

Risk Factors of Lung, Head and Neck, Esophageal, and Kidney and Urinary Tract Carcinomas After Liver Transplantation: The Effect of Smoking Withdrawal

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Liver transplant recipients have an increased risk of malignancy. Smoking is related to some of the most frequent causes of posttransplant malignancy. The incidence and risk factors for the development of neoplasia related to smoking (head and neck, lung, esophageal, and kidney and urinary tract carcinomas) were studied in 339 liver transplant recipients. Risk factors for the development of smoking-related neoplasia were also studied in 135 patients who had a history of smoking so that it could be determined whether smoking withdrawal was associated with a lower risk of malignancy. After a mean follow-up of 7.5 years, 26 patients were diagnosed with 29 smoking-related malignancies. The 5- and 10-year actuarial rates were 5% and 13%, respectively. In multivariate analysis, smoking and older age were independently associated with a higher risk of malignancy. In the smoker subgroup, the variables related to a higher risk of malignancy were active smoking and older age. In conclusion, smoking withdrawal after liver transplantation may have a protective effect against the development of neoplasia. *Liver Transpl* 17:402-408, 2011. © 2011 AASLD.

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One of the most important consequences of immuno-suppression is the risk of de novo malignancies¹ due to the loss of immunovigilance. Thus, liver transplant recipients have an increased risk of neoplasia in comparison with the general population.²⁻⁵ In fact, neoplasia is one of the most frequent causes of late mortality in adult liver transplant recipients.^{1,6}

Smoking is a well-known risk factor for the development of neoplasia both in the general population and in liver transplant recipients.^{1,3,7} It is mainly related to lung,^{8,9} upper aerodigestive tract, and urinary tract carcinomas.^{10,11} As a result, active smokers after transplantation have a higher risk of malignancy than nonsmokers.¹²

The aim of this study was to investigate the risk factors for lung, head and neck, esophageal, and kidney

and urinary tract carcinomas (excluding prostate carcinoma) after liver transplantation. In addition, we investigated whether the risks of developing one of these malignancies were different in patients who ceased smoking and in patients who continued smoking after transplantation.

PATIENTS AND METHODS

Patients

We analyzed all adult patients who underwent liver transplantation for the first time between April 1990 and December 2009 and survived more than 3 months after transplantation. They received

Abbreviation: SRM, smoking-related malignancy.

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cyclosporine- or tacrolimus-based immunosuppression, as previously described.¹³

Follow-Up

All liver transplant candidates underwent urinalysis, a chest X-ray examination, an abdominal ultrasound examination, and gastroscopy when they were evaluated as candidates for transplantation. Furthermore, patients with a smoking history greater than 20 pack-years who were actively smoking or had quit smoking less than 10 years before underwent a computed tomography scan of the chest and an ear-nose-throat evaluation to rule out malignancy.

The frequency of the follow-up and the studies for neoplasia screening after transplantation are described in a recently published article.¹⁴ Our group has introduced a screening protocol based on the risk of neoplasia of every patient. With respect to the neoplasia studied in this study, all patients underwent urinalysis, a chest X-ray examination, and an abdominal ultrasound examination every year. Patients with a smoking history greater than 20 pack-years who were actively smoking or had quit smoking less than 10 years before were seen every year in the ear-nose-throat outpatient clinic (since 2000) and underwent a low-radiation computed tomography scan of the chest every year (since 2006).

A smoking history was obtained when patients were referred for transplantation. Smoking cessation was recommended to smokers. After transplantation, patients were asked about their smoking behavior at least 4 times within the first posttransplant year and once a year thereafter.

Definitions

Smoking-related malignancies (SRMs) included de novo lung, head and neck, esophageal, and kidney and urinary tract carcinomas (excluding prostate carcinoma).

The smoking status was classified as follows:

- Nonsignificant smokers: patients who did not have a past history of smoking, who had a history of smoking less than 20 pack-years, or who had ceased smoking more than 10 years before transplantation.
- Previous smokers: patients with a past history of smoking greater than 20 pack-years who had ceased smoking less than 10 years before transplantation or immediately after transplantation and did not resume smoking after transplantation.
- Active smokers: patients with a history of smoking greater than 20 pack-years who continued smoking after transplantation.

Description of the Study

The relative risks of developing lung cancer, head and neck cancer, esophageal cancer, and kidney and urinary tract cancer (excluding prostate cancer) were

obtained through a comparison of the number of observed cases and the number of cases expected according to age- and sex-based rates of neoplasia and cancer mortality rates for Navarra (Spain) in 1998-2002.¹⁵

The relative risks of developing SRM and dying from SRM were obtained in a similar way. Similarly, the relative risks of developing SRM were calculated for each subgroup of patients: nonsmokers, previous smokers, and active smokers.

The following potential risk factors for the development of SRM were studied: age, sex, alcohol abuse (ie, alcohol consumption > 80 g/day for >10 years) before liver transplantation, hepatitis C virus infection, hepatocellular carcinoma at transplantation, primary immunosuppression (cyclosporine or tacrolimus), history of rejection requiring high doses of steroids or anti-lymphocyte globulins in the first 3 months, number of immunosuppressive drugs at 3 months, and smoking history (nonsignificant smokers versus active or previous smokers). A second analysis of risk factors for the development of SRM was performed only for smokers. In this second study, the same potential risk factors were studied, but smoking was studied in terms of active smokers and previous smokers.

The study was revised and approved by the institutional review board of the University of Navarra and by the Spanish Agency for Drugs and Sanitary Products.

Statistical Analysis

For statistical analysis, the Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL), was used. Patients who developed SRMs during follow-up were compared with the rest of the patients. The distribution of categorical variables was compared with the chi-square test or Fisher's exact test (whichever was appropriate). Differences between means were assessed with the Student *t* test or the Mann-Whitney U test. The Kaplan-Meier method was used to obtain survival rates and rates of neoplasia. Comparisons between groups were performed with the log-rank test. The potential influence of a continuous variable on the risk of developing SRM was studied with Cox regression analysis. The primary variable (smoking) and the variables with a *P* value < 0.2 in univariate analysis were included in a Cox regression analysis.

The relative risks of neoplasia and neoplasia-related mortality were obtained through a comparison of the number of observed cases and the number of expected cases. The 95% confidence limits for the relative risks (observed-to-expected ratios) were obtained after a Poisson distribution was assumed for cancer rates and rates of cancer-related mortality.

RESULTS

Characteristics of the Patients

In the studied period, 356 adult patients received their first liver graft at our center. Fourteen patients

TABLE 1. Comparative Features of 26 Liver Transplant Recipients With De Novo SRMs and 313 Patients Without SRMs

Feature	Without SRM	With SRM	P Value
Age (years), mean (standard deviation)	55.56 (9.87)	60.06 (6.60)	0.004
Sex (male/female), %	76/24	96.2/3.8	0.009
Hepatitis C, %	32.6	11.5	0.017
Hepatocellular carcinoma, %	38.3	34.6	> 0.2
Child-Pugh status, %			0.085
A	20.5	11.5	
B	47	34.6	
C	32.6	53.8	
Alcohol abuse, %	37.1	61.5	0.013
Smoking, %			<0.001
Nonsignificant	64.5	7.7	
Previous	17.2	34.6	
Active	18.2	57.7	
Primary immunosuppression, %			>0.2
Cyclosporine	38	34.6	
Tacrolimus	62	65.4	
Treated rejection, %	16.9	3.8	0.08
Number of immunosuppressive drugs at 3 months, %			0.042
1	13.4	30.8	
2	37.7	23.1	
3	48.9	46.3	

NOTE: SRMs included lung, head and neck, esophageal, and kidney and urinary tract carcinomas.

were excluded because they died before the third posttransplant month. In none of them was a malignancy diagnosed before death or at the autopsy. Another 3 patients were excluded from the study because they underwent combined hepatorenal transplantation (2 patients) or had a human immunodeficiency virus infection (1 patient). The general characteristics of the 339 patients included in the study are shown in Table 1. The mean follow-up of the patients was 7.5 years. Patients were followed for a total of 2533 patient-years.

Risk of SRM

Twenty-six patients were diagnosed with 29 SRMs: 9 patients had lung cancer, 8 had head and neck cancer, 3 had esophageal cancer, and 9 had kidney or urinary tract cancer. Their risks are shown in Fig. 1. The 5- and 10-year SRM rates were 5% and 13%, respectively. Data about their stages at diagnosis and outcomes are shown in Table 2.

Evolution After the Diagnosis of SRM

Fifteen (57.7%) of the patients with SRMs had died by the end of follow-up; in 13 cases, their deaths were due to SRMs. The median survival of the patients af-

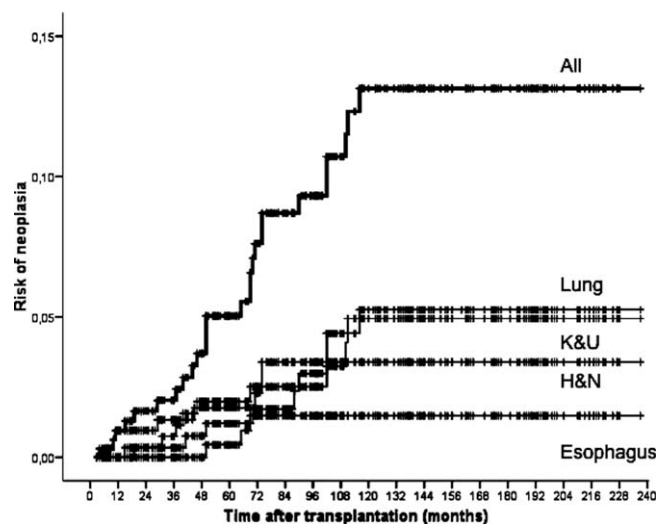


Figure 1. Risk of SRM (lung, head and neck, esophageal, and kidney and urinary tract cancers) in 339 liver transplant recipients.

TABLE 2. Diagnosed SRMs (Including Their Stages) and Patients' Current Status and Survival After the Diagnosis

SRM	Stage at Diagnosis	Current Status and Survival
Lung	I: 5 patients	Alive, 27 and 30 months; dead, 9, 15, and 26 months
	III: 2 patients	Dead, 2 and 14 months
	IV: 2 patients	Dead, 7 and 24 months
Head and neck	I: 2 patients	Alive, 63 and 115 months
	III: 1 patient	Dead, 24 months
	IV: 5 patients	Dead, 2, 3, 9, 11, and 12 months
Esophagus	II: 3 patients	Alive, 123 months; dead, 16 and 32 months
Kidney and urinary tract	0: 4 patients	Alive, 4, 60, and 74 months; dead, 71 months
	I: 3 patients	Alive, 64 and 92 months; dead, 9 months
	II: 1 patient	Alive, 10 months
	IV: 1 patient	Dead, 12 months

NOTE: Twenty-six of 339 patients were diagnosed with SRMs.

ter the diagnosis of SRM was 2 years. The 1-, 2-, and 3-year survival rates after the diagnosis of SRM were 75%, 50%, and 40%, respectively. SRMs were the causes of death for 45% of the patients who died of de

TABLE 3. Observed and Expected Cases of Lung, Head and Neck, Esophageal, and Kidney and Urinary Tract Carcinomas (Excluding Prostate Carcinoma) Among 339 Liver Transplant Recipients Versus a Sex- and Age-Matched General Population

Neoplasia Origin	Observed Cases (n)	Expected Cases (n)	Relative Risk (95% Confidence Interval)
Lung	9	4.142	2.17 (0.99-4.12)
Head and neck	8	2.312	3.46 (1.49-6.82)
Esophagus	3	0.379	7.91 (1.63-23.13)
Kidney and urinary tract	9	2.722	3.31 (1.51-6.28)

TABLE 4. Observed and Expected Cases and Relative Risks of Developing and Dying of SRMs According to Smoking Status Among 339 Liver Transplant Recipients Versus a Sex- and Age-Matched General Population

	Observed Cases (n)	Expected Cases (n)	Relative Risk (95% Confidence Interval)
SRM	29	9.568	3.03 (2.03-4.35)
SRM in nonsignificant smokers	2	5.543	0.36 (0.24-5.57)
SRM in previous smokers	8	1.803	4.44 (1.92-8.74)
SRM in active smokers	19	2.222	8.55 (3.45-15.76)
Mortality due to SRM	13	5.383	2.41 (1.29-4.13)

NOTE: SRMs include lung, head and neck, esophageal, and kidney and urinary tract carcinomas (excluding prostate carcinoma). Smoking terms are defined in the main text.

novo malignancies and for 13.5% of the patients in the global series.

Relative Risk of SRMs

The rates of head and neck, esophageal, and kidney and urinary tract carcinomas were significantly higher in this series of liver transplant recipients versus the general population. The relative risk of lung cancer was greater than 2, but it did not reach significance (Table 3).

TABLE 5. Risk Factors for the Development of Head and Neck, Lung, Esophageal, and Kidney and Urinary Tract Carcinomas in 339 Adult Liver Transplant Recipients

Risk Factor	Hazard Ratio (95% Confidence Interval)	
	Univariate	Multivariate
Tacrolimus-based immunosuppressive drugs (versus cyclosporine)	2.36 (1.03-5.42)	1.00 (0.35-2.89)
Rejection	0.14 (0.02-1.01)	0.30 (0.04-2.39)
Number of immunosuppressive drugs (3 months)	0.67 (0.41-1.11)	0.99 (0.52-1.87)
Alcohol*	2.76 (1.22-5.96)	0.89 (0.36-2.24)
Hepatitis C	0.29 (0.09-0.97)	0.35 (0.09-1.35)
Male sex	9.06 (1.23-66.90)	0.56 (0.06-4.75)
Age (years)	1.07 (1.02-1.12)	1.09 (1.03-1.15)
Significant smoking†	21.90 (5.17-92.73)	19.17 (4.17-88.10)

*The patient's alcohol consumption was greater than 80 g/day for more than 10 years.

†The patient had a past history of smoking greater than 20 pack-years and continued smoking after transplantation or ceased smoking less than 10 years before transplantation.

The cumulative risk of SRM was also significantly higher in the patients versus a sex- and age-matched general population. Nonsignificant smokers did not have an increased risk, but active and previous smokers did have a higher risk (Table 4). Mortality due to SRM was also significantly higher in liver transplant recipients versus the general population.

Risk Factors of SRM

In univariate analysis, alcohol abuse, significant smoking, higher age, male sex, and immunosuppression with tacrolimus were related to a higher risk of developing SRM, and hepatitis C, rejection, and a higher number of immunosuppressive drugs at 3 months were related to a lower risk of SRM (Table 5). In multivariate analysis, only significant smoking and a higher age were independently associated with a higher risk of SRM. Figure 2 shows the risk of SRM in smokers and nonsignificant smokers.

In the smoker group (previous smokers and active smokers), active smoking and older age were the only 2 factors independently related to the diagnosis of SRM (Table 6). Figure 3 shows the risk of developing SRM according to age (≥ 60 years or < 60 years) and

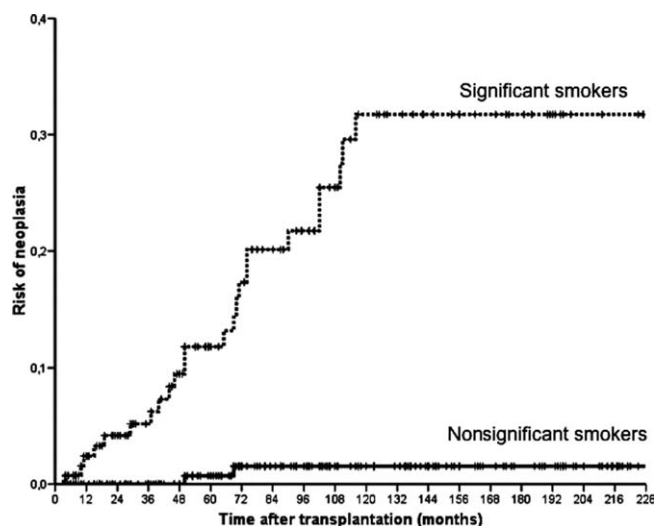


Figure 2. Risk of SRM (lung, head and neck, esophageal, and kidney and urinary tract cancers) in 339 liver transplant recipients according to their smoking status before transplantation.

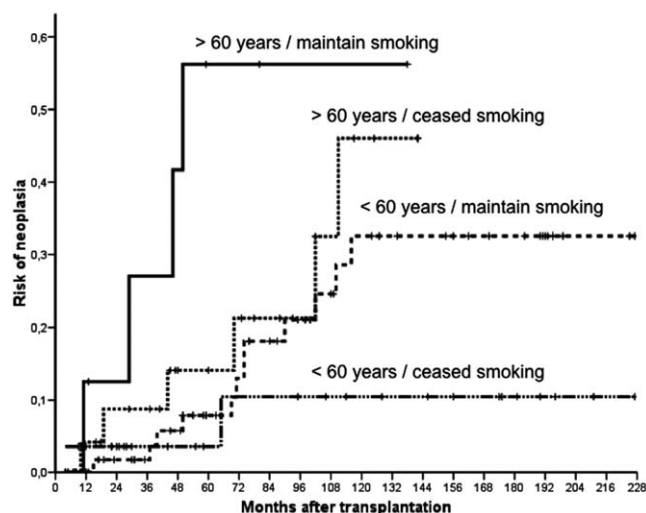


Figure 3. Risk of SRM (lung, head and neck, esophageal, and kidney and urinary tract cancers) in 135 liver transplant recipients who smoked before transplantation according to their age at transplantation (>60 years or <60 years) and their smoking status after transplantation.

TABLE 6. Risk Factors for the Development of Head and Neck, Lung, Esophageal, and Kidney and Urinary Tract Carcinomas in 125 Adult Liver Transplant Recipients With a History of Significant Smoking

Risk Factor	Hazard Ratio (95% Confidence Interval)	
	Univariate	Multivariate
Tacrolimus-based immunosuppressive drugs (versus cyclosporine)	2.66 (1.07-6.63)	1.88 (0.58-6.09)
Rejection	0.22 (0.03-1.66)	0.26 (0.03-2.20)
Number of immunosuppressive drugs (3 months)	0.70 (0.43-1.16)	1.11 (0.55-2.23)
Alcohol*	1.73 (0.76-3.95)	1.05 (0.39-2.83)
Hepatitis C	0.40 (0.12-1.34)	0.48 (0.18-1.99)
Age (years)	1.09 (1.03-1.15)	1.13 (1.05-1.20)
Persistent smoking	1.41 (0.60-3.29)	4.00 (1.42-11.25)

*The patient's alcohol consumption was greater than 80 g/day for more than 10 years.

posttransplant smoking in patients who had smoked before transplantation.

DISCUSSION

The most relevant finding of this study is that liver transplant recipients who quit smoking had a lower rate of SRM than patients who continued to smoke.

This finding could be very important for reinforcing the recommendation of smoking cessation to liver transplant candidates.

Malignancy is one of the most frequent causes of death in liver transplant recipients,^{1,6} and SRMs are some of the most frequent malignancies.^{3-5,7,16-18} In fact, in the present series, SRMs were the cause of death for 13.5% of the deceased patients. Accordingly, the association between posttransplant malignancy and smoking has been previously reported,^{1,3,7,9,12} although other authors have not found a higher risk of neoplasia in smokers.¹⁹

Other complications associated with smoking are increased risks of infection,¹⁹ hepatic artery thrombosis and stenosis,²⁰ and biliary complications.²¹ Furthermore, smoking is also a risk factor for cardiovascular disease,^{19,22} and this is one of the most frequent causes of late mortality after liver transplantation.⁶ With this scenario, if the findings of this article are confirmed in larger series, all liver transplant candidates should be counseled against smoking.

Because smokers have an increased risk of malignancy, they could also benefit from surveillance protocols promoting the early diagnosis of neoplasia at a potentially curable stage. Early experiences with such protocols have shown promising results.^{5,14} The present series is underpowered to evaluate the effect of our surveillance protocols, but a potential benefit could be suggested. Most kidney and urinary tract carcinomas were diagnosed at early stages: 4 at stage 0, 3 at stage I, 1 at stage II, and only 1 at stage IV. Before the initiation of a specific surveillance protocol for head and neck cancer, both patients with this neoplasia were diagnosed at stage IV. Since the initiation of this protocol, 2 patients were diagnosed at stage I, 1 was diagnosed at stage III, and 3 were diagnosed at stage IV. Finally, before 2006, lung cancers were

diagnosed at stages IB (1 patient), III (2 patients), and IV (1 patient). Since 2006, 4 patients were diagnosed at stage IA, and 1 patient was diagnosed at stage IV.

Because immunosuppression is presumably the main risk factor for the increased risk of malignancy in transplant patients, several authors have suggested that a longer duration of immunosuppressive treatment² or stronger immunosuppression could be related to a higher risk of malignancy.^{16,23} In our series, we have not found such an association: in univariate analysis, tacrolimus was associated with a higher risk of malignancy, but this difference was not shown in multivariate analysis. Surprisingly, patients who required antirejection therapy and those who received a higher number of immunosuppressive drugs at 3 months tended to have a lower risk of SRM. This unexpected finding could be due to the association between age and the development of SRM: young patients have a lower risk of malignancy but have a higher risk of rejection,^{24,25} and as a result, they receive stronger immunosuppression. In fact, the only 2 variables that were associated with SRM in this series were age and smoking. This is not surprising because these 2 risk factors have been shown to be related to malignancy both in the general population and in liver transplant recipients.^{1,3,4,7}

The main limitation of the study is that smoking has been considered as a categorical variable. Therefore, it was not possible to evaluate whether the relation between smoking and malignancy in liver transplant recipients has a cumulative dosing effect. A higher cumulative dose of smoking could also explain in part the association between older age and SRM because older patients may have a higher cumulative dose of smoking. Unfortunately, it was not possible to obtain more detailed data about the past history of smoking because this is a retrospective study. Another limitation of the study is the low number of cancer events, which limits the multivariate analysis. Therefore, these findings must be confirmed in larger series or multicenter studies.

In conclusion, smoking withdrawal after liver transplantation may have a protective effect against the development of neoplasia. Because smoking is an important risk factor of malignancy, intervention programs, together with screening programs, may help us to reduce the rate of cancer-related mortality in liver transplant recipients.

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