CHAPTER 3

P53-specific serum antibodies are not associated with a history of skin carcinoma in renal-transplant recipients and immunocompetent individuals

LETTER TO THE EDITOR

p53-Specific serum antibodies are not associated with a history of skin carcinoma in renal transplant recipients and immunocompetent individuals

KEYWORDS
p53-Specific antibodies; Tumor marker; Skin cancer

Alteration of the p53 tumor suppressor gene is the most frequent genetic event found in human cancers [1]. A recent review reported a correlation between the presence of a p53-specific antibody response and p53 mutations in the tumors [1]. Titers of p53-specific antibodies have shown to be prognostic markers of lowered survival in patients with breast and colorectal cancers and may serve to detect lung cancer in early stages [1].

A high rate of p53 mutations is observed in skin carcinomas: in more than 90% of the squamous cell carcinomas (SCC) and in 75–80% of the precursor lesions, solar keratoses (SK) [2]. Also, in renal transplant recipients a large portion (48%) of the skin carcinomas contains p53 mutations [3].

The relevance of p53-specific antibodies to skin cancer is unclear [4]. To our knowledge, only one study reported on p53-specific antibodies in patients with skin carcinomas. Moch et al. [5] found a low prevalence of p53-specific serum antibodies in 105 immunocompetent patients with nonmelanoma skin cancer. Eight per cent (2/25) of the SCC patients and 1.5% (1/68) of the basal cell carcinoma (BCC) patients showed a p53-specific antibody response [5].

Renal transplant recipients run an increased risk of developing cutaneous SCCs compared to immunocompetent patients [6]. In the general population the ratio BCC over SCC is approximately 5:1, this ratio is reversed in renal transplant recipients [6]. Furthermore, SCCs in renal transplant recipients tend to be more aggressive. Therefore, it is important to detect skin cancer in an early stage in this specific population [6].

To determine whether p53-specific serum antibodies could be a relevant marker for the development of skin carcinomas in renal transplant recipients, we resorted to assess p53-specific antibodies in available archived sera (stored at −80 °C) from a well-documented bank collected from renal transplant recipients and immunocompetent subjects with and without a history of skin carcinoma. Data about age, sex and tumors after transplantation were collected. All renal transplant recipients were treated with prednisone and azathioprine [7]. The medical ethical committee of the LUMC approved the study.

In total, sera from 157 patients of the Leiden University Medical Center (LUMC) were studied: thirty-four renal transplant recipients with a history of one or more skin carcinomas, and 43 without skin carcinoma (collected in 1988) [7]. Among the patients who had a carcinoma, 17 individuals had a history of SCC, 7 of BCC, and 10 patients had a history of both tumors. As controls, sera of 80 immunocompetent individuals were randomly selected from the Leiden Skin Cancer Study [8] (collected in 1998). Among them, 39 individuals had a history of SCC and 41 had no skin cancer. None of the individuals displayed lymph node metastases or were known to have a history of other types of cancer (Table 1).

p53-Specific serum antibodies were detected using a quantitated enzyme-linked immunosorbent assay kit (anti-p53 ELISA, PharmaCell, France). The threshold value for presence of antibodies was set at 1.15 U/ml following the instructions of the manufacturer.

The mean age of the immunocompetent individuals was 61 years, while the mean age of renal transplant recipients was 47 years (p < 0.01; two-tailed Student’s t-test). The mean period after transplantation was 13 years in the individuals with a history of skin carcinoma and 12 years in the skin cancer free group (p = 0.32).

Fig. 1 depicts levels of p53-specific antibodies in the renal transplant recipients and immunocompe-
tent patients. The distributions in these two groups were not discernibly different for SCC only, BCC only, or the combination of SCC and BCC (Table 1). The skin cancer groups were, therefore, combined in the statistical analyses.

In 6.5% (5/77) of the renal transplant recipients and 5.0% (4/80) of the immunocompetent patients p53-specific antibodies were present ($p = 0.69$). Altogether, 8.8% (3/34) of the renal transplant recipients with a history of skin carcinoma and 5.1% (2/39) of the immunocompetent patients with a history of skin carcinoma showed p53-specific antibodies ($p = 0.53$). One renal transplant recipient and one immunocompetent individual without skin cancer showed highly elevated levels of p53-specific antibodies: 16.4 and 18.7 U/ml, respectively. No obvious clinical reasons were found for these elevated serum levels. In the analyses the outliers were excluded, but inclusion of these outliers did not alter the outcome. Statistical analyses of the p53-specific serum antibody levels revealed that there were no significant differences in the mean p53-specific antibody levels between the groups. There were no significant age or sex differences between patients with and without p53-specific antibodies either.

Our results show that renal transplant recipients with a history of skin carcinoma and commonly carrying SK rarely display circulating p53-specific IgG antibodies. Despite the limitations of our study on archival sera sampled at various times after removal of skin carcinomas, we infer that there is no indication that circulating p53 antibodies are a useful prognostic marker of skin carcinoma risk in renal transplant recipients (nor in immunocompetent individuals).

Strikingly, 15% (10/66) of a cohort of Japanese renal transplant recipients not bearing any skin carcinomas were reported sero-positive for p53 [9]. Although we used sera of 157 patients, we did not find any indication of elevated titers of p53 antibodies [9]. Because skin carcinomas are extremely rare in Japanese renal transplant recipients [6], these patients cannot simply be compared with their Caucasian counterparts. Interestingly, the sero-positivity in this group of Japanese patients was only found among those who were treated with cyclosporine ($n = 56$), not in those taking only prednisone ($n = 10$) [9]. Cyclosporine treatment can result in p53 accumulation [10], which may well explain the Japanese results. None of the transplant recipients tested in our study was treated with cyclosporine, because they were transplanted before the cyclosporine era.

Likely explanations of the low humoral immunization against p53 in our study could be the low skin tumor mass and lack of necrosis and inflammation, in contrast to what is usually found in colon cancers.

In sum, we conclude that there is no indication of an elevated humoral response against p53 in people treated for skin carcinoma, irrespective of whether these people were on immunosuppressive medication or not.

### Table 1 Description of the patient groups according to the presence of p53-specific antibodies

<table>
<thead>
<tr>
<th></th>
<th>SCC only</th>
<th>BCC only</th>
<th>Both SCC and BCC</th>
<th>No skin cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of renal transplant recipients</td>
<td>17</td>
<td>7</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>p53 pos (no.)</td>
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<td>2</td>
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<td>2</td>
</tr>
<tr>
<td>p53 neg (no.)</td>
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<td>5</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>No. of immunocompetent patients</td>
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<td>0</td>
<td>11</td>
<td>41</td>
</tr>
<tr>
<td>p53 pos (no.)</td>
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<td>—</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>p53 neg (no.)</td>
<td>27</td>
<td>—</td>
<td>10</td>
<td>39</td>
</tr>
</tbody>
</table>

SCC = squamous cell carcinoma; BCC = basal cell carcinoma.

![Fig. 1 Presence of p53-specific antibodies in the different patient groups. RTR = renal transplant recipients; ICP = immunocompetent patients; the dashed line represents the cut-off value for the presence of antibodies (1.15 U/ml); the small horizontal lines represent the mean value after exclusion of the two outliers.](image)
References


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