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MINIREVIEWS

Women's health issues in solid organ transplantation: Breast and gynecologic cancers in the post-transplant population

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Abstract

The success of solid organ transplant has steadily improved which has led to a unique set of post-transplant issues. The rates of *de novo* cancer in the solid organ transplant recipient population are higher than those in the general population. There is growing evidence that breast and gynecologic cancers may have a higher mortality rate in post-transplant patients. Cervical and vulvovaginal cancers specifically have a significantly higher mortality in this population. Despite this increased mortality risk, there is currently no consistent standard in screening and identifying these cancers in post-transplant patients. Breast, ovarian and endometrial cancers do not appear to have significantly increased incidence. However, the data on these cancers remains limited. Further studies are needed to determine if more aggressive screening strategies would be of benefit for these cancers. Here we review the cancer incidence, mortality risk and current screening methods associated with breast and gynecologic cancers in the post-solid organ transplant population.

Key Words: Cancer screening; Solid organ transplant; Female-specific cancer

Core Tip: Survival after solid organ transplant is continually improving. Because of this, patients are living longer and are requiring long-term monitoring for malignancies. There is growing evidence that breast and gynecologic cancers (specifically cervical and vulvovaginal cancers) may have a higher mortality rate in post-transplant patients. Despite this increased mortality risk, there is currently no consistent standard among transplant societies for screening and identifying these cancers in post-transplant patients. Ultimately, data are not robust and further studies are needed to determine if more aggressive screening strategies would be of benefit for these cancers.

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INTRODUCTION

Overall, survival following solid organ transplant (SOT) has improved considerably since the first successful kidney transplant was performed in 1954. The female post-transplant population is growing as well; with women constituting 38% of liver transplant recipients in 2021 *vs* 35% in 2011[1]. Improvement in post-transplant survival, along with the growing female transplant recipient population presents unique concerns with regards to post-transplant sex-specific cancer screening. There are currently no American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Kidney Disease: Improving Global Outcomes (KDIGO) or International Society for Heart and Lung Transplantation (ISHLT) guidelines regarding post-transplant specific screening methods for gynecologic or breast cancers following liver, kidney, heart, or lung transplantation[2-6]. Here we will review the incidence and current screening standards for breast and gynecologic (particularly cervical, ovarian, uterine, and vulvovaginal) cancers following SOT. The data included in this paper is extracted from studies including solid organ transplant recipients (SOTRs). It is challenged to define the rates and true causality of *de novo* cancers in the post-SOT population. There is a growing body of evidence suggesting that cancer diagnosis and cancer-related mortality are increased in post-transplant patients as compared to the general population. Here, we will review the incidence and mortality data available for breast and gynecologic cancers as well as the current screening recommendations for the general population in comparison to the post-transplant population. Although these cancers affect a small proportion of all SOTRs, they bear significance as their mortality rates appear to be considerably higher than in the general population.

CANCER RISK FOLLOWING TRANSPLANTATION

Analysis from SOTRs registries suggests there is a higher incidence of cancers in the post-transplant population as compared to the general population[7]. Most studies analyze the incidence of cancer post-transplant utilizing the standardized incidence ratio (SIR), which depicts the relationship between the observed and expected cancer cases among post-transplant patients compared to the general population. A Swedish study conducted in 2003 demonstrated SIR of 4.0 for developing a first cancer post renal, hepatic or other organs from 1970 to 1997[8]. Watt *et al*[9] found that malignancy was responsible for 22% of deaths greater than one year after liver transplant in a population of 798 patients [9]. Although the cancer risk post-transplant remains high, incidence of *de novo* malignancy following transplantation is improving over time. In a Nordic cohort of greater than 4000 post-liver transplant patients followed over three decades, there was a noted era-dependent decrease in SIR[10]. The SIR for all cancers in this population decreased each decade from the 1980s to the early 2000s, however cancer incidence remained elevated compared to the general population. These findings were attributed to changes in immunosuppression regimens as well as changes in cancer screening protocols and patient follow up. The majority of *de novo* cancers following transplantation are cutaneous and lymphoid, and have been previously linked to the degree of immunosuppression[11-13]. However, there is also a large category of viral infection-related cancers, including cervical, vulvar and vaginal cancers which affect women in particular. 12805 kidney transplant recipients registered in the Netherlands Organ Transplant Registry were followed for a total of 89651 person-years with an incidence of cancer of 7.1 percent as well as a survival reduction of nearly 5 years despite 69 percent dying with a functioning renal graft. The authors also highlighted that 62% of patients diagnosed with *de novo* breast cancer and 64% of patients diagnosed with gynecologic cancers died from their respective cancer; both mortality rates are considerably higher than the general population[14]. This increase in cancer-related mortality is striking and begs the question of its true relationship to SOT or immunosuppression. But the mortality rates

urge those managing post-transplant patients to explore perhaps more aggressive cancer screening strategies.

Cervical cancer

Cervical cancer is primarily caused by the oncogenic human papillomavirus (HPV) infection[15,16]. Although the incidence and mortality of cervical cancer has decreased since the adoption of routine screening with Papanicolaou (Pap) smear, cervical cancer continues to have a considerable impact on the United States population[17]. Cervical cancer had an incidence rate of 7.5 in the general population in 2019[18]. There is varying data on the incidence of cervical cancer in post-transplant populations. However, several studies showed an increased risk of cervical cancer, particularly in the younger post-transplant population[8,19-21]. In a study published by Madeleine *et al*[19] in 2013, there was a SIR of 3.3 for *in situ* cervical carcinoma in SOTRs, and a SIR of 1.0 for invasive cervical cancer[19]. After adjustment for age, this study found that younger recipients (18–34 years old) had a higher incidence of *in situ* cervical cancer. Using incidence rate ratio (IRR), which compares between subgroups of the transplant population (in this case, age), an IRR of 4.7 for *in situ* cervical cancer and an IRR of 2.4 for invasive cervical cancer in the younger transplant recipients was noted compared to older transplant recipients. Another study found a statistically non-significant mild increase in cervical cancer post-SOT with SIR of 2.6 [95% confidence interval (CI): 0.1-15][20]. Adami *et al*[8] found cervical carcinoma *in situ* SIR of 1.3 (95%CI: 1.0-1.8) among patients transplanted with kidney, liver or other organs[8]. A separate study published from data utilizing Swedish and Danish SOTR registries discovered a significantly increased incidence of cervical cancer compared to the general population with SIR 2.6 (95%CI: 1.6–4.5) [21]. Although the rate of cervical cancers varied between these studies, they illustrate a concern for increased risk for cervical cancers in the SOTR. These studies again highlight the concern for a significant change in incidence of cancer post transplantation. These studies also do not clearly delineate the rates of cervical cancer screening in post-transplant patients. But given the incidence, continued diligence seems necessary. Particularly when considering the increased mortality risk related to gynecologic cancers.

Breast cancer

Breast cancer is the most commonly diagnosed cancer among women in the United States and was the second leading cause of cancer-related deaths in 2021[18,22]. The etiology is thought to be multifactorial due to the presence of proliferative breast disease, reproductive factors and genetics and is impacted by several factors such as demographics and environmental exposures[22]. Given the incidence of breast cancer in the general population, most transplant centers require breast cancer screening prior to transplant listing. Several studies have shown a decreased risk of breast cancer which is likely a consequence of pre-transplant screening methods[23-25]. In one study of 1000 post-liver transplant patients, 57 of whom developed cancer after transplantation, the SIR for breast cancer was 0.74 (95%CI: 0.15-2.16, $P > 0.05$)[23]. Another study by Oruc *et al*[24] found the incidence rates of *de novo* breast cancer following liver transplant at the University of Pittsburgh were similar to incidence of breast cancer in the general population with incidence rate of 523.6 per 100000 women in the post-transplant population. Though it is worth noting the incidence rate of breast cancer in the general population at the time was a bit lower than that observed in post-transplant patients, this was not found to be statistically significant [24]. Engels *et al*[25] found a significantly decreased SIR in breast cancer. Among 1700 SOTRs, there was a SIR of 0.85 (95%CI: 0.77-0.93). The authors attribute this significant decrease in risk to pre-transplant cancer screening[25].

Ovarian and endometrial cancer

Ovarian cancer is the second most common gynecologic cancer and the most common cause of gynecologic cancer-related death in the United States[26]. The most common histopathologic type is epithelial ovarian cancer. There are many risk factors for epithelial ovarian cancer; increased age, polycystic ovarian syndrome, endometriosis, infertility, and genetic predisposition (particularly presence of BRCA 1 or 2 mutation and Lynch Syndrome)[26]. Most studies in SOTRs found the SIR for ovarian cancer did not have a statistically significant increase compared to the general population, with a range of 1.2-2[8,9,21,27]. One study did find an increased incidence of *de novo* ovarian cancer arising in patients with a prior breast cancer diagnosis with an incidence of one in 6.5 women *vs* one in 385 for the rest of the study population[28]. Most studies show a statistically non-significant increase in SIR for ovarian cancer One study did show a very mildly decreased SIR of 0.95 for ovarian cancer following SOT, however this was not statistically significant (95%CI: 0.7-1.24)[25]. There is little evidence for ovarian cancer-related mortality within the SOTR population. However, one Korean study found the standardized mortality rate (a comparison in mortality due to the cancer between the transplant population and the general population) for ovarian cancer was 4.0 (95%CI: 2.1-6.5) in female kidney transplant recipients[29]. This study had a higher incidence of ovarian, gynecologic and breast cancer as compared to SOTR studies within North America. The reason for this difference is not clearly elucidated in this paper. The authors postulate the difference may be due to a focus on a later transplant epoch in the Korean population, higher proportion of female transplant recipients (43% *vs* 36%), genetic predis-

position, possible unique environmental exposure of the Korean population, different immunosuppression regimens or different screening and surveillance protocols[11,29].

Endometrial cancer develops in about 3 percent of females in the United States[30]. The more common type 1 endometrial cancer tends to present at an earlier stage and has a better prognosis than type 2 for the general population. Risk factors for type 1 endometrial cancer include excess estrogen unopposed by progestin, genetic predisposition (Lynch Syndrome), obesity, nulliparity, hypertension and diabetes[30]. In most post-SOT studies published, there does not seem to be a statistically significant increase in risk for development of endometrial cancer. Multiple studies have demonstrated SIR ranging from 0.86 to 1.4 without statistical significance[20,21,25]. However one study utilizing data from the Australian and New Zealand SOT registry did find a significant increase in uterine cancer with SIR 1.85 (95%CI: 1.16-2.93)[27,31]. The difference in incidence in this study appears to be anomalous compared to other post-SOT studies.

Vulvar and vaginal cancer

Vulvovaginal cancers are less common in the United States compared to the rest of the world. The incidence of vulvar cancer was 2.5 in 100000 women in 2019; the true incidence of vaginal cancer is unknown, however the estimated incidence of vaginal carcinoma *in situ* is 0.1 in 100000[18,32,33]. Most cases of vaginal cancer in the United States are linked to HPV infection, similar to cervical cancer. Risk factors include multiple lifetime sexual partners, current cigarette smoking, early age at first intercourse [32,33]. Vulvar cancer is less common than the other gynecologic malignancies in the United States, and tends to be diagnosed at earlier stages. Similar to cervical and vaginal cancer, it is also linked to HPV infection. Other risk factors include prior history of cervical cancer or intraepithelial neoplasia, current cigarette smoking, vulvar lichen sclerosis, immunodeficiency syndromes and northern European descent[32]. Most studies found a dramatic increase in rates of vulvar, vaginal or combination of the two malignancies in post-transplant patients which is postulated to be due to viral infection with HPV[34, 35]. In a retrospective study of female renal transplant patients over the age of 40 years, Meeuwis *et al* [36] found 92% of cervical and vulvovaginal cancers were associated with HPV, specifically HPV 16 in 53.8% of cases[36]. In most studies, there was a statistically significant increase in vulvar and vaginal cancers, with SIR ranging from two to forty-five-fold increase compared to the general population[8,19, 20,25,27]. One study found a higher incidence of *in situ* vulvar cancer in younger SOT patients (age 18-34 years) with an increase in IRR to 4.1 (95%CI: 3.0-5.6) for vulvar cancer compared to women transplanted over the age of 35. This study found that younger age at transplant, older immunosuppressive regimens containing azathioprine and cyclosporine, and increased time since transplant were associated with a higher incidence of *in situ* vulvar cancer. Additionally, they found higher incidence of *in situ* rather than invasive genital cancers; potentially due to diagnosis of cancer at earlier stages with screening, or owing to the nature of vulvovaginal cancers being symptomatic, even at early stages[19, 30]. There is sparse data regarding mortality specifically due to vulvar or vaginal cancer across SOTR studies. This may be due to diagnosis at earlier stages and consequently higher rates of remission after treatment.

CURRENT SCREENING STANDARDS

More aggressive cancer screening methods are known to improve detection of cancer and in to thus improve cancer-related mortality rates. Finkenstedt *et al*[37] introduced an intensified surveillance protocol in their post-liver transplant patients and were able to improve the detection of *de novo* cancers from 4.9% to 13%. They also observed more *de novo* malignancies diagnosed in earlier stages[37]. Despite studies such as this, there is no SOTR-specific guideline or guidance for breast or gynecologic cancers aside from cervical cancer surveillance. The ISHLT recommends employing the same general malignancy screening and surveillance methods used for the general population in pre- and post-heart and lung transplant patients with respect to breast and gynecologic cancers[5,38]. The American Society of Transplantation (AST) recommends annual pelvic exam with Pap smear for post-kidney transplant patients[39]. The KDIGO recommends age-appropriate cancer screening in pre- and post-transplant patients in their latest guidance statement, however no specific screening for ovarian, endometrial or vulvovaginal cancers[6,40]. Thusly, the screening strategies included below are those suggested for the general population and, if available, those recommended for the SOTR population (Table 1).

Breast cancer screening: Breast cancer screening, like many other cancer screenings relies heavily upon risk designation of the individual being screened. Screening modality, time at which to start screening and risk-reducing measures differ from the average risk population for women who are considered moderate or high risk. Currently, immunosuppression and transplant status are not considered to increase risk and thus average risk breast cancer screening strategies should be applied to these groups. Screening is recommended by most United States government-sponsored groups and medical societies for average risk women beginning at age 50 with mammography every 1-2 years, with interval frequency based on imaging findings. For women age 40-49 years, it is recommended a conversation

Table 1 Breast and gynecologic cancer screening recommendations and incidence rates as compared to the general population

Cancer type	Current standard guidelines	SOTR specific recommendations	Rates of malignancy in SOTR: Increased (+), Same (=), or Less (-) than general population
Breast cancer	Mammography every 1-2 yr in women > 50 years old (for average risk). Discussion for screening beginning at age 40 yr	Mammography prior to transplantation if > 50 yr; otherwise, same screening interval as the general population	-
Cervical cancer	Women 21 to 29 years old should have a Pap test alone every 3 yr. HPV testing alone can be considered for women who are 25 to 29 years old, but Pap tests are preferred	Pap if younger than 30 years old at transplant, co-testing with Pap and HPV is preferred beginning at age 30 yr but annual Pap is considered adequate	+
	Women who are 30 to 65 years old have three options for testing: Pap and HPV (co-testing) every 5 yr. Pap alone every 3 yr. Or they can have HPV testing alone every 5 yr	If performing co-testing with HPV and Pap: If results of baseline Pap and HPV testing are normal, co-testing can be performed every 3 yr. If the patient is transplanted prior to age 21, it is recommended screening begin within 1 yr of initial engagement of sexual activity	
Vulvar and vaginal cancer	No current screening strategy for the general population, however recommended annual pelvic exam in patients with HIV	AST recommends annual pelvic exam for kidney transplant patients; otherwise, no consistent guidance across societies	+
Endometrial cancer	No current screening strategy	No current screening strategy	=/-
Ovarian cancer	No current screening strategy	No current screening strategy	=/-

SOTR: Solid organ transplant recipient; Pap: Papanicolaou smear; HIV: Human immunodeficiency virus; AST: American Society of Transplantation.

regarding screening is initiated, but screening itself has not shown mortality benefit in this population [41,42].

Cervical cancer screening and prevention: There is considerable data for women post-transplant supporting a more aggressive screening approach than for the general population[13,19]. There is a consensus statement published in 2019 by the American Society for Colposcopy and Cervical Pathology recommending the following: Cervical cytology if the patient is younger than 30 years at transplant, co-testing with cytology and HPV is preferred beginning at age 30 years but cytology is considered adequate. If only performing cytology, annual cytology is recommended; if 3 consecutive cytology results are normal, the interval frequency may be increased to cytology every 3 years. If performing co-testing with HPV and cytology: If results of baseline cytology and HPV testing are normal, co-testing can be performed every 3 years. If the patient is transplanted prior to age 21, it is recommended screening begin within 1 year of initial engagement of sexual activity. Continuation of screening throughout the patient's lifetime is recommended. A discussion regarding quality and duration of life should be pursued prior to discontinuation of screening[43]. There is currently guidance regarding HPV vaccination in pre-transplant populations. Currently, it is recommended by the AASLD to administer the quadrivalent HPV vaccine prior to listing for transplant in women up to the age of 45 years[44]. There is evidence that the HPV vaccine is safe in the immunocompromised population, including SOTRs[45]. However, it is worth noting the immunogenicity of the vaccine is lower in certain circumstances: Lung transplant recipients (57.1% response rate 7 mo after vaccination), high doses of tacrolimus, and vaccination in the early post-transplant period[46]. Further studies are required to assess the benefit of repeating the vaccine series to improve response rates and the effect of this on decreasing vulvovaginal and cervical cancers in the SOTR population.

Vulvovaginal cancer screening: There are currently no screening strategies for vulvovaginal cancer other than pelvic exam. The AST recommends annual pelvic exam in post-kidney transplant patients, however most other SOT societies lack guidance in this area[39]. Diagnosis of vulvovaginal cancers rely upon visual assessment with histopathologic confirmation. The American College of Obstetricians and Gynecologists (ACOG) primarily focuses on methods of prevention including administration of the quadrivalent or nonavalent HPV vaccine[47]. There is growing evidence of increased risk for vulvovaginal cancers among HIV patients due to immunosuppression and concomitant HPV infection. Because of this, annual pelvic exam with close attention paid to visual inspection is recommended in this population[48]. Although the means of immunocompromise/immunosuppression differ between the HIV-infected population and the post-transplant population, the dramatic increased incidence of

vulvovaginal cancers in the HIV-infected population could serve as evidence for more aggressive screening methods in other immunocompromised (or immunosuppressed, in this case) populations. Although there are not specific recommendations regarding screening for vulvovaginal cancers, they are by default screened for by means of pelvic exam during cervical cancer screening-which does have recommendations by transplant societies and the ACOG[2,4-6,13,43]. In one recent review of gynecologic malignancies post-liver transplant, annual pelvic exam is recommended[49]. It is possible that as vulvovaginal cancers are diagnosed in early stages, the mortality rate is relatively low. However, treatment can potentially include chemotherapy, radiation and excision (depending on the stage); all of which have considerable risk and cost to the patient[50].

Ovarian cancer screening: There is currently no recommended screening strategy for ovarian cancer in women of low or average risk within the general population. Furthermore, there is no screening test leading to the early detection of ovarian cancer that reduces ovarian cancer mortality, regardless of risk [51]. One study found an incidence of 1 in 6.5 cases of ovarian cancer in pts with a prior history of breast cancer suggesting closer follow up/screening for this population[28]. Obtaining a detailed family history to identify high risk patients is essential. Patients with family history of breast or ovarian cancer, patients of Ashkenazi Jewish descent, and patients with known hereditary syndromes such a BRCA 1 or 2 mutation or Lynch Syndrome (among others) are identified as high-risk for developing ovarian cancer and should be considered for referral to genetic counseling. Patients with the presence of high-risk genes may benefit from risk-reducing techniques such as bilateral salpingo-oopherectomy[52].

Endometrial cancer screening: Current screening strategies for endometrial cancer rely upon presence of clinical signs/symptoms (such as uterine bleeding) in both average and high-risk patients. It is recommended patients with a genetic predisposition such as Lynch Syndrome or Cowden Syndrome potentially undergo endometrial tissue sampling every 1-2 years starting at age 30-35 years and risk-reducing hysterectomy[53,54].

CONCLUSION

While overall survival and incidence of cancer post-SOT are improving, cancer-related mortality across all cancers remains considerably higher in the post-transplant populations that have been studied as compared to the general population. Despite limited series, cervical and vulvovaginal cancers appear to be the highest risk of incidence of the gynecologic cancers following SOT. Breast cancer does not appear to have a higher incidence following transplantation, and screening methods used in the general population should be sufficient. Ovarian and endometrial cancer rates vary among post-SOT populations[8,9,21,27]. For the most part, they are not significantly increased with exception of patients with a genetic predisposition[28]. Careful history-taking with particular attention to familial cancer syndromes is key in identifying this population.

The lack of uniform gynecologic cancer screening recommendations post-SOT may be due to the small amount of existing evidence. Many studies either combine ovarian, uterine, cervical and vulvovaginal cancers together into a "gynecologic cancer" group or fail to mention vulvovaginal cancers entirely. The incidence of these cancers appears to be small when compared to other cancers. Data regarding mortality from breast and gynecologic cancers is also lacking in these patients. The existing data does appear to indicate a substantially higher mortality rate for SOTRs with breast and gynecologic cancers.

Despite these limitations, there are certain modifiable risk factors to which all Physicians managing the post-transplant population should be aware. As the most common risk factor for vulvovaginal and cervical cancer is infection with HPV, efforts should be focused on prevention (with HPV vaccination in those less than 45) as well as screening in order to decrease the associated morbidity and mortality of these malignancies.

Further studies regarding breast and gynecologic cancer in SOTRs is required to assess the respective incidence and mortality in order to direct screening and surveillance of these cancers. The decreasing age at transplant, growing female transplant population and improved survival post-transplant necessitate improved guidance regarding screening and surveillance of breast and gynecologic cancers among SOTRs.

FOOTNOTES

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