

Association of Methylenetetrahydrofolate reductase (MTHFR) polymorphism and the risk of Squamous Cell Carcinoma in renal transplant patients.

Journal:	<i>Transplantation</i>
Manuscript ID:	TPE-2006-0761
Manuscript Type:	Brief Report
Date Submitted by the Author:	26-Jul-2006
Complete List of Authors:	Laing, mary; Beaumont Hospital, Dermatology Dicker, Patrick; Royal College of Surgeons in Ireland, Department of Molecular and Cellular Therapeutics Moloney, Fergal; Beaumont Hospital, Dermatology Murphy, Gillian; Beaumont Hospital, Dermatology Conlon, Peter; Beaumont Hospital, Nephrology Whitehead, Alexander; University of Pennsylvania, Pennsylvania, USA, Department of Pharmacology and Center for Pharmacogenetics Shields, Denis; Conway Institute, University College Dublin, Institute of Biomolecular and Biomedical Research
Classifications:	02.03 Malignancy/tumor/tumour < 02 Complications of Clinical Transplantation, 01.01 Kidney/Renal < 01 Clinical Transplantation (Adult), 01.09 Skin < 01 Clinical Transplantation (Adult), genetic polymorphism, Methylenetetrahydrofolate reductase
Keywords:	renal transplantation, skin cancer, genetic polymorphisms, folate pathway

1
2
3 **Association of Methylenetetrahydrofolate reductase (MTHFR)**
4
5
6 **polymorphism and the risk of Squamous Cell Carcinoma in renal**
7
8
9 **transplant patients.**
10

11
12
13
14
15
16 Mary E Laing¹, Patrick Dicker², Fergal J. Moloney¹, Gillian M. Murphy¹, Peter Conlon³,
17 Alexander S. Whitehead⁴, Denis C. Shields⁵
18

19
20 ¹Department of Dermatology, Beaumont Hospital, Dublin 9.
21

22 ²Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland
23

24
25 ³Department of Nephrology, Beaumont Hospital, Dublin 9.
26

27
28 ⁴Department of Pharmacology and Center for Pharmacogenetics, University of Pennsylvania
29 School of Medicine, Pennsylvania, USA
30

31
32 ⁵UCD Conway Institute of Biomolecular and Biomedical Research, University
33
34 CollegeDublin, Dublin 4, Ireland.
35
36
37
38
39
40

41
42 Address for correspondence: Dr. Mary Elizabeth Laing. Department of
43
44 Dermatology, Beaumont Hospital, Dublin 9, Ireland 00353 87 7989603
45
46 mrylaing@yahoo.co.uk
47

48
49 Key words: renal transplantation, squamous cell carcinoma, genetic polymorphism,
50 Methylenetetrahydrofolate reductase
51

52
53 Word Count - Main Text - 1427
54

55
56 Word Count – Abstract - 139
57
58
59
60

1
2
3 Tables 2, Figures 0
4
5
6
7
8

9
10 This work was supported by PRTLII Cycle III administered by the Higher Education
11 Authority; a “Higher Research Board” Health Services Research Fellowship, and grants
12 from The Irish Nephrology Society and The Punctestown Kidney Research fund.
13
14
15
16

17
18 I declare no conflicts of interest in the course of this work.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abbreviations:

SCC: Squamous Cell Carcinoma

BCC: Basal Cell Carcinoma

MTHFR : Methylene tetrahydrofolate reductase

VDR: Vitamin D receptor

RTR: Renal Transplant Recipients

ABSTRACT

Background: The relative risk of developing cutaneous squamous cell carcinoma (SCC) is significantly increased following organ transplantation.

Objective: We investigated genetic association with SCC in two pathways associated with cancer risks, with potential for modification by vitamin supplementation.

Methods: 401 renal transplant recipients (117 with SCC and 250 without any skin cancer) were genotyped for key polymorphisms in the folate pathway (MTHFR:C677T; methylene tetrahydrofolate reductase), and the vitamin D pathway (VDR: Intron8G/T; vitamin D receptor).

Results: Individuals carrying the MTHFR 677T allele had a marked increase in risk of SCC (adjusted OR= 2.54, p=0.002, after adjustment for age, sex, skin type, sun exposure score and immunosuppression duration; lower 95% confidence boundary OR of 1.41). In contrast, VDR polymorphisms were not significantly associated.

Conclusion: Folate-sensitive pathways may play a critical role in the elevated rate of SCC in renal transplant recipients.

Risk factors for SCC in the general population include UV radiation, fair skintype and mutations in p53 tumour suppressor gene. ¹ The most important of these risk factors is exposure to UV radiation. UV radiation induces local immunodeficiency as a result of a

1
2
3 decrease in the density of epidermal Langerhan cells. Immunosuppressive treatments, such
4
5 as those used in organ transplant recipients also inhibit Langerhan cells. A recent
6
7 population-based study demonstrated the risk for invasive SCC in renal transplant recipients
8
9 (RTR) was increased 82-fold compared with the nontransplanted population.² Increased
10
11 duration of patient survival and older average age at transplant has led to a steady increase
12
13 in the incidence of post transplant squamous cell carcinoma (SCC). The current
14
15 recommendations for the prevention of post-transplant skin cancer focus on reducing the
16
17 cumulative ultraviolet radiation to which the RTR is exposed. The possibility that vitamin
18
19 supplementation might reduce the subsequent risk of SCC has not been investigated.
20
21
22
23
24
25
26

27 The polymorphisms investigated in this study were the common polymorphisms in vitamin
28
29 D receptor (*VDR*), and methylenetetrahydrofolate-reductase (*MTHFR*), Vitamin D has
30
31 potent anti-tumour properties.³ Calcitriol (1,25(OH)2D3), the hormonal derivative of
32
33 vitamin D3, is an antiproliferative and prodifferentiation factor for squamous cells of the
34
35 head and neck³ and in vitro possesses multiple anti-cancer activities.⁴ Folate deficiency is
36
37 associated with genome-wide DNA hypomethylation⁵. Sequence specific alterations of
38
39 DNA methylation in critical cancer-related genes may be involved in folate deficiency
40
41 mediated colorectal carcinogenesis⁶. Long-term folic acid supplementation appears to
42
43 reduce colorectal cancer risk.⁷ The *MTHFR* C677 T polymorphism results in an Alanine to
44
45 valine substitution at codon 222.⁸ Individuals with this polymorphisms have reduced
46
47 enzyme activity.⁹ This polymorphism is associated with major pathologies ranging from
48
49 neural tube defects¹⁰ to cardiovascular diseases.¹¹ *MTHFR* C677T polymorphism is also
50
51 implicated in colorectal cancer, pancreatic cancer endometrial cancer, gastric cancer and
52
53
54
55
56
57
58
59
60

1
2
3 leukaemia^{9,12-16}. To date, there have been no investigations of *MTHFR* C677 T
4
5 polymorphism association and the risk of SCC in transplant or non-transplant patients.
6

7
8 In the gene for *VDR*, the FokI (exon 2 C to T) transition creates a start codon three
9
10 codons upstream of the usual translation start site. The ApaI (G1281T intron 8) variant is in
11
12 close linkage disequilibrium with several other variants in Caucasians, including Bsm I and
13
14 Taq I variants in introns 8 and 9. Thus, G1281T is representative of the major two
15
16 haplotypes. The role of *VDR* polymorphism has been investigated in a number of cancers.
17
18 In a meta-analysis, the TaqI/BsmI variants have been shown to confer little or no risk of
19
20 prostate cancer; nor did the FokI variant make a significant contribution¹⁷; there is,
21
22 however, a suggestion that TaqI/BsmI variation may impact on BCC risk¹⁸, and malignant
23
24 melanoma outcome.¹⁹
25
26
27
28

29
30 In this study, our objective was to determine whether the above *MTHFR* or *VDR*
31
32 polymorphisms modify SCC risk in RTRs.
33

34
35 This study was carried out in Beaumont Hospital, the national renal transplant
36
37 centre in Ireland. All RTR > 16 years old attending the renal and dermatology out patient
38
39 departments were invited to participate in this study which was approved by the Beaumont
40
41 ethics committee.
42

43
44 Each patient was interviewed and examined by one observer (FM). Data was
45
46 collected on age, gender, patient skin type, duration since transplant, duration exposed to
47
48 each immunosuppressive drug, and personal or family history of non-melanoma skin cancer,
49
50 using a standardised questionnaire as previously described.²⁰
51
52

53
54
55 Immunosuppressants used in these patients included Azathioprine, Cyclosporin and
56
57
58
59
60

1
2
3 Mycophenolate Mofetil. No patient was on the folate antagonist Methotrexate.

4
5
6 Genotyping was carried out using the AmplifluorTM method by K Biosciences
7
8 (www.kbioscience.co.uk). Genomic DNA was isolated from a peripheral venous blood
9
10 sample. Genotyping was performed in 384-well microplates using a fluorescence
11
12 resonance energy transfer (FRET)-based genotyping method. Amplification relied on
13
14 allele-specific primers and a common downstream primer.
15
16

17
18
19 The frequency of genotypes *MTHFR* C677T, *MTHFR* 677TT, a *VDR* FokI carrier, and a
20
21 *VDR* ApaI carrier were each considered. The primary comparison was the genotype
22
23 distributions in SCC patients, compared to those in patients with no skin cancer. Logistic
24
25 regression was performed, correcting for the covariates of age, sex, time elapsed since
26
27 transplant, skin type, and sun exposure score. All covariates were dichotomised into binary
28
29 variables (similar results were obtained when the quantitative models were fitted) except
30
31 skin type. The significance threshold adopted, allowing for testing of four genotypic
32
33 hypotheses, was a p-value of 0.0125. Statistical analysis was performed using SAS®
34
35
36
37
38 Version 9.2.

39
40
41 The known risk factors for SCC in an RTR population are strongly overrepresented
42
43 among the RTR presenting with SCC (Table 1). There was however, also a significant
44
45 association of the *MTHFR* 677T variant with SCC (Table 2). The increase in risk estimated
46
47 by the logistic regression analysis is substantial (OR= 2.54, Table 2). Based on the 95%
48
49 confidence interval (Table 2), we can conclude that there is an Odds Ratio (OR) in excess of
50
51 1.41.
52
53

54
55 When *MTHFR* 677T allele carrier status in SCC was compared to the no cancer
56
57 group, without adjustment for other risk factors, we found a weaker association (OR=1.52;
58
59
60

1
2
3 p=0.07). The lowered OR without correction for other risk factors largely reflected the
4 importance of *MTHFR* genotype in the younger patients, fewer of whom have SCC (Table
5 1): 18% of carriers under 50 had SCC, compared to 7% of non-carriers. When those with
6 SCC were compared to those with no SCC (including in the controls those patients with
7 non-SCC skin cancers i.e. BCC, melanoma and Merkel cell carcinoma) there was still an
8 association of SCC with *MTHFR* carrier status (odds ratio= 2.37, p-value=0.0027). Other
9 cancers were less frequent than SCC: we noted no strong genotypic trends (data not shown).
10 The *MTHFR* 677TT genotype showed a similar risk to carrier status (OR=1.59, CI 0.77-
11 3.28).
12
13
14
15
16
17
18
19
20
21
22
23

24 We investigated whether available serum folate measurement was associated with either
25 SCC or genotype. There was no significant association when serum folate was added to the
26 logistic regression model (with low folate was defined as ≤ 2.8 ng/ml, OR=0.672, CI=0.29-
27 1.55). One study has demonstrated that homozygosity for the C677T polymorphism in the
28 *MTHFR* gene significantly increases total homocysteine concentrations and lowers folate
29 levels in kidney graft recipients.²¹ Current studies are underway to evaluate red cell folate in
30 this cohort.
31
32
33
34
35
36
37
38
39
40
41
42

43 We noted no significant association of the VDR genotypes with SCC outcome
44 (FokI: OR=1.14, 95% CI=0.65-2.00; ApaI: OR=1.41, 95% CI=0.77-2.57).
45
46
47
48
49

50 The data presented here indicate that the *MTHFR* 677T variant contributes strongly to risk
51 of SCC in RTR, with the increase in risk most marked among younger patients. While this
52 is a relatively small study, the risk is sufficiently pronounced, with a lower 95% confidence
53 limit of 1.41. Perturbation of DNA methylation patterns occurs in cancer cells and has an
54
55
56
57
58
59
60

1
2
3 important role in tumorigenesis.²² Changes in genomic DNA methylation associated with
4 cancer can be global DNA hypomethylation or and gene specific hyper or hypomethylation.
5
6 Aberrant DNA methylation causes silencing of tumour suppressor genes. The promoters of
7
8 both p14 ARF and p16 tumour suppressor genes encoded by the CDKN2A gene are often
9
10 hypermethylated in SCC. E-cadherin gene, which encodes for E-Cadherin cell adhesion
11
12 molecule which is important in the structural integrity of the epidermis, is one of the genes
13
14 most frequently hypermethylated in SCC^{23 24}. DNA hypomethylation has been
15
16 demonstrated to result in genomic instability and is a feature of melanoma, e.g melanoma
17
18 antigen (MAGE) often hypomethylated in melanoma.²² Therefore aberrant methylation has
19
20 an effect on skin cancer development. The methylation status of SCC in RTR is unknown
21
22 but in those individuals with *MTHFR* polymorphisms, low folate levels may predispose to
23
24 abnormalities in DNA methylation and contribute to skin cancer risk.
25
26
27
28
29
30
31
32
33
34
35

36 The genetic findings detailed in this paper may have implications for the
37
38 management of SCC risk in other clinical conditions. Specifically, patients treated with
39
40 methotrexate may be at increased risk of SCC. Although methotrexate is not one of the
41
42 immunosuppressants used in renal transplant patients it is used extensively in patients with
43
44 psoriasis. This possibility is supported in a study by Paul et al where exposure to
45
46 methotrexate was a significant risk factor for squamous cell carcinoma in patients with
47
48 psoriasis.²⁵ Folic acid supplementation may ameliorate the oncogenic side effects of such
49
50 treatments and may be particularly important in those with risk conferring *MTHFR*
51
52 genotypes. Our hypothesis that the excess risk of SCC in RTR patients associated with
53
54
55
56
57
58
59
60 MTHFR 677T allele carrier status could be reduced or eliminated by folic acid

1
2
3 supplementation requires evaluation in adequately powered prospective studies.
4
5
6
7

8 9 **ACKNOWLEDGEMENTS**

10
11
12 We acknowledge the help of Drs J.Donohoe, J.Walsh, D.Hickey, B.Kneafsey, B.Kirby,
13
14 B.Kehoe, and G.Mellotte for permission to include their patients in the study.
15
16
17
18
19
20
21
22
23
24

25 **REFERENCES**

- 26
27
28
29 1. McGregor KM, Berkhout RJM, Roycka M et al. p53 mutations implicate sunlight in
30
31 post transplant skin cancer irrespective of human papilloma virus status. *Oncogene*
32
33 1997; 15:1737-1740
34
35
36
37
38
39
40 2. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A
41
42 population-based study of skin cancer incidence and prevalence in renal
43
44 transplant recipients. *Br J Dermatol.* 2006 ;154(3):498-504.
45
46
47
48
49
50
51
52 3. Liu Z, Calderon JI, Zhang Z, Sturgis EM, Spitz MR, Wei Q. Polymorphisms of
53
54 vitamin D receptor gene protect against the risk of head and neck cancer.
55
56
57 *Pharmacogenet Genomics.* 2005 Mar;15(3):159-65.
58
59
60

- 1
2
3
4
5
6 4. Luong QT, Koeffler HP. Vitamin D compounds in leukemia. *J Steroid Biochem*
7
8 *Mol Biol.* 2005;97 (1-2):195-202.
9
10
- 11
12 5. Pufulete M, Al-Ghnaniem R, Rennie JA, Appleby P, Harris N, Gout S et al.
13
14 Influence of folate status on genomic DNA methylation in colonic mucosa of
15
16 subjects without colorectal adenoma or cancer. *Br J Cancer.* 2005
17
18 14;92(5):838-42.
19
20
21
- 22
23 6. Kim YI. Folate and DNA Methylation: A Mechanistic Link between folate
24
25 deficiency and colorectal cancer? *Cancer Epidemiology Biomarkers and Prevention*
26
27 2004; 13: 511-519
28
29
30
31
32
33
34
35
36
37
- 38 7. Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA et
39
40 al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. *J Natl*
41
42 *Cancer Inst.* 1993. 2;85(11):875-84.
43
44
45
46
47
48
- 49 8. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG et al. A
50
51 candidate genetic risk factor for vascular disease: a common mutation in
52
53 methylenetetrahydrofolate reductase. *Nat Genet.* 1995 ;10(1):111-3.
54
55
56
57
58
59
60

- 1
2
3 9. Kono S, Chen K. Genetic polymorphisms of methylenetetrahydrofolate reductase
4 and colorectal cancer and adenoma. *Cancer Sci.* 2005;96(9):535-42.
5
6
7
8
9
10 10. De Franchis R, Sebastio G, Mandato C, Andria G, Mastroiacovo P.
11 Spina bifida, 677T-->C mutation, and role of folate.
12 *Lancet.* 1995;346(8991-8992):1703.
13
14
15
16
17
18
19 11. Klerk M, Verhoef P, Clarke R, et al. *JAMA* 2002; 288: 2023-2031
20
21
22
23
24 12. Li D, Ahmed M, Li Y, Jiao L, Chou TH, Wolff RA et al.
25 10-Methylenetetrahydrofolate reductase polymorphisms and the risk of pancreatic
26 cancer. *Cancer Epidemiol Biomarkers Prev.* 2005;14(6):1470-6.
27
28
29
30
31
32
33
34
35
36 13 Esteller M, Garcia A, Martinez-Palones JM, Xercavins J, Reventos J.
37 Germ line polymorphisms in cytochrome-P450 1A1 (C4887 CYP1A1) and
38 methylenetetrahydrofolate reductase (MTHFR) genes and endometrial cancer
39 susceptibility. *Carcinogenesis.* 1997 ;18(12):2307-11.
40
41
42
43
44
45
46
47
48
49
50
51
52
53 14. Graziano F, Kawakami K, Ruzzo A, Watanabe G, Santini D, Pizzagalli F et al.
54 Methylenetetrahydrofolate reductase 677C/T gene polymorphism, gastric cancer
55
56
57
58
59
60

1
2
3 susceptibility and genomic DNA hypomethylation in an at-risk Italian population.

4
5
6 *Int J Cancer*. 2006;1;118(3):628-32

7
8
9
10 15. Robien K, Ulrich CM. 5,10-Methylenetetrahydrofolate reductase polymorphisms
11 and leukemia risk: a HuGE minireview. *Am J Epidemiol*. 2003; 1;157(7):571

12
13
14
15
16
17 16 Skibola CF, Smith MT, Kane E, et al. Polymorphisms in MTHFR gene are
18 associated with susceptibility to acute leukemia in adults. *PNAS* 1999; 96: 22
19
20
21
22 12810-12815

23
24
25
26
27 17. Tais C, Polycarpou A, Ioannidis JP. Vitamin D receptor gene polymorphisms
28 and risk of prostate cancer: a meta- analysis. *Cancer Epidemiol Biomarkers*
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

19 . Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: is this relevant to
malignant melanoma? *Br J Dermatol*. 2002;147(2):197-213.

- 1
2
3
4
5
6
7
8 20. Moloney FJ, Almarzouqi E, O'Kelly P, Conlon P, Murphy GM. Sunscreen use
9
10 before and after transplantation and assessment of risk factors associated with
11
12 skin cancer development in renal transplant recipients. *Arch Dermatol.*
13
14 2005;141(8):978-82.
15
16
17
18
19 21. Fodinger M, Wolfl G, Fischer G et al. Effect of MTHFR 677C>T on plasma total
20
21 homocysteine levels in renal graft recipients. *Kidney Int.* 1999 Mar;55(3):1072-80.
22
23 PMID: 10027946
24
25
26
27
28
29
30
31
32
33 22. Van Doorn R, Gruis NA, Willemze R et al. Aberrant DNA methylation in
34
35 cutaneous malignancies. *Semin Oncol* 2005; 32:479-487
36
37
38
39
40
41
42
43
44
45 23. Chiles MC, Ai L, Zuo C et al: E-cadherin promoter hypermethylation in
46
47 preneoplastic and neoplastic skin lesions. *Mod Pathol* 2003; 16: 1014-1018
48
49
50
51
52 24 Fraga MF, Herranz M , Espada J et al: A mouse skin multistage carcinogenesis
53
54 model reflects the aberrant DNA methylation patterns of human tumours. *Cancer*
55
56 *Res* 2004; 64: 5527-5534
57
58
59
60

- 1
2
3
4
5
6 25. Paul CF, Ho VC, McGeown C, Christophers E, Schmidtman B, Guillaume JC et al.
7
8 Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 year cohort
9
10 study. *J Invest Dermatol.* 2003;120(2):211-6.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 Table 1: Basic Clinical Features of the Study Population Based on SCC status
38
39
40
41
42

		SCC	No skin cancer	Total
Total		117	250	367
Gender	Males	74 (63%)	143 (57%)	217 (59%)
	Females	43 (37%)	107 (43%)	150 (41%)
Age	>50 years	90 (77%)	82 (33%)	172 (47%)
	<= 50 years	27 (23%)	165 (67%)	192 (53%)

Time since transplant	>= 8 years	69 (59%)	97 (46%)	166 (51%)
	<8 years	47 (41%)	115 (54%)	162 (49%)
Skin Type	I	39 (33%)	52 (21%)	91 (25%)
	II	52 (44%)	109 (44%)	161 (44%)
	III	22 (19%)	63 (25%)	85 (23%)
	IV	4 (3%)	20 (8%)	24 (7%)
	V	0	4 (2%)	4 (1%)
Sun Exposure score	> 8	80 (70%)	84 (39%)	164 (50%)
	<= 8	35 (30%)	129 (61%)	164 (50%)
MTHFR_677T	T allele carrier	78 (67%)	142 (57%)	220 (60%)
	Non carrier	39 (33%)	108 (43%)	147 (40%)

Note: Percentages are based on column totals for each covariate, for patients with available data.

Table 2 Risk of Squamous Cell Carcinoma in Renal Transplant Patients

□

Exposure (Factor)	P-value	Odds Ratio ²	Lower 95% CI	Upper 95% CI
Univariate Analysis				
MTHFR_677T carrier	0.0726	1.52	0.96	2.41
Multivariate Analysis				
Male gender	0.9700	0.99	0.55	1.80
Age > 50 years	<.0001	7.47	3.94	14.16
Time since transplant ≥ 8 years	<.0001	3.31	1.84	5.97

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Skin Type	0.0262	1.47	1.05	2.06
Sun Exposure score > 8	0.0069	2.45	1.28	4.70
MTHFR_677T carrier	0.0019	2.54	1.41	4.56

Comparison is between patients with no history of skin cancer (N=250), and those with a diagnosis of SCC (n=117), and full information on covariates.