BREAST CANCER AND IMMUNOSUPPRESSION IN KIDNEY TRANSPLANT RECIPIENTS: A LITERATURE REVIEW?

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Breast cancer is the most common neoplasm and the fifth cause of death among females. The etiology and pathogenesis of this malignancy are multifactorial. The occurrence of neoplasms in solid organ recipients treated with immunosuppressive drugs is 2 to 3 times higher than in the general population. Females with kidney transplants are also in the at-risk population. The aim of this article is to review recent literature on immunosuppression and the effect it has on breast cancer prevalence in kidney transplant recipients; to discuss the proposed pathologic mechanisms of breast cancer owing to concurrent immunosuppressive treatments; and to review breast cancer screening recommendations for kidney transplant recipients. To attain relevant literature, we conducted literature search using PubMed databases, see PRISMA Diagram (Figure 1). The following MeSH Terms were used in the search: "breast cancer"; "risk factors"; "cancer screening"; "kidney transplantation"; "immunosuppression"; and "cancer". We reviewed a total of 409 articles after having applied exclusion criteria. These articles included randomized controlled trials, reviews, and systematic reviews. Importantly, we also utilized references from other review/primary research articles to attain additional relevant information previously not captured from our initial research. Breast cancer is the third leading malignant cause of death in Croatia, preceding lung and colorectal carcinoma. Generally, breast cancer develops due to a combination of hormonal, genetic and age-related factors. However, a significant risk factor and critical motif in carcinogenesis is immunosuppression. Carcinogenic environmental factors, disturbed function of the immune system due to chronic use of immunosuppressive drugs, and genetic make-up influence the process of carcinogenesis in transplant patients. Immunosuppression reduces immunosurveillance that predisposes patients to increased viral oncogenesis and general carcinogenesis causing cancer to be the second most frequent cause of death in post-kidney transplant patients. Particularly, kidney transplant recipients are prone to carcinogenesis due to lifelong immunosuppressive regimens. Importantly, differences in cancer risk depend on the kidney recipient's cancer type. Certain malignancies, such as breast cancer, are not affected by immunosuppression as their relative risk is comparable to that of the general population. Due to the limited number of articles addressing post-transplant breast cancer (PTBC), we present here a comprehensive review of the topic, current understanding of its pathophysiology, and the role of screening in its diagnosis, treatment and overall management. The risk of developing PTBC in kidney transplant recipients is not increased when compared to the general population. It appears that the development of breast cancer in kidney transplant recipients is unrelated to transplantation immunosuppressive regimen and is mostly associated with aging and independent risk factors that can lead by themselves to kidney transplantation such as diabetes mellitus. Due to screening programs, PTBC is usually diagnosed early. However, if PTBC is diagnosed in advanced grades, it is associated with significantly increased mortality risk. Therefore, it is recommended that patients be screened periodically compared to their age- and gender-matched counterparts from the general population. Notably, this is an area of ongoing research and requires further investigation. Due to the rarity of PTBC and scarce resources on the topic, most guidelines are extrapolated from the general population and are not corresponding to the minimal risk of developing PTBC. Similarly, treatment guidelines are inferred from the general population and do not account for the particular considerations in these patients such as graft survival, graft rejection, nephrotoxic chemotherapeutic drugs, and concurrent administration of immunosuppression. It is worth mentioning that the heterogeneity of results discussed in our review is perhaps due to differing immunosuppressive regimens, type of organ transplantation, concomitant comorbidities, length of follow-up, and screening protocols used. To draw clear guidelines tailored for this population, further investigation into the mechanisms of disease is warranted, with prolonged follow-up time in patients on differing immunosuppressive regimens to allow for subsequent comparison.

Key words: breast cancer, risk factors, cancer screening, kidney transplantation, immunosuppression

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BREAST CANCER

Epidemiology and outcomes

Breast cancer has surpassed lung cancer as the most commonly diagnosed cancer and is the fifth leading cause of death among women. These patterns and trends differ from country to country. However, approximately 2.3 million women were diagnosed with breast cancer in 2020 worldwide. These cases were associated with 685,000 deaths (1). Currently, 1 in 8 women worldwide has a lifetime risk of developing breast cancer (2). In Croatia, breast cancer is the third leading malignant cause of death, preceded by lung and colorectal cancer. In 2017, 2797 patients were diagnosed (rate 132.1/100,000), and by 2019, 752 women died from the disease, yielding a rate of 35.9/100,000 (3,4). Despite significant advancements in the prevention, diagnosis and treatment, various fundamental unresolved problems remain.

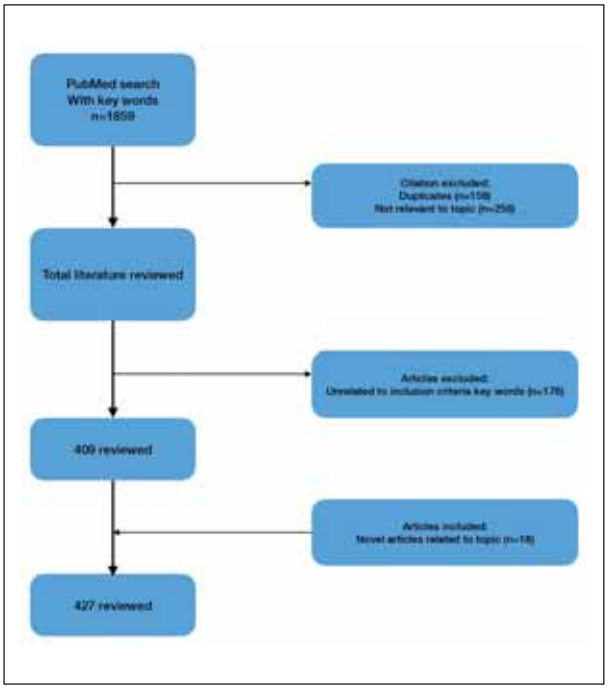

Figure 1. *PRISMA Diagram illustrating search methods with inclusion and exclusion process.*

Pathogenesis

Breast cancer development is multifactorial, and the exact pathogenesis of this disease has not yet been clarified. Understanding its heterogeneity is essential for both preventive and targeted interventions. The cancer stem cell theory and the stochastic theory are two hypotheses on breast cancer initiation and development. Notably, both assumptions are supported by numerous data, but neither can ultimately shed light on its origin (5).

Screening

Breast cancer metastases account for its incurability, and 90% of deaths are associated with the disease. If breast cancer is diagnosed while it remains a primary tumor, treatment strategies may be effective (6). Consequently, timely detection remains the foundation of breast cancer treatment, which has led mainly to better prognosis together with a higher survival rate. Current screening tools include mammography, magnetic resonance imaging (MRI), and ultrasound as an adjuvant. Mammography is an effective modality to acquire high-resolution images of the breast. Despite its shortcomings, it remains the most widely validated method for early detection. It is recommended that women over 50 be screened every two years. Unlike mammography, MRI is highly sensitive, and results are not altered based on density of the breast. In contrast, the specificity of this modality is lower than that of mammography. Thus, this is especially useful in high-risk patients who present with negative mammography results (7).

Risk factors

Multiple risk factors have been identified as contributors to breast tumorigenesis. For many years, it has been understood that genetic and environmental modifications predominantly drive the initiation and progression of breast cancer. Moreover, recent investigations have determined that epigenetic alterations also promote carcinogenesis within the tumor microenvironment (5,8).

Breast cancer incidence is highly related to both age and female sex. According to Siegel *et al.*, 99.3% of deaths associated with breast cancer in America occurred in women over 40 (9). Family history of breast cancer accounts for a quarter of all cases. The inherited susceptibility to breast cancer rises 2.5-fold in women with two affected first-degree relatives (10,11). This is partially accredited to breast cancer-related genes, including BRCA1 and 2. Additional genes associated with breast cancer encompass p53, PTEN, and RB1 (11).

Reproductive factors that increase the risk of breast cancer comprise premature menarche, late onset of menopause, low parity, later age of first pregnancy, and estrogen exposure (12,13). Considerable evidence from epidemiological studies demonstrates that a modern sedentary lifestyle, excessive drinking habits, diets rich in saturated fats, and low physical activity levels are related to higher breast cancer risk. The mechanism by which physical activity influences the risk of developing the disease is altered body composition, insulin resistance, and modified levels of steroid hormones. Therefore, it is now understood that obesity and insulin increase the risk of breast cancer (14,15).

The rising incidence of breast cancer is multifaceted. This trend may be related to the augmentation of risk factors, screening strategies, health inequalities, growing populations, and a lengthier life expectancy (16). The variation in these factors in different regions may explain disparity in the burden of the disease. For example, developed countries such as the United States of America (USA) and the United Kingdom make extensive use of screening tools. Consequently, these countries have encountered the current concern of overdiagnosis (17). Furthermore, the prevalence of obesity and insulin resistance have noteworthy regional dissimilarities; in 2015, the population of obese individuals was 38.2% in the USA compared to 3.7% in Japan (18,19).

Standish *et al*. demonstrated the importance of a functional immune system and its implication in preventing primary and recurring breast cancer (20). There is much to unpack regarding the upsurge of this disease; this paper subsequently aims to explore the role of immune status and immunomodulatory therapy in cancer patients after immunosuppression in general and, more specifically, after breast cancer in kidney transplantation.

CANCER IN PATIENTS RECEIVING IMMUNOSUPPRESSIVE THERAPY

Epidemiology

Solid organ transplant recipients are treated with immunosuppressive drugs to avoid graft rejection. The occurrence of neoplasms in solid organ recipients is 2-3 times higher than in the general population (21). There are many contributing factors to the increased risk of carcinogenesis in post-transplant patients. Carcinogenic environmental factors such as sun exposure, disturbed function of the immune system due to chronic use of immunosuppressive drugs, and genetic make-up of each person influence the process of carcinogenesis in transplant patients (22). Skin and lip cancers, lymphomas, and Kaposi sarcomas appear to be the leading cancers in solid organ transplant recipients (23).

On the other hand, the incidence of some solid neoplasms (such as breast and colon cancers) does not appear to be increased compared to the general population, and some studies even indicate a decreased occurrence of certain malignancies in transplant recipients (24-26). Although immunosuppressants decrease the incidence of graft rejection and prolong life in organ recipients, many of them are associated with an increased risk of carcinogenesis, which compromises patient survival (21,27,28). Carcinogenesis due to chronic immunosuppression poses a severe threat to the health of transplant recipients and complicates their post-transplantation period, being the primary reason for late failure in patients with well-preserved graft function (23).

Transplant recipients tend to have an overall poorer prognosis than other oncologic patients, which could be explained by the concomitant presence of other diseases, immunosuppressive therapy, and the general worse tolerance of cancer treatment (29-31). Furthermore, at the time of diagnosis, cancers in immunosuppressed patients tend to present at the clinically advanced stage (29,30). The literature has noted a noticeable intensification in the biologic aggressiveness of those neoplasms (30).

Pathogenesis

There are three proposed pathophysiological mechanisms of cancer development in solid-organ transplant recipients. First, it is possible for the direct transmission of neoplastic cells from the donor to the recipient to occur during transplantation (29,32). This complication could be avoided by thorough clinical examinations and screenings of donors for a possible undiscovered malignancy. Despite the screening protocols, donor neoplasms sometimes go unnoticed and present as lesions in organ recipients (33,34). The other two mechanisms of carcinogenesis include *de novo* carcinogenesis and relapse of a recipient's pre-transplant malignancy (29,32).

Multiple factors are thought to be interconnected in the process of *de novo* carcinogenesis in organ transplant recipients. Chronic immunosuppressive therapy as one of the main contributing factors results in altered immune response against oncogenic viruses and deranged immunosurveillance points of cancer cells (29,35). Host factors, such as certain viral infections and genetic predisposition to carcinogenesis, also contribute to cancer-promoting potential (22,35). Epstein-Barr virus (EBV), human papillomavirus (HPV), herpesvirus 8 (HHV-8), hepatitis B (HBV) and C (HCV) viruses, and Merkel cell polyomavirus are some of the frequently encountered oncogenic viruses. Each virus is linked to a different type of cancer, and viruses affect the normal host cell cycle by disrupting mitotic checkpoints, inhibiting tumor suppressor genes, activating oncogenes, blocking apoptosis, and leading to uninhibited cell proliferation (36). Organ transplant recipients have a higher possibility of developing a virally driven neoplasm (37,38).

Moreover, some immunosuppressive drugs appear to be directly involved in the process of carcinogenesis. Based on the mechanism of action, immunosuppres-

sive agents can be divided into the following subtypes: corticosteroids, calcineurin inhibitors (cyclosporin, tacrolimus), biologic agents, antimetabolites (azathioprine, mycophenolate mofetil), and mechanistic target of rapamycin (mTOR) inhibitors (rapamycin [sirolimus], everolimus) (39). The rate of *de novo* carcinogenesis in chronically immunosuppressed patients is influenced by the type of immunosuppressive drugs and the level of immunosuppression, the number of immunosuppressant medications, and the duration of the immunosuppressive therapy applied (40-43). Low-dose cyclosporin groups experienced a lower incidence of cancer compared to higher doses (44).

Calcineurin inhibitors (cyclosporin and tacrolimus) directly influence malignancy development by inhibiting DNA repair mechanisms, programmed cell death, and production of interleukin 2 (IL-2) (35,39,45). Anti-oncogenic properties of IL-2 are mediated by its effects on the natural killer, lymphokine-activated killer (LAK), and other cytotoxic cells (46). Inhibition of DNA repair mechanisms leads to mutations in activated T-cells, therefore promoting apoptosis and helping cancer cells escape cell-mediated immunosurveillance (47). Additionally, calcineurin inhibitors increase the production of transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF), resulting in the promotion of tumor angiogenesis and facilitation of tumor growth and progression (48,49). Besides, cyclosporin use positively correlates with the incidence of post-transplantation lymphoproliferative disorder (PTLD), and the abovementioned impairment of T-cell immunosurveillance could explain this phenomenon (50). However, there is also *in vitro* evidence for cyclosporin direct oxidative effect on human "B-cells", which causes promotion of EBV-induced transformation of "B-cells" (51). Cyclosporin also increases IL-6 production in "B-cells", promoting "B-cell" activation and proliferation, possibly contributing to PTLD (52). Finally, oncogenic RAS-RAF pathways appear to be affected by cyclosporin favoring tumorigenesis (53).

Conversely, some studies indicate a potential for anti-oncogenic effects of concomitant use of cyclosporin and other immunosuppressive agents for certain cancers. In a cohort of immunosuppressed female patients (N=25,914), mainly treated with cyclosporin (n= 21,439), Stewart *et al.* observed lower breast cancer incidence (25). Another study analyzed the effect of chronic use of cyclosporin combined with other immunosuppressive drugs (26). It showed a significant reduction in rectal cancer incidence for both sexes.

Azathioprine is a purine antimetabolite that inhibits DNA synthesis and cell proliferation and disrupts the post-replicative DNA mismatch repair system (54,55). Both cyclosporine and azathioprine have been connected to the development of skin cancer (56). Azathioprine promotes skin cancer development by photosensitization of the dermis and increases the production of reactive oxygen species when exposed to ultraviolet A radiation (57). Consequently, an increased occurrence rate of non-melanoma skin cancer (NMSCs) has been reported in organ transplant recipients, myasthenia gravis, and inflammatory bowel disease patients receiving high-dose azathioprine (58-61). A meta-analysis from 2016 of azathioprine exposure showed a significantly increased risk of squamous cell carcinoma (SCC) (57). Another population-based cohort study on the liver, heart, and lung transplant recipients proved that higher doses of azathioprine increased the risk of lip cancer (62). Furthermore, several studies showed a correlation between azathioprine use and the development of lymphoproliferative disorders (63-66). However, expert opinion on the carcinogenic potential of azathioprine remains controversial; in a meta-analysis of 5 studies, no significantly increased risk of neoplasm development was observed among individuals who received long-term azathioprine treatment (66).

T cell-depleting agents used during induction therapy have been associated with a 30%-80% increased risk of non-Hodgkin lymphoma (nHL) compared to transplant patients not receiving induction therapy. A recent study found >20 times higher incidence of lymphoma in patients receiving anti-thymocyte globulin or muromonab. Additionally, a large study observed a 70%-200% increase in the incidence of nHL, colorectal cancer, and thyroid cancer compared to no induction (67).

A novel generation of immunosuppressants?

A promising feature of a novel generation of immunosuppressive agents appears to be their anticarcinogenic effect. Mycophenolate mofetil (MMF), ester prodrug form of mycophenolic acid (MPA), and mTOR inhibitors (sirolimus/rapamycin) do not seem to be associated with an overall increased risk of cancer, and even show anti-oncogenic and anti-angiogenic properties. Rapamycin is believed to exhibit anti-oncogenic properties by reducing VEGF production in tumor cells, which results in diminished endothelial response (68). Moreover, it inhibits tumor growth through cell cycle arrest and initiation of apoptosis (48), while MMF acts as an antioxidant (69).

According to Hirunsatitpron *et al.*, MPA exposure does not appear to be associated with an increased risk of cancer compared to azathioprine use or no exposure to other additional treatments; it may even be associated with a lower risk of cancer when com-

pared to azathioprine or no therapy (70). Cancer risk comparison between MPA and rapamycin revealed no significant difference. mTOR inhibitors exhibit reduced cancer incidence rates in transplant populations compared to calcineurin inhibitors, with marked reduction in NMSCs (71). Results were echoed in the RESCUE study, which showed a 50% reduction in invasive cutaneous SCC (72). Furthermore, the time to development of new SCC lesions after conversion to sirolimus was significantly longer than in patients on calcineurin inhibitors.

In 2015, Yanick *et al.* conducted a meta-analysis and found no correlation between sirolimus (rapamycin) and lower overall cancer incidence in 39,039 kidney transplant recipients receiving sirolimus-based immunosuppressive therapy (73). Nevertheless, lower kidney cancer and higher prostate cancer incidence were noted in those patients (73).

Cancers in chronically immunosuppressed patients have been the subject of ongoing research, and a significant body of knowledge has been gathered through single or multiple author experiences. Different types and combinations of immunosuppressive regimens, different types of organ transplantation, patient comorbidities, length of follow-up, screening protocols, and various statistical methods all contribute to heterogeneity in the results and the inability to draw clear guidelines from them.

CANCER IN KIDNEY TRANSPLANT RECIPIENTS

Epidemiology of cancer in kidney transplant recipients

The incidence of cancer in kidney transplant recipients is well defined. The incidence of solid cancers shows an increasing trend years after kidney transplantation, specifically 4%-5% after five years to 10% at ten years and >25% after 20 years (74-77). Importantly, analysis has found that differences in cancer risk depend on the kidney recipient's cancer type. In particular, Kaposi sarcoma shows the most significant increase in incidence (>300 fold higher than the average population) (78). Other notable increases include NMSCs, lip cancer, and cancer with viral oncogenesis, such as anogenital cancers with HPV infection. As mentioned previously, common cancers such as breast and prostate do not show increased risk compared to age- and gender-matched general populations.

A recent case-control study conducted by van de Wetering *et al.* in 2010 found that 56% of kidney transplant patients had cancer following transplantation (79). The survival of these patients was significantly lower than in those without cancer (2.1 *vs.* 8.3 years) when matched for age, gender, and years of transplantation (80). It has been suggested that the increased mortality in kidney transplant recipients compared with patients with the same cancer from the general population could be due to differences in immunity, influence of immunosuppression, and differing chemotherapeutic regimens.

Interestingly, the time at which cancer is diagnosed differs according to type. A recent study found that transplant recipients with cancer were diagnosed early (American Joint Committee on Cancer, AJCC 0-II) for renal cell carcinoma (RCC). In contrast, for advanced stages (AJCC >II) of non-small-cell lung cancer (NSCLC), breast cancer, prostate cancer, bladder cancer and malignant melanoma all demonstrated worse survival when compared to the general population (81). This is perhaps due to kidney parameters increased or more robust diagnostic sensitivity in kidney transplant recipient management. It has been suggested that cancers that present more advanced are due to increased biologic aggressiveness due to concomitant immunosuppression. However, more investigation is needed.

Data from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) found that the standardized mortality ratio (SMR) for cancer was 1.7 (95% CI 1.6-1.8). These SMR data have been replicated in other studies worldwide, including in Canada, Australia, United Kingdom, and USA (30,79,80). Absolute cancer mortality varied according to age; the 20-29 year age category had the lowest incidence of cancer (0.5 *per* 1,000 patients), increasing to 25 *per* 1,000 in >80-year-old transplant recipients (78). However, the relative risk of recipients developing cancer in 20-29 age group in comparison to >80 age group was much higher (16-18-fold increase in 20-29 *vs.* two-fold increase in >80 years) (82). The increased risk of cancer in kidney recipients is multifactorial and attributed to oncogenic viruses (such as HPV, EBV, etc.), immunosuppression, and altered T cell immunity. As a result, prospective recipients with a history of cancer are recommended to wait for 2-5 years after oncologic intervention before kidney transplantation.

Etiology and risk factors

Following observation studies, risk factors for developing cancer in this subpopulation include (but are not limited to) increased age at transplantation, male gender, white ethnicity, and extended time of dialysis before transplantation (83,84).

The etiologic cause, i.e., end-stage renal disease (ESRD) affects cancer risk following transplantation. Observational studies show an increased risk of breast, liver, and pancreatic cancer in patients with diabetes mellitus. Conversely, their age- and gender-matched counterparts in the general population have a marked reduction of 20%-30% (85). The risk of cancer relating to diabetes type 1 compared to type 2 requires investigation. Patients with polycystic kidney disease (PKD) demonstrate increased rates of liver, colorectal and kidney cancer compared to the general population and a reduced risk in specific subpopulations of patients. This is proposed to be due to lifestyle, genetic differences, and a higher frequency of nephrectomies before transplantation. Conversely, those with acquired PKD have shown increased rates of RCC (86).

Cancers that can lead to ESRD (myeloma, kidney cancers, urinary tract cancers) occur at higher rates in patients on dialysis and in kidney transplant recipients than in the general population (21). The etiology of urinary tract cancers may also involve aristolochic acid and cyclophosphamide, both of which have been shown to cause tubulointerstitial nephropathy. A cohort study found that 14% of patients who developed ESRD from analgesia were found to have urothelial cancers (87).

Transplant and immune factors can influence the incidence of cancers in this population. Patients with a panel reactive antibody (PRA) score >80% have a twofold increased risk compared to baseline (88). HLA mismatching has been shown to influence the incidence of diffuse large "B-cell" lymphoma (89). Additionally, specific HLA subtypes have been associated with differing post-transplant cancer risks (90). Patients receiving live-donor kidneys have a significantly reduced cancer risk compared to deceased expanded criteria donor kidneys (91). Other transplant-related factors include oncogenic virus activation such as cytomegalovirus and BK polyomavirus.

Proposed pathogenic mechanisms for cancer development in kidney transplant recipients

According to recent literature, the pathophysiological mechanisms/etiologies are threefold:
1) etiologies leading to ESRD;
2) immunosuppression leading to an increased risk post-transplantation; and
3) etiologies that do not show an immediate or clear increase in risk following transplantation.

Myeloma and kidney cancers are the most frequent type among kidney transplant patients; this reflects their recurrence post-transplantation. The second group relates to cancers related to viral oncogenesis and prolonged immunosuppression. Enhanced oncogenesis in this category is associated with reduced immunosurveillance, leading to a reduced removal of malignant and virally infected cells. Notably, natural killer cell activity is reduced, which lowers activity against virally infected and cancerous cells (92). Further, kidney transplant recipients diagnosed with specific types of cancers were shown to have excess immunosenescent T cells and regulatory T cells. Overall, tumor-induced immune dysfunction can affect both innate and adaptive immunity. This combination enhances tumor progression and subsequently increases the opportunity for tumor escape and subsequent proliferation.

As discussed, some cancer risks are reduced while using calcineurin inhibitors. This introduces the third group of cancers, which we must be aware of and exhibit caution as not to generalize the mechanisms of cancer development. It has been suggested that immunosuppressive drugs have a direct immunosuppressive effect on cancer. Interestingly, it was shown that cyclosporin reduces the levels of pyruvate kinase isoform M2 (PMK2), an essential metabolite for oncogenic glycolysis and tumor proliferation (93).

Screening: to be or not to be?

Screening for common cancers such as breast and colorectal cancer has proven beneficial in reducing the risk of cancer-related deaths in the general population. The same cannot be said for kidney transplant recipients, and it is currently recommended to screen these patients the same as with the general population. However, this is based on literature that failed to consider reduced life expectancy and the competing risks of death in these patients. Female transplant recipients were found to have a higher incidence of benign breast disease on mammography with a higher risk of false positives leading to potential harms associated with overdiagnosis (unnecessary core fine needle biopsies or surgery, etc.) (94).

Cost-effectiveness studies found that screening for cervical cancer (cytology) and colorectal cancer (fecal immunocytology) may be cost-effective, while RCC and breast cancer in average risk-kidney transplant patients are less beneficial and more costly (84,95).

There appears to be variation in the results of screening tests in kidney transplant recipients; therefore, an individualized and more multidisciplinary approach is warranted. This will take into account individual risks of cancer, competing priorities of other comorbidities, and patient preferences. This older version of the 'one-size-fits-all' medicine model is no longer beneficial to patients of specialist subpopulations such

as kidney transplant recipients. As specialists, we must strive for individualized management strategies to ensure every patient benefits the most. For example, kidney transplant recipients with higher cancer risks may benefit from more frequent testing. Conversely, those at a lower risk of cancer but a higher incidence of comorbidities may prefer to focus on rehabilitation relating to their comorbidities and a less aggressive approach to screening. In this way, it creates a management strategy that allows high-risk cancer patients to get screened and subsequently managed on time while creating a cost-benefit system that saves on those that do not require screening but rather comorbidity management (74).

Post-transplantation cancer management

Management is complex and requires consideration of dosing and safety of chemotherapeutic agents. Chemotherapeutic agents reduce renal function and have the potential to cause nephrotoxicity and drug-drug interactions. Therefore, the consensus is to reduce the immunosuppressive dose after cancer diagnosis, especially for cancers with viral or immunosuppression-related etiology. However, this must be balanced against the risk of acute graft rejection. Interestingly, development of breast cancer in immunosuppressed patients, namely kidney transplant recipients, is somewhat different. Here we discuss this subpopulation of patients.

BREAST CANCER IN KIDNEY TRANSPLANT RECIPIENTS

Epidemiology

Cancer is the second most frequent cause of death in post-kidney transplant patients and significantly affects life expectancy and overall prognosis (74). Most malignancies are closely related to transplant-associated immunosuppression and infectious origin. However, *de novo* PTBC risk was found to be analogous to the risk of developing breast cancer in the general population (75). Insofar, this equal or slightly increased standardized incidence ratio (SIR) suggests a more complex relationship between breast cancer and kidney recipients than just an immunologic one.

Table 1. *Standardized incidence ratios of post-kidney transplantation breast cancer from mentioned articles*

Article authors	Standardized incidence ratio (95% CI)
Au *et al.* (96)	Canada 1.3 (1.0-1.7)
	Italy[a] 0.8 (0.5-1.2)
	Sweden 1.2 (0.9-1.8)
	Australia and New Zealand 1.0 (0.8-1.3)
	Taiwan 1.1 (0.6-1.9)
	USA 0.95 (0.86-1.0)
	Italy[b] 1.2 (0.8-1.8)
	UK 1.0 (0.8-1.2)
	Hong Kong 1.7 (1.0-2.8)
Collett *et al.* (81)	1.0 (0.8-1.2)
Stewart *et al.* (77)	0.8 (0.6-1.1)[c]
Kim *et al.* (97)	1.3 (1.0-1.8)
Birkeland *et al.* (98)	1.1 (0.6-1.8)
Benoni *et al.* (99)	1.16 (0.93-1.46)
Vajdic *et al.* (21)	1.03[d]
Cheung *et al.* (101)	1.66 (1.0-2.75)
Jung *et al.* (102)	1.4 (1.0-1.9), 2.3 (1.5-3.5)[e]
Huo *et al.* (103)	1.28 (1.08-1.53)
USA registry (74)	1.85 0.77-0.93)[f]

a) fifteen transplant centers in Italy
b) four transplant centers in northern Italy
c) in non-immune related malignancies (breast, rectum, prostate and ovary)
d) calculated from the article (56 observed/54.2 expected cases)
e) adjusted SIR by multivariable Cox model (age, diabetes mellitus, ischemic heart disease, heart failure, liver cirrhosis, chronic obstructive pulmonary disease)
f) in 175,732 solid organ transplants (58.4% kidney, 21.6% liver, 10.0% heart, 4.0% lung)

According to most studies, the SIR of PTBC was equal to or reduced, despite some reports of a statistically significant increase of SIR, as can be surmised from Table 1. Au *et al*. gathered data from nine country registries and systematically analyzed the SIR to be equal, consistently, or slightly increased compared to the general population (96). Collett *et al.* found the SIR to be 1.0 (0.8-1.2, 95% CI) in 25,104 kidney transplant patients in England, Wales, and Scotland (81). Stewart *et al*. (1995) found the relative risk of PTBC in the first year to be 0.49 (0.22-0.77, 95% CI) and grew to 0.84 (0.64-1.03, 95% CI) in subsequent years (25). Stewart *et al*. (2009) found the SIR to be 0.8 (0.6-1.1, 95% CI)

in non-immune-related malignancies (breast, rectum, prostate, and ovary) (77). Kim *et al*. found the SIR to be 1.3 (1.0-1.8, 95% CI) in 14,842 South Korean kidney transplant recipients (97). Birkeland *et al*. found the SIR to be 1.1 (0.6-1.8, 95% CI) in 5,692 Nordic kidney transplant recipients (98). Benoni *et al*. report on a SIR of 1.16 (0.93-1.46, 95% CI) in the Nordic kidney recipient population in 2020 (99). Penn reports on an equal, expected prevalence of PTBC compared to the general population (330 cases of breast cancer out of 9,032 post-transplant malignancies) (50). Likewise, Vajdic *et al*. extracted data from the Australian population and found the SIR to be 1.03 (56 observed/54.2 expected cases) (21). However, a recent 2021 study by Anderson *et al*. found an increased incidence risk of PTBC compared to the national USA rate (0.35% *vs*. 0.28%) (100). Supporting that evidence, Cheung *et al*. report on SIR of 1.66 (1.0-2.75, 95% CI) in the Hong Kong population (101). Jung *et al*. extracted incidence rates from the Korean national database and found the crude SIR for PTBC to be 1.4 (1.0-1.9, 95% CI), and once a multivariable model (age, diabetes mellitus, ischemic heart disease, etc.) was taken into account, the adjusted SIR became 2.3 (1.5-3.5, 95% CI) (102). A comprehensive 2020 study analyzing 21 cohort studies found the SIR to be 1.28 (1.08-1.53, 95% CI) (103). Supporting the overall trend, the SIR of breast cancer after a solid organ transplant (175,732 solid organ transplants {58.4% kidney, 21.6% liver, 10.0% heart, 4.0% lung}) in the USA was 0.85 (0.77-0.93, 95% CI) in the 1987-2008 period (74). Data on PTBC in long-term patients are scarce, but Fuhrmann *et al*. found the risk of developing breast cancer to be related mainly to patient age and not directly to the number of years post-transplantation (104).

Albeit a relatively established reduced/equal SIR, the mortality risk of PTBC is still uncertain. Several institutions have reported an increased mortality rate for advanced-stage breast cancer post-kidney transplantation. Cheung *et al*. found the SMR from PTBC to be 1.9 higher than that of the general population (101). Wong *et al*. extracted data from the Australian and New Zealand Dialysis and Transplant Registry and found PTBC patients to have 40% excess mortality compared to the same age in the general population (105). Correspondingly, Miao *et al*. found *de novo* breast carcinoma in organ transplants to have a poorer prognosis (30). Likewise, and probably anecdotally, Yasumura *et al*. described cases (n=2) of advanced breast cancer in kidney recipients and their poor prognosis (106).

Conversely, Kwak *et al*. found the prognosis similar to the general population. However, it is important to note the possible limitations of the small sample size and short follow-up period (107). Similarly, Jeong *et al*. found survival rates identical to the general population (16 PTBC patients) (108). While the general mortality rates were equivocal, advanced breast carcinoma (stages 3 and 4) was found to have a poorer prognosis than in the general population (109). This led to the hypothesis that although immunosuppression does not increase the risk of developing breast cancer, it is needed for the progression and malignancy of breast carcinoma.

Pathogenesis and risk factors

Unlike infectious-related malignancies, which flourish with immunosuppression, breast cancer seems to be related to hormonal, genetic, and aging factors (11). Moreover, breast cancer oncogenesis relation to inflammation is controversial, with recent conflicting meta-analyses reporting both a positive and negative prognostic value of neutrophil to lymphocytes ratio (66,110). It has even been postulated that immunosuppression has a protective role in post-transplant patients with breast cancer, as this kind of malignancy requires immune activation (25).

Independent risk factors for developing breast cancer can concurrently lead to kidney transplantation and may influence breast carcinoma oncogenesis. Here we discuss diabetes mellitus and aging as the key risk factors. Diabetes mellitus has been consistently reported to elevate the risk of developing breast cancer due to various general and local factors, even when excluding obesity and asserting diabetes mellitus is an independent factor (111). Supporting this finding, Larsson *et al*. conducted a meta-analysis and found diabetes mellitus to affect breast cancer risk positively (112). Diabetes mellitus is one of the leading causes of chronic kidney disease and significantly influences the need for kidney transplantation (113,114). Another rare and more lethal mechanism of developing PTBC is direct transmission when unidentified and disseminated from the donor (108).

Aging is another independent risk factor for developing breast cancer (108). Specifically, the age at presentation of PTBC is controversial. While some studies find no change, others found patients presenting at a younger age (108,115). Jeong *et al*. report on a median age for PTBC of 45.2 (±4.5) years compared to 48.6 (±10.04) years in the general breast cancer population, which argues for extensive screening post-transplantation (108). Additionally, Webster *et al*. stratified the risk of developing PTBC by age and found the SIR to be 3.12 (1.17-8.31, 95% CI) in females under 35 years of age with normalization of SIR with patient age (83). Nevertheless, most observational cohorts report an age correlating to the general population.

Screening

Screening has been consistently reported to decrease breast cancer mortality by early detection and is a standard preventive measure in public health institutions. The recommended screening guidelines for post-transplant patients are currently extrapolated from the general population and are based primarily on age (116). Kato *et al*. advocated frequent follow-ups to allow breast cancer to be detected early and managed to detect eight out of nine PTBCs in an early asymptomatic stage in their screening program (117). However, this is based on the assumption that there is a more aggressive presentation in younger patients with subsequent poor prognoses. Acuna *et al*. assessed 13 screening program guidelines in solid organ recipients and found most breast cancer screening guidelines to parallel those of the general population, with a minority advocating for earlier screening age (118). However, this approach is challenged by Kiberd *et al*. when considering the reduced incidence of PTBC, cost-effectiveness of screening, and the reduced life expectancy of transplant recipients (119). Furthermore, increased screening in the post-transplant population can lead to potential overdiagnosis of breast cancer due to heightened unnecessary surveillance (120). Supporting this notion, Wong *et al*. report that most nephrologists would recommend screening in their patients despite a mostly reported equal/slightly increased SIR of PTBC, thereby increasing the chances of diagnosing them with breast cancer (121).

Depending on the malignancy, pre-transplantation evaluation includes a specific disease-free period before transplant, as patients with malignancy are considered to have a poorer prognosis and higher chance for recurrence (122). Current evaluation guidelines for kidney transplantation candidates are two years without early breast cancer (*in situ*) or five years without an advanced breast cancer diagnosis (stage 2) and absolute contraindication with stage 3-4 breast cancer (123). Lim *et al*. challenged this classification and offered the TNM grading system instead of early/advanced to be more precise and to correlate to the overall prognosis (124). To achieve a yet even more accurate prognostic tool, some encourage incorporating genomic profiling assays as a more comprehensive tool for evaluating the risk of developing PTBC (125). This disease-free period before transplantation may contribute to the observed lower SIR of PTBC compared to other malignancies.

Management

The treatment for PTBC is mostly extrapolated from the general population with special considerations given to nephrotoxicity of certain chemotherapeutics, graft-survival expectancy, concurrent comorbidities, and immunosuppression dosage adjustment. The latter poses a great challenge that could induce other iatrogenic malignancies or graft rejection (126,127). However, due to the infrequency of PTBC and the relatively small sample size of cohort studies, further investigation is needed to draw more specific guidelines for the post-transplantation population.

CONCLUSION

In conclusion, the risk of developing breast cancer in kidney transplant recipients does not increase owing to the previously described mechanisms. Instead, the mechanisms seem to be unrelated to transplantation immunosuppression regimen. The mortality rates from PTBC are increased with younger age and advanced carcinoma at the time of presentation, even more so than in the general population. Pre-transplantation evaluation and heightened screening may also contribute to the overall incidence of PTBC. In contrast, other factors that lead to ESRD and kidney transplantation, such as diabetes mellitus, can contribute to the development and prognosis of PTBC.

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SAŽETAK

KARCINOM DOJKE I IMUNOSUPRESIJA U PRIMATELJA BUBREŽNOG PRESATKA: PREGLED LITERATURE

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Rak dojke najčešća je novotvorina i peti uzrok smrti žena. Etiologija i patogeneza ovoga zloćudnog tumora su multifaktorske. Pojava neoplazma u primatelja solidnih organa liječenih imunosupresivnim lijekovima je 2 do 3 puta veća nego u općoj populaciji. U rizičnoj populaciji su i žene s presađenim bubregom. Cilj ovoga pregleda literature je istražiti povezanost pojavnosti karcinoma dojke u primatelja bubrežnog presatka i imunosupresivnih režima, opisati njihovu ulogu u tom procesu te istražiti trenutne preporuke probira za rano otkrivanje karcinoma dojke u toj populaciji. Kako bismo pristupili potrebnoj literaturi koristili smo bazu podataka PubMed-a. MeSH pojmovi uporabljeni za pretragu baze literature su bili: *"breast cancer"*; *"risk factors"*; *"cancer screening"*; *"kidney transplantation"*; *"immunosuppression"* i *"cancer"*. Nakon primjene kriterija isključenja ukupno je pregledano 409 članaka. Članci su uključivali randomizirana kontrolna istraživanja, preglede i sustavne preglede literature. Uporabljene su i reference s drugih pregleda literature kako bi se pribavile dodatne relevantne informacije koje potencijalno nisu bile dohvaćene pri inicijalnoj pretrazi. Karcinom dojke najdijagnosticiraniji je karcinom i ujedno peti vodeći uzrok smrti žena u svijetu. Karcinom dojke je na trećem mjestu liste malignih uzročnika smrti, odmah iza karcinoma pluća i kolorektalnog karcinoma. Karcinom dojke je uzrokovan kombinacijom hormonskih i genetskih čimbenika te čimbenika vezanih uz starenje. Značajan čimbenik procesa kancerogeneze je imunosupresija, što potvrđuje dva do tri puta češća pojavnost malignih bolesti u populaciji primatelja transplantiranih organa. Kronična imunosupresivna terapija, okolišni čimbenici (izlaganje sunčevu zračenju) i genetički zapisi pojedinaca utječu na proces razvoja malignih bolesti u primatelja transplantiranih organa. Imunosupresivni lijekovi smanjuju imuni nadzor, što pospješuje proces virusne onkogeneze te opće karcinogeneze. Primatelji bubrežnog presatka skloniji su razvoju karcinoma upravo zbog doživotne imunosupresivne terapije pa je karcinom drugi uzročnik smrtnosti kod te populacije. Od iznimne važnosti je spomenuti da razlike u procijenjenom riziku razvoja karcinoma ovise upravo o vrsti karcinoma. Pokazalo se da imunosupresija ne utječe na određene maligne bolesti poput karcinoma dojke, jer je njihov relativni rizik usporediv s onim u općoj populaciji. Zbog ograničenog broja radova koji se bave tematikom karcinoma dojke nakon transplantacije bubrega ovom prigodom predstavljamo sveobuhvatan pregled dosadašnje literature, trenutnog razumijevanja patofiziologije bolesti, uloge probira u njenoj dijagnozi i liječenju. Opsežnim pregledom literature došli smo do zaključka da rizik razvoja karcinoma dojke nakon transplantacije u primatelja bubrežnog presatka nije povećan u usporedbi s općom populacijom. Iz pregledanih radova proizlazi zaključak da razvoj karcinoma dojke u primatelja bubrežnog presatka nije povezan s post-transplantacijskim imunosupresivnim režimom te je uglavnom povezan sa starenjem i neovisnim čimbenicima rizika koji sami po sebi mogu dovesti do transplantacije bubrega, kao što je dijabetes melitus. Zbog programa probira za rano otkrivanje karcinoma post-transplantacijski karcinom dojke obično se dijagnosticira rano. Međutim, ako ga se dijagnosticira u uznapredovalim stadijima povezan je sa značajno lošijim ishodom i povećanom razinom smrtnosti u usporedbi s općom populacijom. Preporuka je da se probir bolesnika provodi zajedno s općom populacijom koja odgovara dobi i spolu bolesnika s presatkom, uz naglasak na individualni pristup svakom bolesniku. Iznimno je važno napomenuti da je ovo područje medicine koje zahtijeva daljnje istraživanje. Zbog rijetkosti post-transplantacijskog karcinoma dojke i oskudnih resursa na tu tematiku većina smjernica ekstrapolirana je iz opće populacije i ne odgovara minimalnom riziku od razvoja te bolesti. Slično tome, smjernice za liječenje izvedene su iz podataka opće populacije i ne uzimaju u obzir posebna razmatranja kod populacije pacijenata s bubrežnim presatkom kao: održavanje funkcionalnog presatka, odbacivanje presatka, nefrotoksične kemoterapijske lijekove i istodobnu primjenu imunosupresivnih lijekova. Potrebno je spomenuti da je heterogenost rezultata o kojima se raspravlja u našem pregledu literature posljedica različitih vrsta imunosupresivnih režima, transplantiranih organa, pridruženih bolesti, duljine praćenja bolesnika i programa probira. Kako bi se definirale jasne smjernice prilagođene ovoj populaciji, potrebno je daljnje istraživanje mehanizama nastanka bolesti, uz produljeno vrijeme praćenja pacijenata na različitim imunosupresivnim režimima kako bi se omogućila naknadna usporedba.

Ključne riječi: karcinom dojke, čimbenici rizika, probir, transplantacija bubrega, imunosupresija