Arg72Pro Polymorphism of TP53 Gene and the Risk of Skin Cancer: a Meta-Analysis

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Abstract

Background: TP53 gene is one of the most important tumor suppressor genes. We undertook this meta-analysis to explore the association between TP53 Arg72Pro polymorphism and the risk of skin cancer mainly in Caucasians.

Methods: We searched PubMed for case-control studies published up to March 2013. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association.

Results: A total of 5276 skin cancer cases and 5315 controls from 20 studies were included. Overall, no significant association between TP53 Arg72Pro polymorphism and skin cancer was observed in all genetic contrast models (Pro/Pro versus Arg/Arg, Pro/Arg versus Arg/Arg, Pro/Pro + Pro/Arg versus Arg/Arg, Pro/Arg versus Arg/Pro + Pro/Arg, Pro allele versus Arg allele). Similar results were obtained in the stratified analysis by ethnicity and histological types of skin cancer, such as melanoma, squamous cell carcinoma and basal cell carcinoma. Power calculations indicated that some studies were underpowered. No publication bias was found by using the funnel plot and Egger’s test.

Conclusions: This meta-analysis indicated that TP53 Arg72Pro polymorphism probably had little association with skin cancer susceptibility mainly in Caucasians. However, larger sample-size studies are required to verify the conclusion as low statistical powers.

Introduction

According to epidemiology, skin cancer including melanoma and non-melanoma is the most common type of cancer in white populations [1]. Statistics show that the incidence of skin cancer has been increasing in Europe and the USA, especially melanoma, in the past two decades [2,3]. Skin cancer has several histological subtypes, including melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [4]. Many studies indicate that ultraviolet (UV) exposure is a major risk factor of skin cancer development [5-7]. However, on the molecular level, the carcinogenic mechanism of UV has not been expounded yet.

TP53 gene is a tumor suppressor gene which can regulate cell cycle arrest, cell apoptosis and DNA repair [8]. Hence, it is called guardian of genome. Mutations of TP53 gene are the most common genetic abnormality found in many kinds of human cancers, such as lung cancer, colon cancer, gastric cancer, skin cancer, et al [9]. Arg72Pro polymorphism of TP53 gene is a G-C transversion at codon 72, resulting in an amino acid change from arginine (Arg) to proline (Pro) [10]. Studies have shown that TP53 gene plays an important role in the cellular genome protection from UV exposure [11,12]. But the detailed molecular mechanism is unclear.

Many studies in recent years have investigated the association between TP53 Arg72Pro polymorphism and the risk of skin cancer, but their results remain inconclusive. Thus, we performed this meta-analysis of all eligible case–control studies to help us for a better understanding of the influence of TP53 Arg72Pro polymorphism.

Methods

Publication Search

We searched PubMed for publications up to March 2013, using the terms “TP53,” “polymorphism,” and “skin cancer.”
The search was performed without any restrictions on language. Besides, we searched the reference lists of reviews and retrieved articles manually. When the same patient population appeared in several articles, we chose the largest sample size or the most recent one.

**Inclusion Criteria**

The selected studies must have met the following major criteria: (1) well-designed case-control studies to evaluate TP53 Arg72Pro polymorphism and the risk of skin cancer; (2) skin cancer was diagnosed by pathology; (3) containing useful genotype frequencies; and (4) the distribution of genotypes among controls were in Hardy-Weinberg equilibrium.

**Exclusion Criteria**

The exclusion criteria included: (1) the genotype frequencies or number not presented; (2) animal studies, reviews, case reports, abstracts and family-based studies; (3) duplication of a previous publication.

**Data Extraction**

Two investigators extracted information from eligible studies independently, according to the inclusion and exclusion criteria above. Disagreements were resolved by discussion or a third investigator. The following information was collected: first authors, publication year, ethnicity, characteristics of cases and controls (mean age, distribution of gender), histological type of skin cancer, cases, genotyping method, number of genotypes and total number of cases and controls.

In the paper of Rizzato et al the non coding strand has been genotyped, so we inverted the genotypes in his paper.

**Statistical Analysis**

The strength of the association between TP53 Arg72Pro polymorphism and the risk of skin cancer was evaluated by pooled odds ratios (ORs) with 95% confidence intervals (CIs). The pooled ORs for dominant model (Arg/Arg + Pro/Arg versus Pro/Pro), recessive model (Arg/Arg versus Arg/Pro + Pro/Pro), codominant model (Arg/Arg versus Pro/Pro and Arg/Pro versus Pro/Pro) and the allele contrast (Pro allele versus Arg allele) were calculated, respectively. Stratified analyses were performed by ethnicity and histological type of skin cancer. The heterogeneity assumption was assessed by the Chi-square-based Q-test. If P<0.05 of the Q-test which indicated heterogeneity, the random-effects model was used to calculate the pooled ORs. Otherwise, the fixed-effects model was adopted. The Z test was applied to determine the pooled OR with the significance set at P<0.05. Potential publication bias was estimated by Begg’s funnel plot [13] and Egger’s test [14]. P>0.05 meant no significant publication bias. All above statistical analyses were performed with the STATA software, version 12.0 (StataCorp, College Station, TX, USA). Power analysis was performed using the Power and Sample Size Calculation (PS) program (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) [15].

**Results**

**Study Characteristics**

A total of 165 papers were obtained by the publication search published until March 2013, among which twenty met the inclusion criteria [16-35] (Figure S1). The ultimate twenty studies were all in English, involving 5276 skin cancer cases and 5315 controls. The main characteristics were summarized in Table 1.

Most of the studies (16 of 20) were conducted in Caucasians. Of the twenty case-control studies, four only focused on melanoma [24,29-31], five on SCC [17,20,22,34,35] and two on BCC [26,33]. Four studies investigated both SCC and BCC [16,21,27,32]. Two explored melanoma, SCC and BCC [18,25]. Two studies investigated non-melanoma skin cancer, without subtype specified [19,28]. And one explored skin cancer, histological subtype not mentioned [23]. The publication year was from 2000 to 2012. The sample sizes ranged from 43 to 1643. All cases were pathologically confirmed. The controls were healthy populations and matched for age, gender and ethnicity. All polymorphisms in the controls were in Hardy-Weinberg equilibrium.

**Meta-analysis Results**

As shown in Table 2, no significant association between TP53 Arg72Pro polymorphism and the risk of skin cancer was observed in any genetic model and allele contrast (Pro/Pro versus Arg/Arg, odds ratio (OR) =1.07, 95% confidence interval (CI): 0.81-1.41; Pro/Arg versus Arg/Arg, OR=0.93, 95% CI: 0.77-1.13; Pro/Pro + Pro/Arg versus Arg/Arg, OR=0.93, 95% CI: 0.78-1.12; Pro/Pro versus Arg/Arg + Pro/Arg, OR=1.08, 95% CI: 0.86-1.35; Pro allele versus Arg allele, OR=0.96, 95% CI: 0.84-1.10) (Figure 1-5). Power calculations on the pooled frequencies indicated that the statistical powers were all lower than 80% for all the above meta-analyses.

In the stratified analysis by histological types of skin cancer, there was no evidence of a significant association between TP53 Arg72Pro polymorphism and the risk of melanoma, SCC and BCC. Similar results were found in the stratified analysis by ethnicity. Different from other subgroups, power calculations on the SCC gene models were all more than 80%, which revealed adequate sample sizes (Table 2).

**Publication Bias**

The publication bias was assessed by Begg’s funnel plot and Egger’s test. The shape of the funnel plots was seemed symmetrical and the results of Egger’s test were not significant in all the genetic models (Pro/Pro versus Arg/Arg, Arg allele, OR=0.96, Pro allele versus Arg allele), which indicated no publication bias. Figure 6 shows Begg’s funnel plot of overall Pro/Pro versus Arg/Arg. In the stratified analyses by ethnicity and histological types, neither Begg’s funnel plot nor Egger’s test presented any obvious evidence of publication bias (data not shown). These results indicated no publication bias in our meta-analysis.
susceptibility of skin cancer, but their conclusions are non-Caucasian populations are needed to demonstrate our induction of skin cancer by UV radiation [11,12,38]. The most common polymorphism of TP53 gene locates at codon 72, which is a G-C transversion, causing an amino acid change from arginine (Arg) to proline (Pro) [10]. The functions of the two polymorphic variants of TP53 gene are different. According to the study conducted by Dumont et al, the Arg72 variant induces cell apoptosis markedly better than the Pro72 variant does [39]. Recently, many studies have explored the association between TP53 Arg72Pro polymorphism and the susceptibility of skin cancer, but their conclusions are contradictory. Hence, we performed this meta-analysis to further investigate the influence of TP53 Arg72Pro polymorphism on the development of skin cancer.

Discussion

TP53 tumor suppressor gene plays an important role in the cell cycle arrest and activation of programmed cell death [8,36]. Mutations of TP53 gene have been detected in 50% of all human cancers and in almost all skin carcinomas [37]. Studies have proved that inactivation of TP53 gene involves in the induction of skin cancer by UV radiation [11,12,38]. The most common polymorphism of TP53 gene locates at codon 72, which is a G-C transversion, causing an amino acid change from arginine (Arg) to proline (Pro) [10]. The functions of the two polymorphic variants of TP53 gene are different. According to the study conducted by Dumont et al, the Arg72 variant induces cell apoptosis markedly better than the Pro72 variant does [39]. Recently, many studies have explored the association between TP53 Arg72Pro polymorphism and the susceptibility of skin cancer, but their conclusions are contradictory. Hence, we performed this meta-analysis to further investigate the influence of TP53 Arg72Pro polymorphism on the development of skin cancer.

The results suggested that no significant association between TP53 Arg72Pro polymorphism and the risk of skin cancer in any genetic model (Pro/Pro versus Arg/Arg, Pro/Arg versus Arg/Arg, Pro/Pro + Pro/Arg versus Arg/Arg, Pro/Pro versus Arg/Arg + Pro/Arg). In the stratified analysis by ethnicity and histological types of skin cancer, there was no evidence of a significant association, neither. Our results were similar to the meta-analysis conducted by Jiang in 2011 [40].

However, the results of our meta-analysis should be interpreted with caution. Except SCC subgroup, most of the power calculations on the pooled frequencies were lower than 80%, which demonstrated inadequate sample sizes.

This meta-analysis also had some limitations. First, given that only twenty studies were included, publication bias could potentially exit, even though we tried to find as many studies as we could, carefully assessed the literature and used statistical methods to minimize the publication bias, and no statistically significant publication bias was observed in this meta-analysis. Second, in the stratified analyses by ethnicity, most studies were conducted in Caucasians, and information about other ethnicities, such as African, was insufficient. Thus, more studies with larger sample size and high quality, especially for non-Caucasian populations are needed to demonstrate our

Table 1. Characteristics of studies included in the meta-analysis.

| First author | Year | Ethnicity | Country | Cases | Controls |
|---------------|------|-----------|---------|-------|----------|
| Dokianakis    | 2000 | Caucasian | Greece  | 3     | 5        |
| Marshall      | 2000 | Caucasian | England | 3     | 18       |
| Bastiaens     | 2001 | Caucasian | The Netherlands | 21 | 131|
| O’Connor      | 2001 | Caucasian | Ireland | 1    | 11       |
| Cairey-Remmony| 2002 | Caucasian | France  | 4    | 16       |
| McGregor      | 2002 | Caucasian | England | 0    | 58       |
| Gustafsson    | 2004 | Caucasian | Sweden  | 5    | 19       |
| de Oliveira   | 2004 | Other     | Brazil  | 0    | 0        |
| Gwosdz        | 2006 | Caucasian | Germany | 7    | 24       |
| Han           | 2006 | Caucasian | USA     | 55   | 294      |
| Pezeshki      | 2006 | Asian     | Iran    | 10   | 47       |
| Stefanaki     | 2007 | Caucasian | Greece  | 11   | 44       |
| Bendesky      | 2007 | Other     | Mexico  | 25   | 94       |
| Quelle         | 2007 | Caucasian | France  | 2    | 15       |
| Li            | 2008 | Caucasian | USA     | 40   | 300      |
| Capasso       | 2010 | Caucasian | Italy   | 30   | 87       |
| Almquist      | 2011 | Caucasian | USA     | 94   | 551      |
| Rizzato       | 2011 | Caucasian | Hungary, Romania, Slovakia | 40 | 186 |
| Leob          | 2012 | Caucasian | USA     | 4    | 16       |
| Pandish       | 2012 | Asia      | India   | 19   | 62       |
| Melanomas     |      |           |         |      |          |
| Bastiaens     | 2001 | Caucasian | The Netherlands | 7 | 48  |
| Gwosdz        | 2006 | Caucasian | Germany | 7    | 24       |
| Han           | 2006 | Caucasian | USA     | 15   | 82       |
| Stefanaki     | 2007 | Caucasian | Greece  | 11   | 44       |
| Li            | 2008 | Caucasian | USA     | 40   | 300      |
| Capasso       | 2010 | Caucasian | Italy   | 30   | 87       |
| SCC           |      |           |         |      |          |
| Dokianakis    | 2000 | Caucasian | Greece  | 0    | 1        |
| Marshall      | 2000 | Caucasian | England | 2    | 14       |
| Bastiaens     | 2001 | Caucasian | The Netherlands | 6 | 40  |
| Cairey-Romanny| 2002 | Caucasian | France  | 4    | 16       |
| McGregor      | 2002 | Caucasian | England | 0    | 35       |
| Gustafsson    | 2004 | Caucasian | Sweden  | 5    | 19       |
| Han           | 2006 | Caucasian | USA     | 17   | 104      |
| Bendesky      | 2007 | Other     | Mexico  | 3    | 21       |
| Almquist      | 2011 | Caucasian | USA     | 37   | 220      |
| Leob          | 2012 | Caucasian | USA     | 4    | 16       |
| Pandish       | 2012 | Asia      | India   | 19   | 62       |
| BCC           |      |           |         |      |          |
| Dokianakis    | 2000 | Caucasian | Greece  | 3    | 3        |
| Bastiaens     | 2001 | Caucasian | The Netherlands | 8 | 43  |
| McGregor      | 2002 | Caucasian | England | 0    | 23       |

Table 1 (continued).

| First author | Year | Ethnicity | Country | Cases | Controls |
|---------------|------|-----------|---------|-------|----------|
| Han           | 2006 | Caucasian | USA     | 23   | 108      |
| Pezeshki      | 2006 | Asian     | Iran    | 10   | 47       |
| Bendesky      | 2007 | Other     | Mexico  | 22   | 74       |
| Almquist      | 2011 | Caucasian | USA     | 57   | 295      |
| Rizzato       | 2011 | Caucasian | Romania, Slovakia | 40 | 186 |

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conclusions in the future. Finally, the case-control study belongs to retrospective research that has methodological deficiencies. Despite of limitations, this meta-analysis indicated that TP53 Arg72Pro polymorphism probably had little association with the risk of skin cancer mainly in Caucasians. Nevertheless, it is still necessary to conduct larger size and better-designed studies to explore TP53 Arg72Pro polymorphism as low statistical powers.

Table 2. Main results of meta-analysis for TP53 Arg72Pro polymorphism and skin cancer risk.

| Comparative models                  | n   | Case/Control | OR(95%CI) | P<sub>OR</sub> | I² (%) | P<sub>H</sub> | Model | Power calculation |
|-------------------------------------|-----|--------------|-----------|----------------|--------|------------|-------|-------------------|
| Total                               | 20  | 5276/5315    | 0.96(0.84-1.10) | 0.588          | 62.46  | <0.001     | random | 26.0%             |
| Pro allele vs. Arg allele           |     |              | 1.07(0.81-1.41) | 0.654          | 40.9   | 0.002      | random | 20.2%             |
| Pro/Pro vs. Arg/Arg                |     |              | 0.93(0.77-1.13) | 0.468          | 65.85  | <0.001     | random | 41.2%             |
| Pro/Pro+Pro/Arg vs. Arg/Arg        |     |              | 0.93(0.78-1.12) | 0.459          | 69.52  | <0.001     | random | 44.5%             |
| Pro/Pro vs. Arg/Arg+Pro/Arg        |     |              | 1.08(0.86-1.35) | 0.52           | 31.04  | 0.04       | random | 26.9%             |
| Caucasians                         | 16  | 4822/4385    | 0.94(0.81-1.09) | 0.385          | 47.54  | <0.001     | random | 44.4%             |
| Pro allele vs. Arg allele           |     |              | 1.05(0.77-1.43) | 0.768          | 32.41  | 0.006      | random | 11.5%             |
| Pro/Pro vs. Arg/Arg                |     |              | 0.88(0.72-1.06) | 0.177          | 46.99  | <0.001     | random | 81.0%             |
| Pro/Pro+Pro/Arg vs. Arg/Arg        |     |              | 0.88(0.73-1.07) | 0.203          | 50.61  | <0.001     | random | 84.4%             |
| Pro/Pro vs. Arg/Arg+Pro/Arg        |     |              | 1.12(0.86-1.46) | 0.417          | 25.99  | 0.038      | random | 44.5%             |
| Non-Caucasians                     | 4   | 454/930      | 1.06(0.68-1.65) | 0.791          | 77.2   | 0.004      | random | 10.8%             |
| Pro allele vs. Arg allele           |     |              | 1.10(0.52-2.31) | 0.801          | 63.1   | 0.043      | random | 8.8%              |
| Pro/Pro vs. Arg/Arg                |     |              | 1.22(0.61-2.42) | 0.577          | 79.6   | 0.002      | random | 36.5%             |
| Pro/Pro+Pro/Arg vs. Arg/Arg        |     |              | 1.16(0.59-2.26) | 0.671          | 80.5   | 0.001      | random | 24.4%             |
| Pro/Pro vs. Arg/Arg+Pro/Arg        |     |              | 0.95(0.66-1.36) | 0.764          | 37.9   | 0.185      | fixed  | 6.0%              |
| Melanoma                           | 6   | 1522/2433    | 1.10(0.87-1.39) | 0.437          | 75.4   | 0.001      | random | 45.2%             |
| Pro allele vs. Arg allele           |     |              | 1.36(0.82-2.28) | 0.232          | 65.9   | 0.012      | random | 67.1%             |
| Pro/Pro vs. Arg/Arg                |     |              | 1.22(0.61-2.42) | 0.910          | 63     | 0.019      | random | 5.2%              |
| Pro/Pro+Pro/Arg vs. Arg/Arg        |     |              | 1.05(0.79-1.39) | 0.745          | 71.1   | 0.004      | random | 11.6%             |
| Pro/Pro vs. Arg/Arg+Pro/Arg        |     |              | 1.33(0.87-2.03) | 0.191          | 54.4   | 0.052      | fixed  | 62.3%             |
| SCC                                | 11  | 1455/2643    | 0.76(0.55-1.06) | 0.110          | 85.7   | <0.001     | random | 100.0%            |
| Pro allele vs. Arg allele           |     |              | 0.62(0.31-1.25) | 0.182          | 78.2   | <0.001     | random | 98.2%             |
| Pro/Pro vs. Arg/Arg                |     |              | 0.85(0.61-1.19) | 0.340          | 73.8   | <0.001     | random | 80.6%             |
| Pro/Pro+Pro/Arg vs. Arg/Arg        |     |              | 0.75(0.51-1.22) | 0.158          | 83.1   | <0.001     | random | 99.2%             |
| Pro/Pro vs. Arg/Arg+Pro/Arg        |     |              | 0.72(0.42-1.22) | 0.219          | 64.1   | 0.002      | random | 83.2%             |
| BCC                                | 8   | 2159/3179    | 0.90(0.75-1.08) | 0.245          | 66.3   | 0.004      | random | 65.5%             |
| Pro allele vs. Arg allele           |     |              | 1.01(0.81-1.26) | 0.931          | 30.7   | 0.183      | fixed  | 5.1%              |
| Pro/Pro vs. Arg/Arg                |     |              | 0.83(0.64-1.08) | 0.163          | 72.5   | 0.001      | random | 88.1%             |
| Pro/Pro+Pro/Arg vs. Arg/Arg        |     |              | 0.83(0.64-1.07) | 0.140          | 74.1   | <0.001     | random | 79.1%             |
| Pro/Pro vs. Arg/Arg+Pro/Arg        |     |              | 1.03(0.83-1.28) | 0.787          | 22.9   | 0.247      | fixed  | 5.7%              |

Abbreviations: OR, odds ratio; CI, confidence interval; n, number of case-control studies; P<sub>OR</sub>, P value of Z-test; P<sub>H</sub>, P value for heterogeneity analyses; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

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Figure 1. Forest plot of Pro allele versus Arg allele.
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Figure 2. Forest plot of Pro/Pro versus Arg/Arg for all studies.
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Figure 3. Forest plot of Pro/Arg versus Arg/Arg for all studies.
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Figure 4. Forest plot of Pro/Pro+ Pro/Arg versus Arg/Arg for all studies.
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Figure 5. Forest plot of Pro/Pro versus Arg/Arg+ Pro/Arg for all studies.
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Figure 6. Begg's funnel plot of Pro/Pro versus Arg/Arg for all studies (Begg's Test: \( P = 0.284 \), Egger's test: \( P = 0.455 \)).
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Supporting Information

Figure S1. Flow chart of the literature.

Checklist S1. PRISMA checklist.

References

1. Leiter U, Garbe C (2008) Epidemiology of melanoma and nonmelanoma skin cancer—the role of sunlight. Adv Exp Med Biol 624: 89-103. doi:10.1007/978-0-387-77574-6_6. PubMed: 18348450.
2. Gdotar DE (2011) Worldwide increasing incidences of cutaneous malignant melanoma. Skin Cancer, 2011: 2011:858425. PubMed: 22007306.
3. Cancer Research UK website. Available: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/incidence/uk-skin-cancer-incidence-statistics. Assessed 2013 Apr 13
4. Mueller CS, Reichrath J (2008) Histology of melanoma and nonmelanoma skin cancer. Adv Exp Med Biol 624: 215-226. doi: 10.1007/978-0-387-77574-6_17. PubMed: 18348459.
5. Ewoldt JM (1996) Melanoma and sun exposure. Semin Oncol 23(6): 650-666. PubMed: 8970584.
6. Oliveria SA, Saraiya M, Geller AC, Heneghan MK, Jorgensen C (2006) Sun exposure and risk of melanoma. Arch Dis Child 91(2): 131-138. PubMed: 16326797.
7. Young C (2009) Solar ultraviolet radiation and skin cancer. Occup Med (Lond) 59(2): 82-88. doi: 10.1093/occmed/kxp170. PubMed: 19920182.
8. Levine AJ, Finlay CA, Hinds PW (2004) p53 is a tumor suppressor gene. Cell 116:571-585.
9. Greenblatt MS, Bennett WP, Hollstein M, Harris CC (1994) Mutations in p53 gene and pathogenesis of melanoma. Cancer Res 54(18): 4855-4878. PubMed: 7526320.
10. Egerer G, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109): 629-634. PubMed: 7786990.
11. Mattlachewski GJ, Tuck S, Pim D, Lamb P, Schneider J et al. (1987) Primary structure polymorphism at amino acid residue 72 of human p53. Mol Cell Biol 7(2): 961-963. PubMed: 3547088.
12. Benjamin CL, Ananthaswamy HN (2007) p53 and the pathogenesis of skin cancer. Toxicol Appl Pharmacol 224(3): 241-248. doi:10.1016/j.taap.2006.12.006. PubMed: 17270229.
13. Benjamin CL, Melnikova VO, Ananthaswamy HN (2008) p53 protein and pathogenesis of melanoma and nonmelanoma skin cancer. Adv Exp Med Biol 624: 265-282. doi:10.1007/978-0-387-77574-6_21. PubMed: 18348463.
14. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4): 1088-1101. doi: 10.2307/2533446. PubMed: 7786990.
15. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(709): 629-634. doi:10.1136/bmj.315.709.629. PubMed: 9310563.
16. Dudt WP, Plummer WD Jr. (1998) Power and sample size calculations for studies involving linear regression. Control Clin Trials 19: 589-601. doi:10.1016/S0197-2456(98)00037-3. PubMed: 9875838.
17. Dokianakis DN, Koumantaki E, Billiri K, Spandidos DA (2000) P53 codon 72 polymorphism, sunburns, and risk of non-melanoma skin cancer. J Invest Dermatol 118(1): 577-582. doi:10.1002/jid.21366. PubMed: 18046622.
18. Han J, Cox DG, Colditz GA, Hunter DJ (2006) The p53 codon 72 polymorphism and susceptibility to skin cancer in US Caucasian women. Mol Carcinog 45(6): 694-700. doi:10.1002/mc.20190. PubMed: 16739124.
19. Pezeshki A, Sari-Aslani F, Ghaderi A, Doroudchi M (2006) p53 codon 72 polymorphism in basal cell carcinoma of the skin. Pathol Oncol Res 12(1): 29-33. doi:10.1007/BF02893428. PubMed: 16554913.
20. Benkeser AD, Rosealla S, Salazar AM, Sordo M, Peniche J et al. (2007) p53 codon 72 polymorphism, DNA damage and repair, and risk of non-melanoma skin cancer. Mutat Res 619(1-2): 38-44. doi:10.1016/j.mrmm.2007.01.001. PubMed: 17403527.
21. Queille S, Luron L, Spatz A, Avril MF, Ribrag V et al. (2007) Analysis of skin cancer risk factors in immunosuppressed renal transplant patients shows high levels of UV-specific tandem CC to TT mutations of the p53 gene. Carcinogenesis 28(3): 724-731. PubMed: 17065198.
22. Stefanaki I, Stragias AJ, Dimisianos G, Nikolou V, Papadopoulou O et al. (2007) p53 codon 72 Pro homozygosity increases the risk of cutaneous melanoma in individuals with dark skin complexion and among noncarriers of melanocortin 1 receptor hair variant. Br J Dermatol 156(2): 357-362. doi:10.1111/j.1365-2133.2006.07645.x. PubMed: 17223878.
23. Li C, Chen K, Liu Z, Wang LE, Gershensonwald JE et al. (2008) Polymorphisms of TP53 Arg72Pro, but not p73 G4C14A4TA4 and p21 Ser31Arg, contribute to risk of cutaneous melanoma. J Invest Dermatol 128(6): 1585-1588. doi:10.1016/j.jid.2007.11.006. PubMed: 18043450.
24. Capasso M, Ayala F, Rivarola RA, Russo R, Gambale A et al. (2010) MDM2 SNP309 and p53 Arg72Pro in cutaneous melanoma: association between SNP309 GG genotype and tumor Breslow thickness. J Hum Genet 55(8): 518-524. doi:10.1038/jhg.2010.62. PubMed: 20535124.
25. Almouisti LM, Karagas MR, Christensen BC, Welsh MM, Perry AE et al. (2011) The role of TP53 and MDM2 polymorphisms in TP53 mutagenesis and risk of non-melanoma skin cancer. Carcinogenesis 32(3): 327-330. doi:10.1093/carcin/bgr256. PubMed: 21123835.
26. Rizzotto C, Scherer D, Rudnai P, Gurzaui E, Koppova K et al. (2011) POMC and TP53 genetic variability and risk of basal cell carcinoma of skin: Interaction between host and genetic factors. J Dermatol Sci 63(1): 47-54. doi:10.1016/j.jdermsci.2011.03.006. PubMed: 21536413.
27. Loeb KR, Asgari MM, Hawes SE, Feng Q, Stern JE et al. (2012) Analysis of TP53 codon 72 polymorphisms, TP53 mutations, and HPV infection in cutaneous squamous cell carcinomas. PLOS ONE 7(4): e34422. doi:10.1371/journal.pone.0034422. PubMed: 22545084.
28. Pandith AA, Khan NP, Rashid N, Azad N, Zaroo I et al. (2012) Impact of codon 72 Arg > Pro single nucleotide polymorphism in TP53 gene in the risk of kangi cancer: a case control study in Kashmir. Tumour Biol 33(4): 927-933. doi:10.1007/s13277-012-0315-2. PubMed: 22249977.
36. Hartwell LH, Weinert TA (1989) Checkpoints: controls that ensure the order of cell cycle events. Science 246(4930): 629-634. doi: 10.1126/science.2683079. PubMed: 2683079.

37. Bassett-Séguin N, Moles JP, Mils V, Dereure O, Guilhou JJ (1994) TP53 tumor suppressor gene and skin carcinogenesis. J Invest Dermatol 103(5 Suppl): 102S-106S. doi: 10.1038/jid.1994.18. PubMed: 7963669.

38. Benjamin CL, Ananthaswamy HN (2007) p53 and the pathogenesis of skin cancer. Toxicol Appl Pharmacol 224(3): 241-248. doi: 10.1016/j.taap.2006.12.006. PubMed: 17270229.

39. Dumont P, Leu JI, Della Pietra AC 3rd, George DL, Murphy M (2003) The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet 33(3): 357-365. doi: 10.1038/ng1093. PubMed: 12567188.

40. Jiang DK, Wang WZ, Ren WH, Yao L, Peng B et al. (2011) TP53 Arg72Pro polymorphism and skin cancer risk: a meta-analysis. J Invest Dermatol 131(1): 220-228. doi: 10.1038/jid.2010.270. PubMed: 20861852.