Incidence of Second Primary Cancer in Transplanted Patients

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Background. Solid organ transplanted patients have a three- to fourfold higher lifetime risk of developing a cancer than the general population. However, the incidence of a second primary cancer in transplanted patients has never been studied, despite the fact that the presence of regular follow-ups and the increased survival of these patients make them a very attractive model.
Methods. We investigated the incidence of a second primary cancer (SPC) in 7,636 patients who underwent a kidney, liver, lung or heart transplant between 1970 and 2004, and were followed-up for 51,819 person-years.
Results. During the follow-up, 499 subjects developed a first cancer (annual incidence: 98.6×10,000 PY), and 22 of them developed a SPC (annual incidence: 3.9×10,000 PY). The annual incidence of a SPC in the transplanted patients who developed a first cancer was 107.8×10,000 PY, giving a standardized incidence ratio of 1.1 (95% CI: 0.83–1.41).
Conclusions. This result shows that the incidence of the SPC was the same as the incidence of a first cancer. Our study does not indicate an increased risk of SPC in transplanted subjects who already suffered a first malignancy.

Keywords: Epidemiology, Cohort study, Solid organ transplant.

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The increasing access to sophisticated tools for early detection of cancer and the improving therapeutic schemes have modified the natural history of several types of cancer, and have largely increased the population size of cancer survivors. These subjects are exposed to the possibility of recurrence, or to the development of a second primary cancer (SPC) (*1–4*); this is a cancer that based on time of occurrence, histological type, and site could be defined as a new event, rather than a metastasis or a recurrence of the first neoplasm. The risk of developing a SPC could be related to the persistence of environmental risk factors associated with the first cancer, and this is particularly evident for tobacco-related cancers (*5–10*). Individual susceptibility to carcinogens as well as other genetic factors could be responsible for the development of a SPC (*11–13*). Furthermore, cancer patient survivors undergo more frequent and accurate screening programs and diagnostic scrutiny than non cancer patients, thus increasing the possibility of a detection bias.

Solid organ transplanted patients have a three- to fourfold higher lifetime risk of developing a cancer than the general population, with several hundred fold higher risks for certain types of virus related cancers, such as Kaposi's sarcoma (KS) and posttransplant lymphoproliferative diseases (PTLD) (*14–16*). At the best of our knowledge, the incidence

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of a SPC in transplanted patients has never been studied, despite the fact that the presence of regular follow-ups and the increased survival of these patients make them a very attractive model.

The aim of the present study was to investigate the incidence of a SPC in a network of Italian cohorts of kidney, liver, lung, and heart transplanted patients.

MATERIALS AND METHODS

The study represents the combination of a cohort collected through the North Italian Transplant program (NITp), and a network of cohorts collected through the Spallanzani Institute.

The design of the NITp cohort has been described elsewhere (*14*). Briefly, all the subjects who underwent a kidney transplant from 1990 to 2004 in 10 transplant centers included in the NITp area (San Raffaele and Policlinico, Milan; San Martino, Genoa; Verona; Padova; Ca' Foncello, Treviso; Santa Maria della Misericordia, Udine; Ospedali Riuniti, Bergamo; Spedali Civili, Brescia; San Bortolo, Vicenza) were recruited.

The second network of cohorts includes anonymous information on 2,755 transplants performed in five transplant centers in Northern or Central Italy, 1,340 of which are kidney transplants performed in the period 1972-2003 at Niguarda Hospital, Milan, 504 kidney transplants performed between 1970 and 2000 at Policlinico Gemelli Hospital, Rome; 702 cardiac transplants performed between 1985 and 2004 at Policlinico S. Matteo, Pavia; 159 liver transplants performed between 1990 and 2000 at Azienda Ospedale Università, Padua; and 50 lung transplants performed between 1991 and 2000 at Niguarda Hospital, Milan.

All patients have signed an informed consent, which included the possibility to be contacted for follow up information. Along with an annual, active follow-up for each transplanted subject, the centers were asked to register all newly diagnosed cancers, identified either during their programmed usual clinical follow-up, or through telephone contact of the patients or their family members. This strategy of active surveillance has been put in place in order to avoid underreporting of cases. Data were entered in an electronic data base furnished by our Institute, which included personal information (age at transplant, sex, blood group, anti-HLA antibodies), transplant's information (date, transplant center, donor data, HLA mismatch, cold ischemic time, length of follow-up) and cancer data (site, type, date of diagnosis). Patients who survived less than 10 days after transplant, patients with a pretransplant history of any cancer, and patients who developed cancer within 30 days from transplant were excluded from this study, according to the protocol applied at the time of the cohort's recruitment (*16*). Both basal cell and squamous carcinomas of the skin were excluded from the data base because of possible underreporting; however, they were included if they appeared as a SPC, since underreporting of a second cancer in subjects who already suffered a first malignancy is an unlikely event. A secondary analysis was performed including skin squamous cell carcinoma in the calculation of the incidence of both first and second primary cancer.

A cancer diagnosed in a subject who already suffered a malignancy after transplant, but was located in a different site from the first cancer and was histologically defined by the physician in charge of the patient as a "nonmetastatic" cancer, was recorded in this study as a SPC.

Each patient included in the cohort was actively followed up from the date of transplant to the date of cancer development, or death, and from the date of cancer development to the date of SPC development or death or study end date, for a total of 51,819 person-years (PY). First and second cancer incidence rates were calculated as the observed number of cases divided by PY at risk in the whole cohort, and according to gender and type of transplant. Standardized Incidence Ratio was calculated as the ratio between the incidence of SPC in subjects who had a first cancer divided by the incidence of the first cancer. 95% Confidence Intervals (CI) were calculated assuming a Poisson distribution.

RESULTS

The whole cohort included 7,636 transplanted patients, 6,725 of which were kidney, 159 were liver, 702 were heart, and 50 were lung transplants. During the follow-up period, 499 subjects were diagnosed with cancer, for an overall annual incidence of 98.6×10,000 PY (95% CI: 90.0–107.2). Differences in cancer incidence rate were observed according to gender: the incidence was 105.2×10,000 PY in males vs. 77.5×10,000 PY in females. Among the 7,636 patients included in this analysis, 22 (0.3%) developed a SPC, with an overall annual incidence of 3.9×10,000 PY (95% CI 2.2–5.6) (Table 1). When the analysis was restricted to transplanted patients who developed a first cancer, the incidence rate of a SPC was 107.8×10,000 PY (95% CI 63.0–152.6), yielding a SIR=1.1 (95% CI: 0.83–1.41).

TABLE 1. Incidence of second primary cancer in transplanted patients and patients who developed a first malignancy after the transplant

			Overall incidence of SPC		Incidence in patients with a first cancer after transplant	
		N	Person-years	Incidence rate×10,000 person-years (95% CI)	Person-years	Incidence rate 10,000 person-years (95% CI)
Total		22	51,819	3.9 (2.2–5.6)	2,041	107.8 (63.0–152.6)
Sex	Male	18	34,987	4.6 (2.3–6.8)	1,503	119.8 (64.8–174.8)[a]
	Female	4	16,833	2.4 (0.1–4.7)	538	74.4 (1.8–147.1)[b]

[a] Standardized incidence ratio=1.1.
[b] Standardized incidence ratio=1.0.

When squamous cell carcinoma of the skin was included in the analysis, the incidence of first cancer was 117.7 ×10,000 PY, while the incidence of SPC in transplanted patients who developed a first cancer was 107.5, yielding a SIR of 0.97.

The details on the first and second cancers in subjects who developed a SPC are reported in Table 2. Among solid tumors, the most frequent combination was kidney followed by skin cancer (n=3), while among lymphoproliferative diseases, two cases of Non Hodgkin Lymphoma (NHL) were followed by KS and kidney cancer; 1 case of Hodgkin Lymphoma (HL) was followed by NHL. Among SPC sites, skin cancer was the most frequent (n=11), followed by liver, and kidney (2 cases each).

The time of occurrence of the first tumor ranged from 33 to 5,585 days (mean 1,943±1,648 days), while the time of occurrence of the SPC after the first cancer ranged from 0 to 3,591 days (mean 778±963 days).

DISCUSSION

We report for the first time the incidence rates of a SPC in a network of cohorts of transplanted patients. Previous work on SPC has focused on samples of cancer patients, in order to analyze the carcinogenic mechanisms behind the development of both the first and the second cancer. For example, smoking related SPC in subjects affected by smoking related cancers (*1*, *5–10*), and SPC of the reproductive organs in subjects with reproductive related cancers have been described (*3*, *11*), as well as skin cancer following melanoma (*4*).

Among the 7,636 patients included in the present cohort, 0.3% of the subjects developed a SPC; when considering only the transplanted individuals who developed a first cancer (n=499) 4.0% of them were diagnosed with a SPC. This figure is comparable to what has been previously published, where the percentage of SPC ranges from 1 to 5% (*1*, *2*, *5*, *6*, *17*). However, such previous studies were restricted to subjects with a specific type of first cancer, while the present study has a cohort design, thus allowing calculation of the overall incidence of a SPC. As far as the type of SPC is concerned, the small number of second primary cases does not allow detecting any specific pattern of occurrence. Although the inclusion of squamous skin cancer may be questionable because of the specific nature of this cancer, we have decided to include it in order to give a global picture of SPC incidence in this population. In order to reach a large enough population to study patterns of occurrence of SPC, pooled analyses of transplanted patient registries would be necessary. This effort would also allow the study of SPC in relation to type of solid organ transplant and type of therapeutic regimen. In fact, a limitation of our study is that the small number of second primaries, along with the fact that immunosuppressive protocols have changed in Italy during the large time frame in which the study was conducted, did not allow the analysis of the association between drug type and dosage and SPC incidence.

The incidence of cancer in transplanted patients is known to be higher than in the general population, due to immunosuppressive treatments and possible viral infections. In the cohort described here, the overall annual incidence of first cancer was 98.6×10,000 PY, corresponding to an increased risk of nearly 2.3 fold compared to that in the general population of the same sex and age (www.registri-tumori.it/incidenza/main.htm). This result is in agreement with previously published data (*14–16*). However, the incidence of

TABLE 2. Description of the subjects who developed a SPC

Subject number	Type of transplant	Type of first cancer	Type of SPC	Time between transplant—first cancer (days)	Time between first cancer—SPC (days)
1	Kidney	Cervix	Breast	2912	931
2	Kidney	Gastric	Liver	5585	0
3	Kidney	Larynx	Lung	4638	2215
4	Heart	NHL	Kidney	4130	1270
5	Kidney	Kaposi's Sarcoma	Nasal mucosa	571	2761
6	Heart	Bladder	Skin—basal cell carcinoma	3892	0
7	Kidney	Kidney	Skin—squamous	4179	50
8	Kidney	Melanoma	Anus	502	3591
9	Liver	Kaposi's Sarcoma	Liver	1167	1077
10	Kidney	Burkitt lymphoma	Skin—squamous	2698	20
11	Kidney	Kidney	Skin—basal cell carcinoma	1937	309
12	Kidney	Kaposi's Sarcoma	Skin—squamous	313	440
13	Kidney	Kidney	Skin—basal cell carcinoma	1175	1180
14	Kidney	Breast	Skin—squamous	2416	960
15	Heart	Colon	Skin—basal cell carcinoma	174	406
16	Kidney	Rectum	Skin—squamous	2038	524
17	Kidney	Hodgkin Lymphoma	NHL	1405	713
18	Kidney	Kaposi's Sarcoma	Skin—squamous	308	171
19	Kidney	NHL	Kaposi's Sarcoma	1214	0
20	Kidney	Kaposi's Sarcoma	Kidney	1297	14
29	Kidney	Prostate	Skin—squamous	33	185
22	Kidney	Colon	Melanoma	312	298

NHL, non-Hodgkin lymphoma.

SPC in the subjects who developed a first cancer was 107.8×10,000 PY, suggesting an incidence comparable to the incidence of the first cancer in the same population (Standardized Incidence Ratio=1.1). This result suggests that transplanted subjects who developed a first cancer do not have a significantly higher risk of developing a second cancer compared to their baseline risk of developing the first cancer, at least in our sample.

In conclusion, our study does not indicate a significant increased risk of SPC in transplanted subjects who already suffered of a first malignancy. Therefore, the clinical indication deriving from this study is that regular screening procedures should be applied to transplanted patients who had cancer, while no special indication to more frequent screenings or screening of specific sites in patients who already suffered a first cancer is suggested by this study.

REFERENCES

1. Duchateau CSJ, Stokkel MPM. Second primary tumors involving non-small cell lung cancer. Prevalence and its influence on survival. *Clinc Invest* 2005; 127: 1152.
2. Aydiner A, Karadeniz A, Uygun K, et al. Multiple primary neoplasms at a single Institution. *Am J Clin Oncol* 2000; 23: 364.
3. Bernstein JL, Lapinki RH, Thakore SS, et al. The descriptive epidemiology of second primary breast cancer. *Epidemiology* 2003; 14: 552.
4. Crocetti E, Carli P. Risk of second primary cancer, other than melanoma, in an Italian population - based cohort of cutaneous malignant melanoma patients. *Europ J Cancer Prev* 2004; 13: 33.
5. Teppo L, Slminen E, Pukkala E. Risk of a new primary cancer among patients with lung cancer of different histological types. *Europ J Cancer* 2001; 37: 613.
6. Levi F, Randimbison L, Te VC, La Vecchia C. Second primary cancers in patients with lung carcinoma. *Cancer* 1999; 86: 186.
7. Bhattacharyya N, Nayak VK. Survival outcomes for second primary head and neck cancer: a matched analysis. *Otolaryn Head Neck Surg* 2005; 132: 63.
8. Franco EL, Kowalski IP, Kanda JL. Risk factors for second cancers of the upper respiratory and digestive systems: a case control study. *J Clin Epidemiol* 1991; 11: 615.
9. Day GL, Blot WJ, Shore RE, et al. Second cancers following oral and pharyngeal cancers: role of tobacco and alcohol. *J Natl Cancer Inst* 1994; 86: 137.
10. Barbone F, Franceschi S, Talamini R, et al. A follow-up study of determinants of second tumor and metastasis among subjects with cancer of the oral cavity, pharynx, and larynx. *J Clin Epidemiol* 1996; 49: 367.
11. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. *Cancer Epidemiol Biomarkers Prev* 1999; 8: 855.
12. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li-Fraumeni syndrome. *J Natl Cancer Inst* 1998; 90: 606.
13. Li FP, Abramson DH, Tarone RE, et al. Hereditary retinoblastoma, lipoma, and second primary cancers. *J Natl Cancer Inst* 1997; 89: 83.
14. Pedotti P, Cardillo M, Rossini G, et al. Incidence of cancer after kidney transplant: results from the North Italy transplant program. *Transplantation* 2003; 76: 1448.
15. Penn I. Tumors after renal and cardiac transplantation. *Hem/Oncol Clin North Am* 1993; 7: 431.
16. Serraino D, Piselli P, Angeletti C, et al. Risk of Kaposi's sarcoma and of other cancers in Italian renal transplant patients. *Br J Cancer* 2005; 92: 572.
17. Kaneko S, Yamaguchi N. Epidemiological analysis of site relationships of synchronous and metachronous multiple primary cancers in the National Cancer Center, Japan, 1962–1996. *Jpn J Clin Oncol* 1999; 29: 96.