The Risk of Internal Malignancy Following a Prior Diagnosis of Non-Melanoma Skin Cancer in Solid Organ Transplant Recipients

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ABSTRACT Background: Solid organ transplant recipients (SOTRs) are at increased risk for both skin and internal malignancies (IM). The risk of IM after the occurrence of non-melanoma skin cancer (NMSC) has been studied in the general population but very little is known about this association in SOTRs. Objectives: To evaluate the risk of IM following a prior diagnosis of post transplantation NMSC in SOTRs. Methods: This single center retrospective cohort study included a study population of 329 SOTRs from Rabin Medical Center who had a post-transplant diagnosis of skin malignancy, internal malignancy, or both from 2012 to 2018. Results: In total, 135 (41.03%) SOTRs were diagnosed with IM without a preceding diagnosis of NMSC while only 42 (12.76%) patients diagnosed with IM had a preceding diagnosis of NMSC. SOTRs with a diagnosis of NMSC showed a significantly decreased risk of developing subsequent IM (hazard ratio [HR] 0.64, 95% confidence interval [95%CI] 0.44–0.94, P = 0.02) compared to those without a prior NMSC diagnosis. Liver and lung transplant patients showed a significantly decreased risk of developing subsequent IM after a diagnosis of NMSC (HR 0.09 and 0.43, respectively). When stratified by type of IM, only patients who were diagnosed with a hematological malignancy had a significantly lower risk of developing this malignancy if they had a prior NMSC (HR 0.26). Conclusions: The findings of this study suggest a protective effect of NMSC on subsequent IM in the organ transplant population.

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KEY WORDS: internal malignancy, non-melanoma skin cancer, organ transplantation, skin cancer, vitamin D

Solid organ transplantation is a lifesaving procedure that has become more and more common over the years. In the United States, an average of 30,000 solid organ transplants is performed every year [1]. The success of organ transplants has allowed patients with end stage failure of essential organs (e.g., kidney, liver, lung, heart) the possibility of a prolonged survival, a possibility they did not have before the era of organ transplants. Data show that long-term survival after organ transplantation is increasing. This survival is due in part to the anti-rejection therapy these patients receive [2]. These anti-rejection medications are immunosuppressive medications taken for life by solid organ transplant recipients (SOTRs) to prevent graft rejection and to ensure adequate graft function. The heart and lung are the most immunogenic organs with the highest risk of rejection followed by the kidney and the liver, which is least prone to rejection. The strength of immunosuppression these patients receive is in accordance to the immunogenicity of the organ transplanted [3]. However, the chronic use of immunosuppressive agents has major downsides as it increases the long-term risk of malignancy in these patients compared with that of the general population. Other risk factors for malignancy in SOTRs, apart from iatrogenic immunosuppression, are the direct carcinogenic features of some immunosuppressive agents such as azathioprine and Cyclosporine A, which are known to be human carcinogens. In addition, viral infections (mainly human papillomavirus [HPV], Epstein-Barr virus [EBV], and Human Herpesvirus-8 [HHV-8]), age, genetics, and environmental factors such as sunlight exposure pose a risk for malignancy in these patients. The incidence of specific malignancies varies depending on the organ transplanted and the type, intensity, and duration of immunosuppressive therapy [4,5].

Skin cancers are the most common malignancies in SOTRs and account for substantial morbidity and mortality in such patients; therefore, dermatological care and follow-up are considered currently a standard part of patient care [6]. The most common skin cancers in this population are squamous-cell carcinoma (SCC), basal-cell carcinoma (BCC), melanoma, Kaposi sarcoma, and Merkel cell carcinoma. Of these, SCC and BCC, which are known collectively as non-melanoma skin cancer (NMSC), account for more than 90% of all skin cancers. The incidence of NMSCs increases with the duration of immunosuppressive therapy, ultimately affecting up to 70% of Caucasian transplant recipients [4,7,8]. In the general Caucasian population, this incidence is less than 1%.
population, BCC is the most common cancer followed by SCC with a 4:1 ratio. In the SOTRs this ratio is reversed and SCC is the most common skin cancer. Post-transplant risk of SCC is highly increased (65-fold to 250-fold) compared with the general population. Risk of post-transplant BCC is increased 6-fold to 16-fold [9]. The overall risk for internal malignancies (IM) in the transplant population is also increased compared to the general population as has been shown in many studies. Immunosuppressed SOTRs have a 2-fold to 6-fold increased risk of developing internal malignancies. The risk is even higher for specific infection-related malignancies including post-transplant lymphoproliferative disorders (PLPD) (associated with EBV), anogenital, and cervix cancers (associated with HPV), and Kaposi sarcoma (associated with HHV-8) [4,6,10,11].

The risk of IM after cutaneous SCCs and BCCs has been studied in the general population. While some studies showed that patients with NMSC have an increased risk of IMs [12-14] other studies showed no increased risk or even a decreased risk of IMs, after the occurrence of NMSC [15-17]. This controversy has created two conflicting hypotheses regarding the association between a personal history of NMSC and the risk of subsequent IM. One hypothesis is that NMSC represents a risk for IM in accordance with the multiple primary cancer model and therefore NMSC can be considered as a helpful red flag first marker of increased risk of subsequent primary IM diagnoses. Alternatively, it has been suggested that NMSC has a protective effect and is associated with a decreased risk of subsequent IM. Due to the fact that SOTRS have unique exposures and risk factors for developing new malignancies, prior studies on the risk of malignancy following NMSC in the general population may not be generalizable to transplant recipients. To the best of our knowledge, after a thorough search, only two published studies have addressed the association between IMs and NMSCs in transplant recipients [18,19]. Due to contradicting data in the literature regarding the association between IMs and NMSCs in the general population and sparse data about this association in the unique population of SOTRS, we conducted this study to further investigate the topic.

**PATIENTS AND METHODS**

This is a single center retrospective cohort study conducted in Rabin Medical Center in Petah Tikva, Israel, which holds the largest transplantation unit and follow-up center for SOTRs in Israel (approximately 70% of Israeli transplants). One of the specialized follow-up clinics is the dermatology clinic for SOTRS where many of these patients are screened periodically for the development of skin cancer. As such, we had access to medical records of transplant patients who were followed at Rabin Medical Center.

For the purpose of this study a computerized search was conducted on a comprehensive list of patients who had undergone an organ transplant procedure at Rabin Medical Center and visited one of the multi-disciplinary follow-up clinics for transplant recipients. Of these patients, a cohort was constructed of patients who had a diagnosis of post-transplant skin malignancy, IM, or both from the year 2012 to 2018.

The diagnosis of malignancy (both cutaneous and internal) and date of diagnosis was retrieved from the computerized system at the department of pathology. The IMs found were categorized into eight groups of cancers (lung and airway, blood, breast, endocrinological, gastrointestinal tract, genitourinary tract, sarcoma, unknown primary).

Patient data such as demographics, transplanted organ, date of transplantation, date of death and type of malignancy were retrieved from patient digital medical records. As occurrence of NMSC is not captured by cancer registries but is ascertained in transplant recipients based on patient medical records, as reported in periodical dermatology follow-ups, patient medical records were hand searched and data were collected on type of skin cancer, number of skin cancers, and date of diagnosis. Hand search of patient medical records was also used as a means of quality assurance for data on IM.

To establish the correct chronology of events for the investigation of NMSC as a potential risk factor for the subsequent outcome cancers, only patients with a diagnosis of IM at least one year after diagnosis of NMSC were analyzed.

Serum vitamin D levels were also collected from the computerized medical record, but as there was no generalized policy, the frequency of serum vitamin D testing was inconsistent with individuals in the study population, preventing us from using the data.

Inclusion criteria included a history of solid organ transplantation and documented diagnosis of malignancy (internal and/or skin) that was made after organ transplantation. Exclusion criteria included patients who had a diagnosis of cancer in the transplanted organ (liver, kidney, lungs) as a sole diagnosis of malignancy, patients who had a diagnosis of malignancy (skin or internal) prior to organ transplantation as a sole diagnosis of malignancy.

The main outcome was the risk of IM following a prior diagnosis of NMSC compared to the risk of IM without a prior diagnosis of NMSC in SOTRS.

**STATISTICAL ANALYSES**

The institutional ethics committee approved the study, which was in accordance with the provisions of the Declaration of Helsinki. The statistical analysis for this paper was generated using SAS Software, Version 9.4. Continuous variables were presented by mean ± standard deviation. Categorical variables were presented by (N, %). We used $t$-test to compare the value of continuous variables between study groups and Fisher's exact test was used to compare the value of categorical variables between study groups. Hazard ratio (HR) for IM following a prior...
diagnosis NMSC compared to the risk of IM without a prior diagnosis of NMSC was calculated using the Cox proportional hazards model, where death with no prior internal malignancy was treated as a competing risk and NMSC status was treated as a time varying covariate. Two-sided $P$ values $< 0.05$ were considered statistically significant.

RESULTS

The cohort was comprised of 329 single SOTRs with a post-transplant diagnosis of skin and/or IM between the years 2012 and 2018. To establish the correct chronology of events for the investigation of NMSC as a potential risk factor for the subsequent outcome cancers, only patients with a diagnosis of IM at least one year after diagnosis of NMSC were analyzed. The characteristics of the study population are presented in Table 1.

There was no significant difference in the type of immunosuppressive therapy taken by patients in the different groups. The most common immunosuppressive regimens in our medical center included tacrolimus, mycophenolate mofetil, and corticosteroids. The cohort included 152 patients who had NMSC or other types of skin cancer but no IM. Of the NMSCs diagnosed in our cohort of transplant patients, there were 71 diagnosed with SCC, 30 diagnosed with BCC, and 74 diagnosed with both SCC and BCC. We analyzed SCC and BCC together as a group to increase the chance of statistical significance. In total, 24 patients were diagnosed with skin cancers other than NMSC, 12 with Kaposi sarcoma, 9 with malignant melanoma, 2 with Merkel cell carcinoma, and 1 with sebaceous carcinoma. Skin photo-type of patients according to the Fitzpatrick scale ranged from 2–4 with the vast majority of patients having skin type 3. All NMSC diagnosed were on sun exposed skin.

The risk of post-transplant IM in SOTRS with and without prior NMSC is presented in Table 2. Transplant patients with a diagnosis of NMSC showed a significantly decreased risk of developing subsequent IM (HR 0.64, 95% confidence interval [95%CI] 0.44–0.94, $P = 0.02$) compared to those transplant patients without a prior NMSC diagnosis.

When stratified by type of organ transplanted, patients who underwent a liver transplant showed a significantly decreased risk of developing subsequent IM after a diagnosis of NMSC compared to those with IM and no prior NMSC, with a HR of 0.09 (95%CI 0.01–0.86, $P = 0.03$). The HR for lung transplant patients was 0.43 (95%CI 0.18–1, $P = 0.05$). The HR for kidney transplant patients was 0.77 (95%CI 0.46–1.29), which was not statistically significant. The number of heart transplant recipients in both groups was very small [2,3] and as such the HR was not significant.

The two groups were also stratified by type of IM diagnosed (malignancies were grouped into categories according to groups as described in the methods section). Of these groups, only patients who were ultimately diagnosed with a hematological malignancy had a significantly lower risk of developing this malignancy if they had a prior NMSC compared to patients who developed this malignancy but did not have a prior NMSC (HR 0.26, 95%CI 0.08–0.83, $P = 0.02$). In all other cancer groups, the HR was not statistically significant.

Patients with only SCC ($n=74$) and patient with only BCC ($n=30$) were also analyzed separately. Those with a post-transplant diagnosis of BCC had a significantly decreased risk for subsequent IM with an HR of 0.57 (95%CI 0.34–0.95, $P = 0.03$).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the study population</th>
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<tr>
<td>Total study population</td>
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<tr>
<td>Number</td>
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<td>Sex</td>
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<td>Female</td>
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<td>Transplanted organ</td>
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<td>Lung</td>
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<td>Age at transplantation, years</td>
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<td>Mean (range)</td>
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<td>Age at death, years (range)</td>
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<td>Deaths, n (%)</td>
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NMSC = non-melanoma skin cancer
Those with a post-transplant diagnosis of SCC also had a decreased risk for subsequent IM with an HR of 0.7 that was not statistically significant (95%CI 0.45–1.08, P = 0.1).

In our cohort of SOTRs from the Rabin Medical Center with a post-transplant diagnosis of skin and IM, the majority of patients, 41.03%, developed an IM without a prior diagnosis of NMSC while only 12.76% patients diagnosed with an IM had a preceding diagnosis of NMSC. The HR for developing an IM after a diagnosis of NMSC was 0.64 (95%CI 0.44–0.94, P = 0.02) meaning that patients with a post-transplant diagnosis of NMSC had a significantly lower risk (< 36%) of developing subsequent IM compared to those transplant patients without a prior NMSC diagnosis. When the main types of NMSCs were analyzed separately (patients with only SCC or only BCC), the decreased risk for subsequent IM was maintained in each group separately (although statistically significant only in the BCC group). This result can be considered as a protective effect of NMSC on the subsequent development of IM in SOTRS.

The protective effect of NMSC on the subsequent development of IM in the majority (95%) of organ transplant recipients. Patients who underwent a liver transplant had the strongest protective effect of NMSC on the development of IM with a HR of 0.09 (95%CI 0.01–0.86; P = 0.03). Lung transplant patients also demonstrated a protective effect of NMSC on the subsequent development of IM with a HR of 0.43 (95%CI 0.18–1, P = 0.05). Kidney transplant patients had a non-statistically significant HR of 0.77; however, it did show the same trend of less risk for IM after NMSC. In heart transplant patients the HR was not statistically significant due to a very small number of heart transplant patients in our cohort.

When stratified by type of organ transplanted, there is a clear trend toward the protective effect of NMSC on the subsequent development of IM in the majority (95%) of organ transplant recipients. Patients who underwent a liver transplant had the strongest protective effect of NMSC on the development of IM with a HR of 0.09 (95%CI 0.01–0.86; P = 0.03). Lung transplant patients also demonstrated a protective effect of NMSC on the subsequent development of IM with a HR of 0.43 (95%CI 0.18–1, P = 0.05). Kidney transplant patients had a non-statistically significant HR of 0.77; however, it did show the same trend of less risk for IM after NMSC. In heart transplant patients the HR was not statistically significant due to a very small number of heart transplant patients in our cohort.

When stratified by type of internal malignancy diagnosed, only patients with hematological malignancies had a statistically significant HR (0.26, 95%CI 0.08–0.83, P = 0.02), meaning that transplant patients with a post-transplant diagnosis of

<table>
<thead>
<tr>
<th>Internal malignancy by site</th>
<th>Internal malignancy with prior NMSC, n (%)</th>
<th>Internal malignancy without prior NMSC, n (%)</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Lung and airway</td>
<td>9 (21.42%)</td>
<td>24 (17.77%)</td>
<td>1.08 (0.43–2.4)</td>
<td>0.96</td>
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<tr>
<td>Hematology</td>
<td>3 (7.14%)</td>
<td>24 (17.77%)</td>
<td>0.26 (0.08–0.83)</td>
<td>0.02</td>
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<tr>
<td>Breast</td>
<td>0</td>
<td>7 (5.18%)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Endo</td>
<td>4 (9.52%)</td>
<td>6 (4.44%)</td>
<td>0.63 (0.12–3.07)</td>
<td>0.56</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>10 (23.8%)</td>
<td>26 (19.25%)</td>
<td>1.09 (0.57–2.07)</td>
<td>0.78</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>15 (62.5%)</td>
<td>37 (27.4%)</td>
<td>0.89 (0.44–1.82)</td>
<td>0.76</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>0</td>
<td>1 (0.74%)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Unknown primary</td>
<td>1 (2.38%)</td>
<td>6 (4.44%)</td>
<td>0.44 (0.014–4.01)</td>
<td>0.46</td>
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NMSC = non-melanoma skin cancer, NA = not applicable

DISCUSSION

In our cohort of SOTRs from the Rabin Medical Center with a post-transplant diagnosis of skin and or IM, the majority of patients, 41.03%, developed an IM without a prior diagnosis of NMSC while only 12.76% patients diagnosed with an IM had a preceding diagnosis of NMSC. The HR for developing an IM after a diagnosis of NMSC was 0.64 (95%CI 0.44–0.94, P = 0.02) meaning that patients with a post-transplant diagnosis of NMSC had a significantly lower risk (< 36%) of developing subsequent IM compared to those transplant patients without a prior NMSC diagnosis. When the main types of NMSCs were analyzed separately (patients with only SCC or only BCC), the decreased risk for subsequent IM was maintained in each group separately (although statistically significant only in the BCC group). This result can be considered as a protective effect of NMSC on the subsequent development of IM in SOTRS.

The protective effect of NMSC on the subsequent development of IM in the general population has been investigated previously. This protective effect in patients with a prior diagnosis of NMSC has been demonstrated for a variety of IM: colorectal, prostate, stomach, liver, gallbladder, pancreas, lung, female breast, bladder, and kidney cancers [17]. Solar UV radiation (UVR) is not only the primary cause of NMSC, but is also the major source of serum vitamin D by stimulating cutaneous synthesis of vitamin D. It is not uncommon to find higher levels of serum vitamin D in patients with NMSC arising from chronic sun exposure. Vitamin D has been shown to have anti-cancer activity by various mechanisms including inhibition of cellular proliferation, induction of apoptosis, stimulation of differentiation, suppression of tumor invasion, metastasis, and angiogenesis [20]. Therefore, this protective effect of NMSC on the subsequent development of internal malignancy is thought to be mediated by higher levels of serum vitamin D in patients with prolonged sun exposure.

When stratified by type of organ transplanted, there is a clear trend toward the protective effect of NMSC on the subsequent development of IM in the majority (95%) of organ transplant recipients. Patients who underwent a liver transplant had the strongest protective effect of NMSC on the development of IM with a HR of 0.09 (95%CI 0.01–0.86; P = 0.03). Lung transplant patients also demonstrated a protective effect of NMSC on the subsequent development of IM with a HR of 0.43 (95%CI 0.18–1, P = 0.05). Kidney transplant patients had a non-statistically significant HR of 0.77; however, it did show the same trend of less risk for IM after NMSC. In heart transplant patients the HR was not statistically significant due to a very small number of heart transplant patients in our cohort.

When stratified by type of internal malignancy diagnosed, only patients with hematological malignancies had a statistically significant HR (0.26, 95%CI 0.08–0.83, P = 0.02), meaning that transplant patients with a post-transplant diagnosis of
NMSC had significantly less risk of developing a hematological cancer compared to those who did not have a prior NMSC.

The long-term risk of malignancy in the SOTRs increased compared to that of the general population. Post-transplant lymphoproliferative disorder (PTLD) is one of the more common malignancies diagnosed in this population with some studies showing up to 7 times higher risk of lymphoproliferative cancers as compared to the general population. In most affected patients, PTLD is an EBV-positive B cell proliferation occurring in the setting of immunosuppression and decreased T cell immune surveillance [21]. In our cohort of SOTRs with a post-transplant diagnosis of a hematological malignancy, the majority was classified as PTLD.

Vitamin D has important roles in addition to its classic effects on calcium and bone homeostasis and its anti-cancer effects. Vitamin D also affects the immune system and can modulate the innate and adaptive immune responses. Deficiency in vitamin D has been shown to be associated with increased susceptibility to several infections [22,23]. It has recently been proposed that vitamin D might even have a possible role in reducing the risk or severity of COVID-19 and as such vitamin D supplementation is recommended by some authorities as a preventative measure for COVID-19 infection [24,25].

Our results show a significantly reduced risk of post-transplant hematological malignancies in SOTRs with a prior diagnosis of NMSC, which in theory may be explained by a higher serum vitamin D level in these patients (as a marker of extensive sun exposure causing NMSC) that acts as an immune modulator reducing infectiveness of EBV and thereby reducing incidence of EBV associated post-transplant lymphoproliferative disorder (PTLD). More research is needed to strengthen this hypothesis.

In contrast to our findings, previous studies that have investigated the association between IMs and NMSCs in transplant recipients found an increased risk for IM in SOTRs with previous NMSCs. Wisgerhof and colleagues [18] investigated the risk of IMs occurring after SCCs in kidney transplant recipients in the Netherlands. They found this risk to be increased compared to transplant recipients without prior SCCs [19]. Their study showed a 3-fold increased risk of IMs in kidney transplant recipients with a prior cutaneous SCC compared to those without a prior diagnosis of SCC. A major limitation of the study was that the time interval between diagnosis of NMSC and IM was not reported; therefore, the association might be questionable in some cases. Zamoiski and colleagues [19] investigated the risk of second malignancies after NMSCs in solid organ transplant recipients in the United States. Their results suggested that transplant recipients with cutaneous SCC but not BCC have an increased risk of developing other SCCs. Cutaneous SCC occurrence was associated with a 1.44-fold increased risk for developing later malignancies. The authors concluded that cutaneous SCC occurrence after transplantation could serve as a marker for elevated malignancy risk. A possible explanation for the disagreement between the results of our study and the previous studies might be in part due to higher levels of ambient UVR in Israel compared to the Netherlands and the United States, which resulted in higher levels of serum vitamin D in our cohort of SOTRs. If this explanation is correct, these higher levels of vitamin D might contribute to a lower incidence of IM after NMSC through its anti-cancer effects. Further research on this subject will allow additional understanding of the association between IM and NMSC in the unique population of SOTRs and of the role vitamin D takes in this complex matter.

CONCLUSIONS

In our cohort of SOTRs, we demonstrated that a post-transplant diagnosis of NMSC has a statistically significant protective effect on the subsequent development of IM with a HR of 0.64.

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References

Based on statistical modeling, Suzuki et al. suggested that Omicron has spread more rapidly than the Delta variant in several countries including, South Africa. Cell culture experiments showed Omicron to be less fusogenic than Delta and than an ancestral strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the spike (S) protein of Delta is efficiently cleaved into two subunits, which facilitates cell–cell fusion, the Omicron S protein was less efficiently cleaved compared to the S proteins of Delta and ancestral SARS-CoV-2. Furthermore, in a hamster model, Omicron showed decreased lung infectivity and was less pathogenic compared to Delta and ancestral SARS-CoV-2. These multiscale investigations reveal the virological characteristics of Omicron, including rapid growth in the human population, lower fusogenicity and attenuated pathogenicity.