Association between the STK15 F31I Polymorphism and Cancer Susceptibility: A Meta-Analysis Involving 43,626 Subjects

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Abstract

The association between the Serine/threonine kinase 15 (STK15) F31I polymorphism (rs2273535) and cancer susceptibility remains controversial. To further investigate this potential relationship, we conducted a comprehensive meta-analysis of 27 published studies involving a total of 19,267 multiple cancer cases and 24,359 controls. Our results indicate statistical evidence of an association between the STK15 F31I polymorphism and the increased risk of overall cancer in four genetic models: AA vs. TA+TT, AA vs. TT, AA vs. TA, and A vs. T. In a stratified analysis by cancer type, there was an increased risk of breast cancer in four genetic models: AA vs. TA+TT, AA vs. TT, AA vs. TA, and A vs. T, as well as esophageal cancer in two genetic models: AA vs. TA+TT and AA vs. TA. In a stratified analysis by ethnicity, there was a significant increase in cancer risk among Asians, but not Caucasians, in four genetic models: AA vs. TA+TT, AA vs. TT, AA vs. TA and A vs. T. In addition, a stratified analysis by ethnicity in the breast cancer subgroup revealed a significant increase in cancer risk among Asians in two genetic models: AA vs. TA+TT and AA vs. TT, as well as among Caucasians in one genetic model: AA vs. TA. In summary, this meta-analysis demonstrates that the STK15 F31I polymorphism may be a risk factor for cancer.

Introduction

Cancer is a complex disease that results from interactions between multiple genetic and environmental factors [1-3]. A characteristic of cancer is genetic instability, which can be caused by transgenation and acquired aneuploidy [4]. Genetic instability mostly occurs at the chromosomal level, including losses and gains of whole or large portions of chromosomes [5]. Chromosomal segregation is accomplished by the mitotic spindle, which links whole chromosomes to opposite poles of the cell, and segregates the duplicated DNA equally into two daughter cells [6]. In mammalian cells, centrosomes are the major microtubule organizing centers (MTOC) and play a vital role in symmetrical mitotic spindle formation and mitosis. Serine/threonine kinase 15 (STK15), a centrosome-localized serine/threonine kinase, acts as a critical regulator of mitotic centrosome maturation and spindle assembly. It has a particular role in G2 to M phase, primarily through its phosphorylation functions, and plays an important role in the development and progression of cancer malignancy [7].

A non-synonymous single nucleotide polymorphism (SNP) of STK15, the F31I polymorphism (rs2273535), has been identified in the coding region of STK15. The STK15 F31I polymorphism (91 T→A), a SNP in exon 3 of STK15, encodes a phenylalanine→isoleucine substitution at amino acid residue 31 (F31I) [8]. In recent years, the F31I polymorphism has been intensely investigated for its association with the risk of multiple cancers. Many studies have indicated that the STK15 F31I polymorphism is a general low penetrance susceptibility gene in a number of cancers, particularly breast, colorectal, and esophageal cancer [9-11]. However, results from these studies remain inconsistent, perhaps due to small sample size limitations, ethnic diversity in allele frequencies, and publication bias. Therefore, to confirm the role of the STK15 F31I polymorphism in tumorigenesis, we conducted a comprehensive meta-analysis on eligible case-control studies.
published to date. To the best of our knowledge, this is the most comprehensive meta-analysis regarding the STK15 F31I polymorphism and its association with cancer risk.

Materials and Methods

This meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Table S1, PRISMA checklist) [12].

Search Strategy

Genetic association articles published on cancer and the STK15 F31I polymorphism, up to May 29, 2013, were investigated by searching PubMed, EMBASE, CBM (Chinese BioMedical Disc) and CNKI (Chinese National Knowledge Infrastructure) with combinations of the following terms: "stk15", "Aurora-A", "BTAK", "AIKI", "polymorphism", "SNP", "mutation", "carcinoma", "cancer", "neoplasm", and "malignance". In addition, the publication language was restricted to English and Chinese. All bibliographies listed in these studies and published reviews were checked for original and relevant studies.

Inclusion and Exclusion Criteria

Eligible studies had to meet the following criteria: 1) evaluated the STK15 F31I polymorphism and cancer risk, 2) designed as a case-control study, 3) provided data on genotype or allele frequency in case groups and control groups, 4) provided the genotyping method and ethnicity, and 5) control genotype distributions consistent with Hardy-Weinberg equilibrium (HWE). Exclusion criteria included the following: 1) overlapping data, 2) not case-control studies, and 3) review publication.

Data Extraction

Information from all eligible publications was carefully and independently extracted through three reviewers (W. Tang, H. Qiu, and H. Ding). In case of conflicting evaluations, differences were resolved by further discussion among all reviewers. For each included study the following data was extracted: first author, cancer type, year of publication, country, ethnicity of study subjects, number of cases and controls, genotype method, allele and genotype frequency, and HWE in controls.

Statistical Analysis

Deviation from the HWE among the controls was evaluated for each single study using an internet-based HWE calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The crude odds ratio (OR) with the corresponding 95% confidence intervals (95% CI) was used to measure the strength of the association between the STK15 F31I polymorphism and cancer risk. The significance of the pooled OR was assessed using the Z-test and P-value (two-tailed), and P<0.05 was considered statistically significant. In our study, a Chi-square-based I² test was used to check potential heterogeneity among studies; I²<25% indicated low heterogeneity, 25%≤I²≤50% indicated moderate heterogeneity, and I²>50% indicated large heterogeneity [13]. The heterogeneity was considered statistically significant if I²>50% or P<0.10. If heterogeneity existed, the pooled ORs were calculated according to the random-effects model (the DerSimonian–Laird method) or the fixed-effects model was used (the Mantel–Haenszel method). Subgroup analyses were conducted according to ethnicity and cancer type to measure ethnicity-specific and cancer type-specific effects (any cancer type evaluated by less than three individual case-control studies was combined into "other cancers"). Sensitivity analysis was also carried out to determine whether any excluded studies affected the stability of our results. Galbraith radial plot and further stratified analyses were used to analyze the source the heterogeneity. In our studies, the funnel plot and Egger's test were used to assess potential publication bias, which was measured by visual inspection of an asymmetric plot. In addition, for the interpretation of Egger's test, statistical significance was defined as P<0.05. Statistical analyses were performed using STATA (v12.0) statistical software.

Results

Characteristics

After an initial search, a total of 151 published articles relevant to the topic were identified from databases (PubMed, Embase, CBM and CNKI). With additional filters, 120 of these articles were excluded (26 for duplication of titles, 10 for not being case-control studies, five for an association with cancer treatment, 72 for irrelevance to gene polymorphisms and cancer, six reviews and one case-control study for overlapping data). After this step, 31 qualified and original papers fit the inclusion criteria. After a manual search of the bibliography lists from retrieved articles, another two articles were included (Figure 1). Afterwards, six case-control studies were excluded because the number of genotypes in the control group statistically deviated from HWE. Overall, 27 total case-control studies on the association between the STK15 F31I polymorphism and cancer risk were recruited in this meta-analysis. Among the 27 case-control studies, ten investigated breast cancer [8,9,14-21], four investigated colorectal cancer [10,22-24], and three investigated esophageal cancer [11,25,26]. The other studies investigated gastric cancer, lung cancer, renal cell carcinoma, bladder cancer, glioblastoma, hepatocellular carcinoma, and ovarian cancer [27-36]. As for subjects in these studies, 11 were Asian [9,11,19-21,23,25-29] and 16 were Caucasian [8,10,14-18,22,24,30-36]. Characteristics of populations and cancer types in each individual study recruited in the meta-analysis are listed in Table 1. The distribution of the STK15 F31I polymorphism and allele among patients and controls is listed in Table 2. Results of the meta-analysis from different comparative genetic models are summarized in Table 3, Table 4, and Table 5.

Quantitative Synthesis

In total, 19,267 multiple cancer cases and 24,359 controls from 27 eligible and original case–control studies were recruited for meta-analysis of the association between the
STK15 F31I polymorphism and cancer risk. Divided by ethnicity, 11 case-control studies were focused on Asian subjects and 16 case-control studies focused on Caucasian subjects. After combining all qualified studies, there was statistical evidence of an association between the STK15 F31I polymorphism and increased overall cancer risk in four genetic models: AA vs. TA+TT (OR, 1.18; 95% CI, 1.06–1.31; P=0.002), AA vs. TT (OR, 1.16; 95% CI, 1.01–1.32; P=0.035), AA vs. TA (OR, 1.18; 95% CI, 1.06–1.30; P=0.001), and A vs. T (OR, 1.08; 95% CI, 1.01–1.14; P=0.015) (Table 3, Figure 2). In a stratified analysis by cancer type, there was an increased risk of breast cancer in four genetic models: AA vs. TA+TT (OR, 1.20; 95% CI, 1.05–1.37; P=0.007), AA vs. TT (OR, 1.22; 95% CI, 1.10–1.35; P=0.000), AA vs. TA (OR, 1.19; 95% CI, 1.04–1.36; P=0.011), and A vs. T (OR, 1.08; 95% CI, 1.01–1.15; P=0.017) and of esophageal cancer in two genetic model: AA vs. TA+TT (OR, 1.28; 95% CI, 1.08–1.53; P=0.005) and AA vs. TA (OR, 1.32; 95% CI, 1.10–1.58; P=0.003) (Table 4). In a stratified analysis by ethnicity, significant increases in cancer risk were observed for Asians, but not Caucasians, for four genetic models: AA vs. TA+TT (OR, 1.27; 95% CI, 1.10–1.47; P=0.001), AA vs. TT (OR, 1.26; 95% CI, 1.01–1.56; P=0.039), AA vs. TA (OR, 1.28; 95% CI, 1.12–1.47; P=0.000) and A vs. T (OR, 1.14; 95% CI, 1.02–1.28; P=0.023) (Table 3). In addition, in a stratified analysis by ethnicity in the breast cancer subgroup, significant increases in cancer risk were observed among Asians for two genetic models: AA vs. TA+TT (OR, 1.23; 95% CI, 1.00–1.50; P=0.049) and AA vs. TT (OR, 1.21;
Tests for Publication Bias, Sensitivity Analyses, and Heterogeneity

In this meta-analysis, Begg’s Funnel plot and Egger’s test were both conducted to assess publication bias (Figure 3). The shape of funnel plot showed the evidence of funnel plot symmetry in all the genetic model. The results indicated that there were no publication bias for overall cancer in current meta-analysis (A vs. T; Begg’s test P=0.802, Egger’s test P=0.553; AA vs. TT; Begg’s test P=1.000, Egger’s test P=0.938; TA vs. TT; Begg’s test P=0.532, Egger’s test P=0.509; AA+TA vs. TT; Begg’s test P=0.900, Egger’s test P=0.856; AA vs. TT+TA; Begg’s test P=0.739, Egger’s test P=0.784; AA vs. TA; Begg’s test P=0.802, Egger’s test P=0.585).

Sensitivity analyses were conducted to evaluate the influence of each individual dataset on the pooled OR by deleting each particular dataset dropped at a time. The statistical significances of the overall results did not alter when any individual study was omitted, confirming the stability of the results (Figure 4). Trim and fill method was also used to perform sensitivity analyses. The findings showed the results of this meta-analysis were reliable (Figure 5).

The results showed there were large heterogeneities among the studies enrolled. Because tumor origin and ethnicity can influence the results from meta-analyses, we performed subgroup analyses by cancer type and ethnicity (Table 3 and Table 4). The results indicated that esophageal cancer, colorectal cancer, Asian population subgroup may contribute to the heterogeneity. As shown in Table 3, heterogeneity was significant in allele comparison. Galbraith radial plot also was used to analyze the heterogeneity in allele comparison (Figure 6). The results identified eight outliers which might contribute to the major sources of heterogeneity. Further stratified meta-analysis suggested an association of studies published after 2006, conducted in Chinese population and small sample size design (≤1000 subjects) with more prominent heterogeneity (data not shown).

Table 1. Characteristics of populations and cancer types of the individual studies included in the meta-analysis.

| Study          | Year | Ethnicity | Country    | Cancer type       | Sample size (case/control) | Genotype method |
|----------------|------|-----------|------------|-------------------|----------------------------|-----------------|
| Sang et al.    | 2012 | Asians    | China      | esophageal cancer | 380/380                    | MALDI-TOF MS    |
| Ruan et al.    | 2011 | Asians    | China      | breast cancer     | 1334/1568                  | TaqMan          |
| Navaratne et al.| 2010 | Caucasians| USA        | glioblastoma      | 96/93                      | PCR-RFLP        |
| Akkiz et al.   | 2010 | Caucasians| Turkey     | hepatocellular carcinoma | 128/128                   | PCR-RFLP        |
| Song et al.    | 2010 | Asians    | China      | bladder cancer    | 60/60                      | PCR-RFLP        |
| Chen et al.    | 2009 | Asians    | China      | esophageal cancer | 188/324                    | PCR-RFLP        |
| MARIE-GENICA   | 2009 | Caucasians| German     | breast cancer     | 3136/5466                  | MALDI-TOF MS    |
| Ricketts et al. | 2009 | Caucasians| Polish     | renal cell carcinoma | 328/311                    | MLPA            |
| Dogan et al.   | 2008 | Caucasians| Turkey     | lung cancer       | 102/102                    | Direct sequencing|
| Chen et al.    | 2007 | Caucasians| USA        | colorectal cancer | 60/65                      | Direct sequencing|
| Wang et al.    | 2007 | Caucasians| USA        | lung cancer       | 1518/1518                  | TaqMan          |
| Vidarsdottir et al. | 2007 | Caucasians| Iceland     | breast cancer     | 759/653                    | TaqMan          |
| Tchatchou et al.| 2007 | Caucasians| German     | breast cancer     | 727/819                    | TaqMan          |
| Hammerschmied et al. | 2007 | Caucasians| USA         | colorectal cancer | 2556/2680                  | IlluminaseXentric bead array |
| Webb et al.    | 2006 | Caucasians| UK         | colorectal cancer | 507/875                    | PCR-RFLP        |
| Fletcher et al. | 2006 | Caucasians| UK         | breast cancer     | 235/283/283                | PCR-RFLP        |
| Zhang et al.   | 2006 | Asians    | China      | colorectal cancer | 1259/1742                  | TaqMan          |
| Ju et al.      | 2006 | Asians    | Korea      | gastric cancer    | 501/427                    | MALDI-TOF MS    |
| Chen et al.    | 2005 | Asians    | China      | gastric cancer    | 68/75                      | PCR-RFLP        |
| Hienonen et al.| 2005 | Caucasians| Finland    | colorectal cancer | 235/94                     | Direct sequencing|
| Lo et al.      | 2005 | Asians    | China(Taiwan) | breast cancer   | 709/1972                   | TaqMan          |
| DiCioceci et al.| 2004 | Caucasians| UK,Denmark| ovarian Cancer    | 1821/2467                  | TaqMan          |
| Sun et al.     | 2004 | Asians    | China      | breast cancer     | 520/520                    | PCR-RFLP        |
| Egan et al.    | 2004 | Caucasians| USA        | breast cancer     | 940/830                    | Direct sequencing|
| Mao et al.     | 2004 | Asians    | China      | esophageal cancer | 656/656                    | PCR-RFLP        |
| Dai et al.     | 2004 | Asians    | China      | breast cancer     | 1193/1310                  | TaqMan          |

MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry
PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism
MLPA: Multiplex Ligation Dependent Probe Amplification
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conducted a comprehensive meta-analysis to assess the development and progression to the amplification and risk. In a stratified analysis by ethnicity, the association of STK15 polymorphisms (AA vs. TA+TT, AA vs. TT, AA vs. TA, and A vs. T) significantly increased overall cancer risk. In a stratified analysis by cancer type, STK15 F31I polymorphisms (AA vs. TA+TT, AA vs. TT, AA vs. TA, and A vs. T) were also associated with a significant increase in breast cancer risk and esophageal cancer (AA vs. TA+TT and AA vs. TA). In a stratified analysis by ethnicity, the association of STK15 F31I polymorphisms was significant in Asians but not Caucasians.

**Table 2. Distribution of stk15 F31I polymorphisms genotype and allele among multiple cancer patients and controls.**

| Case          | Control          | Case          | Control          |
|---------------|------------------|---------------|------------------|
|               | AA   | TA   | TT   | AA   | TA   | TT   | A   | T   | A   | T   |
| Sang et al.   | 46   | 161  | 173  | 39   | 188  | 153  | 253 | 507 | 266 | 494 |
| Ruan et al.   | 167  | 568  | 599  | 161  | 691  | 716  | 902 | 1766| 1013| 2123|
| Navarath et al.| 4    | 33   | 59   | 6    | 33   | 54   | 41  | 151 | 45  | 141 |
| Aköz et al.   | 4    | 47   | 77   | 2    | 27   | 99   | 55  | 201 | 31  | 225 |
| Song et al.   | 33   | 15   | 12   | 18   | 25   | 17   | 81  | 39  | 61  | 59  |
| Chen et al.   | 66   | 79   | 43   | 118  | 168  | 38   | 211 | 165 | 404 | 244 |
| MARIE-GENICA  | 167  | 1096 | 1673 | 249  | 1927 | 3290 | 1430| 4842| 2425| 8507|
| Rickets et al.| 207  | 105  | 16   | 171  | 122  | 18   | 519 | 137 | 464 | 158 |
| Dogan et al.  | 6    | 38   | 58   | 3    | 40   | 59   | 50  | 154 | 46  | 158 |
| Chen et al.   | 3    | 13   | 44   | 6    | 21   | 38   | 19  | 101 | 33  | 97  |
| Wang et al.   | 36   | 373  | 692  | 51   | 320  | 594  | 445 | 1757| 422 | 1508|
| Vidarsdottir et al. | 42  | 288  | 429  | 21   | 231  | 401  | 372 | 1146| 273 | 1033|
| Tchatchou et al. | 433 | 257  | 37   | 485  | 287  | 47   | 1123| 331 | 1257| 381 |
| Hammerschmed et al. | 7  | 57   | 92   | 12   | 65   | 81   | 71  | 241 | 89  | 227 |
| Webb et al.   | 114  | 880  | 1564 | 125  | 888  | 1667 | 1108| 4008| 1138| 4222|
| Fletcher et al.| 18   | 154  | 335  | 48   | 280  | 547  | 190 | 824 | 376 | 1374|
| Zhang et al.  | 142  | 111  | 30   | 104  | 137  | 42   | 395 | 171 | 345 | 221 |
| Cox. et al.   | 66   | 401  | 774  | 65   | 571  | 1075 | 533 | 1949| 701 | 2721|
| Ju et al.     | 211  | 215  | 75   | 179  | 190  | 58   | 637 | 365 | 548 | 306 |
| Chen et al.   | 36   | 27   | 5    | 33   | 32   | 10   | 99  | 37  | 98  | 52  |
| Hienonen et al.| 19   | 94   | 122  | 5    | 43   | 46   | 132 | 338 | 53  | 135 |
| Lo et al.     | 348  | 288  | 71   | 866  | 887  | 196  | 984 | 430 | 2659| 1279|
| Dicioccio et al. | 71  | 502  | 821  | 99   | 649  | 1213 | 644 | 2144| 847 | 3075|
| Sun et al.    | 256  | 214  | 50   | 192  | 262  | 66   | 726 | 314 | 646 | 394 |
| Egan et al.   | 50   | 331  | 559  | 31   | 283  | 516  | 431 | 1449| 345 | 1315|
| Miao et al.   | 308  | 290  | 58   | 249  | 316  | 91   | 906 | 406 | 814 | 498 |
| Dai et al.    | 490  | 491  | 121  | 534  | 503  | 503  | 149 | 1471| 733 | 1571|

HWE: Hardy–Weinberg equilibrium.
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**Discussion**

Accumulating evidence suggests environmental factors, genetic components, and gene–environment interactions play important roles in cancer development and progression [37-42]. Recently, a growing interest in the associations between genetic polymorphisms and cancer risk has led to increasing studies on tumor etiology. Many studies have linked tumor development and progression to the amplification and overexpression of STK15 in multiple human cancers (such as breast cancer, colorectal cancer, esophageal cancer, as well as other types of cancer) [43-46]. The STK15 F31I polymorphism has been extensively investigated, and many studies have examined the hypothesis that this polymorphism is relevant to the risk of a variety of cancers; however, the results remain inconclusive and ambiguous. Therefore, we conducted a comprehensive meta-analysis to assess the strength of the association between the STK15 F31I polymorphism and overall cancer risk, and further performed a stratified analysis by ethnicity and cancer type. This meta-analysis, including 27 case-control studies, identified associations between STK15 F31I polymorphism and cancer risk. STK15 F31I polymorphisms (AA vs. TA+TT, AA vs. TT, AA vs. TA, and A vs. T) significantly increased overall cancer risk. In a stratified analysis by cancer type, STK15 F31I polymorphisms (AA vs. TA+TT, AA vs. TT, AA vs. TA, and A vs. T) were also associated with a significant increase in breast cancer risk and esophageal cancer (AA vs. TA+TT and AA vs. TA). In a stratified analysis by ethnicity, the association of STK15 F31I polymorphisms was significant in Asians but not Caucasians.

STK15, also named Aurora A, BTK, and AIk1, encodes a serine/threonine kinase that acts as a crucial component in spindle formation, the centrosome maturation process, and proper cytokinesis during mitosis. It is located on chromosome 20q13, a region associated with a number of human cancers [47]. These threonine kinases belong to a family of mitotic kinases that maintain chromosomal stability through phosphorylation. Thus, any severe defects in STK15, such as mutations, would lead to drastic genomic instability and trigger apoptosis through cell cycle checkpoint surveillance [19,48]. Consequently, a cell harboring a defective STK15 may lead to cancer [19]. Our results demonstrate a significant statistical impact of STK15 F31I polymorphism on cancer risk. The STK15 F31I polymorphism (T→A), which leads to an amino acid residue substitution at codon 31 phenylalanine (Phe) to...
iso|eucine (Ile), is associated with cellular transformation and dramatically increases chromosomal instability [49]. The STK15 F31I polymorphism (T→A) variant changes the activity of the STK15 box 1, leading to an obstruction in p53 binding and the decreased degradation of STK15 [7]. The stabilized overexpression of STK15 results in centrosome amplification, improper cytokinesis, chromosomal instability, and the promotion of tumorigenesis [7]. In this meta-analysis, our results demonstrate that the T→A change in STK15 may lead to STK15-triggered elevation of cell centrosome proliferation, cell transformation, and dramatically increased chromosomal instability, which may increase the risk of multiple cancers.

Since the outcomes from meta-analysis can be affected by cancer origins, stratified analysis was conducted according to cancer type for the STK15 F31I polymorphism. The results demonstrate that the STK15 F31I polymorphism is associated with an increased risk of breast cancer and esophageal cancer, but not colorectal cancer and other cancers. However, all results should be interpreted with caution. For esophageal cancer, only three case-control studies were recruited in the current meta-analysis, which may restrict statistical power to detect a real influence or generate a fluctuated assessment, large heterogeneities among the studies enrolled in current meta-analysis should also be taken into consideration. More large scale studies are needed to verify these results. Stratified analysis was also performed regarding ethnicity for the STK15 F31I polymorphism. The STK15 F31I polymorphism is associated with the risk of cancer in Asians but not Caucasians. This meta-analysis confirmed the mutual effect of genetic diversity and variants in different populations to the risks of various cancers. In addition, cancer risk was affected by genetic and environmental factors on different levels. The possible reason of the conflicting findings among different ethnicities could be that different genetic backgrounds and environmental factors they exposed to may have disproportionate effects on cancer risk. In the future, further investigations with large sample sizes should be conducted to identify these associations, particularly with regard to gene–gene and gene–environment interactions.

Two significant issues should be addressed in this study, that is, heterogeneity and publication bias, which may influence the results of meta-analysis. We don’t detect a significant publication bias in this meta-analysis, suggesting the reliability of our results. Significant heterogeneity was observed between publications for STK15 F31I polymorphisms. Potential sources of heterogeneity include the publication year, ethnicity, country, cancer type, sample size, and so on. When subgroup analyses were carried out according to ethnicity and cancer type, this heterogeneity was greatly reduced or removed in some subgroups, implying different effects on cancer types and ethnic populations, even for the same polymorphism. And then we performed further subgroup analyses by publication year, country, and sample size. The pooled subgroup analysis of a subset of studies published after 2006, esophageal cancer, Asian population, studies conducted in Chinese population and certain that the design of some of the included studies was suboptimal in this meta-analysis. From the forest plot in A vs. T the various susceptibility of cancer in different race or to internal bias in the study design. It is certain that the design of some of the included studies was suboptimal in this meta-analysis. From the forest plot in A vs. T compare genetic model (Figure 2), one can identify that 8
Table 4. Summary of results of the meta-analysis from different comparative genetic models in the subgroup analysis by cancer type.

| Polymorphism       | Genetic comparison | Cancer type  | OR(95%CI) | p-Value | Test of heterogeneity | Model |
|--------------------|--------------------|--------------|-----------|---------|-----------------------|-------|
| AA+TA vs. TT       | All                | Breast cancer| 1.04(0.97-1.12) | 0.265   | 0.002, 50.1%          | R     |
|                    |                    | Colorectal cancer | 1.04(0.94-1.15) | 0.479   | 0.130, 46.9%          | F     |
|                    |                    | Esophageal cancer | 0.86(0.44-1.68) | 0.652   | 0.000, 90.2%          | R     |
|                    |                    | Others        | 1.07(0.90-1.26) | 0.445   | 0.007, 43.2%          | R     |
| AA vs. TA+TT       | All                | Breast cancer | 1.16(1.06-1.31) | 0.002   | 0.000, 56.2%          | R     |
|                    |                    | Colorectal cancer | 1.20(1.05-1.37) | 0.007   | 0.005, 61.5%          | R     |
|                    |                    | Esophageal cancer | 1.28(1.08-1.53) | 0.005  | 0.151, 47.1%          | F     |
|                    |                    | Others        | 1.10(0.84-1.44) | 0.468   | 0.015, 56.3%          | R     |
| AA vs. TT          | All                | Breast cancer | 1.16(1.01-1.32) | 0.035   | 0.000, 55.7%          | R     |
|                    |                    | Colorectal cancer | 1.18(0.72-1.94) | 0.501   | 0.078, 56.1%          | R     |
| STK15 F31I         | Esophageal cancer | 1.02(0.47-2.22) | 0.963   | 0.000 | 88.6%                | R     |
|                    | Others             | 1.04(0.77-1.41) | 0.794   | 0.065 | 44.1%                | R     |
| TA vs. TT          | All                | Breast cancer | 1.01(0.95-1.08) | 0.745   | 0.028, 37.2%          | R     |
|                    |                    | Colorectal cancer | 1.01(0.96-1.07) | 0.667   | 0.752, 0.0%           | F     |
|                    |                    | Esophageal cancer | 1.03(0.93-1.15) | 0.553   | 0.313, 15.7%          | F     |
|                    |                    | Others        | 1.05(0.94-1.16) | 0.392   | 0.664, 0.0%           | F     |
| AA vs. TA          | All                | Breast cancer | 1.18(1.06-1.30) | 0.001   | 0.003, 48.4%          | R     |
|                    |                    | Colorectal cancer | 1.19(1.04-1.36) | 0.011   | 0.011, 57.8%          | R     |
|                    |                    | Esophageal cancer | 1.25(0.80-1.95) | 0.335   | 0.050, 61.7%          | R     |
|                    |                    | Others        | 1.32(1.01-1.68) | 0.003   | 0.853, 0.0%           | F     |
| A vs. T            | All                | Breast cancer | 1.08(1.01-1.14) | 0.015   | 0.000, 64.4%          | R     |
|                    |                    | Colorectal cancer | 1.05(0.80-1.38) | 0.732   | 0.008, 74.7%          | R     |
|                    |                    | Esophageal cancer | 1.00(0.71-1.42) | 0.986   | 0.000, 87.9%          | R     |
|                    |                    | Others        | 1.11(0.95-1.28) | 0.180   | 0.003, 64.5%          | R     |

F indicates fixed model; R indicates random model.

Table of values: 3.0, 2009, http://biochem.mcb.vanderbilt.edu/wiki/bin/view/Main/PowerSampleSize. The power was 1.000 in four genetic models (AA vs. TA+TT, AA vs. TT, AA vs. TA, and A vs. T), 0.526 in AA+TA vs. TT genetic model, and 0.075 in TA vs. TT genetic model.

However, there are certain limitations in this study that should be acknowledged. First, large heterogeneity exists in our meta-analysis, which means the results should be interpreted with caution. Second, all recruited case–control studies were from Asians and Caucasians; thus, our results may only be suitable for these populations. Third, only published studies were eligible in this meta-analysis; therefore, some relevant unpublished studies were inevitably missed, which may lead to bias. Fourth, due to the lack of sufficient and uniform information in original case-control studies, data were not stratified by other factors (e.g., age, smoking, alcohol consumption, and other lifestyle factors). Considering the complexity of cancer etiology and the low penetrance cancer susceptibility gene effects from STK15 F31I SNP, these important environmental factors should not be ignored.

In summary, this meta-analysis suggests the STK15 F31I polymorphism represents a low risk factor for cancer, especially in Asians, in breast cancer and esophageal cancer subgroup. In the future, more studies with large sample sizes should be carried out to clarify the association between STK15 and cancer risk.
Table 5. Summary of results of the meta-analysis from different comparative genetic models in the breast cancer subgroup analysis by ethnicity.

| Polymorphism       | Genetic comparison | Population  | OR(95%CI)   | P       | Test of heterogeneity | Model | Model p-Value | I²   |
|--------------------|--------------------|-------------|-------------|---------|-----------------------|-------|---------------|------|
|                    | AA+TA vs. TT       | All         | 1.05(0.99-1.10) | 0.120   | 0.462                 | 0.0%  | F             |      |
|                    |                    | Asians      | 1.07(0.96-1.20) | 0.211   | 0.482                 | 0.0%  | F             |      |
|                    |                    | Caucasians  | 1.04(0.97-1.10) | 0.284   | 0.309                 | 16.3% | F             |      |
|                    | AA vs. TA+TT       | All         | 1.20(1.05-1.37) | 0.007   | 0.005                 | 61.5% | R             |      |
|                    |                    | Asians      | 1.23(1.00-1.50) | 0.049   | 0.006                 | 75.9% | R             |      |
|                    |                    | Caucasians  | 1.18(0.96-1.44) | 0.109   | 0.055                 | 53.7% | R             |      |
|                    | AA vs. TT          | All         | 1.22(1.10-1.35) | 0.000   | 0.131                 | 34.6% | F             |      |
|                    |                    | Asians      | 1.21(1.01-1.45) | 0.037   | 0.266                 | 24.3% | F             |      |
|                    |                    | Caucasians  | 1.23(0.98-1.54) | 0.075   | 0.061                 | 49.0% | F             |      |
|                    | TA vs. TT          | All         | 1.01(0.96-1.07) | 0.667   | 0.752                 | 0.0%  | F             |      |
|                    |                    | Asians      | 1.02(0.90-1.14) | 0.804   | 0.492                 | 0.0%  | F             |      |
|                    |                    | Caucasians  | 1.01(0.95-1.08) | 0.723   | 0.628                 | 0.0%  | F             |      |
|                    | AA vs. TA          | All         | 1.19(1.04-1.36) | 0.011   | 0.011                 | 57.8% | R             |      |
|                    |                    | Asians      | 1.22(0.98-1.52) | 0.074   | 0.005                 | 76.6% | R             |      |
|                    |                    | Caucasians  | 1.14(1.00-1.29) | 0.042   | 0.136                 | 40.5% | F             |      |
|                    | A vs. T            | All         | 1.08(1.01-1.15) | 0.017   | 0.025                 | 52.8% | R             |      |
|                    |                    | Asians      | 1.15(0.97-1.36) | 0.098   | 0.034                 | 65.5% | R             |      |
|                    |                    | Caucasians  | 1.05(1.00-1.10) | 0.069   | 0.109                 | 44.5% | F             |      |

F indicates fixed model; R indicates random model
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F31I polymorphism and cancer risk, especially for gene–gene and gene–environment interactions.
Figure 2. Meta-analysis with a random-effects model for the association between the risk of cancer and the STK15 F31I polymorphism (A vs. T).
doi: 10.1371/journal.pone.0082790.g002
Figure 3. Begg’s funnel plot of meta-analysis of between the STK15 F31I polymorphism and the risk of cancer in the dominant model.
doi: 10.1371/journal.pone.0082790.g003

Figure 4. Sensitivity analysis of the influence of A vs. T in overall cancer meta-analysis (random–effects estimates).
doi: 10.1371/journal.pone.0082790.g004
Figure 5. Filled funnel plot of meta-analysis of between the STK15 F31I polymorphism and the risk of cancer in the dominant model.

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Figure 6. Galbraith radial plot of meta-analysis (A vs. T compare genetic model).

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