| Yes | 127 | (20.9%) |
| No | 480 | (79.1%) |
| Posttransplant Warts | | |
| Yes | 169 | (27.8%) |
| No | 439 | (72.2%) |
| Family History of Skin Cancer | | |
| Yes | 56 | ( 9.3%) |
| No | 545 | (90.7%) |
| Number of Years lived in Northern Alberta | | |
| Less than 38 years | 295 | (48.5%) |
| Equal or greater than 38 years | 313 | (51.5%) |
| Percentage of Life Lived in Northern Alberta | | |
| Less than 90% | 301 | (49.7%) |
| Equal or greater than 90 % | 305 | (50.3%) |

majority had brown hair (n=349, 57.5%). Most (n=275, 45.2%) reported that their skin would always tan/sometimes burn when in the sun (Fitzpatrick skin type 3). No history of precancerous skin lesions (n=580, 95.4%), warts (n=480, 79.1%), or skin cancer (n=594,

97.9%) were reported pretransplant, as well, the majority did not have precancerous skin lesions (n=503, 83.1%), warts (n=439, 72.2%), or skin cancer (n=533, 88.1%) post renal transplant. Patients also did not have a family history of skin cancer (n=545, 90.7%). Most patients reported they had never seen a dermatologist (n=312, 51.3%), and a majority stated they had never had a skin biopsy (n=420, 69.1%). The median number of years lived in Northern Alberta was 38 years (range 3-78 years) and median percentage of life lived in Northern Alberta was 90% (range 5-100%) (Table 4).

Table 5

Sun Exposure History – Study Cohort Lifestyle Characteristics

| Variable | Frequency (%) | |
|---|---|---|
| Work Outside | | |
| Yes | 320 | (52.6%) |
| No | 288 | (47.4%) |
| Hobby Outside | | |
| Yes | 478 | (79.0%) |
| No | 127 | (21.0%) |
| History of Sunbed Usage | | |
| Yes | 81 | (13.3%) |
| No | 527 | (86.7%) |
| Use of Sunscreen Pretransplant | | |
| Always | 53 | ( 8.8%) |
| Sometimes | 232 | (38.4%) |
| Never | 319 | (52.8%) |
| Use of Sunscreen Posttransplant | | |
| Always | 153 | (25.2%) |
| Sometimes | 261 | (43.0%) |
| Never | 193 | (31.8%) |
| History of Smoking | | |
| Current | 104 | (17.1%) |
| Past | 244 | (40.1%) |
| Never | 260 | (42.8%) |

A majority reported that they worked outdoors as part of their employment (n=320, 52.6%), with the mean time outdoors per day being 4.44 hours (SD=5.10); or 4.67 months of the year (SD=5.20), for an average of 9.69 years (SD=14.86). More males

(n=272) than females (n=48) reported working outdoors (p<0.001). A majority of patients reported that they had hobbies that took them outside (n=478, 79%), for an average of 2.52 hours per day (SD=2.94), or 5.68 months of the year (SD=4.26), for 21.31 years (SD=19.37). More males (n=314) in contrast to females (n=164) had outdoor hobbies (p=0.004). Most patients (n= 365, 60.2%) stated they did not have a history of less than 2 painful sunburns. A majority (n= 527, 86.7%) did not use an artificial sun tanning bed. Of those that reported using an artificial sun tanning bed, the average number of sessions was 61.84 sessions (SD=247.66), or a median of 14 sessions. Most patients (n= 319, 52.8%) reported 'never' using sunscreen pretransplant, in contrast to most patients (n=261, 43%) using sunscreen 'sometimes' post transplant. Most patients had either never smoked (n=260, 42.8%) or had a history of smoking (n=244, 40.1%), with 104 patients (17.1%) currently smoking (Table 5).

## Development of Non-Melanoma Skin Cancer

### Incidence of Non-Melanoma Skin Cancer

Overall, the incidence of a first NMSC lesion in this post renal transplant cohort was 9.7% (n=90). Of these lesions, 27 were Squamous Cell Carcinoma (SCC) and 23 were Bowens disease (Squamous Cell Carcinoma in situ), 37 were Basal Cell Carcinoma (BCC), and 3 had a mixture of SCC and BCC lesions (one patient had a Basosquamous lesion, and two patients had a SCC and BCC lesion biopsied on the same day from two different locations). Due to the mixture of these lesions they were not able to be placed in either an SCC or BCC category. By comparison, the incidence of a first SCC lesion was 5.4% (n=50), a first BCC lesion was 4% (n=37). Of the 90 patients that developed NMSC post renal transplant, the majority had more than one NMSC lesion (n=64, 71.1%), with a

mean of 7.92 lesions (SD=11.23), or a median of 4 (range 2-60 lesions). Of these 90 patients with NMSC lesions, 21.1% had greater than 6 NMSC lesions. The total number of SCC lesions post renal transplant was 376 lesions in comparison to 157 BCC lesions, giving a ratio of SCC to BCC lesions of 2.39:1. Most first NMSC lesions were located on the head and neck (n=61, 67.8%). The majority of first SCC lesions (n=31, 62%) and BCC lesions (n=28, 75.7%) were also located on the head and neck. Patients with greater than 6 NMSC lesions had the majority located on the head and neck (n=165, 54.6%) (Table 6).

Table 6

Non-Melanoma Skin Cancer Post Renal Transplant

| Variable | Non-Melanoma Skin Cancer | | Squamous Cell Carcinoma | | Basal Cell Carcinoma | | Multiple Non-Melanoma (> 6 lesions) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | N | % |
| Incidence | 90 | ( 9.7%) | 50 | ( 5.4%) | 37 | ( 4.0%) | 19 | (21.1%) |
| Location of Lesions | | | | | | | | |
| Head/Neck | 61 | (67.8%) | 31 | (62.0%) | 28 | (75.7%) | 165 | (54.6%) |
| Upper Limbs | 15 | (16.7%) | 13 | (26.0%) | 1 | ( 2.7%) | 87 | (28.8%) |
| Chest | 5 | ( 5.6%) | 3 | ( 6.0%) | 2 | ( 5.4%) | 20 | ( 6.6%) |
| Abdomen | 0 | ( 0.0%) | 0 | ( 0.0%) | 0 | ( 0.0%) | 3 | ( 1.0%) |
| Back | 3 | ( 3.3%) | 0 | ( 0.0%) | 3 | ( 8.1%) | 15 | ( 5.0%) |
| Genitilia | 2 | ( 2.2%) | 2 | ( 4.0%) | 0 | ( 0.0%) | 4 | ( 1.3%) |
| Lower Limbs | 4 | ( 4.4%) | 1 | ( 2.0%) | 3 | ( 8.1%) | 8 | ( 2.7%) |

When comparing those with NMSC and those without NMSC, there was significant differences found on gender, age, ethnicity, cause of death, cause of transplant failure, use of induction medication, transplant year, use of immunosuppressive medications (Azathioprine, Cyclosporin, MMF, Tacrolimus) hair colour, post transplant warts, number of years lived in Northern Alberta, history of sunburn, and use of sunscreen pretransplant (Tables 7, 8, and 9). There were more males (76.7% vs. 61.7%)

than females (23.3% vs. 38.3%) with NMSC in comparison to patients without NMSC ($p=0.006$). More patients with NMSC (70%), in contrast to those without NMSC (48.7%), were over the age of 45 years ($p<0.001$). All patients with NMSC were Caucasian (100%) in comparison than those without NMSC, 77.3% were Caucasian ($p<0.001$). The primary cause of death was malignancy (52.6%) for patients with NMSC, and cardiac factors (25%) for patients without NMSC ($p=0.001$). The primary cause of transplant failure was due to death (57.2%) for patients with NMSC in comparison to patients without NMSC (32.8%) ($p=0.052$). Of patients with NMSC, almost half (45.6%) were transplanted between 1990-1993, and only 17.8% were transplanted in 2000-2003, while those without NMSC were equally divided between transplant years ($p=0.002$). Fewer patients with NMSC (22.2%) had induction therapy in comparison to those without NMSC (36.8%) ($p=0.005$). More patients with NMSC in comparison to those without NMSC were on Azathioprine (54.5% vs. 31.6%, $p<0.001$); Cyclosporin (80.7% vs. 66.8%, $p=0.008$). Less patients with NMSC in comparison to those without NMSC were on Mycophenolate mofetil (44.30% vs. 59.3%, $p=0.008$) and Tacrolimus (17% vs. 32%, $p=0.003$). More patients with NMSC (76.7%) in contrast to patients without NMSC (47%) ($p<0.001$) were on cumulative duration of immunosuppressive therapy $\geq$ 1818.5 days. Of those with NMSC, 76.7% had a graft survival of $\geq$ 1759 days in contrast to 47.1% of those without NMSC ($p<0.001$). Patients with NMSC were blonde (32.3%) in comparison to 19.7% of patients without NMSC ($p=0.003$). More patients with than without NMSC had warts post transplant (50.8% vs. 25%, $p<0.001$). Seventy-two percent of patients with NMSC lived $\geq$ 38 years in Northern Alberta in contrast to only 49% of patients without NMSC

Table 7

Demographics of Patients with No Skin Cancer Versus Non-Melanoma Skin Cancer

| Variable | No Skin Cancer | | Non-Melanoma Skin Cancer | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| DEMOGRAPHIC CHARACTERISTICS | | | | | |
| Gender | | | | | **0.006** |
| Female | 320 | (38.3%) | 21 | (23.3%) | |
| Male | 516 | (61.7%) | 69 | (76.7%) | |
| Age | | | | | **<0.001** |
| Less than 45 years old | 429 | (51.3%) | 27 | (30.0%) | |
| Greater than 45 years old | 407 | (48.7%) | 63 | (70.0%) | |
| Ethnicity | | | | | **<0.001** |
| Caucasian | 646 | (77.3%) | 90 | (100.0%) | |
| Other | 190 | (22.7%) | 0 | ( 0.0%) | |
| CLINICAL CHARACTERISTICS | | | | | |
| Original Renal Disease | | | | | 0.566 |
| Glomerulonephritis | 348 | (41.6%) | 38 | (42.2%) | |
| Hypertension | 18 | ( 2.2%) | 3 | ( 3.3%) | |
| Diabetes Mellitus | 156 | (18.7%) | 11 | (12.2%) | |
| Other | 215 | (25.7%) | 27 | (30.0%) | |
| Unknown | 99 | (11.8%) | 11 | (12.2%) | |
| Cause of Death | | | | | **0.001** |
| Cardiac | 45 | (25.0%) | 3 | (15.8%) | |
| Infection | 38 | (21.1%) | 4 | (21.1%) | |
| Malignancy | 26 | (14.4%) | 10 | (52.6%) | |
| Other | 41 | (22.8%) | 1 | ( 5.3%) | |
| Unknown | 30 | (16.7%) | 1 | ( 5.3%) | |
| Cause of Transplant Failure | | | | | 0.052 |
| Acute Rejection | 29 | (10.2%) | 0 | ( 0.0%) | |
| Chronic Rejection | 75 | (26.4%) | 3 | (10.7%) | |
| Malignancy | 4 | ( 1.4%) | 1 | ( 3.6%) | |
| Death | 93 | (32.8%) | 16 | (57.2%) | |
| Non-Function | 12 | ( 4.2%) | 0 | ( 0.0%) | |
| Recurrent Disease | 25 | ( 8.8%) | 5 | (17.9%) | |
| Technical Problems | 16 | ( 5.6%) | 0 | ( 0.0%) | |
| Other | 20 | ( 7.0%) | 2 | ( 7.1%) | |
| Unknown | 10 | ( 3.5%) | 1 | ( 3.6%) | |
| IMMUNOSUPPRESSIVE MEDICATIONS | | | | | |
| Induction Medications | | | | | **0.005** |
| Yes | 307 | (36.8%) | 20 | (22.2%) | |
| No | 528 | (63.2%) | 70 | (77.8%) | |
| Maintenance Medications at Month 1 | | | | | |
| Prednisone | 708 | (94.9%) | 87 | (98.9%) | 0.112 |
| Azathioprine | 236 | (31.6%) | 48 | (54.5%) | **<0.001** |
| Cyclosporin | 498 | (66.8%) | 71 | (80.7%) | **0.008** |
| Mycophenolate Mofetil (MMF) | 442 | (59.3%) | 39 | (44.3%) | **0.008** |
| Tacrolimus | 239 | (32.0%) | 15 | (17.0%) | **0.003** |
| Sirolimus | 20 | ( 2.7%) | 1 | ( 1.1%) | 0.716 |
| Cumulative Medications | | | | | **<0.001** |
| Less than 1818.5 days | 443 | (53.0%) | 21 | (23.3%) | |
| Equal or Greater than 1818.5 days | 393 | (47.0%) | 69 | (76.7%) | |

Table 8

Transplant Characteristics of Patients with No Skin Cancer Versus Non-Melanoma Skin Cancer

| Variable | No Skin Cancer | | Non-Melanoma Skin Cancer | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| TRANSPLANT CHARACTERISTICS | | | | | |
| Transplant Year | | | | | **0.002** |
| 1990-1994 | 251 | ( 30.0%) | 41 | ( 45.6%) | |
| 1995-1999 | 300 | ( 35.9%) | 33 | ( 36.7%) | |
| 2000-2003 | 385 | ( 34.1%) | 16 | ( 17.8%) | |
| Number of Renal Transplants | | | | | 0.249 |
| First Transplant | 715 | (85.5%) | 71 | (78.9%) | |
| Second Transplant | 98 | (11.7%) | 17 | (18.9%) | |
| Third Transplant | 20 | ( 2.4%) | 2 | ( 2.2%) | |
| Fourth Transplant | 3 | ( 0.4%) | 0 | ( 0.0%) | |
| Type of Donation | | | | | 0.294 |
| Live Donor | 284 | (34.0%) | 36 | (40.0%) | |
| Deceased Donor | 552 | (66.0%) | 54 | (60.0%) | |
| Graft Survival | | | | | **<0.001** |
| Less than 1759 days | 442 | (52.9%) | 21 | (23.3%) | |
| Equal or greater than 1759 days | 394 | (47.1%) | 69 | (76.7%) | |
| HLA A Antigen Mismatch | | | | | 0.066 |
| No mismatch | 189 | (22.8%) | 16 | (18.6%) | |
| One mismatch | 403 | (48.6%) | 53 | (61.6%) | |
| Two mismatch | 237 | (28.6%) | 17 | (19.8%) | |
| HLA B Antigen Mismatch | | | | | 0.332 |
| No mismatch | 110 | (13.3%) | 13 | (15.1%) | |
| One mismatch | 351 | (42.3%) | 42 | (48.8%) | |
| Two mismatch | 368 | (44.4%) | 31 | (36.0%) | |
| HLA AB Antigen Mismatch | | | | | 0.386 |
| No mismatch | 76 | ( 9.2%) | 7 | ( 8.1%) | |
| One mismatch | 103 | (12.4%) | 12 | (14.0%) | |
| Two mismatch | 249 | (30.0%) | 34 | (39.5%) | |
| Three mismatch | 243 | (29.3%) | 20 | (23.3%) | |
| Four mismatch | 158 | (19.1%) | 13 | (15.1%) | |
| HLA DR Antigen Mismatch | | | | | 0.749 |
| No mismatch | 153 | (18.7%) | 13 | (15.5%) | |
| One mismatch | 401 | (49.1%) | 42 | (50.0%) | |
| Two mismatch | 263 | (32.2%) | 29 | (34.5%) | |
| Total Antigen Mismatch | | | | | 0.927 |
| No mismatch | 65 | ( 7.9%) | 6 | ( 7.1%) | |
| One mismatch | 39 | ( 4.8%) | 5 | ( 6.0%) | |
| Two mismatch | 84 | (10.2%) | 9 | (10.7%) | |
| Three mismatch | 198 | (24.1%) | 25 | (29.8%) | |
| Four mismatch | 189 | (23.0%) | 17 | (20.2%) | |
| Five mismatch | 170 | (20.7%) | 15 | (17.9%) | |
| Six mismatch | 76 | ( 9.3%) | 7 | ( 8.3%) | |
| HLA A11 Antigen | | | | | 1.000 |
| Yes | 118 | (14.2%) | 12 | (13.3%) | |
| No | 711 | (85.8%) | 78 | (86.7%) | |
| HLA B27 Antigen | | | | | 0.298 |
| Yes | 67 | ( 8.2%) | 4 | ( 4.5%) | |
| No | 754 | (91.8%) | 85 | (95.5%) | |
| HLA DR7 Antigen | | | | | 1.000 |
| Yes | 154 | (18.7%) | 16 | (18.4%) | |
| No | 670 | (81.3%) | 71 | (81.6%) | |

Table 9

Sun Exposure History of Patients With No Skin Cancer Versus Non-Melanoma Skin Cancer

| Variable | No Skin Cancer | | Non-Melanoma Skin Cancer | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| PERSONAL CHARACTERISTICS | | | | | |
| Eye Color | | | | | 0.056 |
| Blue | 199 | (36.6%) | 34 | (52.3%) | |
| Brown | 230 | (42.4%) | 17 | (26.2%) | |
| Green | 45 | ( 8.3%) | 5 | ( 7.7%) | |
| Hazel | 69 | (12.7%) | 9 | (13.8%) | |
| Hair Color | | | | | **0.003** |
| Blonde | 107 | (19.7%) | 21 | (32.3%) | |
| Red | 16 | ( 3.0%) | 2 | ( 3.1%) | |
| Brown | 309 | (57.0%) | 40 | (61.5%) | |
| Black | 110 | (20.3%) | 2 | ( 3.1%) | |
| Skin Type | | | | | 0.062 |
| Always burns/never tans | 26 | ( 4.8%) | 5 | ( 7.7%) | |
| Always burns/sometimes tans | 92 | (16.9%) | 15 | (23.1%) | |
| Always tans/sometimes burns | 242 | (44.6%) | 33 | (50.8%) | |
| Always tans/never burns | 121 | (22.3%) | 12 | (18.5%) | |
| Never burns/brown skin | 56 | (10.3%) | 0 | ( 0.0%) | |
| Never burns/black skin | 6 | ( 1.1%) | 0 | ( 0.0%) | |
| Pretransplant Warts | | | | | 0.423 |
| Yes | 111 | (20.5%) | 16 | (24.6%) | |
| No | 431 | (79.5%) | 49 | (75.4%) | |
| Posttransplant Warts | | | | | **<0.001** |
| Yes | 136 | (25.0%) | 33 | (50.8%) | |
| No | 407 | (75.0%) | 32 | (49.2%) | |
| Family History of Skin Cancer | | | | | 0.357 |
| Yes | 48 | ( 8.9%) | 8 | (12.7%) | |
| No | 490 | (91.1%) | 55 | (87.3%) | |
| Number of Years Lived in Northern Alberta | | | | | **<0.001** |
| Less than 38 years | 277 | (51.0%) | 18 | (27.7%) | |
| Equal or greater than 38 years | 266 | (49.0%) | 47 | (72.3%) | |
| Percentage of Life Lived in Northern Alberta | | | | | 0.294 |
| Less than 90 % | 273 | (50.5%) | 28 | (43.1%) | |
| Equal or greater than 90% | 268 | (49.5%) | 37 | (56.9%) | |
| Work Outside | | | | | 0.237 |
| Yes | 281 | (51.7%) | 39 | (60.0%) | |
| No | 262 | (48.3%) | 26 | (40.0%) | |
| Hobby Outside | | | | | 1.000 |
| Yes | 426 | (78.9%) | 52 | (80.0%) | |
| No | 114 | (21.1%) | 13 | (20.0%) | |
| History of Sunburn | | | | | **0.030** |
| Yes | 207 | (38.2%) | 34 | (53.1%) | |
| No | 335 | (61.8%) | 30 | (46.9%) | |
| History of Sunbed Usage | | | | | 0.699 |
| Yes | 74 | (13.6%) | 7 | (10.8%) | |
| No | 469 | (86.4%) | 58 | (89.2%) | |
| Use of Sunscreen Pretransplant | | | | | **0.029** |
| Always | 52 | ( 9.6%) | 1 | ( 1.6%) | |
| Sometimes | 211 | (39.1%) | 21 | (32.8%) | |
| Never | 277 | (51.3%) | 42 | (65.6%) | |
| Use of Sunscreen Posttransplant | | | | | 0.056 |
| Always | 141 | (26.0%) | 12 | (18.5%) | |
| Sometimes | 224 | (41.3%) | 37 | (56.9%) | |
| Never | 177 | (32.7%) | 16 | (24.6%) | |
| History of Smoking | | | | | 0.439 |
| Current | 91 | (16.8%) | 13 | (20.0%) | |
| Past | 215 | (39.6%) | 29 | (44.6%) | |
| Never | 237 | (43.6%) | 23 | (35.4%) | |

($p<0.001$). Patients with NMSC reported more sunburns than patients without NMSC (53.1% vs. 38.2%, $p=0.030$). Patients with NMSC in contrast to those without NMSC, reported 'always' using sunscreen pretransplant (1.6% vs. 9.6%, $p=0.029$).

Patients that had > 6 NMSC lesions post renal transplant and those that had $\leq 6$ NMSC lesions differed significantly on gender, age, cumulative duration of immunosuppressive medications, Fitzpatrick skin type, and having hobbies outside. For those with > than 6 NMSC lesions, all were male (100%), in contrast to 70.4% of those with $\leq 6$ NMSC lesions ($p=0.005$). More patients were over 45 years of age with > 6 NMSC lesions than those with $\leq 6$ NMSC lesions (94.7% vs. 63.4%, $p=0.010$). More patients with > 6 NMSC lesions had $\geq 1818.5$ days cumulative duration of immunosuppressive therapy compared to those without NMSC (94.7% vs. 71.8%, $p=0.037$). More patients with > 6 NMSC lesions (23.1%) had Fitzpatrick skin type 1 (always burn/never tan) in comparison to those with out NMSC (3.8%) ($p=0.045$). Less patients with > 6 NMSC lesions had hobbies outside than those with $\leq 6$ NMSC lesions (53.8% vs. 86.5%, $p=0.016$) (Tables 10, 11, and 12).

In examining patients with SCC or BCC, there were no statistically significant differences found on any demographic characteristics, clinical variables, renal transplant variables, and sun exposure variables (Tables 13, 14, and 15).

Table 10

Demographics of Patients With > 6 Non-Melanoma Skin Cancer Lesions Versus ≤ 6 Non-Melanoma Skin Cancer Lesions

| Variable | Non-Melanoma Skin Cancer (> 6 lesions) | | Non-Melanoma Skin Cancer (≤ 6 lesions) | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| DEMOGRAPHIC CHARACTERISTICS | | | | | |
| Gender | | | | | **0.005** |
| Female | 0 | ( 0.0%) | 21 | (29.6%) | |
| Male | 19 | (100.0%) | 50 | (70.4%) | |
| Age | | | | | **0.010** |
| Less than 45 years old | 1 | ( 5.3%) | 26 | (36.6%) | |
| Greater than 45 years old | 18 | (94.7%) | 45 | (63.4%) | |
| Ethnicity | | | | | * |
| Caucasian | 19 | (100.0%) | 71 | (100.0%) | |
| CLINICAL CHARACTERISTICS | | | | | |
| Original Renal Disease | | | | | 0.160 |
| Glomerulonephritis | 6 | (31.6%) | 32 | (45.1%) | |
| Hypertension | 1 | ( 5.3%) | 2 | ( 2.8%) | |
| Diabetes Mellitus | 0 | ( 0.0%) | 11 | (15.5%) | |
| Other | 8 | (42.1%) | 19 | (26.8%) | |
| Unknown | 4 | (21.1%) | 7 | ( 1.9%) | |
| Cause of Death | | | | | 0.515 |
| Cardiac | 0 | ( 0.0%) | 3 | (23.1%) | |
| Infection | 2 | (33.3%) | 2 | (15.4%) | |
| Malignancy | 4 | (66.7%) | 6 | (46.2%) | |
| Other | 0 | ( 0.0%) | 1 | ( 7.7%) | |
| Unknown | 0 | ( 0.0%) | 1 | ( 7.7%) | |
| Cause of Transplant Failure | | | | | 0.205 |
| Acute Rejection | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Chronic Rejection | 0 | ( 0.0%) | 3 | (13.6%) | |
| Malignancy | 1 | (16.7%) | 0 | ( 0.0%) | |
| Death | 4 | (66.7%) | 12 | (54.5%) | |
| Non-Function | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Recurrent Disease | 0 | ( 0.0%) | 5 | (22.7%) | |
| Technical Problems | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Other | 1 | (16.7%) | 1 | ( 4.5%) | |
| Unknown | 0 | ( 0.0%) | 1 | ( 4.5%) | |
| IMMUNOSUPPRESSIVE MEDICATIONS | | | | | |
| Induction Medications | | | | | 0.223 |
| Yes | 2 | (10.5%) | 18 | (25.4%) | |
| No | 17 | (89.5%) | 53 | (74.6%) | |
| Maintenance Medications at Month 1 | | | | | |
| Prednisone | 18 | (94.7%) | 69 | (97.2%) | 1.000 |
| Azathioprine | 12 | (63.2%) | 36 | (50.7%) | 0.296 |
| Cyclosporin | 17 | (89.5%) | 54 | (76.1%) | 0.177 |
| Mycophenolate Mofetil (MMF) | 6 | (31.6%) | 33 | (46.5%) | 0.426 |
| Tacrolimus | 1 | ( 5.3%) | 14 | (19.7%) | 0.289 |
| Sirolimus | 0 | ( 0.0%) | 1 | ( 1.4%) | 1.000 |
| Cumulative Medication | | | | | **0.037** |
| Less than 1818.5 days | 1 | ( 5.3%) | 20 | (28.2%) | |
| Equal or greater than 1818.5 days | 18 | (94.7%) | 51 | (71.8%) | |

*unable to analyze by chi-square due to constant

Table 11

Transplant Characteristics of Patients with > 6 Non-Melanoma Skin Cancer Lesions Versus ≤ 6 Non-Melanoma Skin Cancer Lesions

| Variable | Non-Melanoma Skin Cancer (> 6 lesions) | | Non-Melanoma Skin Cancer (≤ 6 lesions) | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| TRANSPLANT CHARACTERISTICS | | | | | |
| Transplant year | | | | | 0.061 |
| 1990-1994 | 13 | (68.4%) | 28 | (39.4%) | |
| 1995-1999 | 5 | (26.3%) | 28 | (39.4%) | |
| 2000-2003 | 1 | ( 5.3%) | 15 | (21.1%) | |
| Number of Renal Transplants | | | | | 1.000 |
| First Transplant | 15 | (78.9%) | 56 | (78.9%) | |
| Second Transplant | 2 | (10.5%) | 15 | (21.1%) | |
| Third Transplant | 2 | (10.5%) | 0 | ( 0.0%) | |
| Fourth Transplant | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Type of Donation | | | | | 0.798 |
| Live Donor | 7 | (36.8%) | 29 | (40.8%) | |
| Deceased Donor | 12 | (63.2%) | 42 | (59.2%) | |
| Graft Survival | | | | | **0.037** |
| Less than 1759 days | 1 | ( 5.3%) | 20 | (28.2%) | |
| Equal or greater than 1759 days | 18 | (94.7%) | 51 | (71.8%) | |
| HLA A Antigen Mismatch | | | | | 0.651 |
| No mismatch | 2 | (11.8%) | 14 | (20.3%) | |
| One mismatch | 12 | (70.6%) | 41 | (59.4%) | |
| Two mismatch | 3 | (17.6%) | 14 | (20.3%) | |
| HLA B Antigen Mismatch | | | | | 0.117 |
| No mismatch | 0 | ( 0.0%) | 13 | (18.8%) | |
| One mismatch | 11 | (64.7%) | 31 | (44.9%) | |
| Two mismatch | 6 | (34.3%) | 25 | (36.2%) | |
| HLA AB Antigen Mismatch | | | | | 0.535 |
| No mismatch | 0 | ( 0.0%) | 7 | (10.1%) | |
| One mismatch | 2 | (11.8%) | 10 | (14.5%) | |
| Two mismatch | 9 | (52.9%) | 25 | (36.2%) | |
| Three mismatch | 3 | (17.6%) | 17 | (24.6%) | |
| Four mismatch | 3 | (17.6%) | 10 | (14.5%) | |
| HLA DR Antigen Mismatch | | | | | 0.891 |
| No mismatch | 2 | (11.8%) | 11 | (16.4%) | |
| One mismatch | 9 | (52.9%) | 33 | (49.3%) | |
| Two mismatch | 6 | (35.3%) | 23 | (34.3%) | |
| Total Antigen Mismatch | | | | | 0.229 |
| No mismatch | 0 | ( 0.0%) | 6 | ( 9.0%) | |
| One mismatch | 1 | ( 5.9%) | 4 | ( 6.0%) | |
| Two mismatch | 1 | ( 5.9%) | 18 | (11.9%) | |
| Three mismatch | 8 | (47.1%) | 17 | (25.4%) | |
| Four mismatch | 3 | (17.6%) | 14 | (20.9%) | |
| Five mismatch | 1 | ( 5.6%) | 14 | (20.9%) | |
| Six mismatch | 3 | (17.6%) | 4 | ( 6.0%) | |
| HLA A11 Antigen | | | | | 0.448 |
| Yes | 1 | ( 5.3%) | 11 | (15.5%) | |
| No | 18 | (94.7%) | 61 | (84.5%) | |
| HLA B27 Antigen | | | | | 0.574 |
| Yes | 0 | ( 0.0%) | 4 | ( 5.7%) | |
| No | 19 | (100.0%) | 66 | (94.3%) | |
| HLA DR7 Antigen | | | | | 0.292 |
| Yes | 5 | (29.4%) | 11 | (15.7%) | |
| No | 12 | (70.6%) | 59 | (84.3%) | |

Table 12

Sun Exposure History of Patients with > 6 Non-Melanoma Skin Cancer Lesions Versus ≤ 6 Non-Melanoma Skin Cancer Lesions

| Variable | Non-Melanoma Skin Cancer (> 6 lesions) | | Non-Melanoma Skin Cancer ( ≤ 6 lesions) | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| PERSONAL CHARACTERISTICS | | | | | |
| Eye color | | | | | 0.554 |
| Blue | 8 | (61.5%) | 26 | (50.0%) | |
| Brown | 4 | (30.8%) | 13 | (25.0%) | |
| Green | 0 | ( 0.0%) | 5 | ( 9.6%) | |
| Hazel | 1 | ( 7.7%) | 8 | (15.4%) | |
| Hair Color | | | | | 0.382 |
| Blonde | 5 | (38.5%) | 16 | (30.8%) | |
| Red | 1 | ( 7.7%) | 1 | ( 1.9%) | |
| Brown | 6 | (46.2%) | 34 | (65.4%) | |
| Black | 1 | ( 7.7%) | 1 | ( 1.9%) | |
| SkinType | | | | | **0.045** |
| Always burns/never tans | 3 | (23.1%) | 2 | ( 3.8%) | |
| Always burns/sometimes tans | 1 | ( 7.7%) | 14 | (26.9%) | |
| Always tans/sometimes burns | 8 | (61.5%) | 25 | (48.1%) | |
| Always tans/never burns | 1 | ( 7.7%) | 11 | (21.2%) | |
| Never burns/brown skin | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Never burns/black skin | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Pretransplant Warts | | | | | 0.492 |
| Yes | 2 | (15.4%) | 14 | (26.9%) | |
| No | 11 | (84.6%) | 38 | (73.1%) | |
| Posttransplant Warts | | | | | 0.367 |
| Yes | 5 | (38.5%) | 28 | (53.8%) | |
| No | 8 | (61.5%) | 24 | (46.2%) | |
| Family History of Skin Cancer | | | | | 1.000 |
| Yes | 1 | ( 8.3%) | 7 | (13.7%) | |
| No | 11 | (91.7%) | 44 | (86.3%) | |
| Number of Years Lived in Northern Alberta | | | | | 0.489 |
| Less than 38 years | 5 | (38.5%) | 13 | (25.0%) | |
| Equal or greater than 38 years | 8 | (61.5%) | 39 | (75.0%) | |
| Percentage of Life Lived in Northern Alberta | | | | | 0.533 |
| Less than 90 % | 7 | (53.8%) | 21 | (40.4%) | |
| Equal or greater than 90% | 6 | (46.2%) | 31 | (59.6%) | |
| Work Outside | | | | | 1.000 |
| Yes | 8 | (61.5%) | 31 | (59.6%) | |
| No | 5 | (38.5%) | 21 | (40.4%) | |
| Hobby Outside | | | | | **0.016** |
| Yes | 7 | (53.8%) | 45 | (86.5%) | |
| No | 6 | (46.2%) | 7 | (13.5%) | |
| History of Sunburn | | | | | 0.548 |
| Yes | 8 | (61.5%) | 26 | (51.0%) | |
| No | 5 | (38.6%) | 25 | (49.0%) | |
| History of Sunbed Usage | | | | | 0.329 |
| Yes | 0 | ( 0.0%) | 7 | (13.5%) | |
| No | 13 | (100.0%) | 45 | (86.5%) | |
| Use of Sunscreen Pretransplant | | | | | 0.348 |
| Always | 0 | ( 0.0%) | 1 | ( 1.9%) | |
| Sometimes | 2 | (16.7%) | 19 | (36.5%) | |
| Never | 10 | (83.3%) | 32 | (61.5%) | |
| Use of Sunscreen Posttransplant | | | | | 0.115 |
| Always | 0 | ( 0.0%) | 12 | (23.1%) | |
| Sometimes | 8 | (61.5%) | 29 | (55.8%) | |
| Never | 5 | (38.5%) | 11 | (21.2%) | |
| History of Smoking | | | | | 0.168 |
| Current | 5 | (38.5%) | 8 | (15.4%) | |
| Past | 4 | (30.8%) | 25 | (48.1%) | |
| Never | 4 | (30.8%) | 19 | (36.5%) | |

Table 13

Demographics of Patients with SCC Versus BCC

| Variable | Squamous Cell Carcinoma | | Basal Cell Carcinoma | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| DEMOGRAPHIC CHARACTERISTICS | | | | | |
| Gender | | | | | 0.138 |
| Female | 9 | (18.0%) | 12 | (32.4%) | |
| Male | 41 | (82.0%) | 25 | (67.6%) | |
| Age | | | | | 0.478 |
| Less than 45 years old | 13 | (26.0%) | 13 | (35.1%) | |
| Equal or greater than 45 years old | 37 | (74.0%) | 24 | (64.9%) | |
| Ethnicity | | | | | |
| Caucasian | 50 | (100.0%) | 37 | (100.0%) | * |
| CLINICAL CHARACTERISTICS | | | | | |
| Original Renal Disease | | | | | 0.775 |
| Glomerulonephritis | 19 | (38.0%) | 17 | (45.9%) | |
| Hypertension | 2 | ( 4.0%) | 1 | ( 2.7%) | |
| Diabetes Mellitus | 8 | (16.0%) | 3 | ( 8.1%) | |
| Other | 14 | (28.0%) | 12 | (32.4%) | |
| Unknown | 7 | (14.0%) | 4 | (10.8%) | |
| Cause of Death | | | | | 0.930 |
| Cardiac | 2 | (14.3%) | 1 | (20.0%) | |
| Infection | 3 | (21.4%) | 1 | (20.0%) | |
| Malignancy | 7 | (50.0%) | 3 | (60.0%) | |
| Other | 1 | ( 7.1%) | 0 | ( 0.0%) | |
| Unknown | 1 | ( 7.1%) | 0 | ( 0.0%) | |
| Cause of Failure | | | | | 0.596 |
| Acute Rejection | | ( 0.0%) | 0 | ( 0.0%) | |
| Chronic Rejection | 1 | ( 5.3%) | 2 | (22.2%) | |
| Malignancy | 1 | ( 5.3%) | 0 | ( 0.0%) | |
| Death | 11 | (57.9%) | 5 | (55.6%) | |
| Non-Function | | ( 0.0%) | 0 | ( 0.0%) | |
| Recurrent Disease | 3 | (15.8%) | 2 | (22.2%) | |
| Technical Problems | | ( 0.0%) | 0 | ( 0.0%) | |
| Other | 2 | (10.5%) | 0 | ( 0.0%) | |
| Unknown | 1 | ( 5.3%) | 0 | ( 0.0%) | |
| IMMUNOSUPPRESSIVE MEDICATIONS | | | | | |
| Induction Medications | | | | | 0.307 |
| None | 12 | (85.7%) | 31 | (83.8%) | |
| Polyclonal Antibody | 1 | ( 7.1%) | 2 | ( 5.4%) | |
| Interleukin 2 (IL-2) | 0 | ( 0.0%) | 3 | ( 8.1%) | |
| Monoclonal Antibody (OKT3) | 1 | ( 7.1%) | 1 | ( 2.7%) | |
| Maintenance Medications at Month 1 | | | | | |
| Prednisone | 48 | (100.0%) | 36 | (97.3%) | 0.435 |
| Azathioprine | 29 | (76.9%) | 17 | (45.9%) | 0.197 |
| Cyclosporin | 37 | (77.1%) | 32 | (86.5%) | 0.402 |
| Mycophenolate Mofetil (MMF) | 18 | (37.5%) | 20 | (54.1%) | 0.187 |
| Tacrolimus | 9 | (18.8%) | 5 | (13.5%) | 0.570 |
| Sirolimus | 1 | ( 2.1%) | 0 | ( 0.0%) | 1.000 |
| Cumulative Medication | | | | | 0.453 |
| Less than 1818.5 days | 10 | (20.0%) | 10 | (27.0%) | |
| Equal or Greater than 1818.5 days | 40 | (80.0%) | 27 | (73.0%) | |

*unable to analyze by chi-square due to constant.

Table 14

Transplant Characteristics of Patients With SCC Versus BCC

| Variable | Squamous Cell Carcinoma | | Basal Cell Carcinoma | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| TRANSPLANT CHARACTERISTICS | | | | | |
| Transplant Year | | | | | 0.612 |
| 1990-1994 | 24 | ( 48.0%) | 15 | ( 40.5%) | |
| 1995-1999 | 19 | ( 38.0%) | 14 | ( 37.8%) | |
| 2000-2003 | 7 | ( 14.0%) | 8 | ( 21.6%) | |
| Number of Renal Transplants | | | | | 0.410 |
| First Transplant | 38 | (76.0%) | 31 | (83.8%) | |
| Second Transplant | 10 | (20.0%) | 6 | (16.2%) | |
| Third Transplant | 2 | ( 4.0%) | 0 | ( 0.0%) | |
| Fourth Transplant | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Type of Donation | | | | | 1.000 |
| Live Donor | 21 | (42.0%) | 15 | (40.5%) | |
| Deceased Donor | 29 | (58.0%) | 22 | (59.5%) | |
| Graft Survival | | | | | 0.453 |
| Less than 1759 days | 10 | (20.0%) | 10 | (27.0%) | |
| Equal or greater than 1759 days | 40 | (80.0%) | 27 | (73.0%) | |
| HLA A Antigen Mismatch | | | | | 0.888 |
| No mismatch | 8 | (17.4%) | 8 | (21.6%) | |
| One mismatch | 29 | (63.0%) | 22 | (59.5%) | |
| Two mismatch | 9 | (19.6%) | 7 | (18.9%) | |
| HLA B Antigen Mismatch | | | | | 0.321 |
| No mismatch | 5 | (10.9%) | 7 | (18.9%) | |
| One mismatch | 22 | (47.8%) | 20 | (54.1%) | |
| Two mismatch | 19 | (41.3%) | 10 | (27.0%) | |
| HLA AB Antigen Mismatch | | | | | 0.323 |
| No mismatch | 3 | ( 6.5%) | 4 | (10.8%) | |
| One mismatch | 5 | (10.9%) | 6 | (16.2%) | |
| Two mismatch | 21 | (45.7%) | 13 | (35.1%) | |
| Three mismatch | 8 | (17.4%) | 11 | (29.7%) | |
| Four mismatch | 9 | (19.6%) | 3 | ( 8.1%) | |
| HLA DR Antigen Mismatch | | | | | 0.942 |
| No mismatch | 7 | (15.9%) | 6 | (16.2%) | |
| One mismatch | 23 | (52.3%) | 18 | (48.6%) | |
| Two mismatch | 14 | (31.8%) | 13 | (35.1%) | |
| Total Antigen Mismatch | | | | | 0.292 |
| No mismatch | 4 | ( 9.1%) | 2 | ( 5.4%) | |
| One mismatch | 0 | ( 0.0%) | 5 | (13.5%) | |
| Two mismatch | 5 | (11.4%) | 4 | (10.8%) | |
| Three mismatch | 15 | (34.1%) | 9 | (24.3%) | |
| Four mismatch | 8 | (18.2%) | 8 | (21.6%) | |
| Five mismatch | 9 | (20.5%) | 6 | (16.2%) | |
| Six mismatch | 3 | ( 6.8%) | 3 | ( 8.1%) | |
| HLA A11 Antigen | | | | | 0.753 |
| Yes | 7 | (14.0%) | 4 | (10.8%) | |
| No | 43 | (86.0%) | 33 | (89.2%) | |
| HLA B27 Antigen | | | | | 0.637 |
| Yes | 3 | ( 6.0%) | 1 | ( 2.8%) | |
| No | 47 | (94.0%) | 35 | (97.2%) | |
| HLA DR7 Antigen | | | | | 0.781 |
| Yes | 9 | (19.1%) | 6 | (16.2%) | |
| No | 38 | (80.9%) | 31 | (83.8%) | |

Table 15

Sun Exposure History of Patients With SCC Versus BCC

| Variable | Squamous Cell Carcinoma | | Basal Cell Carcinoma | | |
|---|---|---|---|---|---|
| | N | (%) | N | (%) | p value |
| PERSONAL CHARACTERISTICS | | | | | |
| Eye Color | | | | | 0.618 |
| Blue | 17 | (51.5%) | 15 | (51.7%) | |
| Brown | 8 | (24.2%) | 8 | (27.6%) | |
| Green | 4 | (12.1%) | 1 | ( 3.4%) | |
| Hazel | 4 | (12.1%) | 5 | (17.2%) | |
| Hair Color | | | | | 0.186 |
| Blonde | 8 | (24.2%) | 12 | (41.1%) | |
| Red | 2 | ( 6.1%) | 0 | ( 0.0%) | |
| Brown | 23 | (69.7%) | 16 | (55.2%) | |
| Black | 0 | ( 0.0%) | 1 | ( 3.4%) | |
| Skin Type | | | | | 0.430 |
| Always burns/never tans | 2 | ( 6.1%) | 2 | ( 6.9%) | |
| Always burns/sometimes tans | 10 | (30.3%) | 5 | (17.2%) | |
| Always tans/sometimes burns | 14 | (42.4%) | 18 | (62.1%) | |
| Always tans/never burns | 7 | (21.2%) | 4 | (13.8%) | |
| Never burns/brown skin | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Never burns/black skin | 0 | ( 0.0%) | 0 | ( 0.0%) | |
| Pretransplant Warts | | | | | 0.244 |
| Yes | 11 | (33.3%) | 5 | (17.2%) | |
| No | 22 | (66.7%) | 24 | (82.8%) | |
| Posttransplant Warts | | | | | 0.611 |
| Yes | 19 | (57.6%) | 14 | (48.3%) | |
| No | 14 | (42.4%) | 15 | (51.7%) | |
| Family History of Skin Cancer | | | | | 1.000 |
| Yes | 1 | ( 3.0%) | 1 | ( 3.4%) | |
| No | 32 | (97.0%) | 28 | (96.6%) | |
| Number of Years Lived in Northern Alberta | | | | | 0.171 |
| Less than 38 years | 7 | (21.2%) | 11 | (37.9%) | |
| Equal or Greater than 38 years | 26 | (78.8%) | 18 | (62.1%) | |
| Percentage of Life Lived in Northern Alberta | | | | | 0.617 |
| Less than 90% | 16 | (48.5%) | 12 | (41.4%) | |
| Equal or Greater than 90% | 17 | (51.5%) | 17 | (58.6%) | |
| LIFESTYLE CHARACTERISTICS | | | | | |
| Work Outside | | | | | 0.796 |
| Yes | 21 | (63.6%) | 17 | (58.6%) | |
| No | 12 | (36.4%) | 12 | (41.4%) | |
| Hobby Outside | | | | | 0.227 |
| Yes | 24 | (72.7%) | 25 | (86.2%) | |
| No | 9 | (27.3%) | 4 | (13.8%) | |
| History of Sunburn | | | | | 0.611 |
| Yes | 18 | (54.5%) | 13 | (46.4%) | |
| No | 15 | (45.5%) | 15 | (53.6%) | |
| History of Sunbed Usage | | | | | 1.000 |
| Yes | 4 | (12.1%) | 3 | (10.3%) | |
| No | 29 | (87.9%) | 26 | (89.7%) | |
| Use of Sunscreen Pretransplant | | | | | 0.462 |
| Always | 0 | ( 0.0%) | 1 | ( 3.4%) | |
| Sometimes | 10 | (31.3%) | 11 | (37.9%) | |
| Never | 22 | (68.8%) | 17 | (58.6%) | |
| Use of Sunscreen Posttransplant | | | | | 0.968 |
| Always | 6 | (18.2%) | 6 | (20.7%) | |
| Sometimes | 19 | (57.6%) | 16 | (55.2%) | |
| Never | 8 | (24.2%) | 7 | (24.1%) | |
| History of Smoking | | | | | 0.643 |
| Current | 7 | (21.2%) | 6 | (20.7%) | |
| Past | 17 | (51.5%) | 12 | (41.4%) | |
| Never | 9 | (27.3%) | 11 | (37.9%) | |

Time to Development of Non-Melanoma Skin Cancer

The median time to development of a first NMSC lesion post renal transplant was 4.03 years (1472 days; range 51-5324 days) for approximately 6% of this cohort (Figure 2). The median time to development of a first SCC lesion was 4.12 years (1503 days; range 86-5324 days), versus 3.99 years (1457days; range 51-5237days) for development of a first BCC lesion post renal transplant. The time to development of a first NMSC

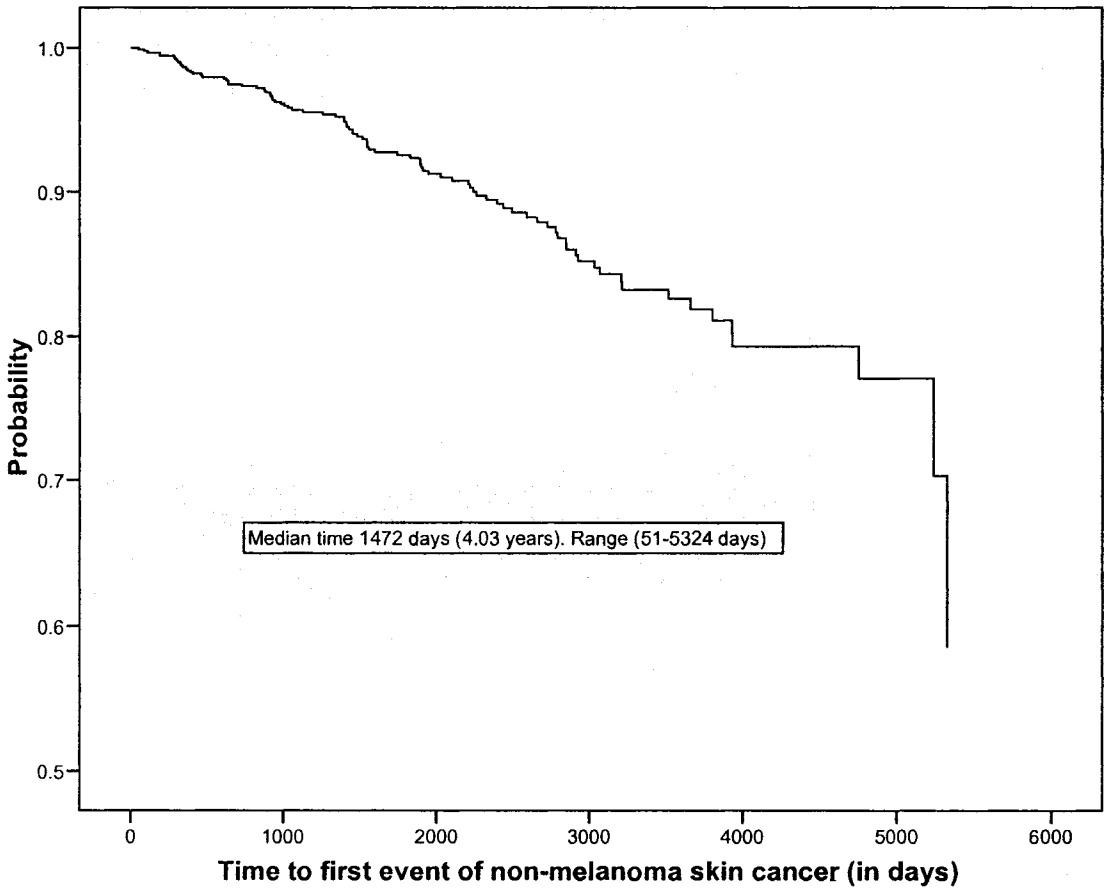


Figure 2. Unadjusted Time to Development of Non-Melanoma Skin Cancer

lesion was then adjusted for demographic characteristics, clinical variables, renal transplant variables, and sun exposure variables. Gender, age, ethnicity, eye colour, hair colour, Fitzpatrick skin type, the presence of warts post transplant, history of more than

two sunburns, and the number of years lived in Northern Alberta were significant for the time to development of NMSC post renal transplantation (Tables 16, 17, 18 and Appendix D). Males had a 2.02 ($p=0.005$) higher risk for the development of NMSC post renal transplantation, and patients greater than 45 years of age had a 3.08 higher risk ($p<0.001$). Patients with warts post renal transplant had a 1.96 increased risk ($p=0.007$) of developing NMSC. Eye colour was combined into light color eyes (blue, green, and hazel) and dark colored eyes (brown). Patients with light colored eyes had a 1.91 increased risk ($p=0.023$) of developing NMSC in comparison to patients with dark coloured eyes. Hair colour was combined into blonde or red hair and brown or black hair. Patients with blonde or red hair had 1.74 increased risk ($p=0.034$) of developing NMSC in contrast to patients with brown or black hair. There was also found to be a difference between light coloured skin (Fitzpatrick skin types 1, 2, and 3) and dark coloured skin (Fitzpatrick skin types 4, 5, and 6). Patients with light coloured skin had a 2.29 increased risk ($p=0.010$) in comparison to those with dark skin. Patients with a history of sunburn had a 1.70 increased risk ($p=0.035$) of developing NMSC than those that did not have a history of sunburn. Number of years lived in Northern Alberta had an increased risk of 1.04 ($p<0.001$).

All statistically significant univariate variables (gender, age, eye colour, hair colour, skin type, warts post transplant, history of sunburn and number of years lived in Northern Alberta) for the time to development of NMSC were then entered into a multivariate model. It was found that gender (HR=2.13, $p=0.013$), age (HR=3.81, $p<0.001$), number of years lived in Northern Alberta (HR=1.02, $p=0.022$), and warts post transplant (HR=2.05, $p=0.005$) remained significant for the development of NMSC post renal transplant (Table 19).

Table 16

Development of Non-Melanoma Skin Cancer Adjusted for Demographic Characteristics

| Variable | B | SE | HR | 95% CI | p value |
|---|---|---|---|---|---|
| Gender | | | | | |
| Female (reference) | | | | | |
| Male | 0.70 | 0.25 | 2.02 | 1.25 - 3.29 | **0.005** |
| Age | | | | | |
| Less than 45 years old (reference) | | | | | |
| Equal or greater than 45 years old | 1.13 | 0.22 | 3.08 | 1.95 - 4.86 | **<0.001** |
| Ethnicity | | | | | |
| Caucasian (reference) | | | | | |
| Other | -3.38 | 1.10 | 0.03 | 0.00 - 0.30 | **0.002** |
| Transplant Year | | | | | |
| 1990-1994 (reference) | | | | | |
| 1995-1999 | 0.00 | 0.25 | 1.00 | 0.61 - 1.64 | 0.995 |
| 2000-2003 | 0.38 | 0.34 | 1.47 | 0.75 - 2.85 | 0.259 |
| Kidney Disease | | | | | |
| GN (reference) | | | | | |
| HTN | 0.17 | 0.60 | 1.18 | 0.36 - 3.84 | 0.781 |
| DM | -0.36 | 0.34 | 0.70 | 0.36 - 1.36 | 0.290 |
| Other | 0.20 | 0.25 | 1.23 | 0.75 - 2.01 | 0.419 |
| Unknown | 0.02 | 0.34 | 1.02 | 0.52 - 1.99 | 0.965 |
| Number of Transplants | | | | | |
| One (reference) | | | | | |
| Greater than one | 0.44 | 0.26 | 1.50 | 0.89 - 2.52 | 0.126 |
| Type of Transplant | | | | | |
| Deceased (reference) | | | | | |
| Living | 0.24 | 0.22 | 1.27 | 0.84 - 1.94 | 0.262 |
| Graft Survival | | | | | |
| Less than 1759 days (reference) | | | | | |
| Equal or greater than 1759 days | -0.43 | 0.30 | 0.65 | 0.36 - 1.17 | 0.150 |
| Induction Therapy | | | | | |
| No | 0.16 | 0.26 | 1.17 | 0.71 - 1.94 | 0.540 |
| Yes (reference) | | | | | |
| Prednisone | | | | | |
| Yes (reference) | | | | | |
| No | -0.58 | 1.01 | 0.56 | 0.08 - 4.07 | 0.568 |
| Azathioprine | | | | | |
| Yes (reference) | | | | | |
| No | -0.09 | 0.23 | 0.92 | 0.58 - 1.45 | 0.711 |
| Cyclosporin | | | | | |
| Yes (reference) | | | | | |
| No | 0.28 | 0.29 | 1.32 | 0.75 - 2.32 | 0.339 |
| Mycophenolate mofetil | | | | | |
| Yes (reference) | | | | | |
| No | -0.14 | 0.23 | 0.87 | 0.56 - 1.37 | 0.559 |
| Tacrolimus | | | | | |
| Yes (reference) | | | | | |
| No | -0.17 | 0.30 | 0.84 | 0.47 - 1.53 | 0.575 |
| Sirolimus | | | | | |
| Yes (reference) | | | | | |
| No | 0.00 | 1.01 | 1.00 | 0.14 - 7.26 | 1.000 |
| Cumulative Days of Immunosuppressive | | | | | |
| Less than 1818.5 days (reference) | | | | | |
| Equal or greater than 1818.5 days | -0.35 | 0.29 | 0.70 | 0.40 - 1.24 | 0.224 |

Table 17

Development of Non-Melanoma Skin Cancer Adjusted for HLA Antigens

| Variable | B | SE | HR | 95% CI | p value |
|---|---|---|---|---|---|
| HLA A Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.45 | 0.29 | 1.57 | 0.90 - 2.75 | 0.112 |
| Two mismatch | -0.01 | 0.35 | 0.99 | 0.50 - 1.95 | 0.970 |
| HLA B Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.02 | 0.32 | 1.02 | 0.55 - 1.91 | 0.939 |
| Two mismatch | -0.15 | 0.33 | 0.86 | 0.45 - 1.66 | 0.661 |
| HLA AB mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.19 | 0.48 | 1.21 | 0.48 - 3.07 | 0.693 |
| Two mismatch | 0.44 | 0.42 | 1.55 | 0.69 - 3.50 | 0.292 |
| Three mismatch | -0.01 | 0.44 | 0.99 | 0.42 - 2.35 | 0.983 |
| Four mismatch | 0.12 | 0.47 | 1.13 | 0.45 - 2.83 | 0.799 |
| HLA DR mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.22 | 0.32 | 1.24 | 0.67 - 2.32 | 0.493 |
| Two mismatch | 0.47 | 0.34 | 1.60 | 0.83 - 3.08 | 0.162 |
| HLA Total mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.27 | 0.61 | 1.31 | 0.40 - 4.29 | 0.659 |
| Two mismatch | 0.14 | 0.53 | 1.15 | 0.41 - 3.22 | 0.797 |
| Three mismatch | 0.34 | 0.46 | 1.40 | 0.58 - 3.43 | 0.456 |
| Four mismatch | 0.06 | 0.48 | 1.06 | 0.42 - 2.69 | 0.904 |
| Five mismatch | 0.14 | 0.48 | 1.15 | 0.44 - 2.96 | 0.777 |
| Six mismatch | 0.38 | 0.56 | 1.46 | 0.49 - 4.37 | 0.494 |
| Recipient positive for HLA A 11 | | | | | |
| Yes (reference) | | | | | |
| No | 0.02 | 0.31 | 1.02 | 0.55 - 1.87 | 0.956 |
| Recipient positive for HLA B27 | | | | | |
| Yes (reference) | | | | | |
| No | 0.56 | 0.51 | 1.76 | 0.64 - 4.79 | 0.272 |
| Recipient positive for HLA DR7 | | | | | |
| Yes (reference) | | | | | |
| No | 0.10 | 0.28 | 1.11 | 0.64 - 1.91 | 0.710 |

Table 18

Development of Non-Melanoma Skin Cancer Adjusted for Sun Exposure History

| Variable | B | SE | HR | CI 95% | p value |
|---|---|---|---|---|---|
| PERSONAL CHARACTERISTICS | | | | | |
| Eye Colour | | | | | |
| Blue, Green , and Hazel | 0.64 | 0.28 | 1.91 | 1.10 - 3.31 | **0.023** |
| Brown (reference) | | | | | |
| Hair Colour | | | | | |
| Blonde, Red | 0.55 | 0.26 | 1.74 | 1.04 - 2.89 | **0.034** |
| Brown, Black (reference) | | | | | |
| Fitzpatrick Skintype | | | | | |
| Skin typesl, 2, and 3 | 0.83 | 0.32 | 2.29 | 1.22 - 4.28 | **0.010** |
| Skin types 4, 5, and 6 (reference) | | | | | |
| Warts Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.01 | 0.29 | 0.99 | 0.56 - 1.75 | 0.974 |
| Warts Posttransplant | | | | | |
| Yes | 0.67 | 0.25 | 1.96 | 1.20 - 3.20 | **0.007** |
| No (reference) | | | | | |
| Family History of Non-Melanoma Skin | | | | | |
| Yes (reference) | | | | | |
| No | -0.10 | 0.38 | 0.91 | 0.43 - 1.92 | 0.798 |
| Number of Years Lived in Northern Alberta | 0.04 | 0.01 | 1.04 | 1.02 - 1.06 | **<0.001** |
| Percentage of Life in Northern Alberta | 0.01 | 0.01 | 1.01 | 1.00 - 1.02 | 0.121 |
| LIFESTYLE CHARACTERISTICS | | | | | |
| Work Outside | | | | | |
| Yes (reference) | | | | | |
| No | -0.35 | 0.25 | 0.71 | 0.43 - 1.16 | 0.168 |
| Hobby Outside | | | | | |
| Yes (reference) | | | | | |
| No | -0.01 | 0.31 | 0.99 | 0.54 - 1.82 | 0.975 |
| History of 2 or More Sunburns | | | | | |
| Yes | 0.53 | 0.25 | 1.7 | 1.04 - 2.78 | **0.035** |
| No (reference) | | | | | |
| Sun Bed Use | | | | | |
| Yes (reference) | | | | | |
| No | 0.21 | 0.40 | 1.23 | 0.56 - 2.70 | 0.605 |
| Sunscreen Use Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.49 | 0.26 | 1.64 | 0.98 - 2.74 | 0.061 |
| Sunscreen Use Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.30 | 0.29 | 0.74 | 0.42 - 1.31 | 0.304 |
| History of Smoking | | | | | |
| Yes (reference) | | | | | |
| No | -0.28 | 0.26 | 0.76 | 0.46 - 1.26 | 0.290 |

Table 19

Development of Non-Melanoma Skin Cancer – Multivariate Analysis

| Variable | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | p value | Hazard Ratio | CI 95% | p value | Hazard Ratio | CI 95% |
| DEMOGRAPHIC CHARACTERISTICS | | | | | | |
| Gender | | | | | | |
| Female (reference) | | | | | | |
| Male | **0.005** | 2.02 | 1.25 - 3.29 | **0.013** | 2.13 | 1.17 - 3.86 |
| Age | | | | | | |
| Less than 45 years old (reference) | | | | | | |
| Equal or greater than 45 years old | **<0.001** | 3.08 | 1.95 - 4.86 | **<0.001** | 3.81 | 2.07 - 7.04 |
| PERSONAL CHARACTERISTICS | | | | | | |
| Eye Colour | | | | | | |
| Blue, Green , and Hazel | **0.023** | 1.91 | 1.10 - 3.31 | 0.194 | 1.55 | 0.80 - 2.99 |
| Brown (reference) | | | | | | |
| Hair Colour | | | | | | |
| Blonde, Red | **0.034** | 1.74 | 1.04 - 2.89 | 0.127 | 1.56 | 0.88 - 2.76 |
| Brown, Black (reference) | | | | | | |
| Fitzpatrick Skintype | | | | | | |
| Skin typesl, 2, and 3 | **0.010** | 2.29 | 1.22 - 4.28 | 0.453 | 1.32 | 0.64 - 2.70 |
| Skin types 4, 5, and 6 (reference) | | | | | | |
| Warts Posttransplant | | | | | | |
| Yes | **0.007** | 1.96 | 1.20 - 3.20 | **0.005** | 2.05 | 1.24 - 3.40 |
| No (reference) | | | | | | |
| History of 2 or more sunburns | | | | | | |
| Yes | **0.035** | 1.70 | 1.04 - 2.78 | 0.103 | 1.59 | 0.91 - 2.79 |
| No (reference) | | | | | | |
| Number of Years Lived in Northern Alberti | **<0.001** | 1.04 | 1.02 - 1.06 | **0.022** | 1.02 | 1.00 - 1.04 |

## Predictors of Non-Melanoma Skin Cancer

Univariate logistic regression analyses were first performed to examine the predictors of non-melanoma skin cancer post renal transplantation. Gender, age, transplant year, graft survival, eye colour, hair colour, Fitzpatrick skin type, presence of warts post transplant, a history of sunburn, use of sunscreen post renal transplant, and number of years living in Northern Alberta were found to be predictors of NMSC post renal transplant (Tables 20, 21, 22and Appendix E) . Males had a 2.04 times greater risk for NMSC than women (p=0.006). Patients over 45 years of age had a 2.15 times

Table 20

Predictors of Non-Melanoma Skin Cancer Post Renal Transplant - Demographic Characteristics

| Variable | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| DEMOGRAPHIC CHARACTERISTICS | | | | | |
| Gender | | | | | |
| Female (reference) | | | | | |
| Male | 0.71 | 0.26 | 2.04 | 1.23 - 3.39 | **0.006** |
| Age | | | | | |
| Less than 45 years old (reference) | | | | | |
| Equal or greater than 45 years ol | 0.77 | 0.23 | 2.15 | 1.37 - 3.39 | **0.001** |
| Transplant Year(group) | | | | | |
| 1990-1994 | 1.07 | 0.31 | 2.91 | 1.59 - 5.31 | **0.001** |
| 1995-1999 | 0.67 | 0.32 | 1.96 | 1.06 - 3.64 | **0.033** |
| 2000-2003 (reference) | | | | | |
| Kidney Disease | | | | | |
| GN (reference) | | | | | |
| HTN | 0.42 | 0.65 | 1.53 | 0.43 - 5.42 | 0.513 |
| DM | -0.44 | 0.36 | 0.65 | 0.32 - 1.30 | 0.219 |
| Other | 0.14 | 0.27 | 1.15 | 0.68 - 1.94 | 0.599 |
| Unknown | 0.02 | 0.36 | 1.02 | 0.50 - 2.06 | 0.962 |
| Number of Transplants | | | | | |
| One (reference) | | | | | |
| Greater than one | 0.46 | 0.28 | 1.58 | 0.92 - 2.72 | 0.097 |
| Type of Transplant | | | | | |
| Deceased (reference) | | | | | |
| Living | 0.26 | 0.23 | 1.30 | 0.83 - 2.02 | 0.254 |
| Graft Survival | | | | | |
| Less than 1759 days (reference) | | | | | |
| Equal or greater than 1759 days | 1.31 | 0.26 | 3.67 | 2.22 - 6.12 | **<0.001** |
| IMMUNOSUPPRESSIVE MEDICATIONS | | | | | |
| Induction medication | | | | | |
| Yes (reference) | | | | | |
| No | 0.71 | 0.26 | 2.04 | 1.21 - 3.41 | **0.010** |
| Prednisone | | | | | |
| Yes (reference) | | | | | |
| No | -1.54 | 1.02 | 0.21 | 0.03 - 1.58 | 0.131 |
| Azathioprine | | | | | |
| Yes (reference) | | | | | |
| No | -0.95 | 0.23 | 0.39 | 0.25 - 0.60 | **<0.001** |
| Cyclosporin | | | | | |
| Yes (reference) | | | | | |
| No | -0.73 | 0.28 | 0.48 | 0.28 - 0.83 | **0.009** |
| Mycophenolate Mofetil | | | | | |
| Yes (reference) | | | | | |
| No | 0.61 | 0.23 | 1.83 | 1.17 - 2.86 | **0.008** |
| Tacrolimus | | | | | |
| Yes (reference) | | | | | |
| No | 0.83 | 0.29 | 2.29 | 1.29 - 4.08 | **0.005** |
| Sirolimus | | | | | |
| Yes (reference) | | | | | |
| No | 0.87 | 1.03 | 2.40 | 0.32 - 18.08 | 0.397 |
| Cumulative days | | | | | |
| Less than 1818.5 days (reference) | | | | | |
| Equal or greater than 1818.5 day: | 1.31 | 0.26 | 3.70 | 2.23 - 6.15 | **<0.001** |

Table 21

Predictors of Non-Melanoma Skin Cancer Post Renal Transplant – HLA Antigens

| Variables | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| HLA A Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.44 | 0.30 | 1.55 | 0.87 - 2.79 | 0.140 |
| Two mismatch | -0.17 | 0.36 | 0.85 | 0.42 - 1.72 | 0.647 |
| HLA B Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.01 | 0.34 | 1.01 | 0.52 - 1.96 | 0.970 |
| Two mismatch | -0.34 | 0.35 | 0.71 | 0.36 - 1.41 | 0.330 |
| HLA AB Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.24 | 0.50 | 1.27 | 0.48 - 3.36 | 0.638 |
| Two mismatch | 0.39 | 0.44 | 1.48 | 0.63 - 3.48 | 0.366 |
| Three mismatch | -0.11 | 0.46 | 0.89 | 0.36 - 2.19 | 0.806 |
| Four mismatch | -0.11 | 0.49 | 0.89 | 0.34 - 2.33 | 0.818 |
| HLA DR Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.21 | 0.33 | 1.23 | 0.66 - 2.36 | 0.528 |
| Two mismatch | 0.26 | 0.35 | 1.30 | 0.66 - 2.57 | 0.455 |
| HLA Total Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.33 | 0.64 | 1.39 | 0.40 - 4.86 | 0.607 |
| Two mismatch | 0.15 | 0.55 | 1.16 | 0.39 - 3.43 | 0.787 |
| Three mismatch | 0.31 | 0.48 | 1.37 | 0.54 - 3.48 | 0.511 |
| Four mismatch | -0.03 | 0.50 | 0.97 | 0.37 - 2.58 | 0.958 |
| Five mismatch | -0.05 | 0.51 | 0.96 | 0.36 - 2.57 | 0.929 |
| Six mismatch | 0.00 | 0.58 | 1.00 | 0.32 - 3.12 | 0.997 |
| Recipient Positive for HLA A11 | | | | | |
| Yes (reference) | | | | | |
| No | 0.08 | 0.33 | 1.08 | 0.57 - 2.04 | 0.816 |
| Recipient Positive for HLA B27 | | | | | |
| Yes (reference) | | | | | |
| No | 0.64 | 0.53 | 1.89 | 0.67 - 5.31 | 0.228 |
| Recipient Positive for HLADR7 | | | | | |
| Yes (reference) | | | | | |
| No | 0.02 | 0.29 | 1.02 | 0.58 - 1.80 | 0.956 |

greater risk (p=0.001) than patients less than 45 years for NMSC. Having a renal transplant from 1990-1994 was a 2.91 times greater risk (p=0.001), and having a renal transplant from 1995-1999 was a 1.96 increased risk (p=0.033) for NMSC, in comparison to being transplanted from 2000-2003. Graft survival $\geq$ 1759 days had a 3.69 increased risk for NMSC in comparison to graft survival < 1759 days (p<0.001). Having light coloured eyes had an increased risk of 2.08 in comparison to dark coloured eyes (p=0.013); having blonde or red hair had an increased risk of 1.87 in contrast to brown or black hair (p=0.025); light coloured skin (Fitzpatrick skin types 1-3) had an increased risk of 2.25 (p=0.015) in comparison to dark coloured skin (Fitzpatrick skin types 4-6) for NMSC. Patients with warts had a 3.09 increased risk of developing NMSC as compared to patients without warts post transplant (p<0.001). A history of sunburn post renal transplant had a 1.83 increased risk for NMSC in comparison to patients that did not have a history of sunburn (p=0.022). Patients who did not use sunscreen pretransplant had an increased risk of 1.81 in comparison to patients that did use sunscreen pretransplant (p=0.032). Living in Northern Alberta $\geq$ 38 years had a 2.67 increased risk for NMSC compared to those that have lived < than 38 years in Northern Alberta (p=0.001).

All statistically significant univariate variables were entered into a multivariate model and age (OR=4.55, p<0.001), gender (OR=1.88, p=0.063), warts post transplant (OR=2.54, p=0.002), and number of years lived in Northern Alberta (OR=1.94, p=0.041) remained significant predictors for the development of NMSC post renal transplant (Table 23).

In examining predictors for having > 6 NMSC lesions, patients older than 45 years had a 10.40 increased risk in comparison to patients younger than 45 years (p=0.027).

Table 22

Predictors of Non-Melanoma Skin Cancer Post Renal Transplant – Sun Exposure History

| Variable | B | SE | Odds Ratio | CI 95% | p value |
|---|---|---|---|---|---|
| PERSONAL CHARACTERISTICS | | | | | |
| Eye Colour | | | | | |
| Blue, Green, Hazel | 0.73 | 0.3 | 2.08 | 1.16 - 3.70 | **0.013** |
| Brown (reference) | | | | | |
| Hair colour | | | | | |
| Blonde, Red | 0.62 | 0.28 | 1.87 | 1.08 - 3.22 | **0.025** |
| Brown, Black (reference) | | | | | |
| Fitzpatrick Skintype | | | | | |
| Skin types 1-3 | 0.81 | 0.33 | 2.25 | 1.17 - 4.31 | **0.015** |
| Skin types 4-6 (reference) | | | | | |
| Warts Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.24 | 0.31 | 0.79 | 0.43 - 1.44 | 0.439 |
| Warts Posttransplant | | | | | |
| Yes | 1.13 | 0.27 | 3.09 | 1.83 - 5.21 | **<0.001** |
| No (reference) | | | | | |
| Family History of Non-Melanoma Skin Cancer | | | | | |
| Yes (reference) | | | | | |
| No | -0.40 | 0.41 | 0.67 | 0.30 - 1.50 | 0.332 |
| Number of Years Lived in Northern Alberta | | | | | |
| Less than 38 years (reference) | | | | | |
| Equal or greater than 38 years | 0.98 | 0.29 | 2.67 | 1.51 - 4.72 | **0.001** |
| Percentage of Life in Northern Alberta | | | | | |
| Less than median 90% (reference) | | | | | |
| Equal or greater than median 90% | 0.30 | 0.27 | 1.35 | 0.80 - 2.26 | 0.262 |
| LIFESTYLE CHARACTERISTICS | | | | | |
| Work Outside | | | | | |
| Yes (reference) | | | | | |
| No | -0.34 | 0.27 | 0.72 | 0.42 - 1.21 | 0.210 |
| Hobby Outside | | | | | |
| Yes (reference) | | | | | |
| No | -0.07 | 0.33 | 0.93 | 0.49 - 1.78 | 0.835 |
| History of 2 or More Sunburns | | | | | |
| Yes | 0.61 | 0.27 | 1.83 | 1.09 - 3.09 | **0.022** |
| No (reference) | | | | | |
| Sun Bed Use | | | | | |
| Yes (reference) | | | | | |
| No | 0.27 | 0.42 | 1.31 | 0.58 - 2.97 | 0.523 |
| Sunscreen Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.60 | 0.28 | 1.81 | 1.05 - 3.12 | **0.032** |
| Sunscreen Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.40 | 0.30 | 0.67 | 0.37 - 1.22 | 0.191 |
| History of Smoking | | | | | |
| Yes (reference) | | | | | |
| No | -0.35 | 0.27 | 0.71 | 0.41 - 1.21 | 0.205 |

Table 23

Predictors of Non-Melanoma Skin Cancer – Multivariate Analysis

| Variable | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | p value | Odds Ratio | CI 95% | p value | Odds Ratio | CI 95% |
| DEMOGRAPHIC CHARACTERISTICS | | | | | | |
| Gender | | | | | | |
| Female (reference) | | | | | | |
| Male | **0.006** | 2.04 | 1.23 - 3.39 | 0.063 | 1.88 | 0.97 - 3.66 |
| Age | | | | | | |
| Less than 45 years old (reference) | | | | | | |
| Equal or greater than 45 years old | **0.001** | 2.15 | 1.37 - 3.39 | **<0.001** | 4.55 | 2.34 - 8.84 |
| Transplant Group | | | | | | |
| 1990-1994 | **0.001** | 2.91 | 1.59 - 5.31 | 0.107 | 3.05 | 0.79 - 11.82 |
| 1995-1999 | **0.033** | 1.96 | 1.06 - 3.64 | 0.534 | 1.56 | 0.39 - 6.31 |
| 2000-2003 (reference) | | | | | | |
| Graft Survival | | | | | | |
| Less than 1759 days (reference) | | | | | | |
| Equal of greater than 1759 days | **<0.001** | 3.67 | 2.22 - 6.12 | 0.449 | 1.62 | 0.46 - 5.71 |
| Eye Colour | | | | | | |
| Blue, Green , and Hazel | **0.013** | 2.08 | 1.16 - 3.70 | 0.112 | 1.84 | 0.87 - 3.90 |
| Brown (reference) | | | | | | |
| Hair Colour | | | | | | |
| Blonde, Red | **0.025** | 1.87 | 1.08 - 3.22 | 0.093 | 1.78 | 0.91 - 3.47 |
| Brown, Black (reference) | | | | | | |
| Fitzpatrick Skin Type | | | | | | |
| Skin typesl, 2, and 3 | **0.015** | 2.25 | 1.17 - 4.31 | 0.398 | 1.42 | 0.63 - 3.22 |
| Skin types 4, 5, and 6 (reference) | | | | | | |
| Warts Posttransplant | | | | | | |
| Yes | **<0.001** | 3.09 | 1.83 - 5.21 | **0.002** | 2.54 | 1.39 - 4.64 |
| No (reference) | | | | | | |
| History of 2 or More Sunburns | | | | | | |
| Yes | **0.022** | 1.83 | 1.09 - 3.09 | 0.232 | 1.48 | 0.78 - 2.84 |
| No (reference) | | | | | | |
| Sunscreen Pretransplant | | | | | | |
| Yes (reference) | | | | | | |
| No | **0.032** | 1.81 | 1.05 - 3.12 | 0.401 | 0.77 | 0.91 - 3.47 |
| Number of Years Lived in Northern Alberta | | | | | | |
| Less than 38 years (reference) | | | | | | |
| Equal or greater than 38 years | **<0.001** | 2.67 | 1.51 - 4.72 | **0.040** | 1.94 | 1.03 - 3.66 |

Not having a hobby outside had a 5.51 increased risk in comparison to having a hobby outside (p=0.013). In multivariate analyses there were no significant predictors found for multiple lesions (Tables 24, 25, 26, and 27). There were also no significant predictors found for SCC (Tables 28, 29, and 30) or BCC (Table 31, 32, and 33).

Table 24

Predictors of > 6 Non-Melanoma Skin Cancer Lesions Post Renal Transplant – Demographic Characteristics

| Variable | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| DEMOGRAPHIC CHARACTERISTICS | | | | | |
| Gender | | | | | |
| Female (reference) | | | | | |
| Male | 20.24 | 8770.83 | 0.00 | 0.00 | 1.000 |
| Age | | | | | |
| Less than 45 years old (reference) | | | | | |
| Equal or greater than 45 years old | 2.34 | 1.06 | 10.40 | 1.31 - 82.48 | **0.027** |
| Transplant Year(group) | | | | | |
| 1990-1994 | 1.94 | 1.09 | 6.96 | 0.83 - 58.51 | 0.074 |
| 1995-1999 | 0.99 | 1.14 | 2.68 | 0.29 - 25.08 | 0.388 |
| 2000-2003 (reference) | | | | | |
| Kidney Disease | | | | | |
| GN | -1.11 | 0.77 | 0.33 | 0.07 - 1.48 | 0.147 |
| HTN | -0.13 | 1.38 | 0.88 | 0.06 - 12.98 | 0.923 |
| DM | -20.64 | 12118.64 | 0.00 | 0.00 - | 1.000 |
| Other | -0.31 | 0.76 | 0.74 | 0.17 - 3.28 | 0.686 |
| Unknown (reference) | | | | | |
| Number of Transplants | | | | | |
| One (reference) | | | | | |
| Greater than one | 0.07 | 0.64 | 1.07 | 0.31 - 3.72 | 0.919 |
| Type of Transplant | | | | | |
| Deceased (reference) | | | | | |
| Living | -0.17 | 0.53 | 0.85 | 0.30 - 2.40 | 0.752 |
| Graft Survival | | | | | |
| Less than 1759 days (reference) | | | | | |
| Equal or greater than 1759 days | 1.20 | 1.06 | 7.06 | 0.88 - 56.45 | 0.065 |
| IMMUNOSUPPRESSIVE MEDICATIONS | | | | | |
| Induction medication | | | | | |
| Yes | -1.06 | 0.80 | 0.35 | 0.07 - 1.65 | 0.183 |
| No (reference) | | | | | |
| Prednisone | | | | | |
| Yes (reference) | | | | | |
| No | -19.86 | 40192.97 | 0.00 | 0.00 | 1.000 |
| Azathioprine | | | | | |
| Yes (reference) | | | | | |
| No | -0.64 | 0.55 | 0.53 | 0.18 - 1.57 | 0.251 |
| Cyclosporin | | | | | |
| Yes (reference) | | | | | |
| No | -1.62 | 1.07 | 0.20 | 0.02 - 1.61 | 0.130 |
| Mycophenolate Mofetil | | | | | |
| Yes (reference) | | | | | |
| No | 0.58 | 0.55 | 1.78 | 0.60 - 5.29 | 0.297 |
| Tacrolimus | | | | | |
| Yes (reference) | | | | | |
| No | 1.45 | 1.07 | 4.25 | 0.52 - 34.71 | 0.177 |
| Sirolimus | | | | | |
| Yes (reference) | | | | | |
| No | 19.86 | 40192.99 | 0.00 | 0.00 | 1.000 |
| Cumulative days | | | | | |
| Less than 1818.5 days (reference) | | | | | |
| Equal or greater than 1818.5 days | 1.95 | 1.06 | 7.06 | 0.88 - 56.45 | 0.065 |

Table 25

Predictors of > 6 Non-Melanoma Skin Cancer Lesions Post Renal Transplant – HLA Antigens

| Variables | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| HLA A Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.72 | 0.82 | 2.05 | 0.41 - 10.30 | 0.384 |
| Two mismatch | 0.41 | 0.99 | 1.50 | 0.22 - 10.40 | 0.682 |
| HLA B Mismatch | | | | | |
| No mismatch | -19.78 | 11147.52 | 0.00 | 0.00 | 1.000 |
| One mismatch | 0.39 | 0.57 | 1.48 | 0.48 - 4.56 | 0.496 |
| Two mismatch (reference) | | | | | |
| HLA AB Mismatch | | | | | |
| No mismatch | -20.00 | 15191.52 | 0.00 | 0.00 | 1.000 |
| One mismatch | -0.41 | 1.02 | 0.67 | 0.09 - 4.89 | 0.690 |
| Two mismatch | 0.18 | 0.76 | 1.20 | 0.27 - 5.37 | 0.812 |
| Three mismatch | -0.53 | 0.91 | 0.59 | 0.10 - 3.49 | 0.559 |
| Four mismatch (reference) | | | | | |
| HLA DR Mismatch | | | | | |
| No mismatch | -0.36 | 0.90 | 0.70 | 0.12 - 4.03 | 0.687 |
| One mismatch | 0.04 | 0.59 | 1.05 | 0.33 - 3.34 | 0.940 |
| Two mismatch (reference) | | | | | |
| HLA Total Mismatch | | | | | |
| No mismatch | -20.92 | 16408.71 | 0.00 | 0.00 | 1.000 |
| One mismatch | -1.10 | 1.35 | 0.33 | 0.02 - 4.74 | 0.417 |
| Two mismatch | -1.79 | 1.31 | 0.17 | 0.01 - 2.16 | 0.170 |
| Three mismatch | -0.47 | 0.88 | 0.63 | 0.11 - 3.49 | 0.595 |
| Four mismatch | -1.25 | 0.99 | 0.29 | 0.41 - 2.01 | 0.208 |
| Five mismatch | -2.35 | 1.29 | 0.10 | 0.01 - 1.19 | 0.068 |
| Six mismatch (reference) | | | | | |
| Recipient Positive for HLA A11 | | | | | |
| Yes | -1.19 | 1.08 | 0.30 | 0.04 - 2.51 | 0.268 |
| No (reference) | | | | | |
| Recipient Positive for HLA B27 | | | | | |
| Yes (reference) | | | | | |
| No | 19.96 | 20096.49 | 0.00 | 0.00 | 1.000 |
| Recipient Positive for HLA DR7 | | | | | |
| Yes (reference) | | | | | |
| No | -0.80 | 0.63 | 0.45 | 0.13 - 1.53 | 0.199 |

Table 26

Predictors of > 6 Non-Melanoma Skin Cancer Lesions Post Renal Transplant – Sun Exposure History

| Variable | B | SE | Odds Ratio | CI 95% | p value |
|---|---|---|---|---|---|
| PERSONAL CHARACTERISTICS | | | | | |
| Eye Colour | | | | | |
| Blue, Green, Hazel (reference) | | | | | |
| Brown | 0.29 | 0.68 | 1.33 | 0.35 - 5.07 | 0.673 |
| Hair Colour | | | | | |
| Blonde, Red (reference) | | | | | |
| Brown, Black | -0.57 | 0.63 | 0.57 | 0.17 - 1.95 | 0.367 |
| Fitzpatrick Skin Type | | | | | |
| Skin types 1-3 (reference) | | | | | |
| Skin types 4-6 | -1.17 | 1.10 | 0.31 | 0.04 - 2.66 | 0.286 |
| Warts Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.71 | 0.83 | 2.03 | 0.40 - 10.31 | 0.395 |
| Warts Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.62 | 0.63 | 1.87 | 0.54 - 6.47 | 0.325 |
| Family History of Non-Melanoma Skin Cancer | | | | | |
| Yes (reference) | | | | | |
| No | 0.56 | 1.12 | 1.75 | 0.19 - 15.75 | 0.618 |
| Number of Years Lived in Northern Alberta | | | | | |
| Less than 38 years (reference) | | | | | |
| Equal or greater than 38 years | -0.63 | 0.65 | 0.53 | 0.15 - 1.92 | 0.336 |
| Percentage of Life in Northern Alberta | | | | | |
| Less than median 90% (reference) | | | | | |
| Equal or greater than median 90% | -0.54 | 0.62 | 0.58 | 0.17 - 1.97 | 0.384 |
| LIFESTYLE CHARACTERISTICS | | | | | |
| Work Outside | | | | | |
| Yes (reference) | | | | | |
| No | -0.08 | 0.64 | 0.92 | 0.27 - 3.21 | 0.899 |
| Hobby Outside | | | | | |
| Yes (reference) | | | | | |
| No | 1.71 | 0.69 | 5.51 | 1.43 - 21.26 | **0.013** |
| History of 2 or More Sunburns | | | | | |
| Yes | 0.43 | 0.64 | 1.54 | 0.443 - 5.34 | 0.498 |
| No (reference) | | | | | |
| Sun Bed Use | | | | | |
| Yes (reference) | | | | | |
| No | 19.96 | 15191.51 | 0.00 | 0.00 | 1.000 |
| Sunscreen Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | 1.14 | 0.83 | 3.13 | 0.62 - 15.76 | 0.167 |
| Sunscreen Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.85 | 0.66 | 2.33 | 0.64 - 8.55 | 0.202 |
| History of Smoking | | | | | |
| Yes (reference) | | | | | |
| No | -0.26 | 0.67 | 0.77 | 0.21 - 2.85 | 0.698 |

Table 27

Predictors of > 6 Non-Melanoma Skin Cancer Lesions Post Renal Transplant – Multivariate Analysis

| Variable | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | p value | Odds Ratio | CI 95% | p value | Odds Ratio | CI 95% |
| Age | | | | | | |
| Less than 45 years old (reference) | | | | | | |
| Equal or greater than 45 years old | **0.027** | 10.40 | 1.31 - 82.48 | 0.188 | 4.385 | 0.49 - 39.50 |
| Hobby Outside | | | | | | |
| Yes (reference) | | | | | | |
| No | **0.013** | 5.51 | 1.43 - 21.26 | 0.067 | 3.714 | 0.91 - 15.15 |

Table 28

Predictors of Squamous Cell Carcinoma Post Renal Transplant – Demographic Characteristics

| Variable | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| DEMOGRAPHIC CHARACTERISTICS | | | | | |
| Gender | | | | | |
| Female (reference) | | | | | |
| Male | 0.67 | 0.51 | 1.95 | 0.73 - 5.25 | 0.185 |
| Age | | | | | |
| Less than 45 years old (reference) | | | | | |
| Equal or greater than 45 years old | 0.43 | 0.46 | 1.53 | 0.62 - 3.79 | 0.356 |
| Transplant Year(group) | | | | | |
| 1990-1994 (reference) | | | | | |
| 1995-1999 | -0.04 | 0.47 | 0.96 | 0.38 - 2.43 | 0.934 |
| 2000-2003 | -0.60 | 0.60 | 0.55 | 0.17 - 1.77 | 0.317 |
| Kidney Disease | | | | | |
| GN (reference) | | | | | |
| HTN | 0.69 | 1.27 | 2.00 | 0.17 - 23.96 | 0.584 |
| DM | 0.98 | 0.75 | 2.67 | 0.61 - 11.61 | 0.191 |
| Other | 0.07 | 0.50 | 1.08 | 0.40 - 2.89 | 0.883 |
| Unknown | 0.56 | 0.71 | 1.75 | 0.44 - 6.98 | 0.428 |
| Number of Transplants | | | | | |
| One (reference) | | | | | |
| Greater than one | 0.55 | 0.55 | 1.74 | 0.59 - 5.14 | 0.319 |
| Type of Transplant | | | | | |
| Deceased (reference) | | | | | |
| Living | 0.19 | 0.43 | 1.21 | 0.52 - 2.83 | 0.665 |
| Graft Survival | | | | | |
| Less than 1759 days (reference) | | | | | |
| Equal or greater than 1759 days | 0.42 | 0.50 | 1.52 | 0.57 - 4.05 | 0.405 |
| IMMUNOSUPPRESSIVE MEDICATIONS | | | | | |
| Induction Medication | | | | | |
| Yes (reference) | | | | | |
| No | -0.51 | 0.53 | 0.60 | 0.22 - 1.69 | 0.340 |
| Prednisone | | | | | |
| Yes (reference) | | | | | |
| No | -21.41 | 40192.97 | 0.00 | 0.00 | 1.000 |
| Azathioprine | | | | | |
| Yes (reference) | | | | | |
| No | -0.52 | 0.43 | 0.59 | 0.25 - 1.39 | 0.227 |
| Cyclosporin | | | | | |
| Yes (reference) | | | | | |
| No | 0.52 | 0.56 | 1.69 | 0.56 - 5.05 | 0.352 |
| Mycophenolate Mofetil | | | | | |
| Yes (reference) | | | | | |
| No | 0.61 | 0.44 | 1.84 | 0.79 - 4.32 | 0.160 |
| Tacrolimus | | | | | |
| Yes (reference) | | | | | |
| No | -0.27 | 0.58 | 0.77 | 0.25 - 2.37 | 0.642 |
| Sirolimus | | | | | |
| Yes (reference) | | | | | |
| No | -21.04 | 40192.93 | 0.00 | 0.00 | 1.000 |
| Cumulative Days | | | | | |
| Less than 1818.5 days (reference) | | | | | |
| Equal or greater than 1818.5 days | 0.42 | 0.50 | 1.52 | 0.57 - 4.05 | 0.405 |

Table 29

Predictors of Squamous Cell Carcinoma Post Renal Transplant – HLA Antigens

| Variables | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| HLA A Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.19 | 0.57 | 1.21 | 0.40 - 3.70 | 0.740 |
| Two mismatch | 0.12 | 0.70 | 1.13 | 0.29 - 4.41 | 0.866 |
| HLA B Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | 0.57 | 0.65 | 1.76 | 0.49 - 6.27 | 0.383 |
| Two mismatch | 0.93 | 0.68 | 2.53 | 0.67 - 9.59 | 0.171 |
| HLA AB Mismatch | | | | | |
| No mismatch(reference) | | | | | |
| One mismatch | -0.05 | 0.96 | 0.95 | 0.14 - 6.28 | 0.960 |
| Two mismatch | 0.77 | 0.84 | 2.15 | 0.41 - 11.20 | 0.362 |
| Three mismatch | -0.12 | 0.89 | 0.89 | 0.16 - 5.08 | 0.895 |
| Four mismatch | 1.10 | 0.97 | 3.00 | 0.45 - 20.15 | 0.258 |
| HLA DR Mismatch | | | | | |
| No mismatch(reference) | | | | | |
| One mismatch | 0.04 | 0.64 | 1.04 | 0.30 - 3.62 | 0.954 |
| Two mismatch | -0.22 | 0.67 | 0.80 | 0.22 - 2.97 | 0.739 |
| HLA Total Mismatch | | | | | |
| No mismatch(reference) | | | | | |
| One mismatch | 21.86 | 17974.84 | 0.00 | 0.00 | 1.000 |
| Two mismatch | -0.47 | 1.10 | 0.63 | 0.07 - 5.35 | 0.668 |
| Three mismatch | -0.29 | 0.96 | 0.75 | 0.12 - 4.90 | 0.764 |
| Four mismatch | -0.81 | 0.99 | 0.44 | 0.06 - 3.11 | 0.414 |
| Five mismatch | -0.29 | 1.01 | 0.75 | 0.10 - 5.47 | 0.777 |
| Six mismatch | -0.98 | 1.16 | 0.38 | 0.04 - 3.61 | 0.396 |
| Recipient positive for HLA A11 | | | | | |
| Yes (reference) | | | | | |
| No | -0.13 | 0.63 | 0.88 | 0.26 - 3.01 | 0.835 |
| Recipient positive for HLA B27 | | | | | |
| Yes (reference) | | | | | |
| No | -0.89 | 1.18 | 0.41 | 0.04 - 4.13 | 0.451 |
| Recipient positive for HLADR7 | | | | | |
| Yes (reference) | | | | | |
| No | -0.11 | 0.56 | 0.90 | 0.30 - 2.67 | 0.843 |

Table 30

Predictors of Squamous Cell Carcinoma Post Renal Transplant – Sun Exposure History

| Variable | B | SE | Odds Ratio | CI 95% | p value |
|---|---|---|---|---|---|
| PERSONAL CHARACTERISTICS | | | | | |
| Eye Colour | | | | | |
| Blue, Green, Hazel (reference) | | | | | |
| Brown | -0.20 | 0.57 | 0.82 | 0.27 - 2.48 | 0.722 |
| Hair colour | | | | | |
| Blonde, Red (reference) | | | | | |
| Brown, Black | 0.45 | 0.52 | 1.57 | 0.57 - 4.38 | 0.386 |
| Fitzpatrick Skintype | | | | | |
| Skin types 1-3 (reference) | | | | | |
| Skin types 4-6 | 0.37 | 0.65 | 1.45 | 0.41 - 5.17 | 0.563 |
| Warts Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.99 | 0.61 | 0.37 | 0.11 - 1.23 | 0.104 |
| Warts Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.56 | 0.50 | 0.57 | 0.22 - 1.53 | 0.267 |
| Family History of Non-Melanoma Skin Cancer | | | | | |
| Yes (reference) | | | | | |
| No | 0.11 | 0.76 | 1.12 | 0.25 - 4.92 | 0.885 |
| LIFESTYLE CHARACTERISTICS | | | | | |
| Work Outside | | | | | |
| Yes (reference) | | | | | |
| No | -0.31 | 0.51 | 0.74 | 0.27 - 1.99 | 0.544 |
| Hobby Outside | | | | | |
| Yes (reference) | | | | | |
| No | 0.97 | 0.66 | 2.63 | 0.72 - 9.61 | 0.145 |
| History of 2 or More Sunburns | | | | | |
| Yes (reference) | | | | | |
| No | -0.12 | 0.50 | 0.89 | 0.33 - 2.38 | 0.814 |
| Sun Bed Use | | | | | |
| Yes (reference) | | | | | |
| No | -0.29 | 0.81 | 0.75 | 0.15 - 3.65 | 0.722 |
| Sunscreen Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.28 | 0.53 | 1.32 | 0.47 - 3.72 | 0.599 |
| Sunscreen Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.04 | 0.58 | 0.96 | 0.31 - 2.97 | 0.943 |
| History of Smoking | | | | | |
| Yes (reference) | | | | | |
| No | -0.73 | 0.53 | 0.48 | 0.17 - 1.36 | 0.168 |
| Number of Years Lived in Northern Alberta | | | | | |
| Less than 38 years (reference) | | | | | |
| Equal or greater than 38 years | 0.67 | 0.57 | 1.95 | 0.64 - 5.89 | 0.239 |
| Percentage of Life in Northern Alberta | | | | | |
| Less than median 90% (reference) | | | | | |
| Equal or greater than median 90% | -0.45 | 0.51 | 0.64 | 0.24 - 1.71 | 0.372 |

Table 31

Predictors of Basal Cell Carcinoma Post Renal Transplant – Demographic Characteristics

| Variable | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| DEMOGRAPHIC CHARACTERISTICS | | | | | |
| Gender | | | | | |
| Female (reference) | | | | | |
| Male | -0.85 | 0.51 | 0.43 | 0.16 - 1.15 | 0.093 |
| Age | | | | | |
| Less than 45 years old (reference) | | | | | |
| Equal or greater than 45 years old | -0.41 | 0.46 | 0.66 | 0.27 - 1.65 | 0.376 |
| Transplant Year(group) | | | | | |
| 1990-1994 (reference) | | | | | |
| 1995-1999 | 0.25 | 0.48 | 1.28 | 0.50 - 3.26 | 0.609 |
| 2000-2003 | 0.55 | 0.60 | 1.73 | 0.54 - 5.57 | 0.356 |
| Kidney Disease | | | | | |
| GN (reference) | | | | | |
| HTN | -0.48 | 1.27 | 0.62 | 0.05 - 7.41 | 0.704 |
| DM | -0.77 | 0.75 | 0.46 | 0.11 - 2.02 | 0.306 |
| Other | -0.01 | 0.51 | 0.99 | 0.37 - 2.67 | 0.981 |
| Unknown | -0.35 | 0.71 | 0.71 | 0.18 - 2.82 | 0.622 |
| Number of Transplants | | | | | |
| One (reference) | | | | | |
| Greater than one | -0.70 | 0.58 | 0.50 | 0.16 - 1.54 | 0.226 |
| Type of Transplant | | | | | |
| Deceased (reference) | | | | | |
| Living | 0.04 | 0.44 | 1.04 | 0.44 - 2.45 | 0.930 |
| Graft Survival | | | | | |
| Less than1759 days (reference) | | | | | |
| Equal or greater than 1759 days | -0.35 | 0.50 | 0.71. | 0.26 - 1.89 | 0.490 |
| IMMUNOSUPPRESSIVE MEDICATIONS | | | | | |
| Induction medication | | | | | |
| Yes (reference) | | | | | |
| No | 0.62 | 0.54 | 1.86 | 0.64 - 5.39 | 0.256 |
| Prednisone | | | | | |
| Yes (reference) | | | | | |
| No | 21.55 | 40192.97 | 0.00 | 0.00 | 1.000 |
| Azathioprine | | | | | |
| Yes (reference) | | | | | |
| No | 0.60 | 0.44 | 1.82 | 0.77 - 4.30 | 0.170 |
| Cyclosporin | | | | | |
| Yes (reference) | | | | | |
| No | -0.68 | 0.58 | 0.51 | 0.16 - 1.59 | 0.250 |
| Mycophenolate Mofetil | | | | | |
| Yes (reference) | | | | | |
| No | -0.68 | 0.44 | 0.51 | 0.21 - 1.19 | 0.120 |
| Tacrolimus | | | | | |
| Yes (reference) | | | | | |
| No | 0.45 | 0.60 | 1.56 | 0.49 - 5.02 | 0.460 |
| Sirolimus | | | | | |
| Yes (reference) | | | | | |
| No | 20.90 | 40192.93 | 0.00 | 0.00 | 1.000 |
| Cumulative days | | | | | |
| Less than 1818.5 days (reference) | | | | | |
| Equal or greater than 1818.5 days | -0.35 | 0.50 | 0.71 | 0.26 - 1.89 | 0.490 |

Table 32

Predictors of Basal Cell Carcinoma Post Renal Transplant – HLA Antigens

| Variables | B | SE | Odds Ratio | 95% CI | p value |
|---|---|---|---|---|---|
| HLA A Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | -0.34 | 0.57 | 0.71 | 0.31 - 2.18 | 0.549 |
| Two mismatch | -0.36 | 0.70 | 0.70 | 0.18 - 2.77 | 0.611 |
| HLA B Mismatch | | | | | |
| No mismatch (reference) | | | | | |
| One mismatch | -0.25 | 0.64 | 0.78 | 0.22 - 2.71 | 0.695 |
| Two mismatch | -0.90 | 0.68 | 0.41 | 0.11 - 1.54 | 0.185 |
| HLA AB Mismatch | | | | | |
| No mismatch(reference) | | | | | |
| One mismatch | -0.29 | 0.96 | 0.75 | 0.12 - 4.90 | 0.764 |
| Two mismatch | -0.77 | 0.84 | 0.46 | 0.09 - 2.42 | 0.362 |
| Three mismatch | -0.09 | 0.89 | 0.92 | 0.16 - 5.21 | 0.922 |
| Four mismatch | -1.49 | 1.00 | 0.23 | 0.03 - 1.62 | 0.139 |
| HLA DR Mismatch | | | | | |
| No mismatch(reference) | | | | | |
| One mismatch | -0.13 | 0.64 | 0.88 | 0.25 - 3.05 | 0.834 |
| Two mismatch | -0.05 | 0.67 | 0.95 | 0.26 - 3.53 | 0.936 |
| HLA Total Mismatch | | | | | |
| No mismatch(reference) | | | | | |
| One mismatch | 21.90 | 17974.84 | 0.00 | 0.00 | 1.000 |
| Two mismatch | 0.47 | 1.10 | 1.60 | 0.19 - 13.70 | 0.668 |
| Three mismatch | 0.12 | 0.96 | 1.13 | 0.17 - 7.40 | 0.902 |
| Four mismatch | 0.58 | 0.99 | 1.78 | 0.25 - 12.45 | 0.562 |
| Five mismatch | 0.29 | 1.01 | 1.33 | 0.18 - 9.73 | 0.777 |
| Six mismatch | 0.41 | 1.16 | 1.50 | 0.16 - 14.42 | 0.725 |
| Recipient Positive for HLA A11 | | | | | |
| Yes (reference) | | | | | |
| No | 0.38 | 0.65 | 1.47 | 0.41 - 5.28 | 0.558 |
| Recipient Positive for HLA B27 | | | | | |
| Yes (reference) | | | | | |
| No | 0.74 | 1.18 | 2.10 | 0.21 - 21.03 | 0.528 |
| Recipient Positive for HLADR7 | | | | | |
| Yes (reference) | | | | | |
| No | 0.26 | 0.57 | 1.29 | 0.42 - 3.94 | 0.653 |

Table 33

Predictors of Basal Cell Carcinoma Post Renal Transplant – Sun Exposure History

| Variable | B | SE | Odds Ratio | CI 95% | p value |
|---|---|---|---|---|---|
| PERSONAL CHARACTERISTICS | | | | | |
| Eye Colour | | | | | |
| Blue, Green, Hazel (reference) | | | | | |
| Brown | 0.13 | 0.57 | 1.14 | 0.38 - 3.47 | 0.814 |
| Hair colour | | | | | |
| Blonde, Red (reference) | | | | | |
| Brown, Black | -0.47 | 0.52 | 0.62 | 0.22 - 1.74 | 0.366 |
| Fitzpatrick Skintype | | | | | |
| Skin types 1-3 (reference) | | | | | |
| Skin types 4-6 | -0.58 | 0.61 | 0.56 | 0.15 - 2.09 | 0.388 |
| Warts Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.75 | 0.61 | 2.11 | 0.64 - 7.00 | 0.221 |
| Warts Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | 0.18 | 0.50 | 1.20 | 0.45 - 3.19 | 0.718 |
| Family History of Non-Melanoma Skin Cancer | | | | | |
| Yes (reference) | | | | | |
| No | -0.26 | 0.76 | 0.77 | 0.18 - 3.42 | 0.735 |
| Number of Years Lived in Northern Alberta | | | | | |
| Less than 38 years (reference) | | | | | |
| Equal or greater than 38 years | -0.93 | 0.57 | 0.40 | 0.13 - 1.21 | 0.103 |
| Percentage of Life in Northern Alberta | | | | | |
| Less than median 90% (reference) | | | | | |
| Equal or greater than median 90% | 0.13 | 0.51 | 1.13 | 0.42 - 3.05 | 0.804 |
| LIFESTYLE CHARACTERISTICS | | | | | |
| Work Outside | | | | | |
| Yes (reference) | | | | | |
| No | 0.10 | 0.51 | 1.11 | 0.41 - 3.01 | 0.839 |
| Hobby Outside | | | | | |
| Yes (reference) | | | | | |
| No | -0.73 | 0.66 | 0.48 | 0.13 - 1.76 | 0.268 |
| History of 2 or More Sunburns | | | | | |
| Yes (reference) | | | | | |
| No | 0.48 | 0.51 | 1.62 | 0.60 - 4.37 | 0.345 |
| Sun Bed Use | | | | | |
| Yes (reference) | | | | | |
| No | 0.08 | 0.81 | 1.08 | 0.92 - 5.28 | 0.921 |
| Sunscreen Pretransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.57 | 0.53 | 0.57 | 0.20 - 1.61 | 0.285 |
| Sunscreen Posttransplant | | | | | |
| Yes (reference) | | | | | |
| No | -0.05 | 0.58 | 0.96 | 0.31 - 2.98 | 0.936 |
| History of Smoking | | | | | |
| Yes (reference) | | | | | |
| No | 0.20 | 0.52 | 1.22 | 0.44 - 3.39 | 0.700 |

# CHAPTER FIVE

## Discussion

The purpose of this study was to identify the incidence of and risk factors for developing NMSC post renal transplant. A retrospective cohort design was used to examine the relationship between demographic characteristics, clinical variables, renal transplant variables, sun exposure history and the development of NMSC in renal transplant patients in the Northern Alberta Renal Program (NARP). Data were analyzed using descriptive statistics, Chi-Square analysis, Cox Proportional Hazard analysis, and logistic regression analysis.

This cohort (n=926) was predominately male (63.2%) and Caucasian (79.5%), with a mean age of 44.71 (SD=13.55). The majority were transplanted between the years 1990 and 1999 (67.5%) and for most, this was their first renal transplant (84.9%). Overall, 65.4% of transplants were from a deceased donor and had an average HLA mismatch of 3 antigens or greater (77%). The median graft survival was 1759 days (4.92 years) and over 64% of patients did not receive induction of immunosuppressive therapy. The majority were on maintenance medications of Prednisone (95.3%), Mycophenolate Mofetil (57.7%), and Cyclosporin therapy (68.2%). The median cumulative days on immunosuppressive therapy was 1818.5 days (4.98 years). This Northern Alberta cohort had light coloured eyes (59.4%), dark coloured hair (76%), and light coloured skin (67.9%). There was a low proportion of patients with warts pretransplant (20.9%), post transplant (27.8%), or family history of skin cancer (9.3%). The median number of years lived in Northern Alberta was 38 years and the median percentage of life lived in Northern Alberta was 90%. A majority reported outside work (52.6%) and an outside

hobby (79%), with 39.8% having had at least one sunburn. There was less reported use of sunscreen pretransplant in comparison to post transplant (47.2% vs. 68.2%) and 17.1% of patients reported they were currently smoking.

Patients that developed NMSC were predominately male, over the age of 45 years, and Caucasian, with light coloured hair and eyes, presence of warts post transplant and lived greater than 38 years in Northern Alberta. The predominance of males developing of NMSC has been found in several studies (Bordea et al., 2000; Euvrard, Kanitakasis, Pouteil-Noble, Dureau et al.,1995; Liddington et al., 1989). One study specifically attributes this to males having more exposure to the sun, and hence a higher risk (Bordea et al., 2000). Studies that support older patients being more susceptible to NMSC consider this a risk factor mainly due to the higher cumulative exposure to the sun as one ages (Berg & Otley, 2002; Gilchrest, Eller, Gellar, & Yaar, 1999). Gupta et al. (1986) and Sheil (1992) also found patients with NMSC being predominately Caucasian. This can be attributed to less melanin in the skin, which is a natural protector from the harmful UV rays. Fair skin, light coloured hair and eyes are in the Caucasian population and consequently have also been cited as risk factors in the development of NMSC. (Euvrard, Kanitakasis, Pouteil-Noble, Dureau et al.,1995; Lampros et al., 1998). Furthermore, a number of studies also suggested that HPV plays a role in the development of NMSC (Dreno, 1998; Penn,1999). Most patients with NMSC lived in Northern Alberta greater than 38 years, and reported a history of sunburn and less use of sunscreen pretransplant. Adherence with sun protective strategies has been found in other renal transplant programs (Butt & Roberts, 1997; Seukeran et al., 1987).

The majority of patients with NMSC in this cohort were transplanted between 1990-1999, were on their first renal transplant and received their transplant from a deceased donor. This time period reflects an era of immunosuppression and duration of therapy in which most did not receive induction therapy. Azathioprine and Cyclosporin were more commonly used in comparison to Mycophenolate mofetil and Tacrolimus. Most studies on NMSC post transplant have been from the Cyclosporin era due to the predominate use of this medication (Jensen et al., 1999). Euvrard, Kanitakis, and Claudy (2003) recognize that not enough is known about newer immunosuppressive medications and the development of NMSC. Newer findings suggest both Mycophenolate mofetil (Engl et al., 2005) and Sirolimus (Luan et al., 2005) may be protective against some cancers. Patients that developed NMSC in this cohort had a longer cumulative duration of immunosuppressive therapy. Bordea et al. (2004) and Liddington et al. (1989) also found that time from transplant and duration of immunosuppression were risk factors for the development of NMSC.

Likewise, patients that developed > 6 NMSC lesions were male, Caucasian, and over the age of 45 years, with a majority of NMSC lesions located on the head and neck. Most were transplanted between 1990-1999 and on their first transplant from a deceased donor. All had grafts that survived $\geq$ 1759 days. Most had a cumulative duration of immunosuppressive therapy $\geq$1818.5 days. For patients that developed > 6 NMSC lesions most were Fitzpatrick skin type 1 (Always burn/never tan). Euvrard, Kanitakis, Pouteil-Noble, Disant et al., (1995) also found that patients with multiple lesions were older with light colour eyes and skin, and with a majority of lesions located on the head. For this cohort, there were no significant differences found amongst demographic

characteristics, clinical variables, renal transplant variables or sun exposure history between patients that developed SCC or BCC post transplant. However, the ratio of SCC:BCC lesions for patients with NMSC was 2.39:1 and was similar to other studies. (Euvrard, Kanatakis, Pouteil-Noble et al., 1995; Bordea et al., 2004).

Development of Non-Melanoma Skin Cancer

The incidence of NMSC post renal transplant in this Northern Alberta cohort was found to be 9.7%. In another Canadian study (Gupta et al., 1986) of only Caucasian renal transplant patients, the incidence was 5.3%. Jemec and Holm (2003) reported higher incidence rates of 22-50% after organ transplant depending on where patients reside. In fact, the incidence of NMSC post renal transplant in this study cohort may be understated, as the Canadian Cancer Society suggests that NMSC is underreported (Canadian Cancer Society, 2006).

The median time to development of a first NMSC lesion post renal transplant was 4.03 years (SD=3.28 years, range 51-5324 days). Similarly, the median time to development of SCC was 4.12 years (mean 4.75 years, SD=3.26years) and the median time to development of BCC was 3.99 years (mean 4.58 years, SD=3.42 years). Gupta et al. (1986) reported a mean time to development of NMSC of 7.2 years (range 24-181 months) for renal transplant patients in Canada. This is in contrast to Euvrard, Kanitakis, Poteil-Noble, Dureau et al. (1995) who found the mean time post renal transplant and the appearance of SCC was $8.6 \pm 6$ years for renal transplant patients in France. The time to development of NSMC in this NARP cohort may be sooner due to the older age at which patients are transplanted. The unadjusted rate for patients in Northern Alberta to develop NMSC post renal transplant was approximately 18% at 10 years. Hartevelt, Bouwes

Bavinck, Kootte, Vermeer, and Vandenbroucke (1990) reported rates of NMSC being 10% in the Netherlands and 45% in Australia at 10 years post renal transplant. A study in Oregon (Lampros et al., 1998) reported a rate of 35% at 10 years for heart transplant patients. This supports that patients living in a temperate environment have higher rates of NMSC than previously thought (Bordea et al., 2004; Hartevelt et al., 1990; Ramsey et al., 2000).

## Risk Factors for Non-Melanoma Skin Cancer

The risk factors found for NMSC post renal transplant in this cohort were older age (>45 years), male gender, having a transplant in 1990-1999, light eyes, hair, and/or skin color, presence of warts post transplant, a history of sunburn, not using sunscreen pretransplant, and years lived in Northern Alberta. On multivariate analysis, risk factors that remained significant were male, older age (> 45 years), presence of warts post transplant, and number of years lived in Northern Alberta. There were no risk factors that remained significant for > 6 NMSC lesions on multivariate analysis, as well as for SCC and BCC.

The mean age of this cohort was 50 years (SD=12.4 years) for the development of NMSC post renal transplant. Euvrard et al. (1995) found the age to be 47-49 years for the development of NMSC. The age of this NARP cohort may be older, reflecting transplanting older patients. Males had over twice the risk of developing of NMSC post renal transplant than females. Naldi et al. (2000) had similar outcomes with respect to gender. As well, only males in this cohort developed multiple NMSC lesions (> than 6 NMSC lesions). The presence of warts post transplant may play a role in the development of NMSC (Dreno, 2003), but the literature remains controversial. In this

cohort, a higher percentage of warts were reported post transplant in all subgroups of NMSC. In this cohort at 10 years post transplant, it was found that approximately 25% of patients with warts post transplant will develop NMSC. It has been recommended that warts be removed pretransplant and that patients be provided with early treatment post transplant (Dreno, 2003)

Number of years lived in Northern Alberta was found to be a risk factor for NMSC post renal transplant. To this date, there have been no studies on how living in Northern Alberta affects the development of NMSC in renal transplant patients. Considering Alberta is known as one of the sunniest provinces in Canada with reports of 312 days per year of sunshine (Environment Canada, 2005) it is logical that time spent in Alberta would be a risk factor for NMSC. However, this study was unable to specifically relate outside work or hobbies as a risk for the development of NMSC post renal transplant. This is consistent with Liddington et al. (1989) who was unable to relate outdoor occupations to the development of NMSC in renal transplant patients in the U.K..

Sun exposure is important in the development of skin cancer as it directly causes DNA damage to the skin and induces further immunosuppression (Bouwes Bavinck, Boer et al., 1993; Boyle, MacKee, Briggs, Junor, & Aitchison, 1984; Parrish, 1983). The majority of NMSC lesions in this cohort were found in sun-exposed areas, with the majority to the head/neck and upper arms. This is supported in the literature (Naldi et al., 2000; Bordea et al.,2004; Euvrard, Kanitakis, Pouteil-Noble, Dureau et al., 1995). The fact NMSC lesions occur predominately in sun-exposed areas suggests the importance sunlight has in the development of NMSC (Bordea et al.,2004; Naldi et al.,2000; Blohme

& Larko, 1992; Lampros et al., 1998). This also stresses the importance of transplant patients adopting sun reduction strategies.

All patients that developed NMSC were Caucasian, and this was consistent with light skin colour (Fitzpatrick 1-3) as a risk factor for the development of NMSC. Ramsey et al. (2003) found in the general population that fair skin and light coloured eyes and hair increase the risk of NMSC.

Smoking was not found to be a risk factor for NMSC in this cohort. There have been studies that have identified smoking in the general population as a risk factor for the development of SCC (De Hertog et al., 2001). This has been attributed to a decreased immune surveillance (Johnson et al., 1990; Wewer et al., 1998) and smoke being directly carcinogenic (Wynder & Hoffman, 1968). Notwithstanding, there have been other studies that have reported that smoking may be overridden by other more important variables (Bordea et al., 2004).

Previous reports have shown that HLA mismatch or presence of certain HLA antigens as significant in the development of NMSC post renal transplant (Bock et al., 2004). Findings of this study did not demonstrate any association with HLA mismatch or presence of certain 'high risk' (HLA A11, B27 or DR7) antigens. This has been supported in other studies (Jensen et al., 1998). This may be a regional affect as this transplant cohort is fairly homogenous and the sample size may have been too small to show an effect.

Induction therapy was not found to be a risk factor for the development of NMSC, a similar finding to Bordea et al. (2004). In addition, maintenance immunosuppressive medications were not a significant predictor. Most studies have been based on

Cyclosporin and/or Azathioprine therapy. This cohort had approximately 8 years with patients on Mycophenolate mofetil, 5 years on Tacrolimus, and 3 years on Sirolimus. The duration of these medications may not have been long enough to determine if they posed a high or low risk. As well, only one patient was on Sirolimus, thus the effect on the development of NMSC could not be determined. Immunosuppressive medications not being a risk factor for NMSC post transplant studies has been reported in other studies (Harden et al., 2001; Liddington et al., 1989).

## Limitations of the Study

Although, the Alberta Cancer Registry captures approximately 95% of all NMSC lesions, it is recognized a small number of NMSC lesions may be removed at physician offices and subsequently not reported. In comparison of patients' self-report of skin cancer to the Alberta Cancer Registry, there were 5 cases of NMSC not reported. This potential incomplete registration of NMSC cases may under estimates the incidence of NMSC. Presence of warts both pre and post renal transplant was obtained by self-report as HPV virus status is not routinely documented, therefore HPV serology was not found upon health record review. Recall in completing the Sun Exposure Questionnaire was another limitation, as time periods in their life may not be remembered. As well, the Sun Exposure Questionnaire was administered to living patients, therefore there were no personal or lifestyle data on patients that had died or were lost to follow up. Subgroup comparisons of SCC and BCC and multiple lesions were hindered by inadequate sample size. The presence of NMSC pretransplant was not addressed as potentially influencing the development of NMSC post transplant. The combination of immunosuppressive medications was also not addressed, nor was the introduction of different agents in

different eras, making it difficult to identify the contribution of individual immunosuppressive medications. Incomplete data or missing data could also alter the findings. Finally, a strength of this study is that patients, for the most part in the NARP, are involved in long-term follow up.

## Implications of the Findings

Identified in this study is a high-risk patient that is older, male, living in Northern Alberta with a history of warts post transplant. Considering the majority of the study cohort is male and over the age of 45 years, and has lived in Northern Alberta for greater than 38 years, one must be vigilant in education about the dangers of the sun and provide close surveillance of these patients. These patients need lesions removed promptly with the possibility of adjusting immunosuppressive therapy. There is also an issue of adherence with renal transplant patients. Butt and Roberts (1997) found 91% of patients were aware of the risks of UVR exposure but 31% were not taking any precautions against UVR. Seukeran et al. (1998) found only 30% of renal transplant recipients knew that they needed to take extra precautions in the sun. Moloney et al. (2005) suggested that the effects of immunosuppressive therapy on the skin may be why patients do not use sunscreen (Cyclosporin can cause sebaceous gland hyperplasia, folliculitis, acne, and hirsutism; Prednisone can cause acne) or it may be due to the cost of sunscreen. Strategies to improve adherence suggested are to find out what the patient knows about the problem, agree on what the problem is, negotiate reasonable goals, provide options, mutually determine a plan of action, and assess for readiness to learn (Lowes, 1998). The International Transplant Society of Skin Cancer (ITSCC) describes prevention strategies for transplant patients as follows: daily sun protection, monthly self-skin examination,

and timely skin examination by a dermatologist. Daily sun protection consists of using a broad spectrum sunscreen daily with SPF greater than 30, long sleeves shirts, a wide-brimmed hat, sunglasses, sun avoidance between 10am and 4pm, avoidance of artificial sources of UVR, and avoidance of prolonged exposure in the sun and if outside to seek shade. Monthly self-skin examination consists of a full body view of your skin. The ITSCC also recommends at least one complete skin examination by a dermatologist post transplant and follow-up exams depending on the number of risk factors the patients has.

## Conclusion

As more renal transplant patients are living longer with their grafts due to improvements in the field of renal transplantation, the development of NMSC is of concern. In this Northern Alberta post renal transplant cohort, the incidence of NMSC post renal transplant was 9.7%. The median time to development was 4.02 years. The risk factors identified for NMSC were older age, male gender, presence of warts post transplant, and number of years lived in Northern Alberta. There were no noted significant risk factors for patients with multiple NMSC lesions or for patients with SCC or BCC. Having identified a high-risk group for NMSC post renal transplant, these patients require education on sun protection, surveillance of their skin, and early treatment.

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# Appendix A

**Data Collection Sheet**

Study # _____

1. Date of Birth _____ Age: _____

2. Gender ☐ Male ☐ Female

3. Ethnicity ☐ Caucasian ☐ Black ☐ Asian ☐ Aboriginal ☐ E. Indian ☐ M. Eastern ☐ Philipino ☐ Other

4. Cause of Renal Disease ☐ GN ☐ DM ☐ HTN ☐ Other

5. If patient is deceased cause of death: _____

6. If patient is alive; current status: ☐ Dialysis ☐ Transplanted

7. Previous Kidney Transplants ☐ Yes ☐ No Number: _____

8. Date of Transplant Surgery _____ Months Since Surgery: _____

9. Donation Type

| | |
|---|---|
| LRD | |
| LURD | |
| DDT | |

10. Induction Medication

| | |
|---|---|
| IL-2 | |
| ALG | |
| OKT3 | |

11. Medications

| | Duration |
|---|---|
| Cyclosporin | |
| Prednisone | |
| Imuran | |
| Cellcept | |
| Tacrolimus | |
| Rapamycin | |

12. HLA Status Recipient

| A | A | B | B | DR | DR |
|---|---|---|---|---|---|
| | | | | | |

13. HLA Status Donor

| A | A | B | B | DR | DR |
|---|---|---|---|---|---|
| | | | | | |

14. Documentation of HPV ☐ Yes ☐ No

15. Skin Cancer Pretransplant ☐ Yes ☐ No

Date _____
Type _____
Location _____
Number of Lesions _____
Treatment _____
Number of Episodes _____

16. Skin Cancer Post Transplant ☐ Yes ☐ No
    Date of First Lesion _____
    Type _____
    Location _____
    Number of Lesions _____
    Treatment _____
    Number of Episodes _____

# Appendix B

**Sun Exposure Questionnaire**

*** Adapted from Moloney, F.J., Almarzouqi, E., O'Kelly, P., Conlon, P., and Murphy, G. (2005) Sunscreen use before and after transplantation and assessment of risk factors associated with skin cancer development in renal transplant recipients. Archives of Dermatology, 141, 978-982.**

Study #: _____

1. Occupation
   (a) Did you work outdoors? ☐ Yes ☐ No ☐ Partially
   (b) For how many hours per day? _____
   (c) For how many months per year? _____
   (d) For how many years? _____

2. Recreation
   (a) Outdoor hobbies? Specify _____
   (b) For how many hours per day? _____
   (c) For how many months per year? _____
   (d) For how many years? _____

3. Eye Colour ☐ Blue ☐ Brown ☐ Green ☐ Hazel

4. Hair Colour ☐ Blonde ☐ Red ☐ Brown ☐ Black

5. Skin Type
   I: Always burns/Never tans ☐
   II: Always burns/Sometimes tans ☐
   III: Always tans/Sometimes burns ☐
   IV: Always tans/Never burns ☐
   V: Never burns/Brown skin ☐
   VI: Never burns/Black skin ☐

6. History of >= 2 painful sunburns: ☐ Yes ☐ No

7. Sun bed use: ☐ Yes ☐ No No. of Sessions: _____

8. If you are going out on a sunny day do you apply sunscreen:
   (a) Pretransplantation? ☐ Always ☐ Sometimes ☐ Never
   (b) Posttransplantation? ☐ Always ☐ Sometimes ☐ Never

9. Pretransplant History of:
   Precancerous Lesions ☐ Yes ☐ No
   Warts ☐ Yes ☐ No
   Skin Cancer ☐ Yes ☐ No

10. Posttransplant History of:
    Precancerous Lesions ☐ Yes ☐ No
    Warts ☐ Yes ☐ No
    Skin Cancer ☐ Yes ☐ No

11. Family history: Skin cancer in a first degree relative? ☐ Yes ☐ No

12. Number and % of total years lived in northern Alberta? _____ % _____

13. History of Smoking ☐ Current ☐ Past ☐ Never

14. Have you ever visited a Dermatologist (Skin Doctor)? ☐ Yes ☐ No

15. Have you ever had a skin biopsy (piece of skin removed)? ☐ Yes ☐ No

## Appendix C

## Information Sheet

**Title: Incidence and Risk Factors for Non-melanoma Skin Cancer Post Renal Transplant**

Principal Investigator: Sherry Comeau, MN Candidate (780) 405-2776

Co-investigators:

| | | |
|---|---|---|
| Dr. Louise Jensen | Faculty of Nursing | 492-6795 |
| Dr. Kristine Martin-MacDonald | Faculty of Nursing | 492-4709 |
| Dr. Sandra Cockfield | Department of Nephrology | 407-7239 |
| Dr. Sita Gourishankar | Department of Nephrology | 407-3627 |
| Dr. Mariuz Sapijaszko | Off-site Dermatologist | 424-4440 |


Introduction:
I am a graduate nursing student doing a study on 'The incidence and risk factors of non-melanoma skin cancer post renal transplant' for my master thesis. Since you had a kidney transplant and are registered in the Northern Alberta Renal Program, you are being asked to take part in this study. This study is looking at skin cancer after a kidney transplant for patients living in Northern Alberta. We hope to gain a better understanding of the risk factors for getting skin cancer after a kidney transplant. If you are willing, you will be asked a few questions regarding your sun exposure history. This would take about 10-15 minutes. All information will be kept private and confidential. Your name and any other personal information will not be attached to the information you provide. Your name will also never be used in any presentations or written work of the study results. Taking part in this study is voluntary. Your consent will be implied with the completion of the questionnaire. You may refuse to answer any questions. The information will be kept in a locked filing cabinet in the researcher's office for a period of 7 years.

Contact Persons:
If you have concerns about your rights as a study participant, you may contact the Patient Relations office of Capital Health, at 407-1040. This office has no affiliation with the study investigators. Please contact Sherry Comeau at 405-2776 if you any questions or concerns.

Thank you for taking the time to complete this questionnaire

# Appendix D

## Hazard Ratio Plots

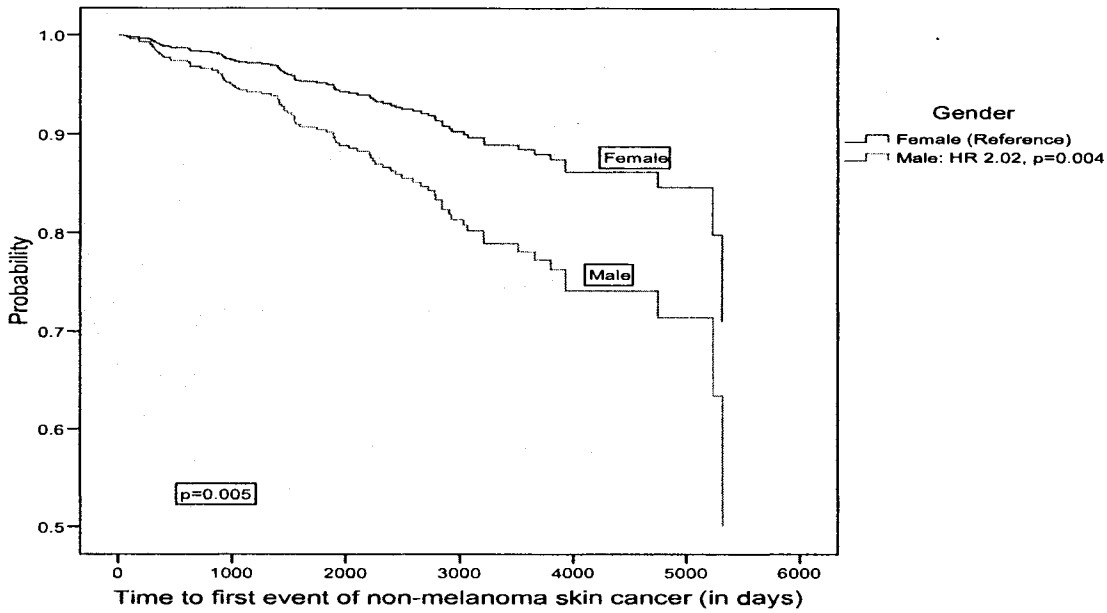


Figure 1. Time to development of non-melanoma skin cancer adjusted for gender

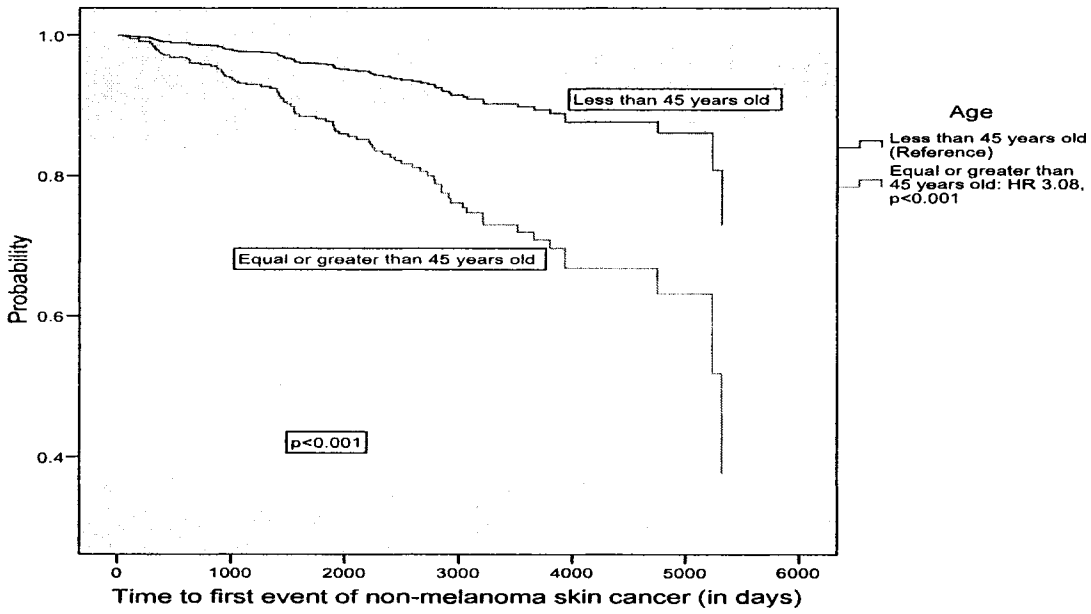


Figure 2. Time to development of non-melanoma skin cancer adjusted for age

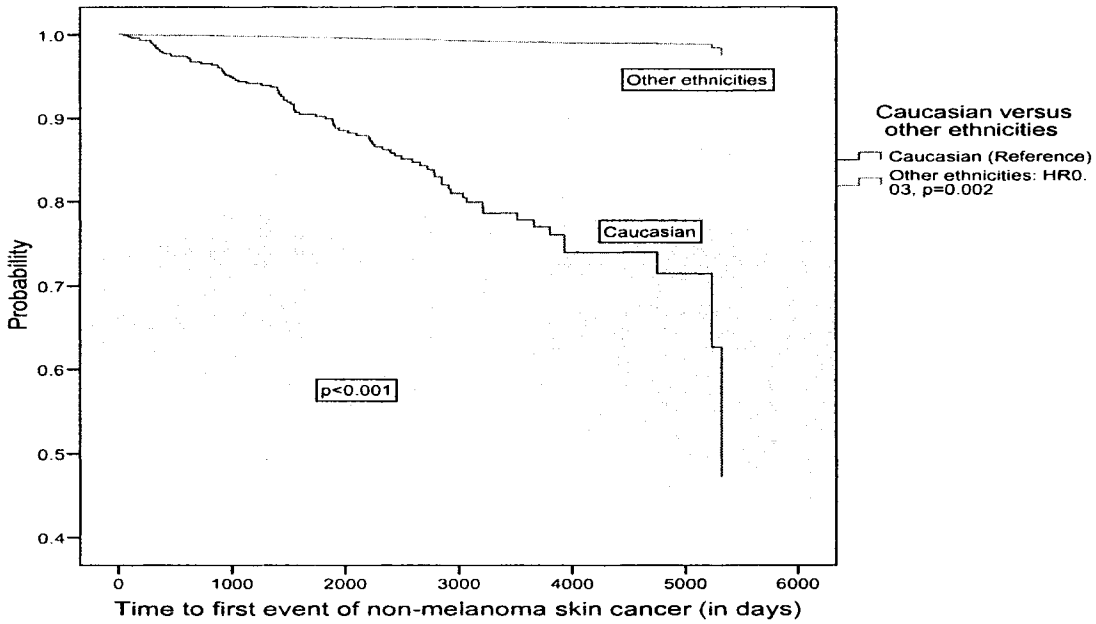


Figure 3. Time to the development of non-melanoma skin cancer adjusted for ethnicity

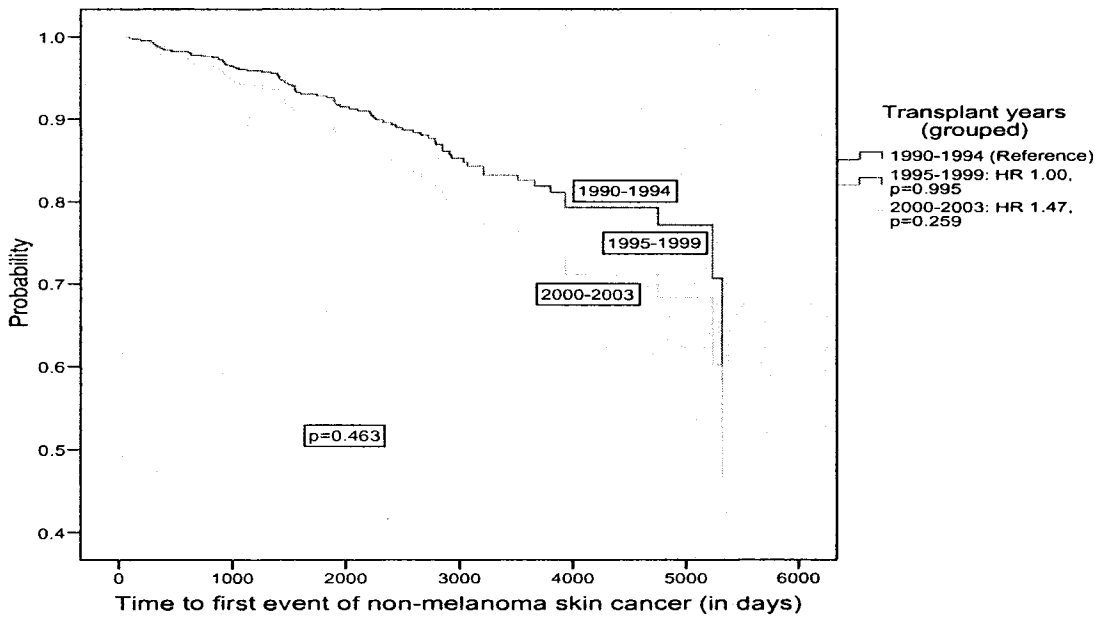


Figure 4. Time to the development of non-melanoma skin cancer adjusted for transplant years

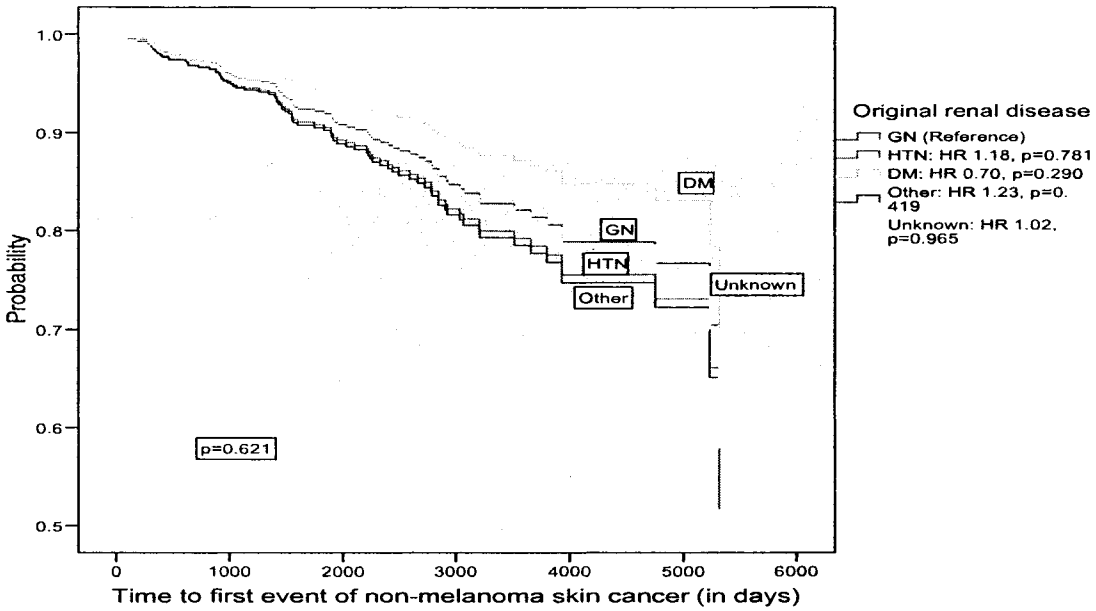


Figure 5. Time to the development of non-melanoma skin cancer adjusted for renal disease

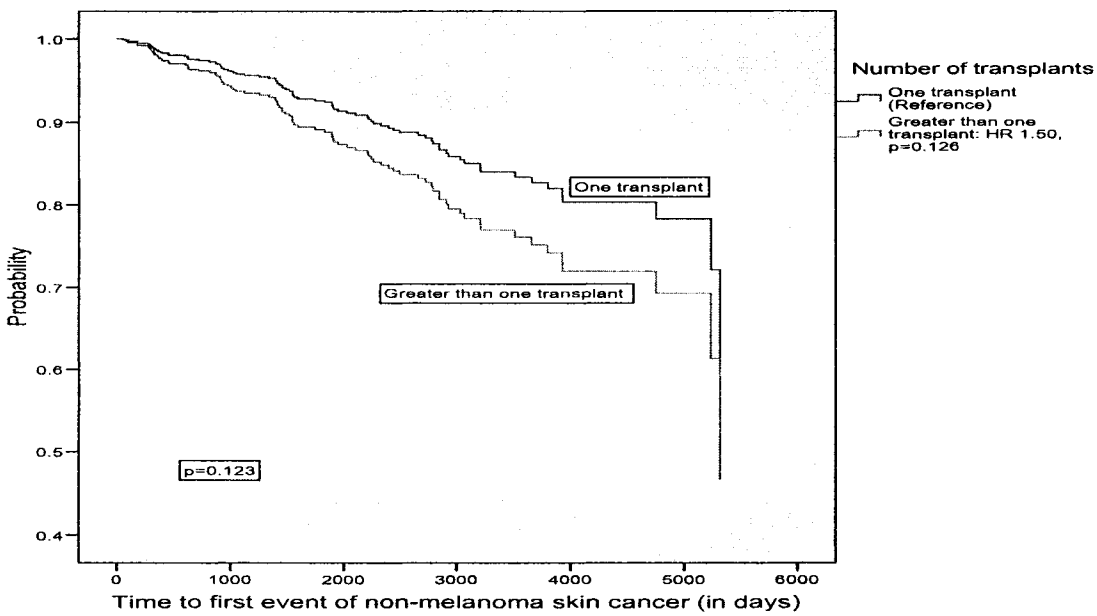


Figure 6. Time to the development of non-melanoma skin cancer adjusted for number of transplants

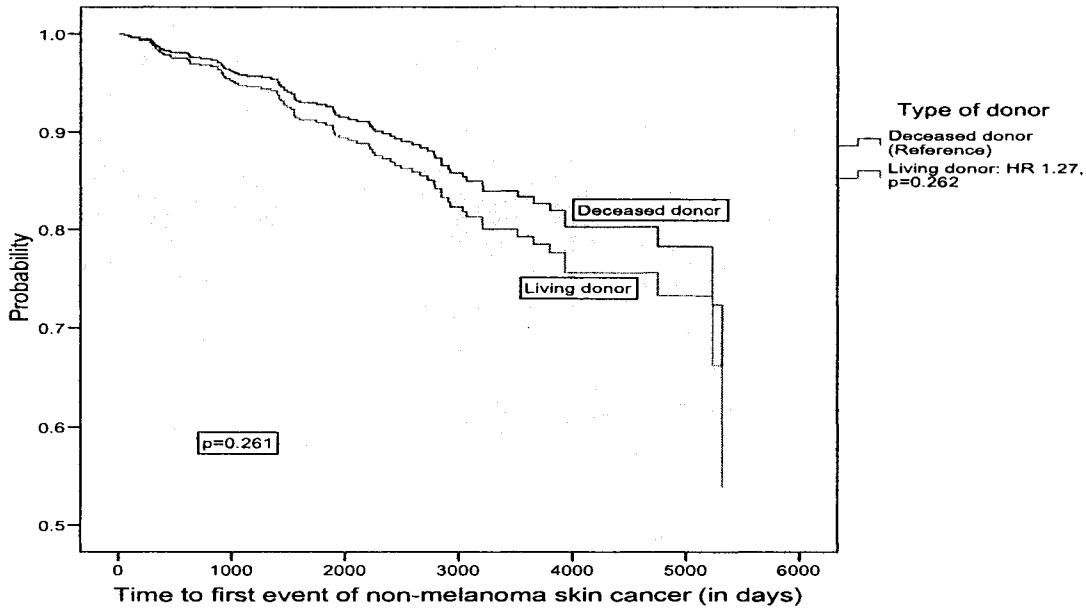


Figure 7. Time to the development of non-melanoma skin cancer adjusted for type of donor

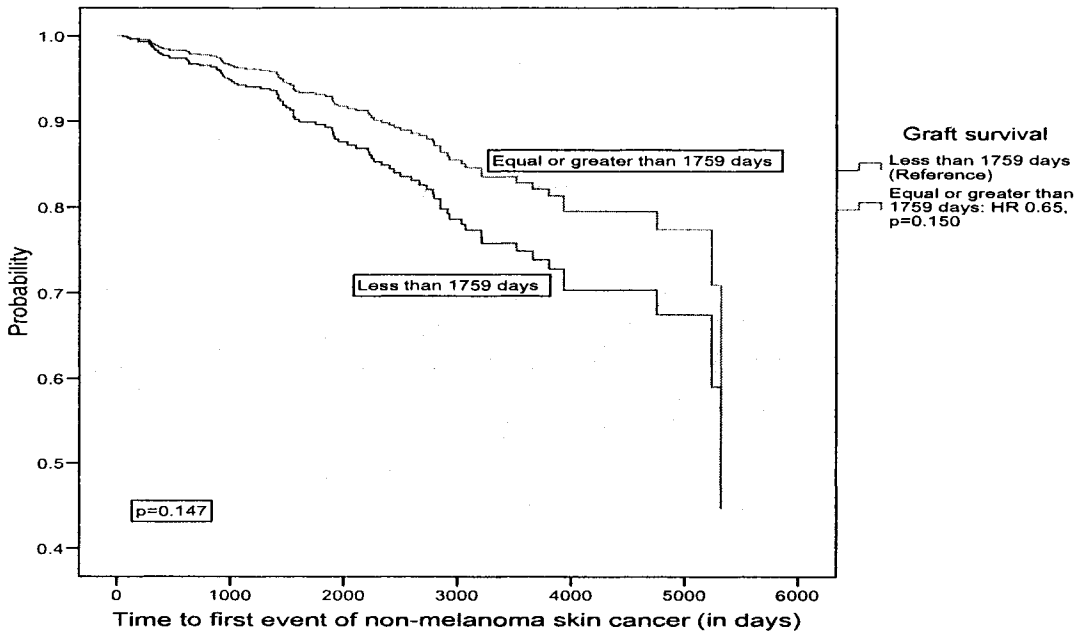


Figure 8. Time to the development of non-melanoma skin cancer adjusted for graft survival

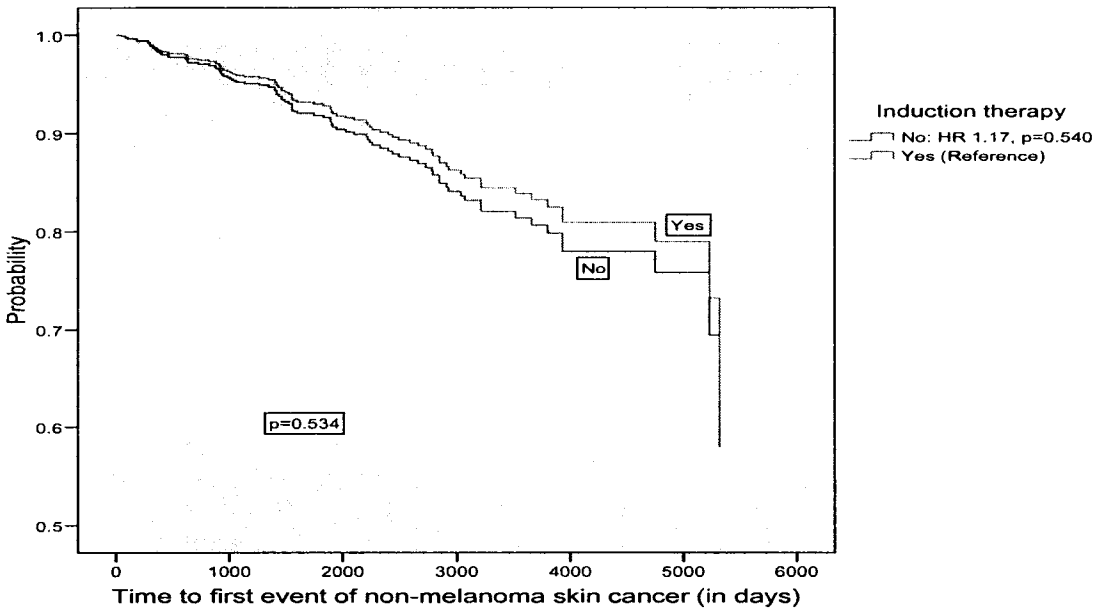


Figure 9. Time to the development of non-melanoma skin cancer adjusted for induction therapy

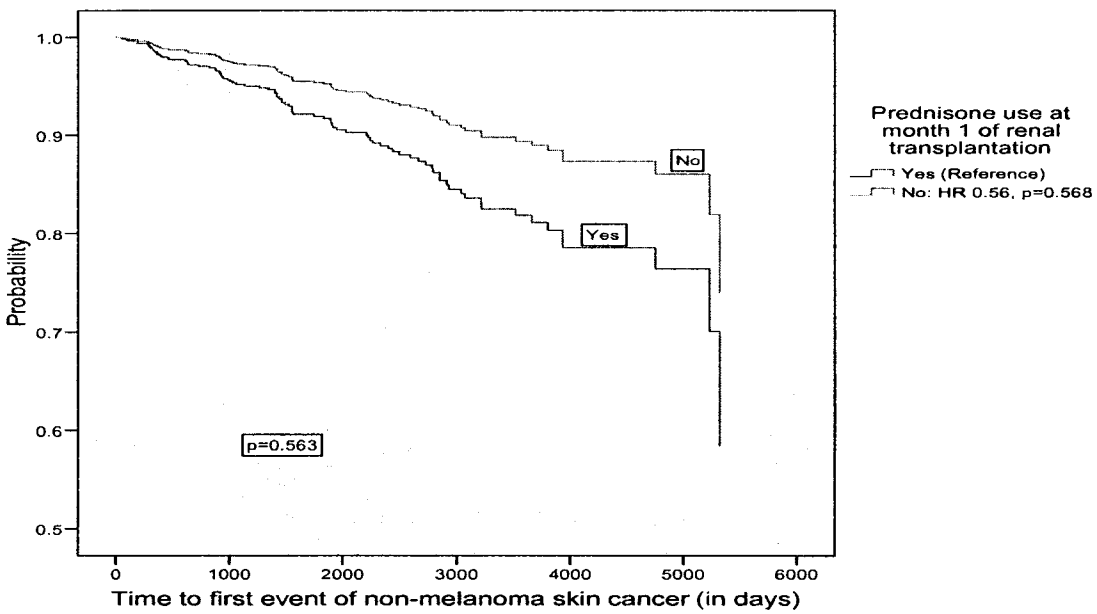


Figure 10. Time to the development of non-melanoma skin cancer adjusted for Prednisone use at month one

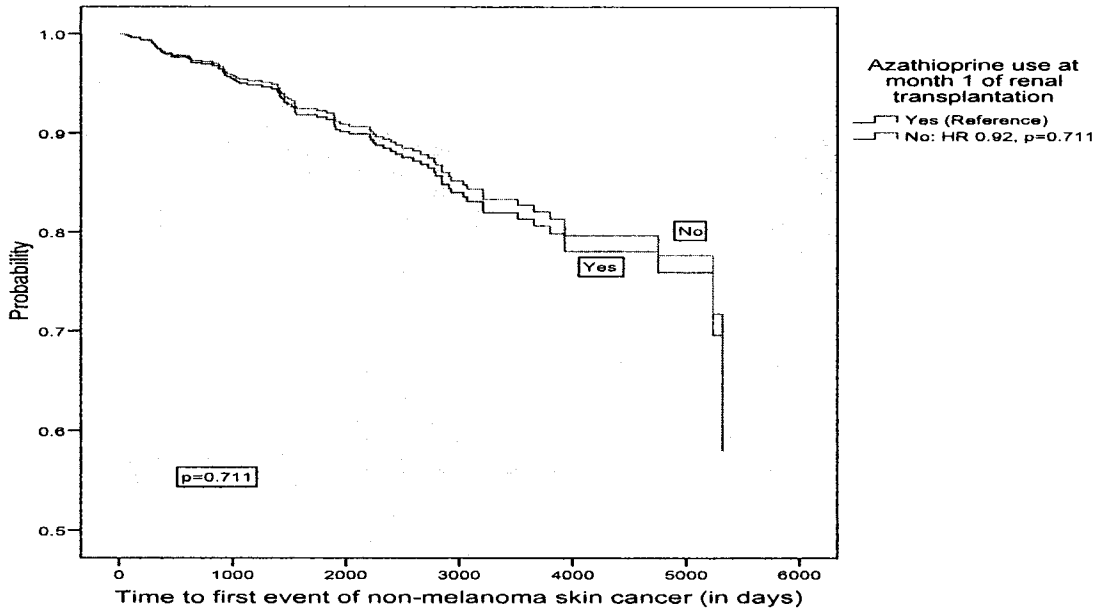


Figure 11. Time to the development of non-melanoma skin cancer adjusted for Azathioprine use at month one

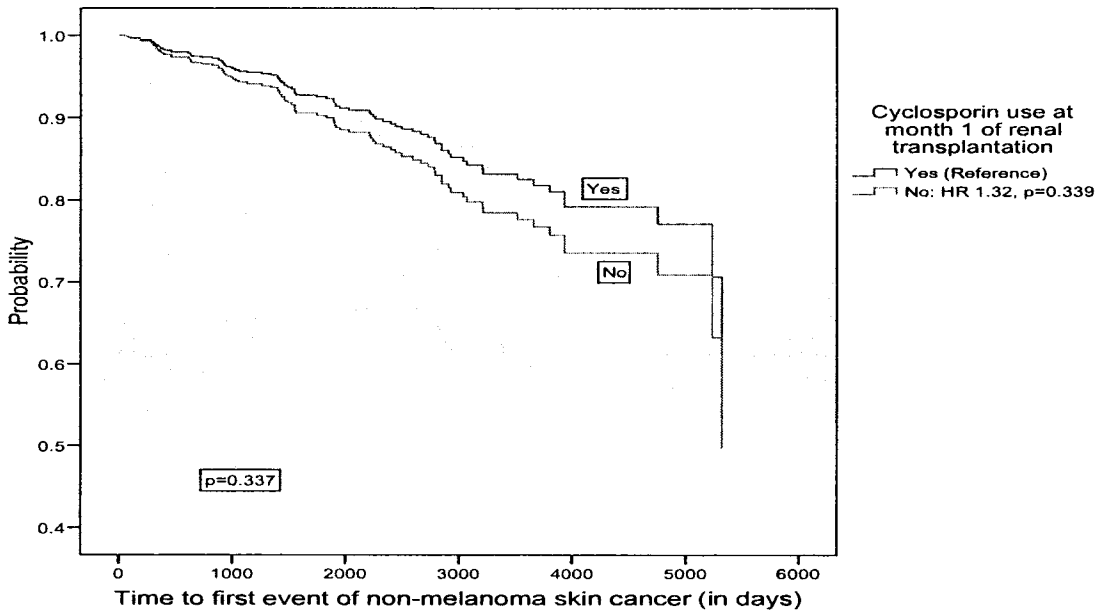


Figure 12. Time to the development of non-melanoma skin cancer adjusted for Cyclosporin use at month one

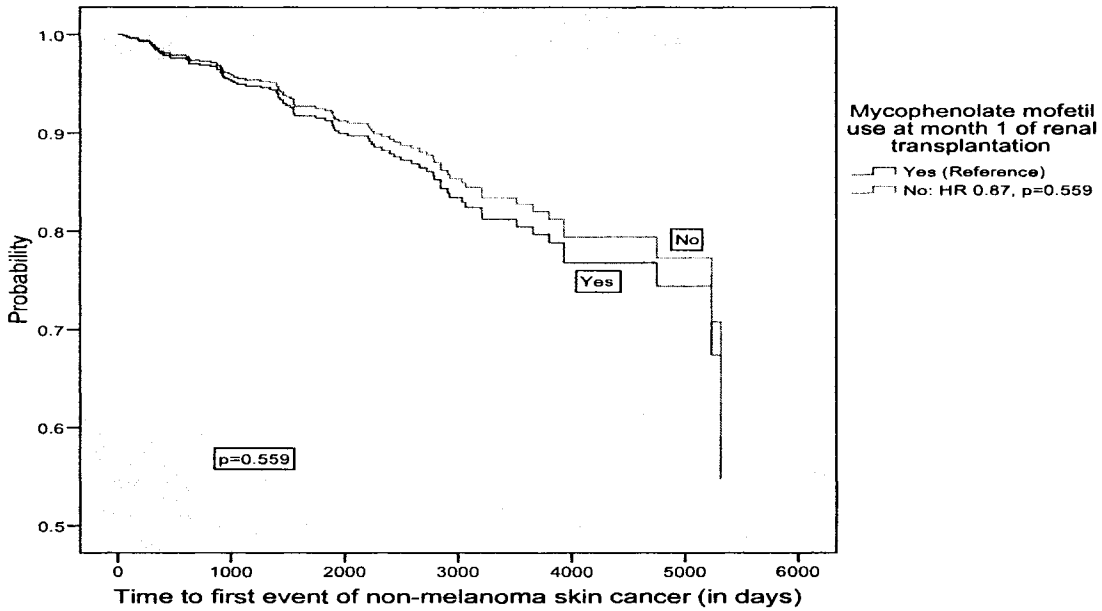


Figure 13. Time to the development of non-melanoma skin cancer adjusted for Mycophenolate mofetil use at month one

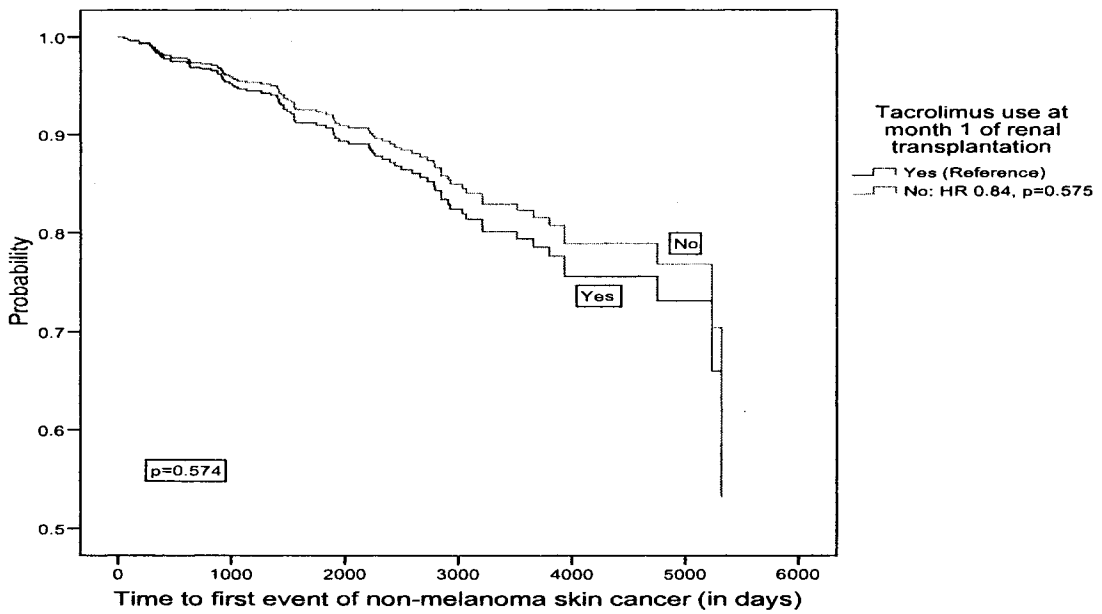


Figure 14. Time to the development of non-melanoma skin cancer adjusted for Tacrolimus use at month one

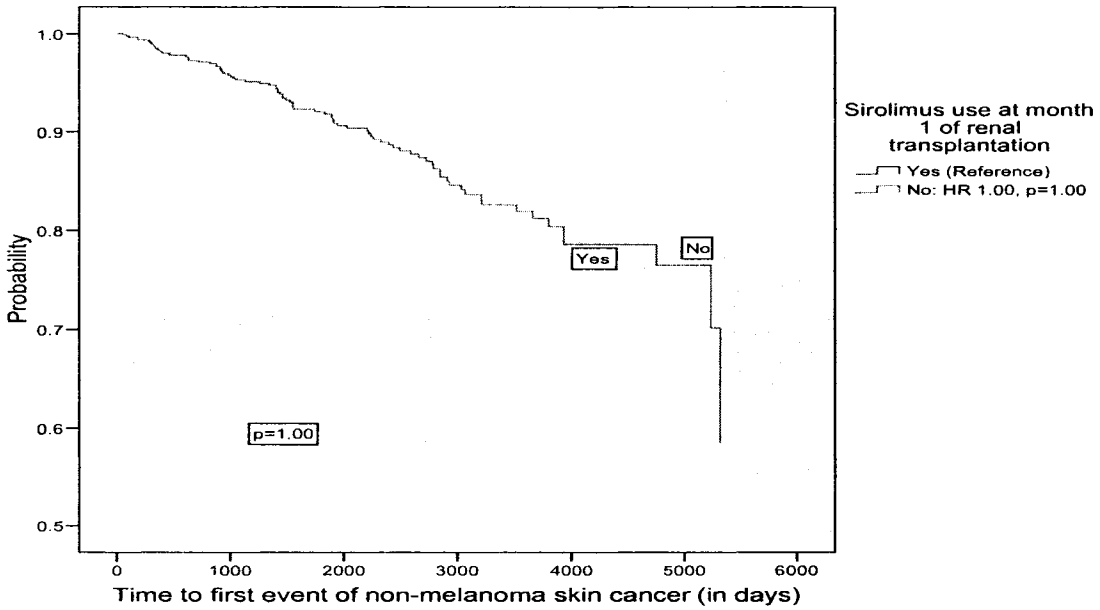


Figure 15. Time to the development of non-melanoma skin cancer adjusted for Sirolimus use at month one

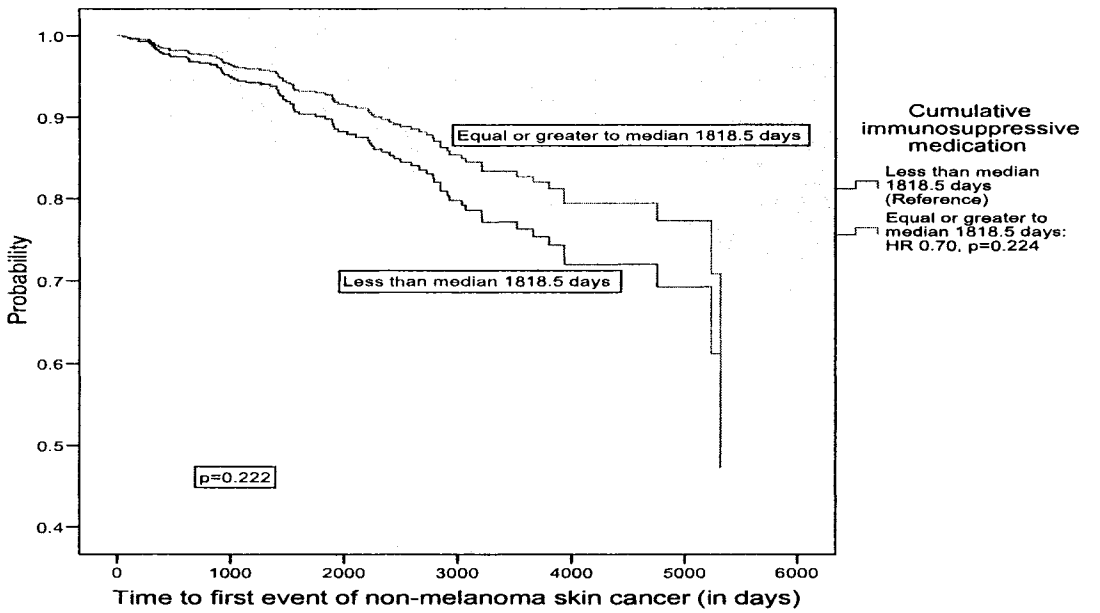


Figure 16. Time to the development of non-melanoma skin cancer adjusted for cumulative immunosuppressive medication

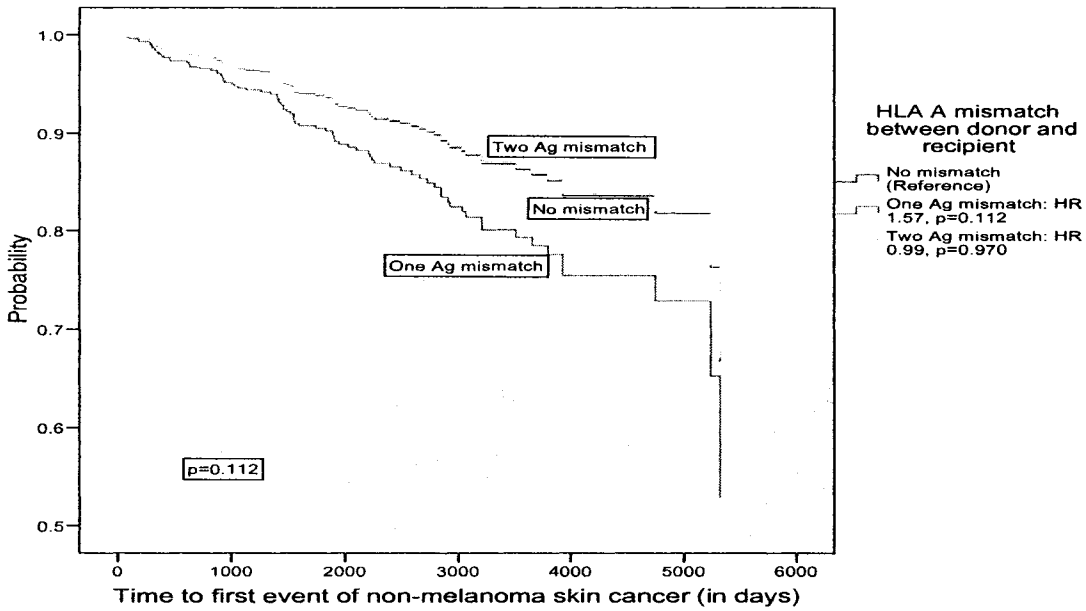


Figure 17. Time to the development of non-melanoma skin cancer adjusted for HLA A mismatch between donor and recipient

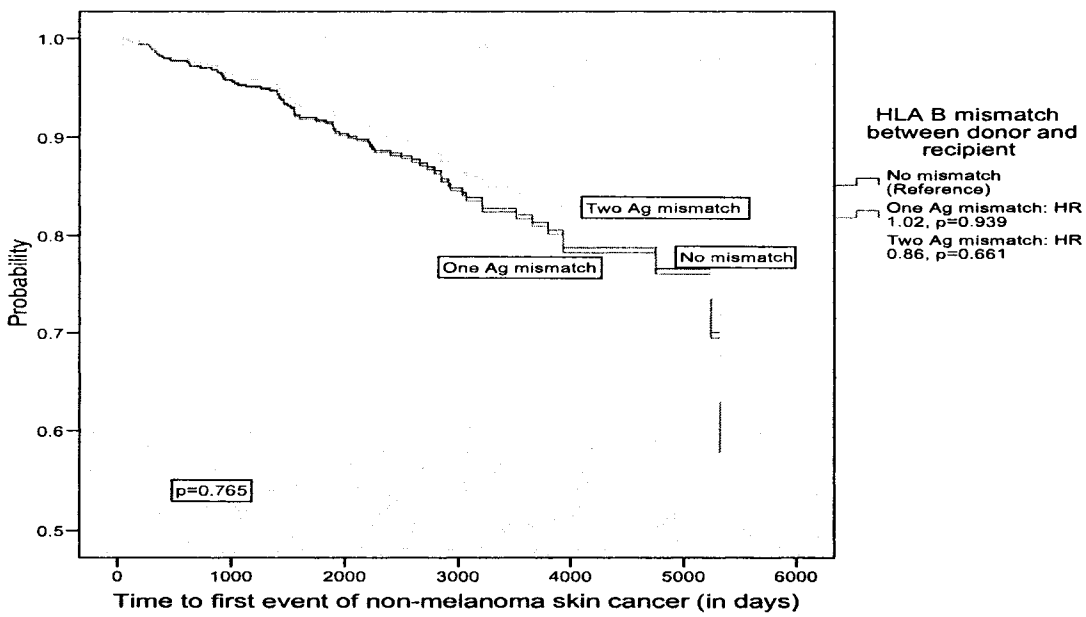


Figure 18. Time to the development of non-melanoma skin cancer adjusted for HLA B mismatch between donor and recipient

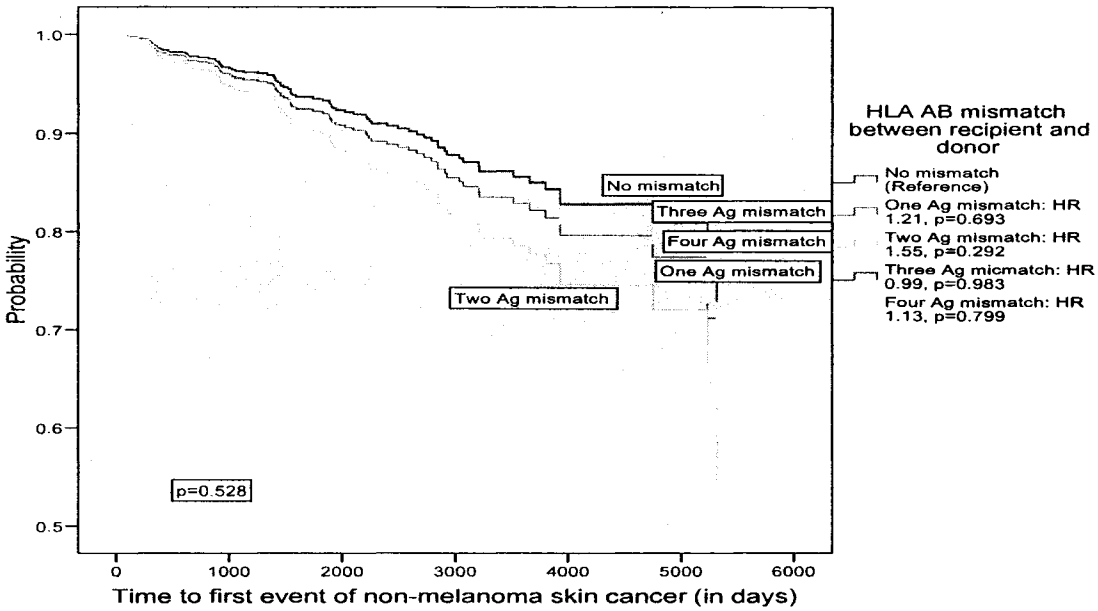


Figure 19. Time to the development of non-melanoma skin cancer adjusted for HLA AB mismatch between donor and recipient

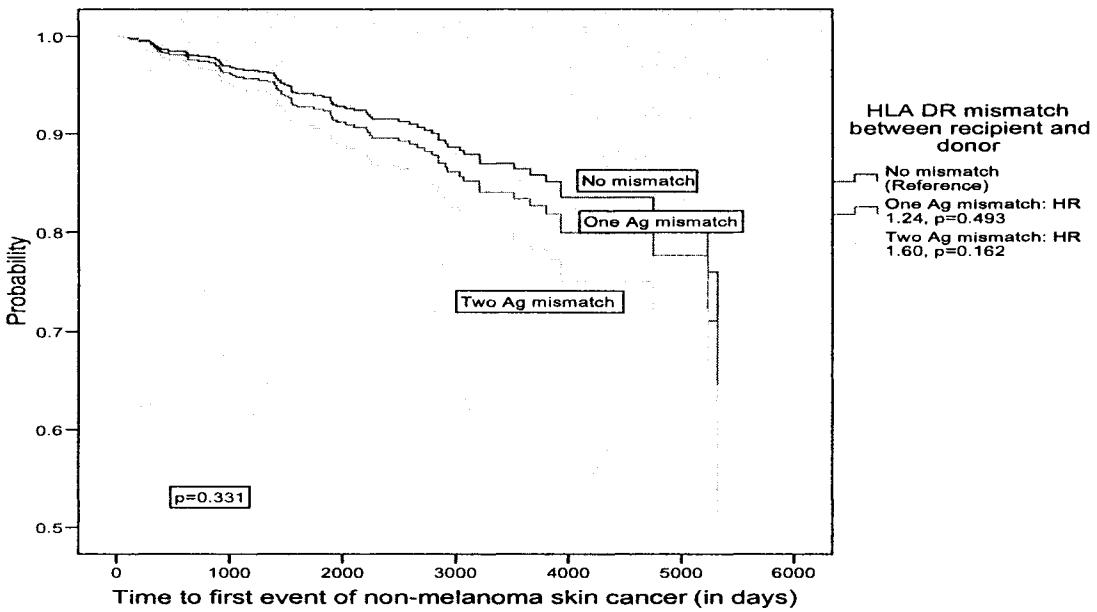


Figure 20. Time to the development of non-melanoma skin cancer adjusted for HLA DR mismatch between donor and recipient

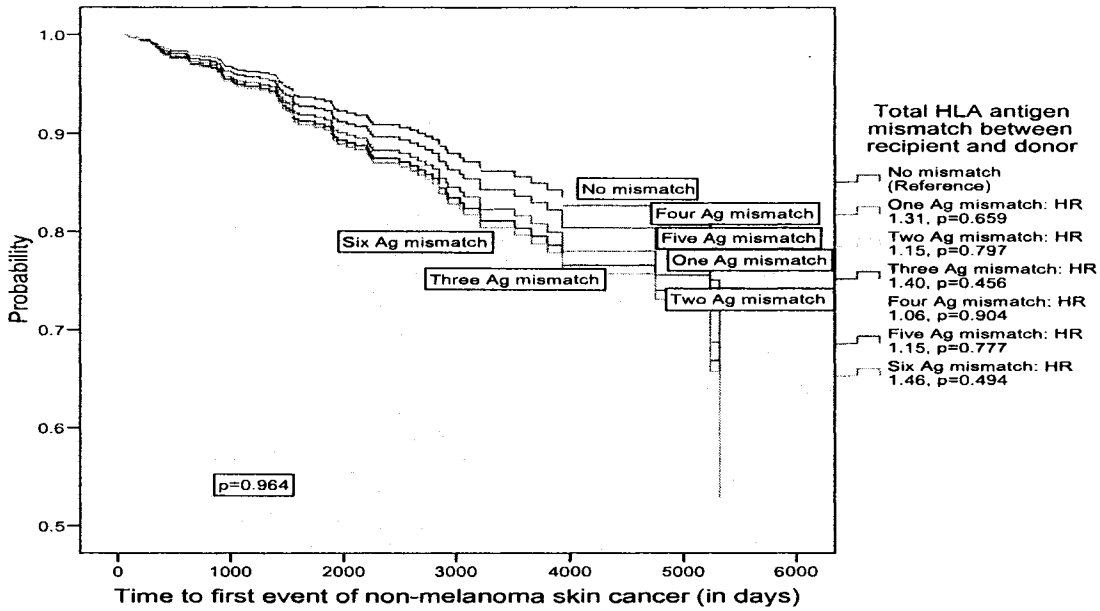


Figure 21. Time to the development of non-melanoma skin cancer adjusted for total HLA mismatch between donor and recipient

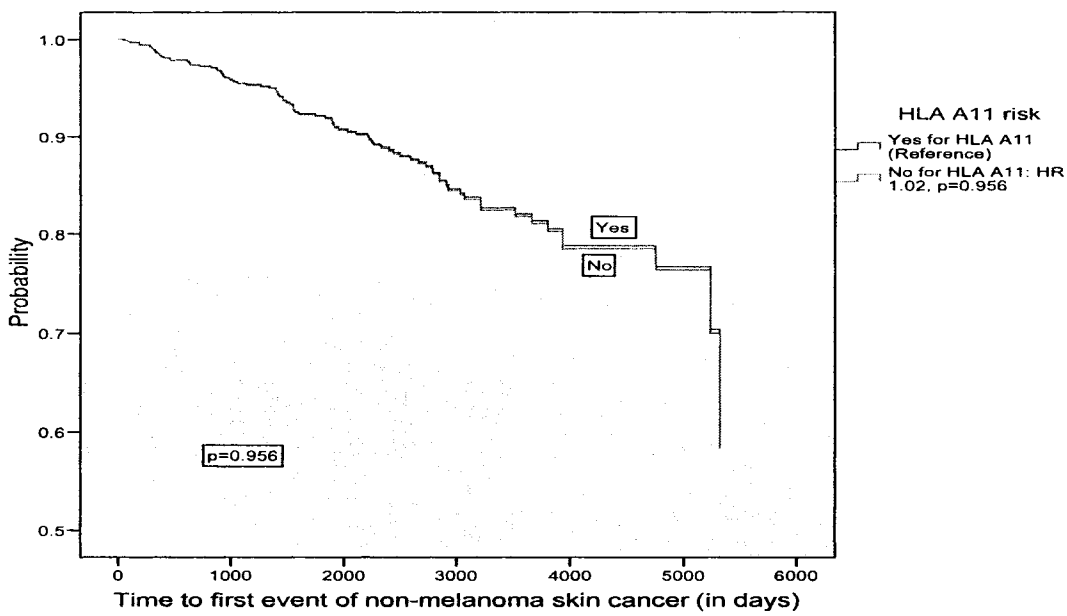


Figure 22. Time to the development of non-melanoma skin cancer adjusted for HLA A 11 antigen

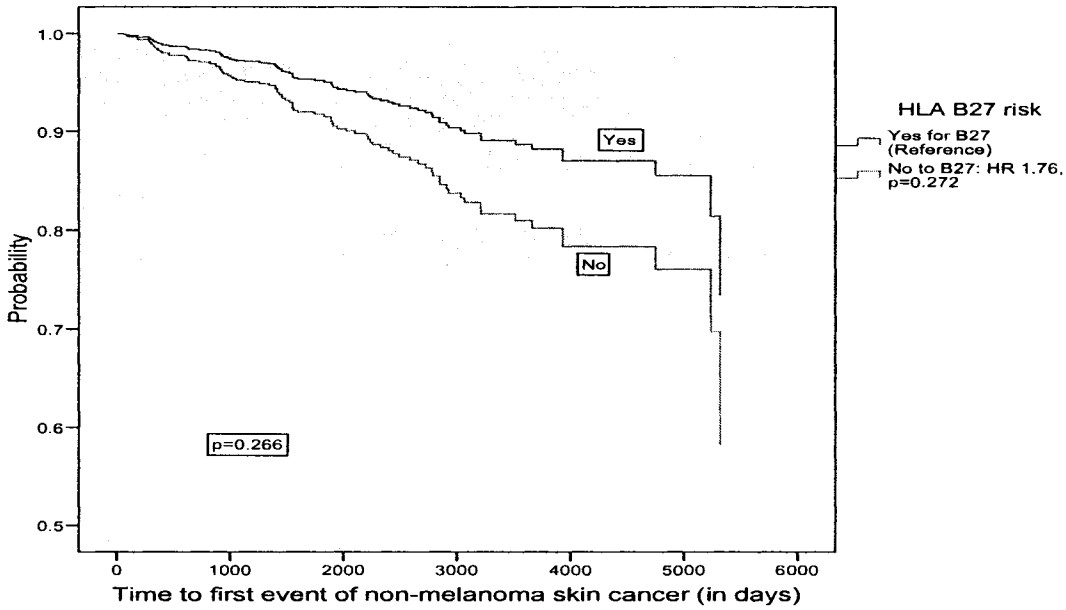


Figure 23. Time to the development of non-melanoma skin cancer adjusted for HLA B 27 antigen

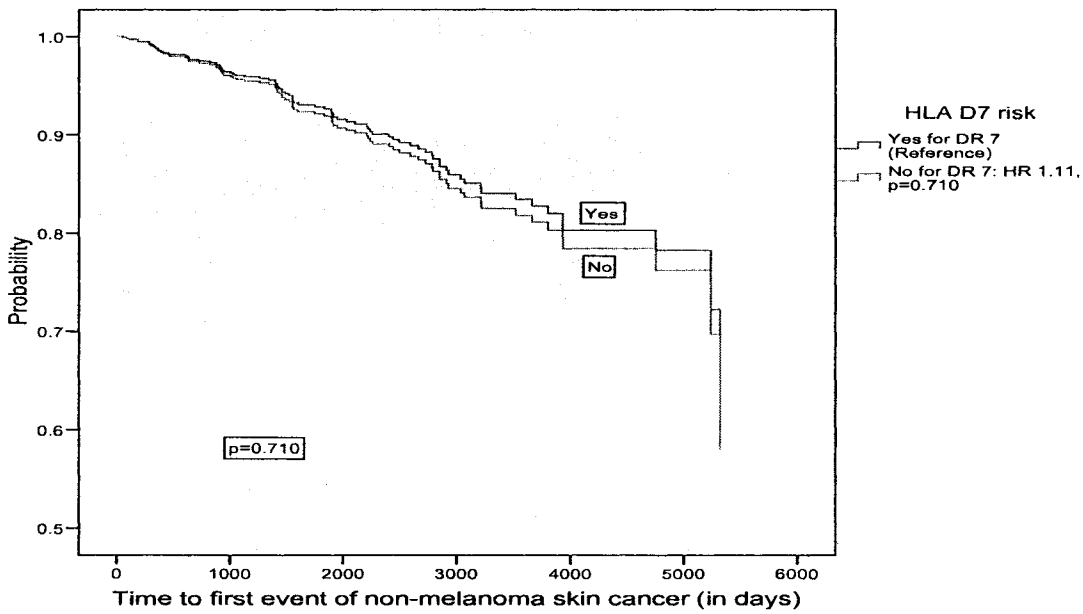


Figure 24. Time to the development of non-melanoma skin cancer adjusted for HLA DR 7 antigen

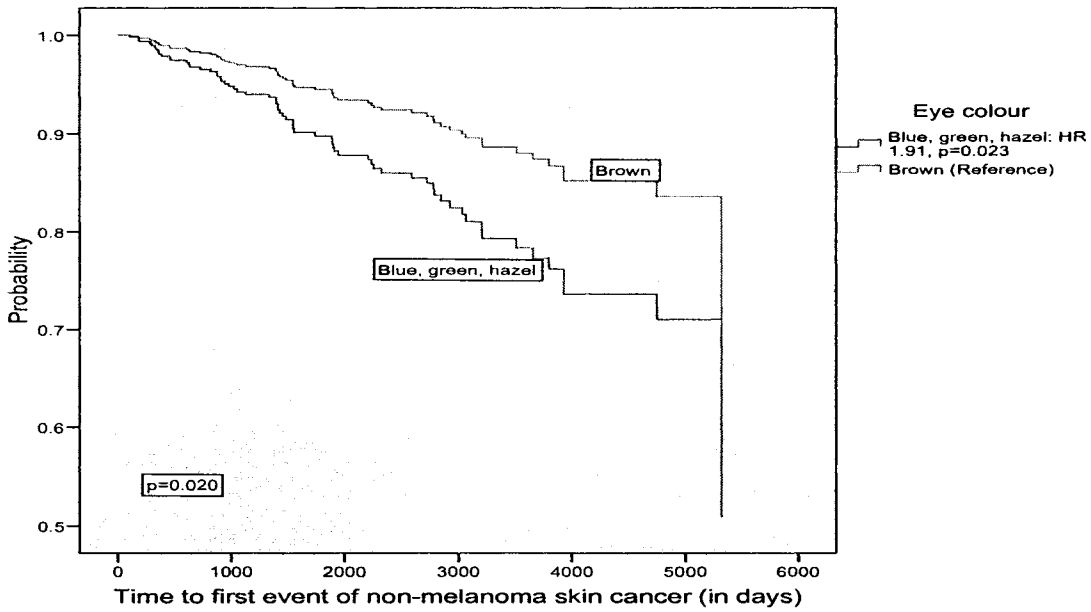


Figure 25. Time to the development of non-melanoma skin cancer adjusted for eye colour

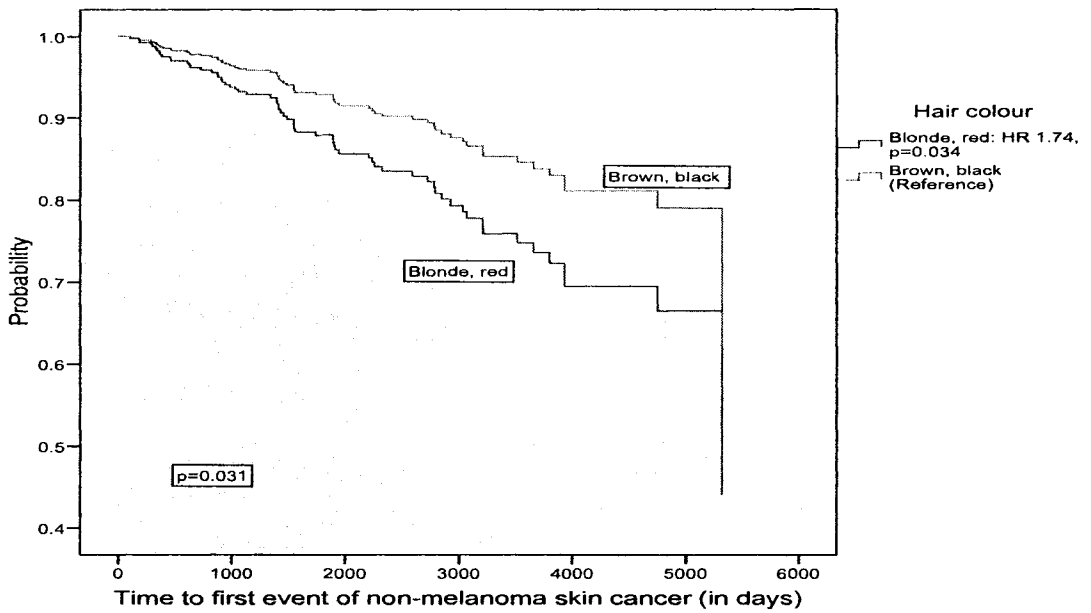


Figure 26. Time to the development of non-melanoma skin cancer adjusted for hair colour

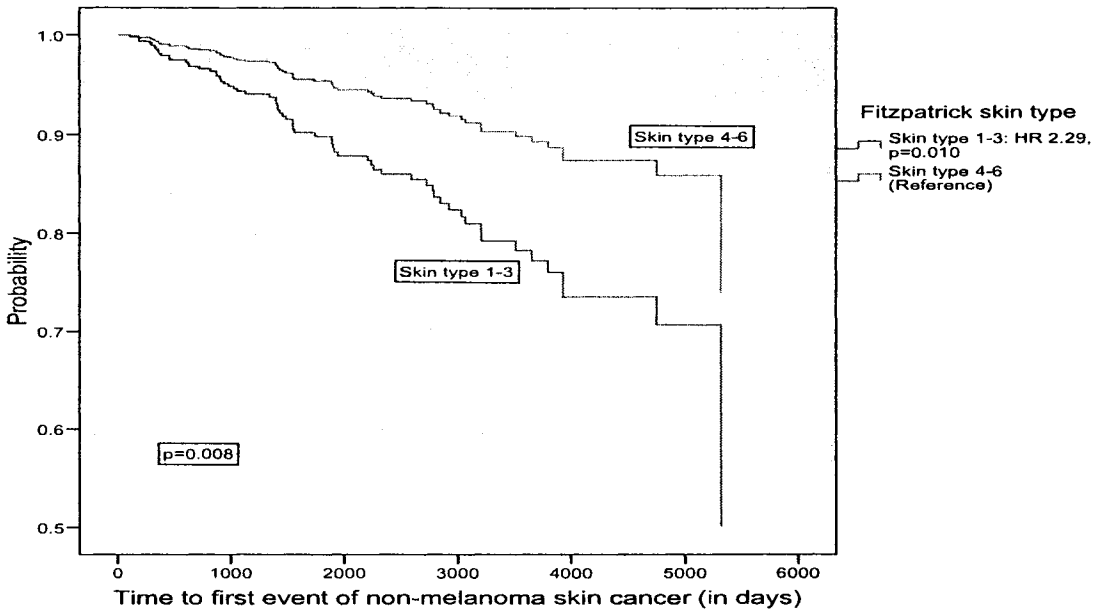


Figure 27. Time to the development of non-melanoma skin cancer adjusted for Fitzpatrick skin type

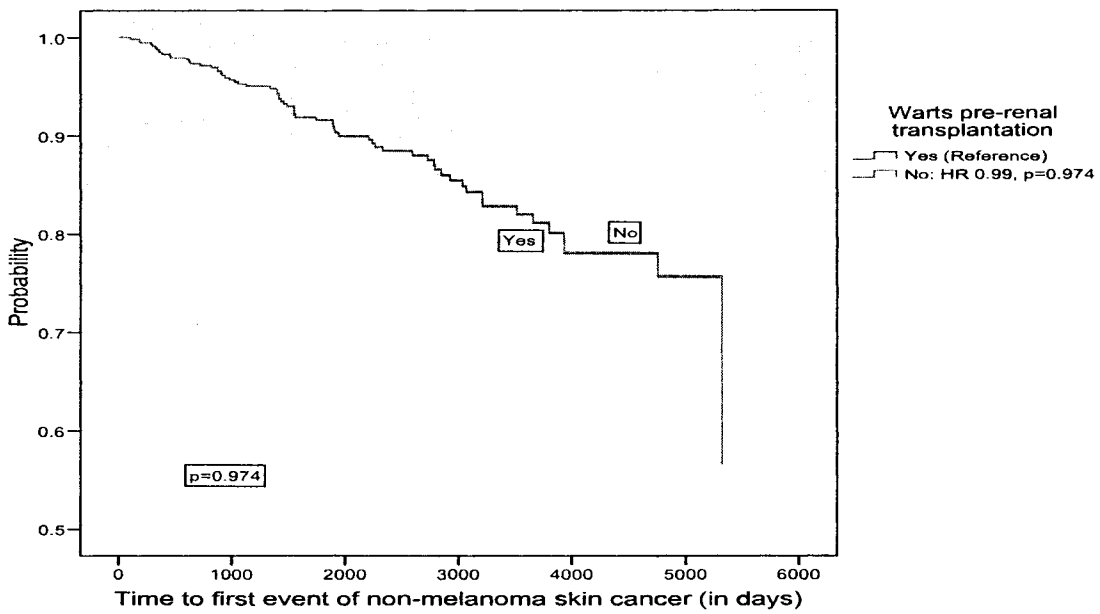


Figure 28. Time to the development of non-melanoma skin cancer adjusted for warts pre-renal transplantation

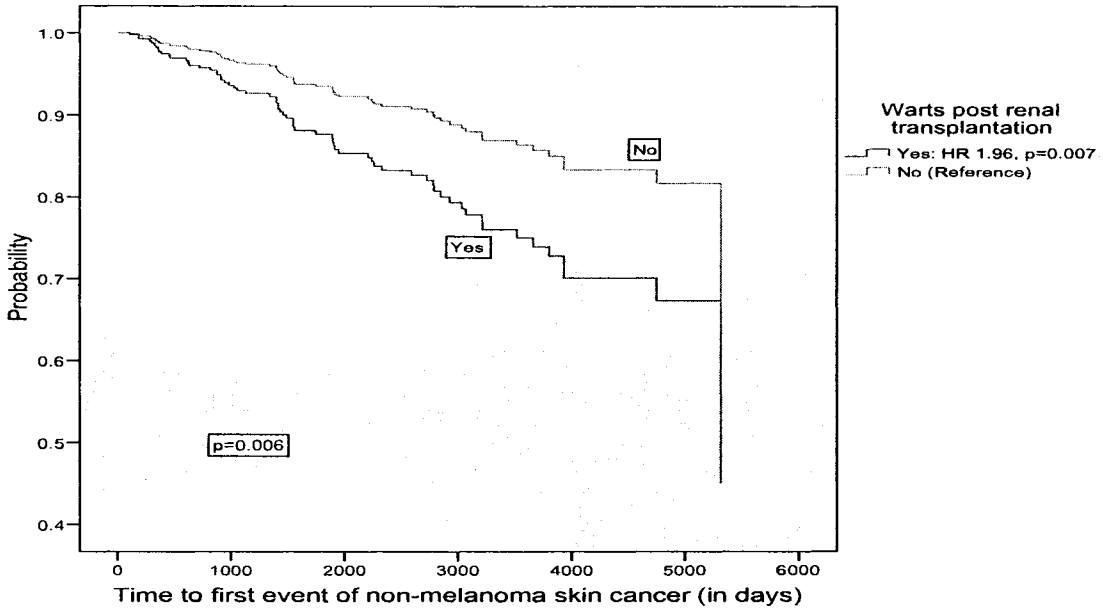


Figure 29. Time to the development of non-melanoma skin cancer adjusted for warts post renal transplantation

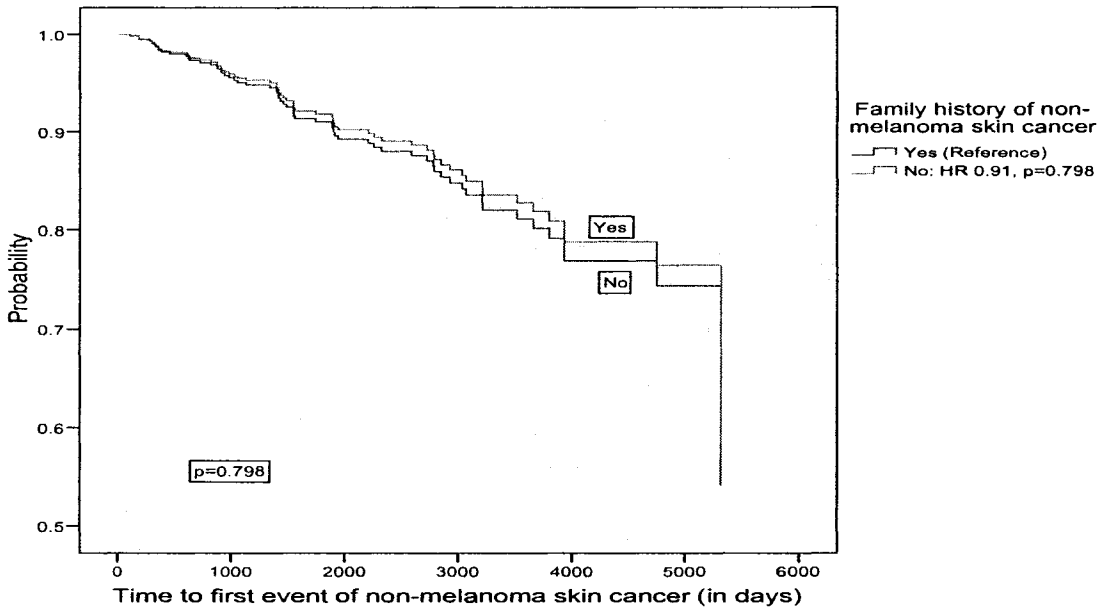


Figure 30. Time to the development of non-melanoma skin cancer adjusted for family history of non-melanoma skin cancer

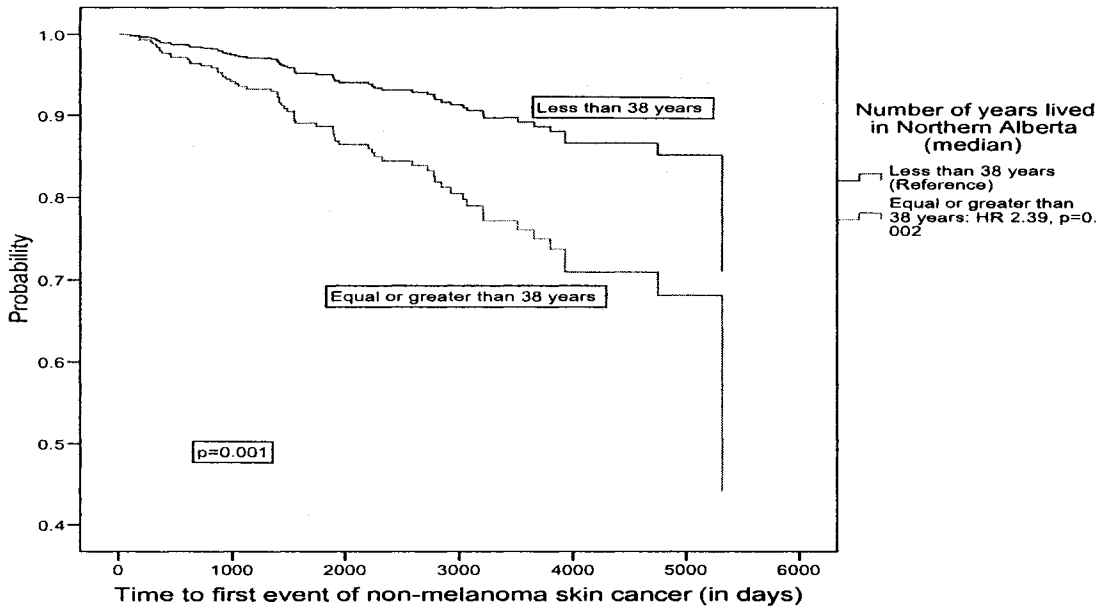


Figure 31. Time to the development of non-melanoma skin cancer adjusted for number of years lived in Northern Alberta

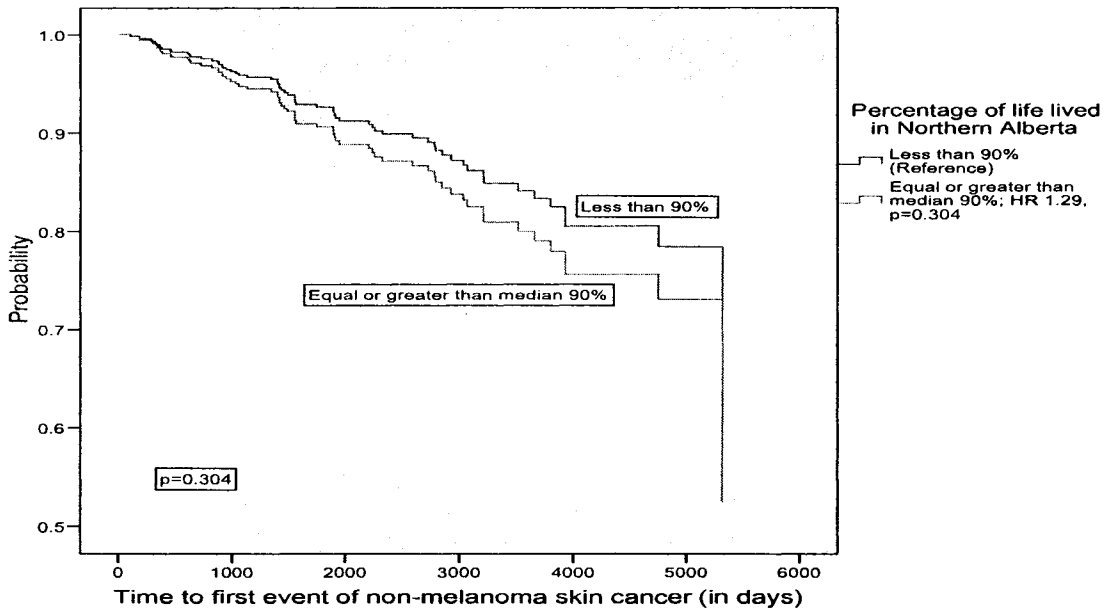


Figure 32. Time to the development of non-melanoma skin cancer adjusted for percentage of life lived in Northern Alberta

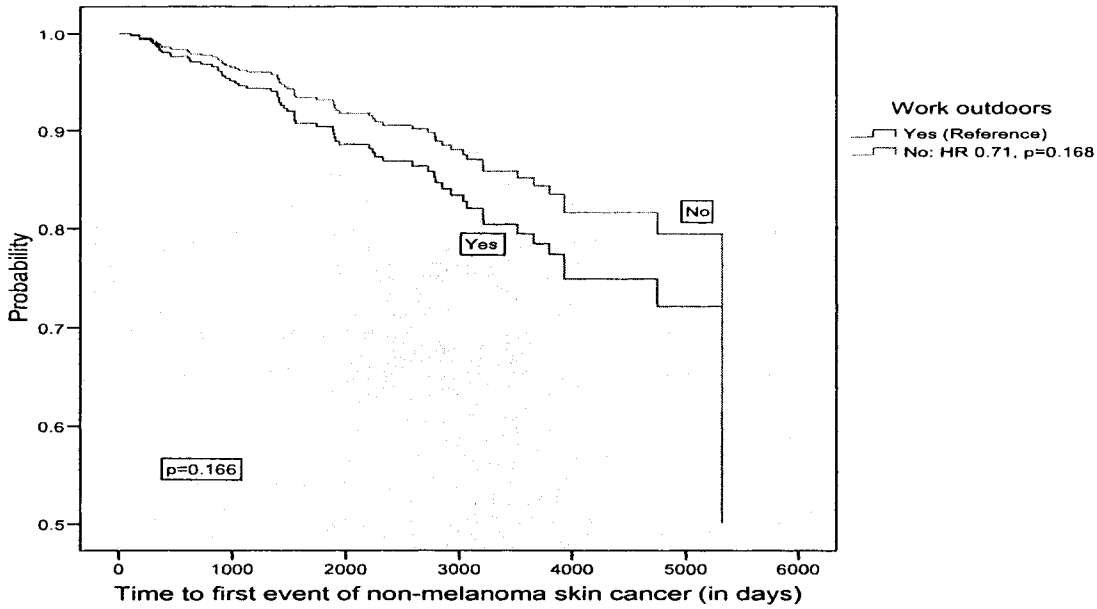


Figure 33. Time to the development of non-melanoma skin cancer adjusted for work outdoors

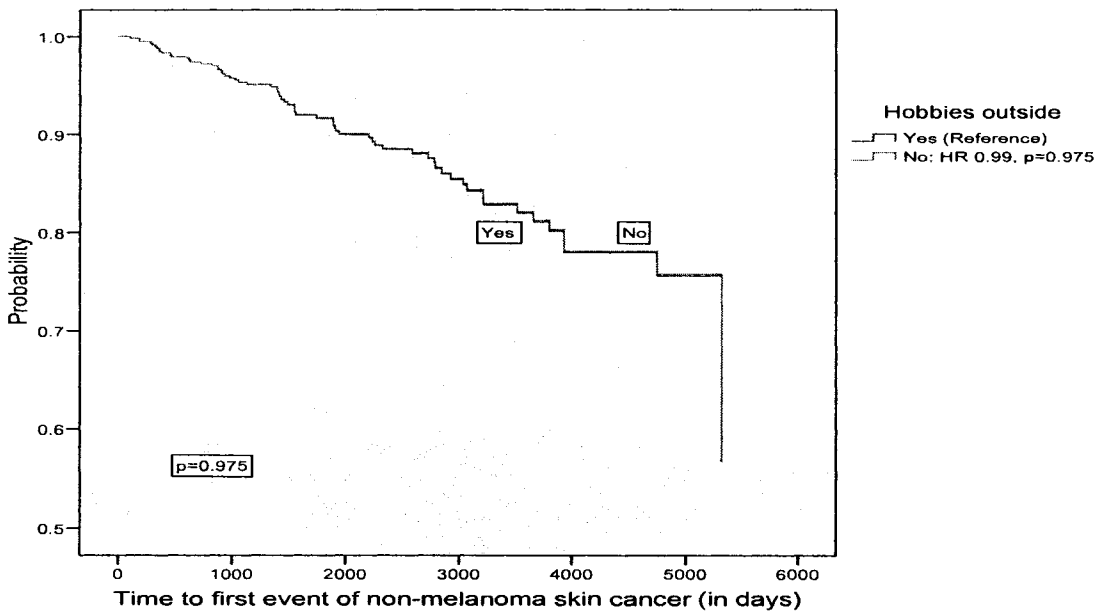


Figure 34. Time to the development of non-melanoma skin cancer adjusted for hobbies outside

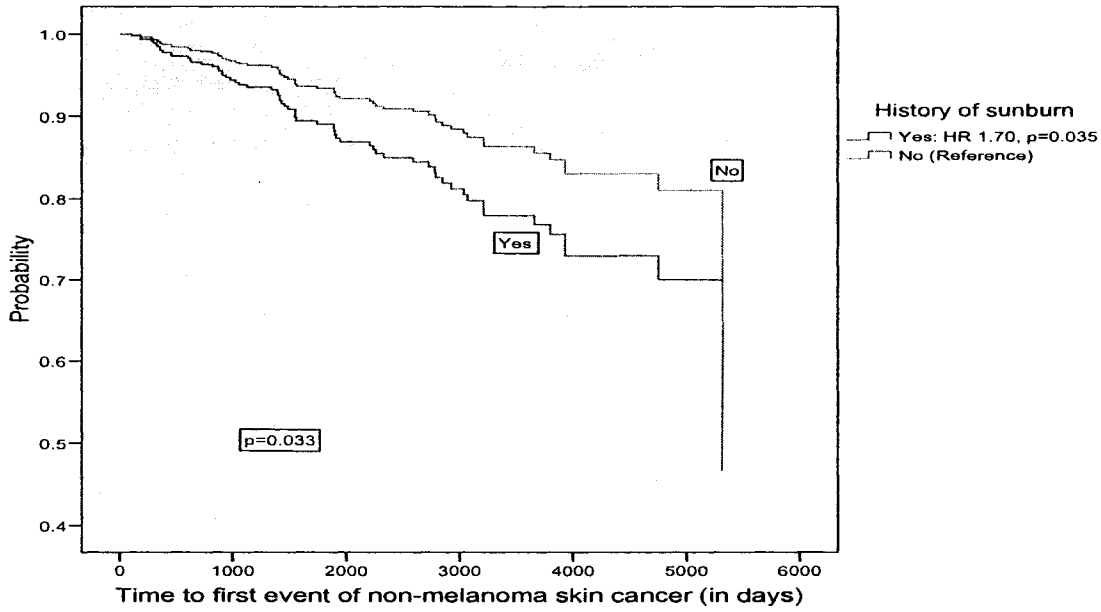


Figure 35. Time to the development of non-melanoma skin cancer adjusted for history of sunburn

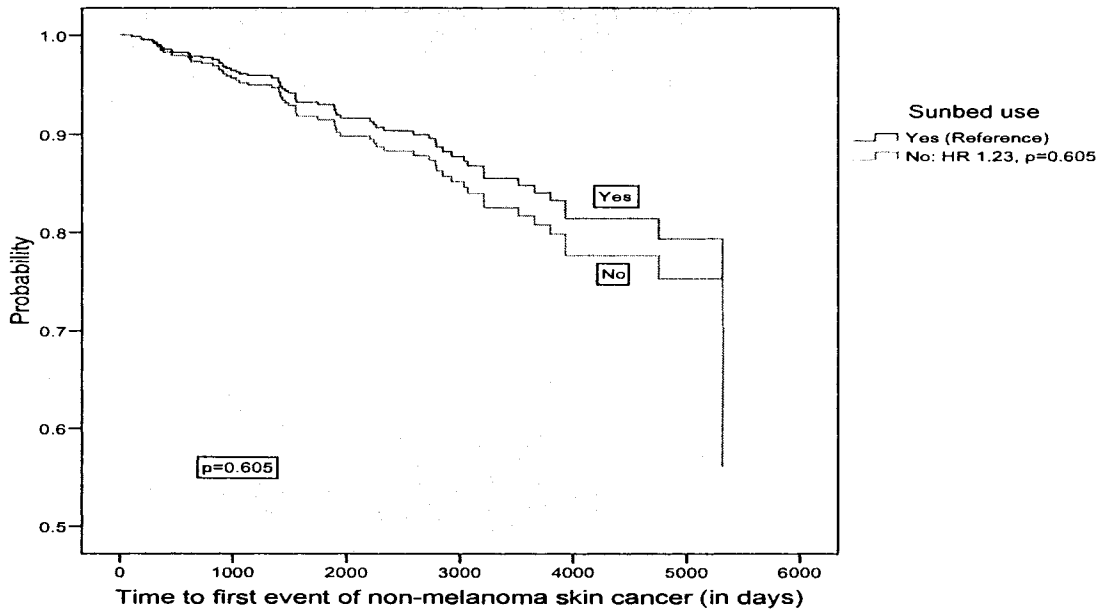


Figure 36. Time to the development of non-melanoma skin cancer adjusted for sunbed use

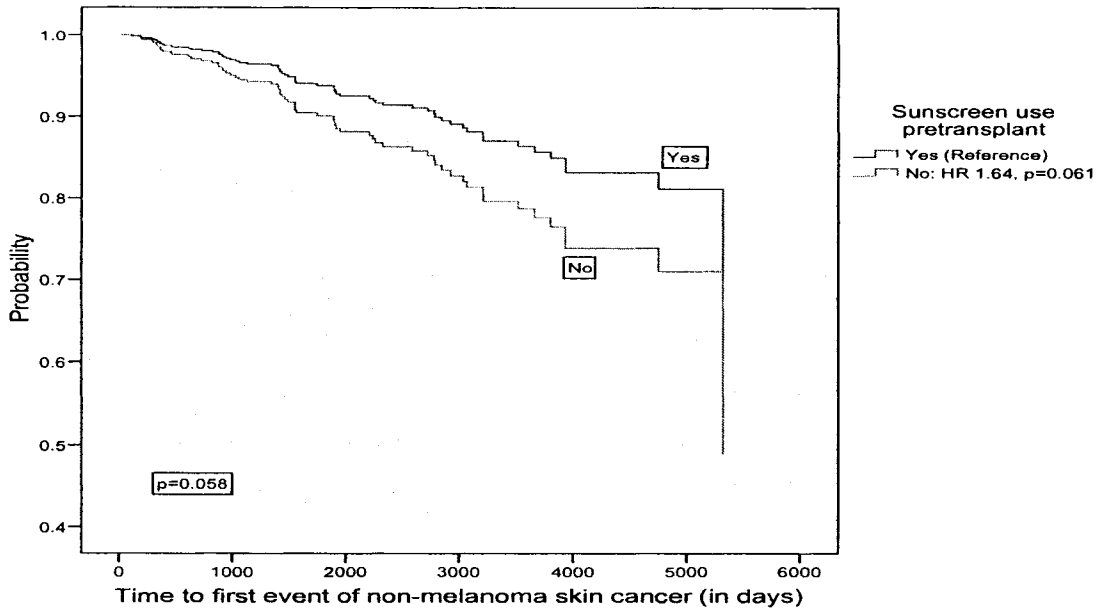


Figure 37. Time to the development of non-melanoma skin cancer adjusted for sunscreen use pre-transplant

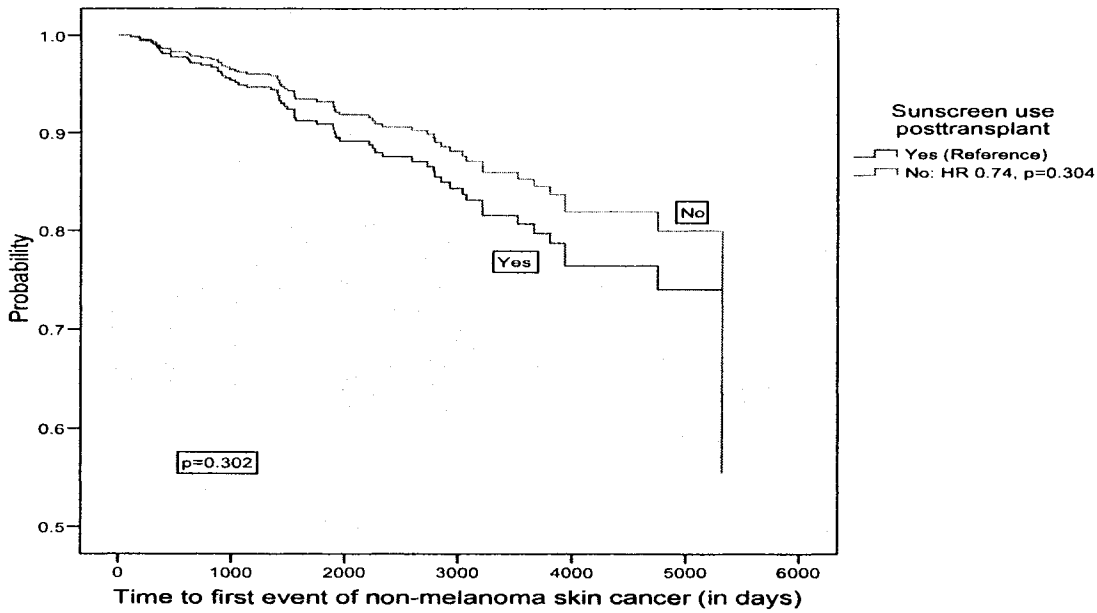


Figure 38. Time to the development of non-melanoma skin cancer adjusted for sunscreen use post transplant

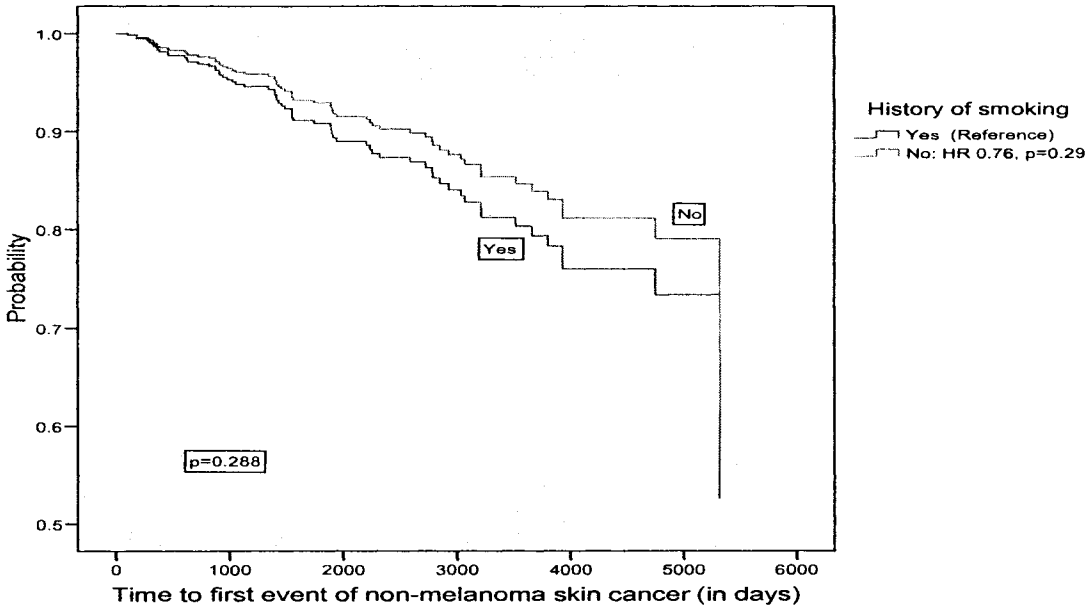


Figure 39. Time to the development of non-melanoma skin cancer adjusted for history of smoking

# Appendix E

## Odds Ratio Plots

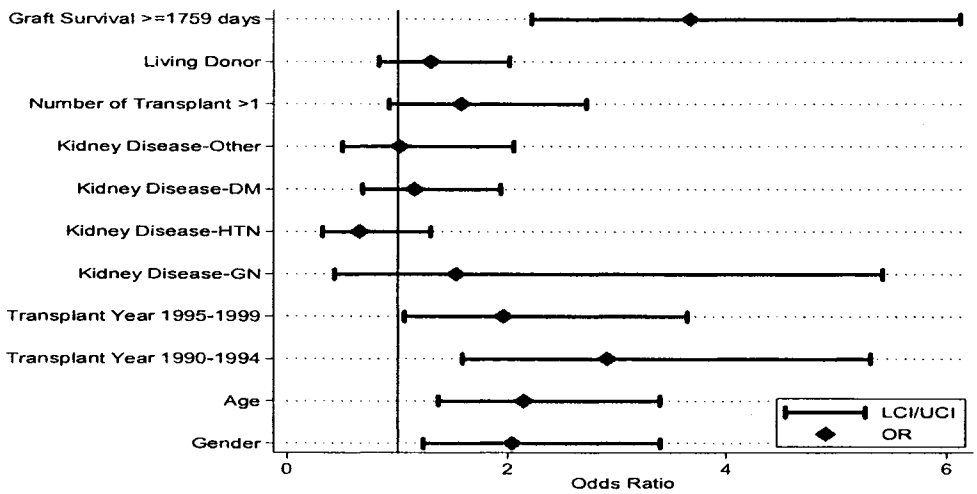


Figure 1. Demographic Characteristics

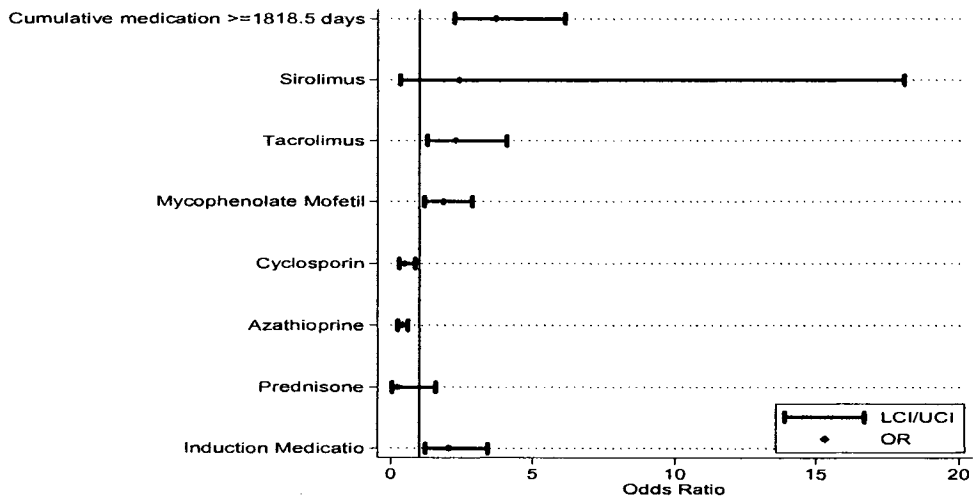


Figure 2. Immunosuppressive Medications

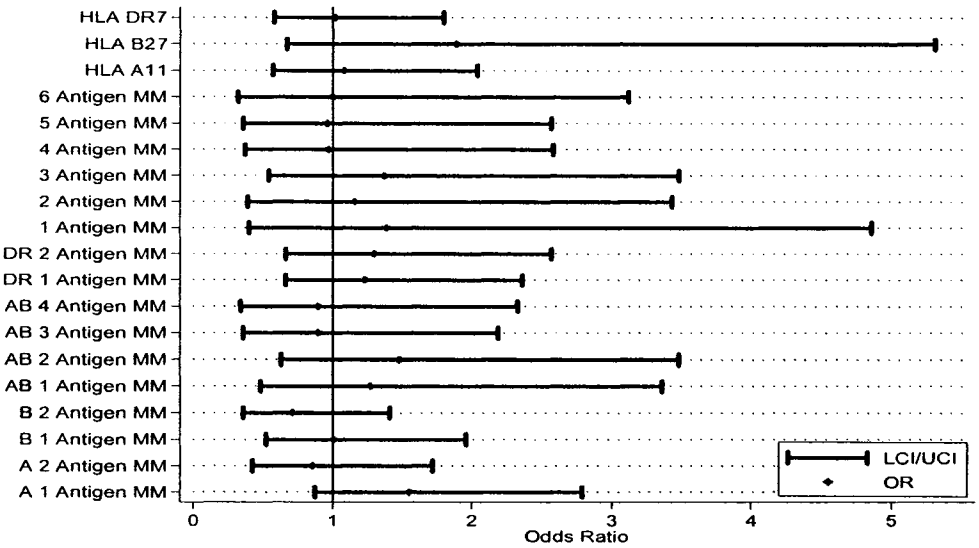


Figure 3. High-risk HLA Antigens and HLA Mismatch Between Donor and Recipient

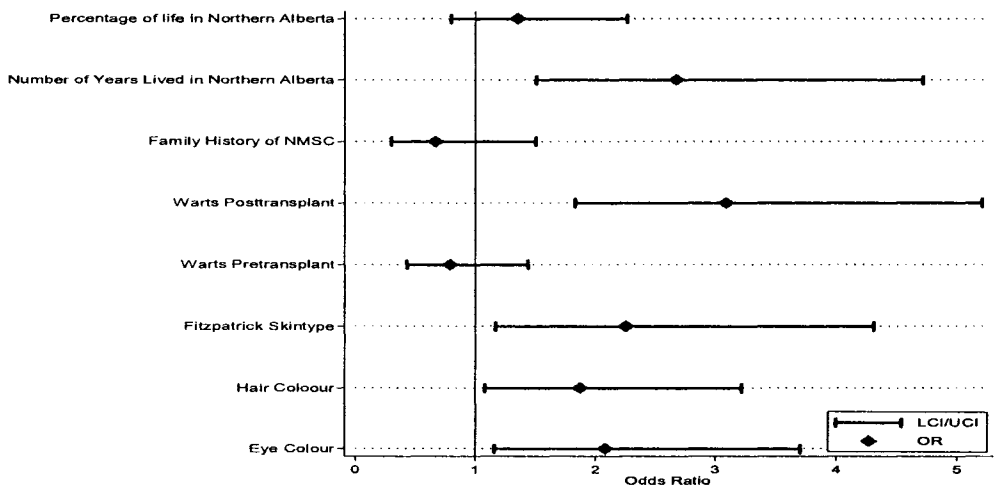


Figure 4. Sun Exposure History – Personal Characteristics

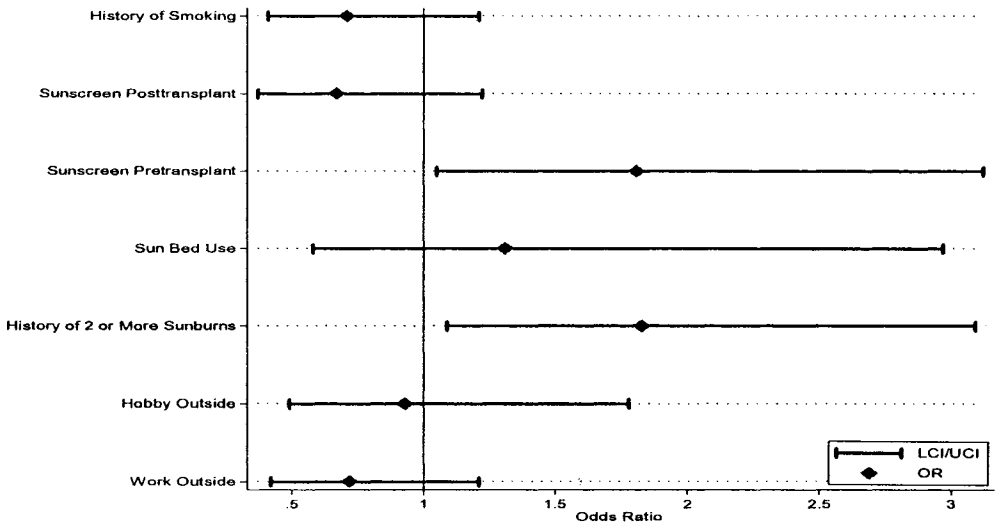


Figure 5. Sun Exposure History – Lifestyle Characteristics