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META-ANALYSIS

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# Association Between Polymorphism rs678653 in Human Cyclin D1 Gene (CCND1) and Susceptibility to Cancer: A Meta-Analysis

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Data Interpretation D
Manuscript Preparation E
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**Background:** To assess the association between polymorphism rs678653 in human Cyclin D1 gene (CCND1) and the risk of cancer.

**Material/Methods:** Multiple biomedical databases were systematically searched. Pooled odds ratios (OR) and 95% confidence intervals (95% CIs) were calculated in the appropriate model.

**Results:** In total, 17 case-control studies from 14 articles were included. When combing all available data, no significant association of rs678653 with cancer risk was observed under different genetic models. Stratification by ethnicity also indicated that rs678653 was not correlated with cancer risk in Taiwanese or Indian populations. When stratified by cancer type, no significant association was found between polymorphism rs678653 and digestive tract cancer, head and neck cancer, and gynecological cancer risk.

**Conclusions:** Our comprehensive meta-analysis suggests that the polymorphism rs678653 in CCND1 has no association with cancer risk in different population and disease contexts, indicating that CCND1 rs678653 does not serve a significant biological function in predicting cancer risk.

**MeSH Keywords:** Drug Screening Assays, Antitumor • Genes, bcl-1 • Neoplastic Stem Cells

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## Background

The cell cycle is a series of organized and monitored activities contributing to proper cell division into 2 daughter cells; cell cycle dysfunction is a hallmark of cancer [1,2]. Cancer cells, which are cell-cycle deregulated cells, represent uncontrolled proliferation [1,3]. Cyclins and their counterparts, cyclin-dependent kinases (CDKs), are essential mediators in cell proliferation [1]. CDKs and cyclins, the potential targets for oncogenic mutation, are overexpression in human tumorigenesis [1,4]. It is reported that CDKs are involved in the transition of G1 phase to S phase of the cell cycle and there are defects in the transition in most human tumors [1].

Cyclin D1 (CCND1), together with cyclin-dependent kinase 4 and 6 (CDK4 and CDK6), which are its binding partners, phosphorylate and inactivate retinoblastoma protein by forming complexes, thus promoting cell cycle progression [5]. CCND1, 1 of the 3 D-type cyclins, is frequently overexpressed in cancer, which shortens the G1 phase and regulates the G1 phase to S phase transition of the cell cycle [6,7]. Accumulating evidence shows that the gene CCND1, located on human chromosome 1q31-32, is a potential gene for initiating carcinogenesis and cancer progression [3].

Gene amplification, posttranslational modifications and rearrangements, and gene polymorphisms can cause abnormal protein levels and impair CCND1 function [8]. G1722C(rs678653) is one of the most commonly investigated CCND1 polymorphisms, but its role in cancer is unclear because only a few studies have focused on the association of this single-nucleotide polymorphism (SNP) with cancer risk [3–15]. For example, a case-control study by Sathyan et al. showed no significant association between rs678653 and oral cancer risk, and the same authors published a study in 2008 reported that CCND1was frequently overexpressed in oral carcinoma and rs678653 polymorphism was significantly associated with CCND1 expression [16,17]. Here, we performed a meta-analysis of all eligible studies to investigate the association between CCND1 rs678653 and cancer risk.

## Material and Methods

### Literature search and data extraction

Published reports assessing the association between polymorphism of CCND1 and risk of cancer were searched through PubMed, MEDLINE, Cochrane Library, and Embase. “G1722C”, “rs678653”, and “CCND1 polymorphism” were set as search terms. The search covered the publications in English from January 1, 2000 to March 31, 2015. Preliminary evaluation was conducted based on titles and abstracts, and then full texts

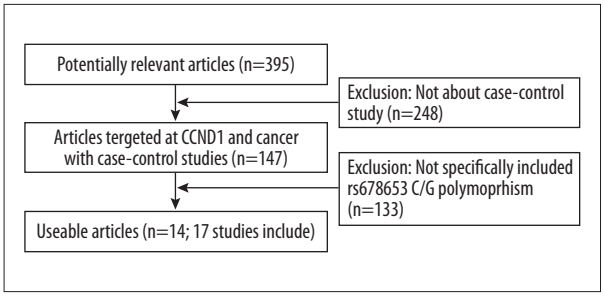


**Figure 1.** Flow chart of study selection and elaborating specific reasons of excluding non-qualified studies from the meta-analysis.

of potentially relevant studies were obtained and re-evaluated for inclusion. Articles without exact quantity information of the genotypes of rs678653 were excluded after careful examination. Studies without case-control design were also removed. Participants in case groups had to be confirmed to have cancer and the control group had to be non-cancer subjects. Detailed data in the remaining articles were checked carefully and studies without exact quantity information of the genotypes of rs678653 were excluded. The following information was extracted: year of publication, first author, race or nationality of samples, cancer type, exact quantity of each genotype for cases and controls, and genotyping method.

### Statistical methods

The data were analyzed with STATA 12 (Stata Corp LP, College Station, Texas, USA) and a P value <0.05 was considered as statistically significant. Pooled odds ratio (ORs) were calculated for dominant model (CC + GC *vs.* GG), recessive model (CC *vs.* GC + GG), co-dominant models (heterozygous: GC *vs.* GG; homozygote: CC *vs.* GG), and allele contrast (C *vs.* G). In the dominant model, we investigated the distribution of genotype CC and GC compared to genotype GG. In the recessive model, the distribution of genotype CC compared to genotype GC and GG was analyzed. In co-dominant models, GG was regarded as the reference genotype and the distribution of GC or CC was investigated. In allele contrast, we investigated the distribution of allele C compared to allele G.

In this meta-analysis, the OR and 95% CI were estimated using Mantel-Haenszel fixed-effects model or DerSimonian-Laird random-effects model. The heterogeneity among different studies was evaluated by $I^2$ index. When there was a significant heterogeneity (P-value <0.1), the random-effects model was used to pool the data, otherwise, the fixed-effects model was selected. For each analysis, the fixed-effects model was used first to test the heterogeneity, and then the appropriate model was chosen based on the test result. Pooled OR and 95% confidence intervals (CI) were calculated, and the corresponding forest plot was generated to summarize the result.





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**Table 1.** Characteristics of studies related to rs678653 and cancers included in our meta-analysis.

| Study | Race or nationality | Cancer type | Case | | | Control | | | Genotyping method |
|---|---|---|---|---|---|---|---|---|---|
| | | | GG | CG | CC | GG | CG | CC | |
| 2015, Huang | Taiwanese | Colorectal cancer | 249 | 85 | 28 | 257 | 80 | 25 | RFLP |
| 2014, Kuo | Taiwanese | Gastric cancer | 245 | 83 | 30 | 252 | 78 | 28 | RFLP |
| 2012, Shih | Taiwanese | Nasopharyngeal carcinoma | 127 | 37 | 12 | 124 | 38 | 14 | RFLP |
| 2011, Tsai | Taiwanese | Oral cancer | 450 | 127 | 43 | 434 | 136 | 50 | RFLP |
| 2011, Hussain | Indian | Esophageal squamous cell carcinoma | 15 | 57 | 79 | 26 | 80 | 45 | RFLP |
| 2011, Hsia | Taiwanese | Lung cancer | 243 | 83 | 32 | 514 | 152 | 50 | RFLP |
| 2011, Lin | Taiwanese | Upper tract urothelial cancer | 125 | 43 | 2 | 205 | 44 | 0 | RFLP |
| 2010, Fernberg | Nordic* | Non-Hodgkin lymphoma | 1011 | 970 | 264 | 818 | 744 | 211 | MALDI-MS |
| 2009, Thakur(a) | Indian | Cervical precancer | 23 | 17 | 6 | 43 | 111 | 46 | RFLP |
| 2009, Thakur(b) | Indian | Cervical invasive carcinoma | 48 | 72 | 34 | 43 | 111 | 46 | RFLP |
| 2009, Gemignani | Caucasian | Malignant pleural mesothelioma | 18 | 26 | 3 | 150 | 157 | 45 | APEX |
| 2008, Driver | Caucasian | Breast cancer | 1697 | 1948 | 560 | 1887 | 2036 | 548 | Taqman |
| 2007, Gayther | White European* | Ovarian cancer | 621 | 661 | 197 | 1017 | 1123 | 328 | Taqman |
| 2007, Rajaraman(a) | Multi-ethnic | Glioma | 138 | 188 | 46 | 198 | 243 | 74 | Taqman |
| 2007, Rajaraman(b) | Multi-ethnic | Meningioma | 72 | 55 | 26 | 198 | 243 | 74 | Taqman |
| 2007, Rajaraman(c) | Multi-ethnic | Acoustic neuroma | 24 | 33 | 13 | 198 | 243 | 74 | Taqman |
| 2006, Sathyan | Indian | Oral squamous cell carcinoma | 44 | 72 | 31 | 44 | 60 | 35 | RFLP |

* Meaned not 100% percent belonged to corresponding population group.

**Table 2.** Meta-analysis of rs678653 with dominant model, recessive model and co-dominant models for entire database and different race (or nationality).

| Group | Pooling model | Analysis model | Heterogeneity | p value | OR (95% CI) | p value |
|---|---|---|---|---|---|---|
| Entire database | Random | Dominant | 57.0% | 0.002 | 1.009 (0.909, 1.119) | 0.868 |
| | Random | Recessive | 39.3% | 0.049 | 1.055 (0.929, 1.199) | 0.410 |
| | Random | Co-dominant, heterozygote | 49.2% | 0.012 | 1.003 (0.905, 1.111) | 0.956 |
| | Random | Co-dominant, homozygote | 42.1% | 0.035 | 1.019 (0.884, 1.175) | 0.794 |
| | Random | Allelic | 61.2% | 0.001 | 1.025 (0.945, 1.112) | 0.548 |
| Taiwanese | Fixed | Dominant | 29.2% | 0.216 | 1.075 (0.943, 1.224) | 0.280 |
| | Fixed | Recessive | 0 | 0.585 | 1.057 (0.838, 1.332) | 0.640 |
| | Fixed | Co-dominant, heterozygote | 0 | 0.448 | 1.075 (0.930, 1.242) | 0.326 |
| | Fixed | Co-dominant, homozygote | 0 | 0.484 | 1.066 (0.844, 1.348) | 0.590 |
| | Fixed | Allelic | 45.2% | 0.104 | 1.064 (0.954, 1.187) | 0.264 |
| Indian | Random | Dominant | 83.9% | <0.001 | 0.921 (0.766, 1.106) | 0.378 |
| | Random | Recessive | 81.9% | 0.001 | 1.048 (0.531, 2.070) | 0.892 |
| | Random | Co-dominant, heterozygote | 76.2% | 0.006 | 0.712 (0.381, 1.332) | 0.288 |
| | Random | Co-dominant, homozygote | 83.6% | <0.001 | 0.841 (0.345, 2.051) | 0.704 |
| | Random | Allelic | 88.9% | <0.001 | 0.917 (0.540, 1.556) | 0.748 |





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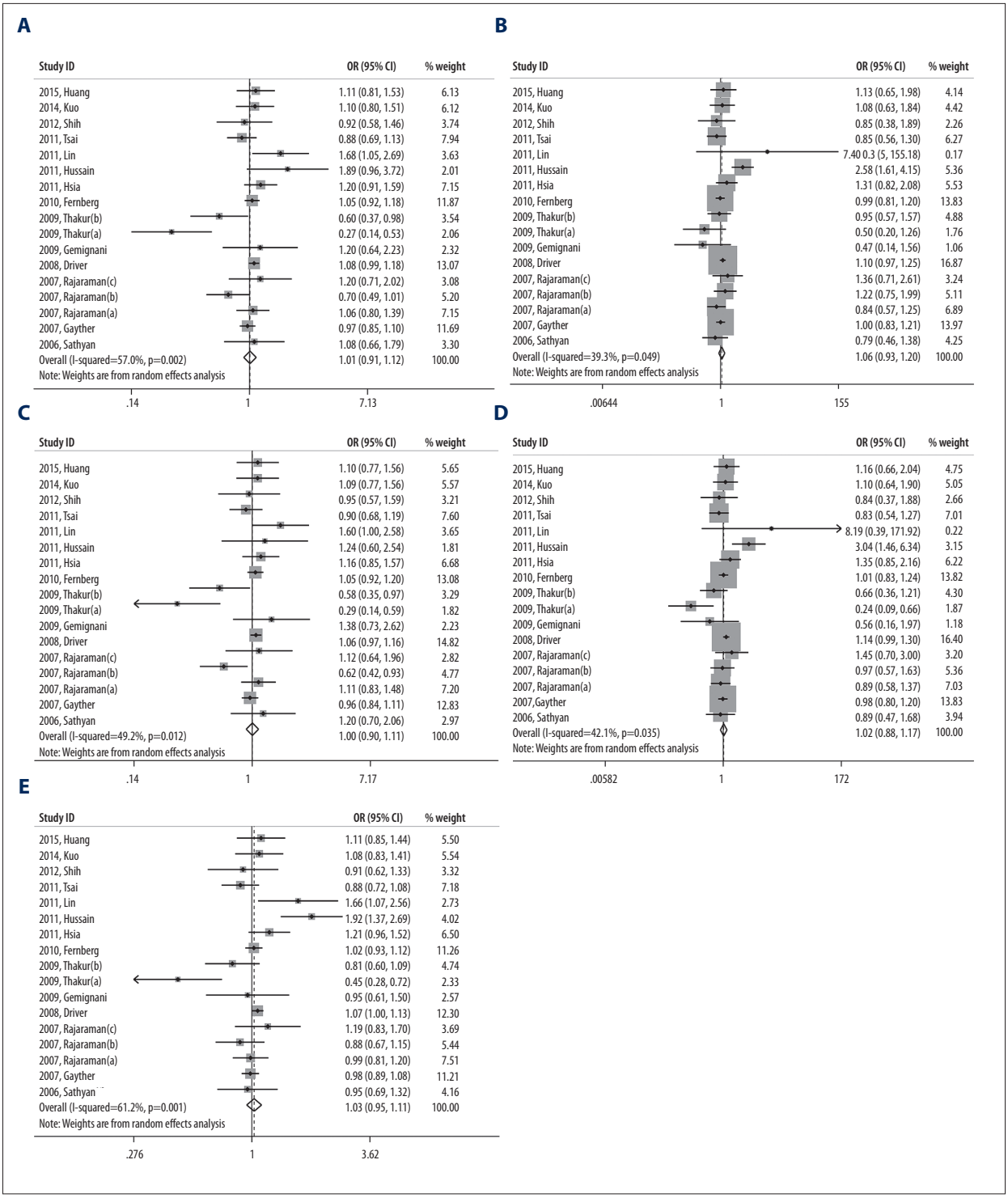


**Figure 2.** Forest plots of studies with all samples under dominant model (**A**), recessive model (**B**), co-dominant heterozygote model (**C**), co-dominant homozygote model (**D**), and allelic model (**E**).





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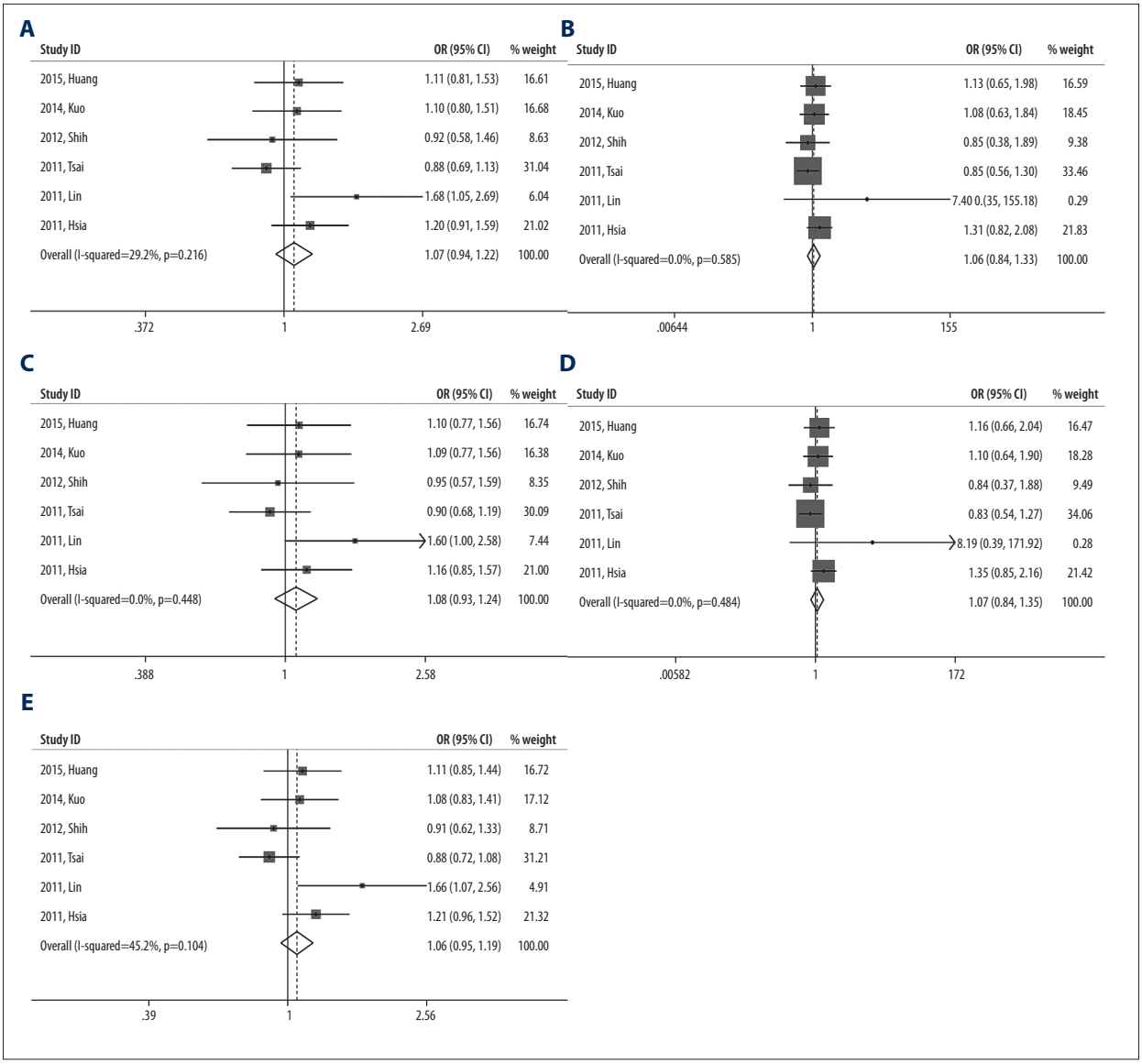


**Figure 3.** Forest plots of studies with Taiwanese samples under dominant model (**A**), recessive model (**B**), co-dominant heterozygote model (**C**), co-dominant homozygote model (**D**), and allelic model (**E**).

Furthermore, for the elaborated evaluation, subgroup analysis was conducted according to the nationality and cancer type.

## Results

### Characteristics of studies

A total of 953 publications were retrieved after the first search: 404 were from PubMed, 291 were from Embase, 249 were from Medline, and the others were from Cochrane Library. We removed 480 duplicated articles, and then excluded other articles that were not based on case-control studies, leaving 147 candidate publications. Of the remaining 147 publications, we eliminated 133. The study selection process and the main reasons for exclusion are illustrated in Figure 1. Eventually, only 14 papers, including 17 case-control studies, met the inclusion criteria and were used for our meta-analysis [3,8–15,17–21]. Characteristics of studies included in the meta-analysis are presented in Table 1.

### Evaluation of the association between rs678653 polymorphism and cancer

We included a total of 17 case-control studies in our analysis to evaluate the association between CCND1 polymorphism rs678653 and cancer risk. For the overall analysis, there was no significant association between cancer risk and the rs678653





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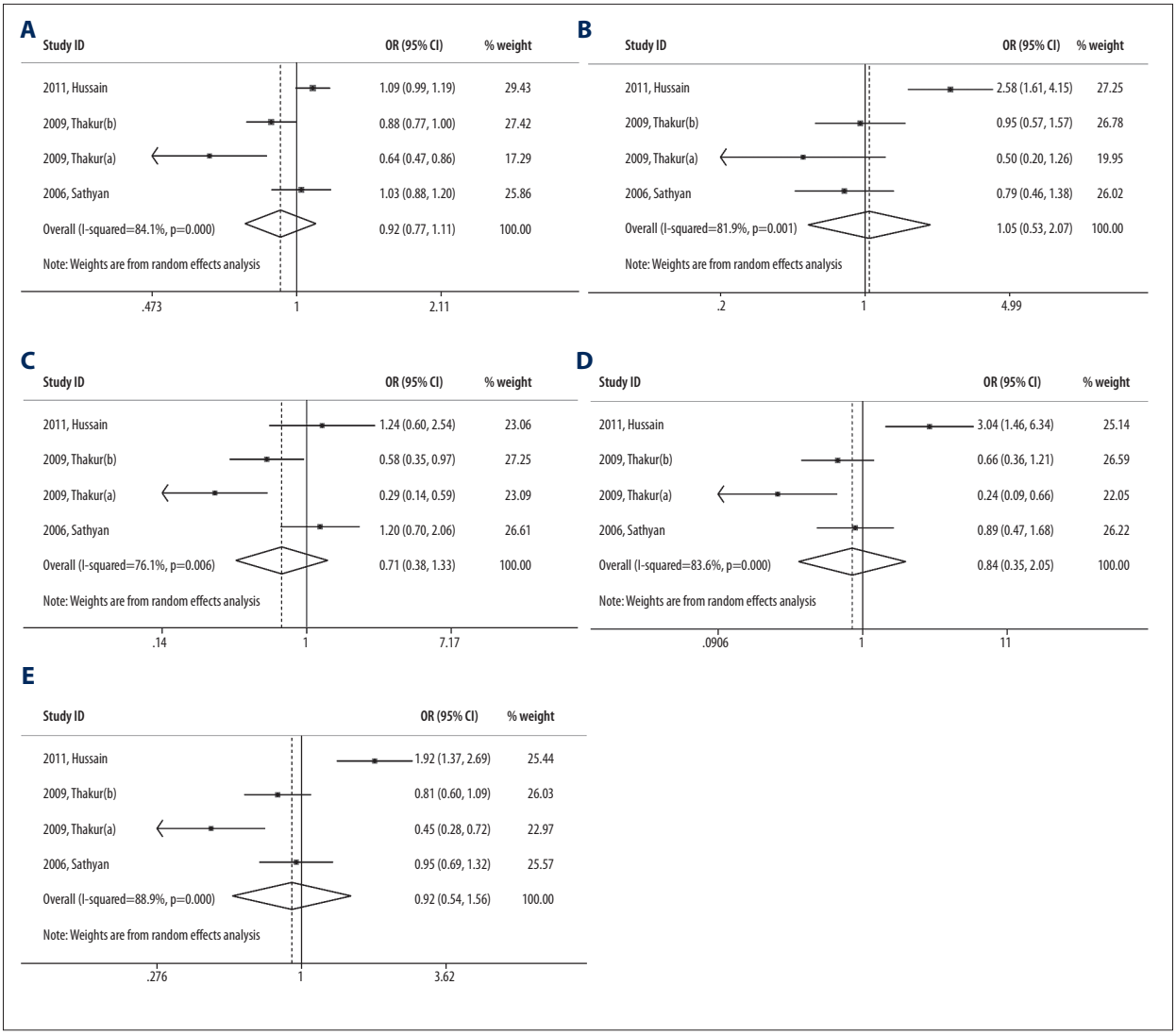


**Figure 4.** Forest plots of studies with Indian samples under dominant model (**A**), recessive model (**B**), co-dominant heterozygote model (**C**), co-dominant homozygote model (**D**), and allelic model (**E**).

polymorphism in all models (Table 2). For the dominant model, the overall OR was 1.009 (95% CI=0.909–1.119, p=0.868, Figure 2A); for the recessive model, the overall OR was 1.055 (95% CI=0.929–1.199, p=0.410, Figure 2B); for the co-dominant heterozygote model, the overall OR was 1.003 (95% CI=0.905–1.111, p=0.956, Figure 2C); for the co-dominant homozygote model, the overall OR was 1.019 (95% CI=0.884–1.175, p=0.794, Figure 2D); and for the allelic model, the overall OR was 1.025 (95% CI=0.945–1.112, p=0.548, Figure 2E). All the analyses showed that CCND1 rs678653 is not associated with cancer risk for the overall population when combining all data.

### Elaborated evaluation in different nationalities

Considering the negative results, we performed subgroup analysis to determine if there is any nationality difference for the association between CCND1 rs678653 polymorphism and cancer risk.

In the Taiwanese subgroup, 6 studies were included, and the main results are shown in Table 2. No significant association was found in any genetic models. For the dominant model, the overall OR was 1.075 (95% CI=0.943–1.224; p=0.280, Figure 3A); for the recessive model, the overall OR was 1.057 (95% CI=0.838–1.332, p=0.640, Figure 3B); for the co-dominant heterozygote model, the overall OR was 1.075 (95% CI=0.930–1.242, p=0.326, Figure 3C); for the co-dominant homozygote model, the overall OR was 1.066 (95% CI=0.844–1.348, p=0.590, Figure 3D); and for the allelic model, the overall OR was 1.064 (95% CI=0.954–1.187, p=0.264, Figure 3E). The results show that there was no association of CCND1 rs678653 with cancer risk in the Taiwanese population.





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**Table 3.** Meta-analysis of rs678653 with dominant model, recessive model and co-dominant models for different cancers.

| Group | Pooling model | Analysis model | Heterogeneity | p value | OR (95% CI) | p value |
|---|---|---|---|---|---|---|
| Digestive tract cancer | Fixed | Dominant | 7.0% | 0.341 | 1.165 (0.942, 1.442) | 0.159 |
| | Random | Recessive | 73.2% | 0.024 | 1.487 (0.830, 2.664) | 0.182 |
| | Fixed | Co-dominant, heterozygote | 0 | 0.954 | 1.110 (0.877, 1.406) | 0.387 |
| | Random | Co-dominant, homozygote | 63.5% | 0.064 | 1.500 (0.838, 2.687) | 0.172 |
| | Random | Allelic | 75.5% | 0.017 | 1.299 (0.930, 1.814) | 0.125 |
| Head neck cancer | Fixed | Dominant | 0 | 0.471 | 0.934 (0.811, 1.077) | 0.348 |
| | Fixed | Recessive | 0 | 0.657 | 0.934 (0.759, 1.150) | 0.522 |
| | Fixed | Co-dominant, heterozygote | 24.8% | 0.248 | 0.946 (0.811, 1.103) | 0.477 |
| | Fixed | Co-dominant, homozygote | 0 | 0.869 | 0.921 (0.738, 1.150) | 0.469 |
| | Fixed | Allelic | 0 | 0.770 | 0.946 (0.850, 1.052) | 0.302 |
| Gynecological cancer | Random | Dominant | 87.5% | <0.001 | 0.580 (0.296, 1.138) | 0.113 |
| | Fixed | Recessive | 4.6% | 0.350 | 0.967 (0.813, 1.151) | 0.707 |
| | Random | Co-dominant, heterozygote | 85.2% | 0.001 | 0.586 (0.303, 1.134) | 0.112 |
| | Random | Co-dominant, homozygote | 76.2% | 0.015 | 0.628 (0.324, 1.220) | 0.170 |
| | Random | Allelic | 81.9% | 0.004 | 0.757 (0.522, 1.097) | 0.141 |

In the Indian subgroup, 4 studies were included, and the main results are presented in Table 2. No significant association was found between rs678653 polymorphism and cancer risk in any models. For the dominant model, the overall OR was 0.921 (95% CI=0.766–1.106; p=0.378, Figure 4A); for the recessive model, the overall OR was 1.048 (95% CI=0.531–2.070, p=0.892, Figure 4B); for the co-dominant heterozygote model, the overall OR was 0.712 (95% CI=0.381–1.332, p=0.288, Figure 4C); for the co-dominant homozygote model, the overall OR was 0.841 (95% CI=0.345–2.051, p=0.704, Figure 4D); and for the allelic model, the overall OR was 0.917 (95% CI=0.540–1.556, p=0.748, Figure 4E). We concluded that there was no association of CCND1 rs678653 with cancer risk in the Indian population.

### Elaborated evaluation in different cancer types

We further evaluated the cancer risk of CCND1 polymorphism rs678653 in different cancer types. Considering the cancer types included in our meta-analysis, 3 general classes of cancer were investigated: digestive tract cancer [3,8,9], head and neck cancer [10,11,17,21], and gynecological cancer [15,20]. The detailed results are shown in Table 3.

For digestive tract cancer, in the dominant model the overall OR was 1.165 (95% CI=0.942–1.442, p=0.159, Figure 5A); in the recessive model the overall OR was 1.487 (95% CI=0.830–2.664, p=0.182, Figure 5B); in the co-dominant heterozygote model the overall OR was 1.110 (95% CI=0.877–1.406, p=0.387, Figure 5C); in the co-dominant homozygote model the overall OR was 1.500 (95% CI=0.838–2.687, p=0.172, Figure 5D); and in the allelic model the overall OR was 1.299 (95% CI=0.930–1.814, p=0.125, Figure 5E). Therefore, no association was observed between the CCND1 rs678653 and digestive tract cancer.

For head and neck cancer, in the dominant model the overall OR was 0.934 (95% CI=0.811–1.077, p=0.348, Figure 6A); in the recessive model the overall OR was 0.934 (95% CI=0.759–1.150, p=0.522, Figure 6B); in the co-dominant heterozygote model the overall OR was 0.946 (95% CI=0.811–1.103, p=0.477, Figure 6C); in the co-dominant homozygote model the overall OR was 0.921 (95% CI=0.738–1.150, p=0.469, Figure 6D); and in the allelic model the overall OR was 0.946 (95% CI=0.850–1.052, p=0.302, Figure 6E). These observations show there is no association between CCND1 rs678653 and head and neck cancer risk. For gynecological cancer, in the dominant model the overall OR was 0.580 (95% CI=0.296–1.138, p=0.113, Figure 7A); in the recessive model the overall OR was 0.967 (95% CI=0.813–1.151, p=0.707, Figure 7B); in the co-dominant heterozygote model the overall OR was 0.586 (95% CI=0.303–1.134, p=0.112, Figure 7C); in the co-dominant homozygote model the overall OR was 0.628 (95% CI=0.324–1.220, p=0.170, Figure 7D); and in the allelic model the overall OR was 0.757 (95% CI=0.522–1.097, p=0.141, Figure 7E). The observations show no association of CCND1 rs678653 with gynecological cancer risk.





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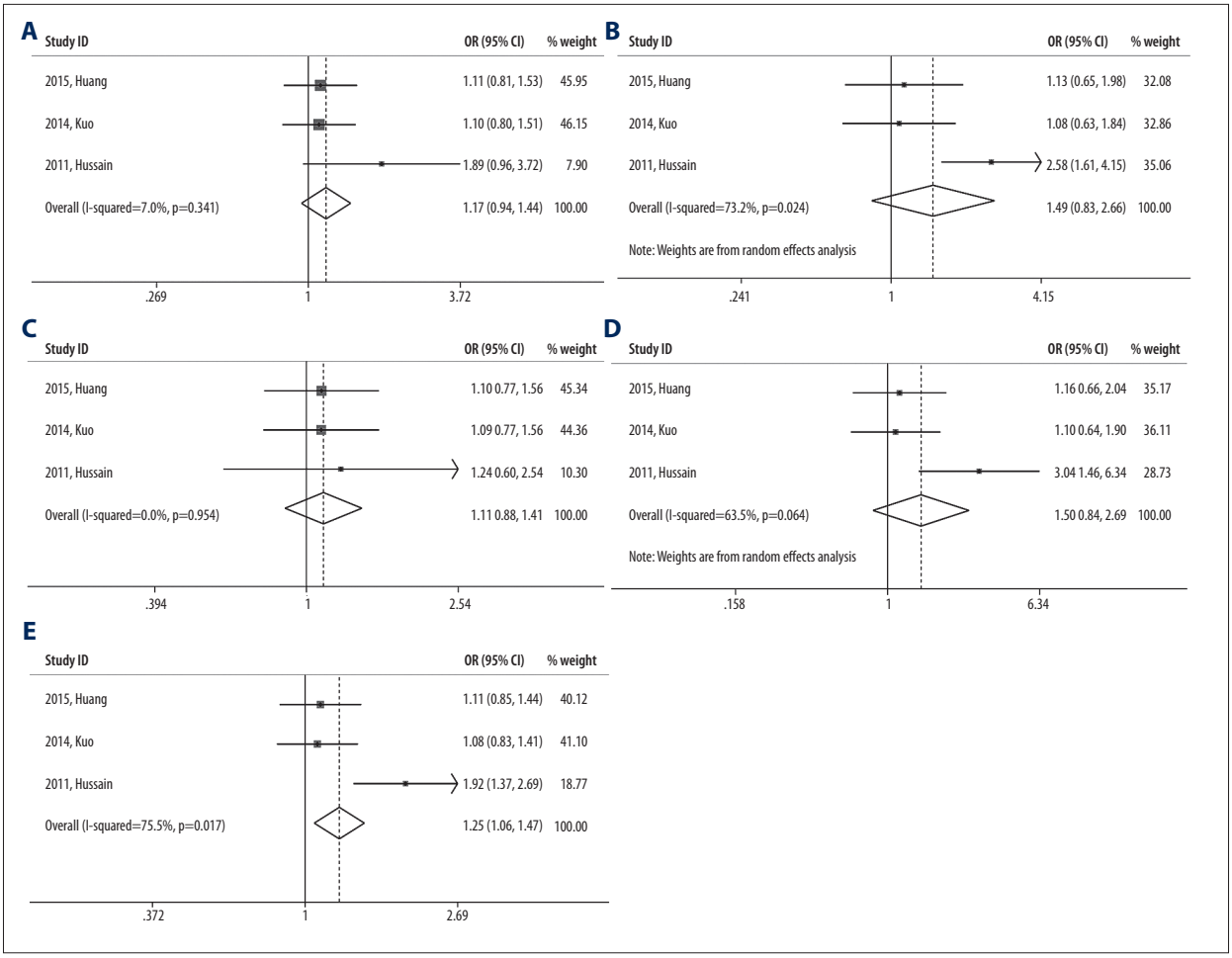


**Figure 5.** Forest plots of studies with digestive tract cancer samples under dominant model (**A**), recessive model (**B**), co-dominant heterozygote model (**C**), co-dominant homozygote model (**D**), and allelic model (**E**).

### Sensitivity analysis

To assess the stability of our meta-analysis, we performed sensitivity analysis for the entire dataset under different models by sequentially removing each study. The results are shown in Supplementary Figure 1. We observed no significant difference after the omission of any study for all the 5 models, signifying that our results are statistically reliable.

## Discussion

We analyzed the association between CCND1 polymorphism rs678653 and cancer risk. The subgroup analysis of different nationalities (Taiwanese and Indian) and different cancer types (digestive tract cancer, head and neck cancer, and gynecological cancer) were also investigated. Results from the meta-analysis showed that, generally, no association was observed between the polymorphism rs678653 and the cancer risk when combining all the available data. For the subgroup analysis of different nationalities, no association was found between the polymorphism rs678653 and cancer risk in the Taiwanese and Indian populations. For the subgroup analysis of different cancer types, no associations were detected between the polymorphism rs678653 and head and neck cancer, gynecological cancer, or digestive tract cancer.

A870G (rs9344), another of the most commonly explored CCND1 polymorphisms, has been reported by several meta-analyses to be associated with risk of esophageal cancer, rectal cancer, brain tumors, and other cancer types [22–26]. However, very few meta-analyses have comprehensively assessed the association between rs678653 and cancer risk. To the best of our knowledge, the only such published meta-analysis is by Lin et al., performed in 2014, which covered 3 eligible studies including 934 cases and 935 controls, to evaluate the association of rs678653 polymorphism with head and neck cancer risk, and no significant association was reported [27]. The result was consistent with that of our subgroup analysis for head and neck cancer. Our study is the first comprehensive





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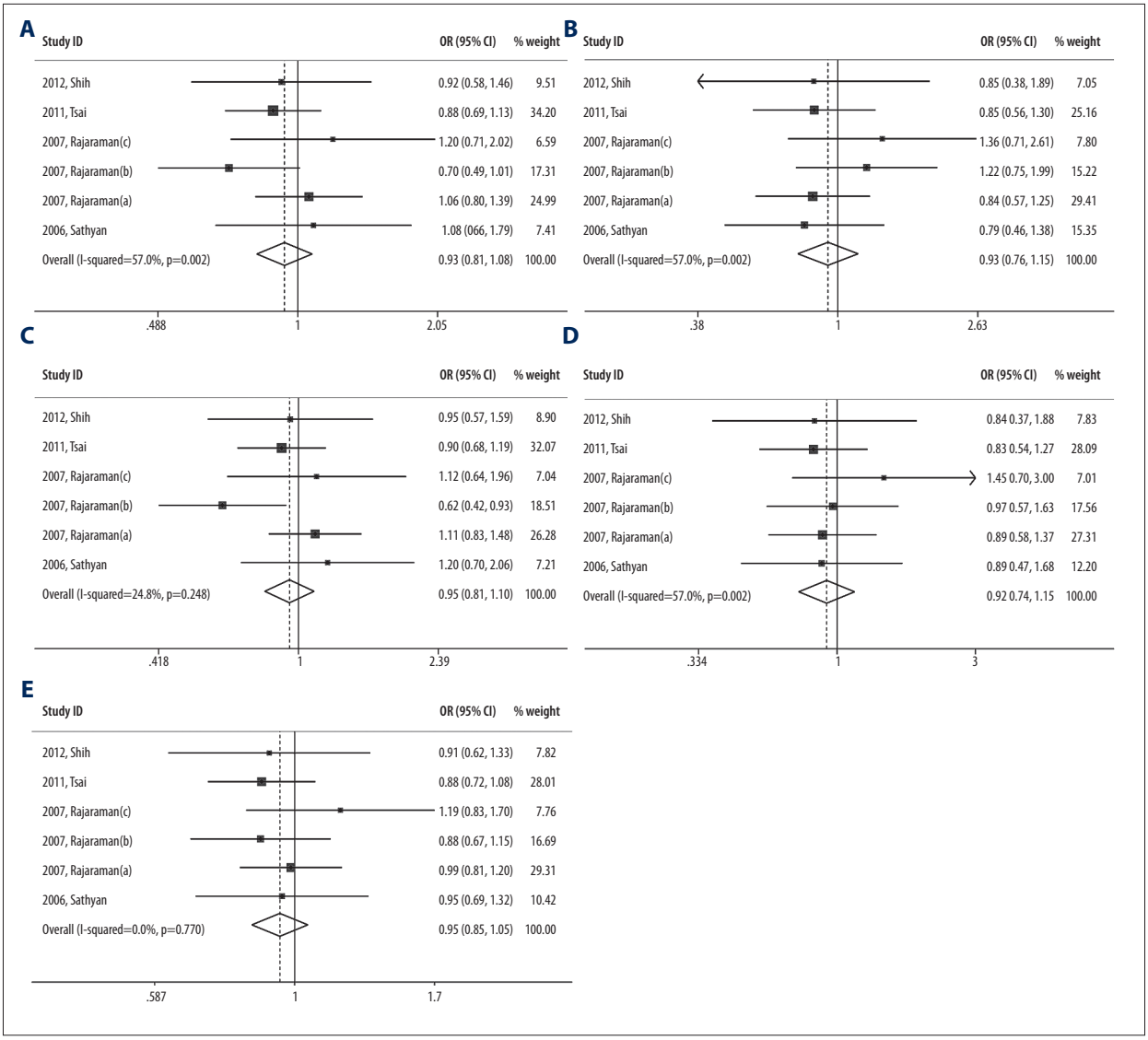


**Figure 6.** Forest plots of studies with head and neck cancer samples under dominant model (**A**), recessive model (**B**), co-dominant heterozygote model (**C**), co-dominant homozygote model (**D**), and allelic model (**E**).

and elaborated meta-analysis to assess the association between rs678653 polymorphism and cancer risk, and the subgroup analysis based on the stratifications of nationalities and cancer types were also performed.

For the subgroup analysis of digestive tract cancer, a case-control study conducted by Hussain et al. in 2011 showed that polymorphism rs678653 in CCND1 gene was strongly associated with digestive tract cancer risk, while the other 2 case-control studies, from Huang et al. and Kuo et al., performed in 2015 and 2014, respectively, suggested that there was no association between rs678653 and digestive tract cancer risk [3,8,9]. In our meta-analysis, no association was observed between rs678653 and digestive tract cancer risk. For the subgroup analysis of gynecological cancer, a case-control study by Thakur et al. reported that polymorphism rs678653 in CCND1 gene was associated with gynecological cancer risk and that rs678653 polymorphism might be a protective factor for gynecological cancer [15], but a case-control study performed by Gayther et al. found no association between the rs678653 polymorphism and gynecological cancer risk. In our meta-analysis, no association was detected between rs678653 and gynecological cancer risk.

The degree of heterogeneity affects the reliability of meta-analyses. In our study, large heterogeneity was detected in the subgroup analyses of Indian population and gynecological cancer, especially in the analysis of the allelic model in the India subgroup ($I^2$=89.9%) and of the dominant and co-dominant heterozygote model in the gynecological cancer subgroup (dominant:





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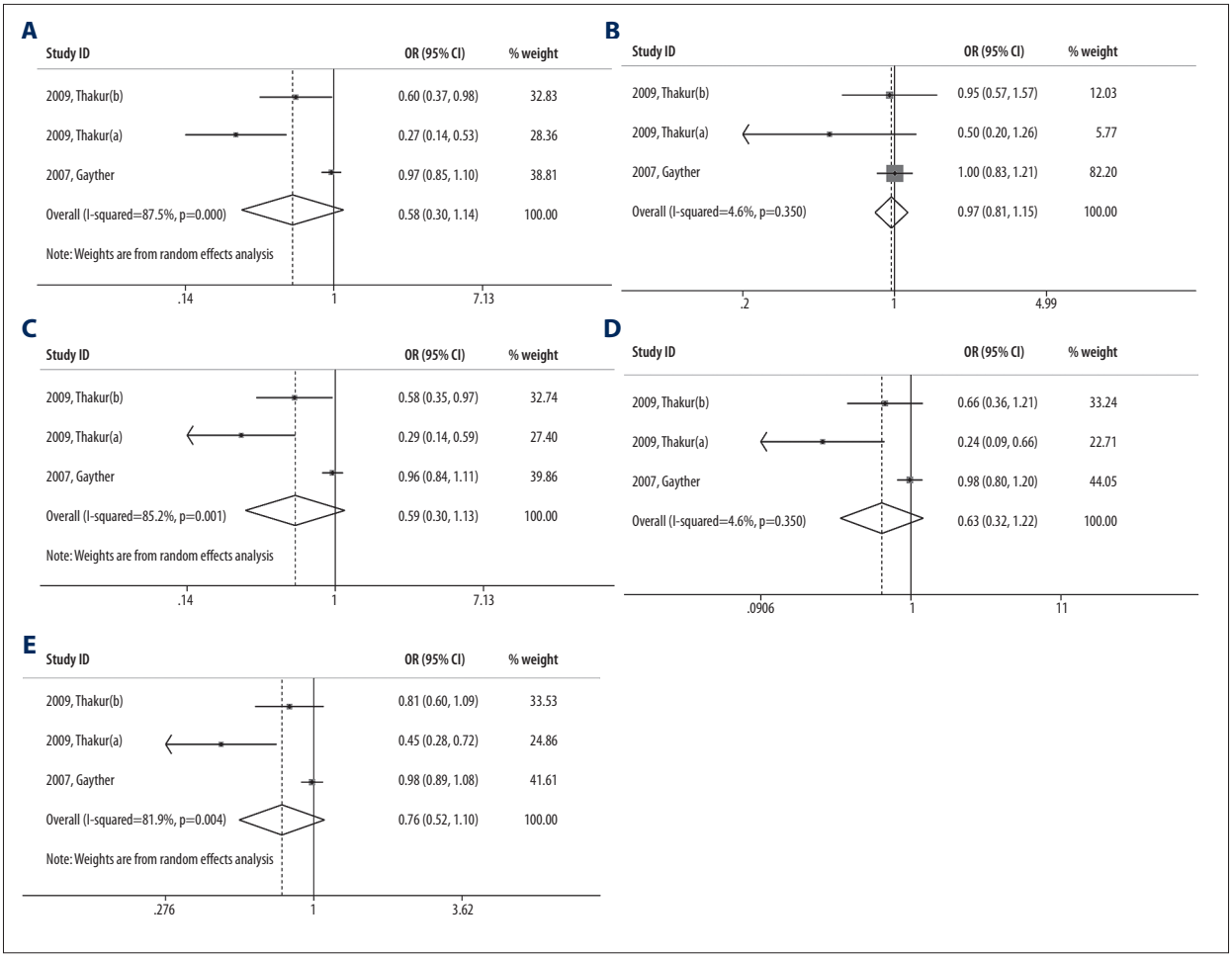


**Figure 7.** Forest plots of studies with gynecological cancer samples under dominant model (**A**), recessive model (**B**), co-dominant heterozygote model (**C**), co-dominant homozygote model (**D**), and allelic model (**E**).

$I^2$=87.5%; co-dominant heterozygote: $I^2$=85.2%). The subgroup analyses stratified by nationality showed that the heterogeneity of the Taiwanese population was moderate, but it was extremely large in the Indian population. Therefore, we deduced that the complicated genetic backgrounds in the Indian population might be responsible for the large heterogeneity. When stratified by cancer type, results showed that the heterogeneity of digestive tract cancer or the heterogeneity of head and neck cancer were acceptable, but it was extremely large in gynecological cancer, indicating that a larger patient population might be needed for the study on gynecological cancer.

Some limitations of our study should be mentioned. Firstly, in the 17 studies included for our analysis, the 4 Indian samples accounted for only 4.77% of all samples, and more studies are needed to update the analysis and arrive at a more confident conclusion. Secondly, the analysis of digestive tract cancer risk only covers India and Taiwanese races; due to the limited sample sizes, different races cannot be further distinguished. As new studies become available, it would be interesting to investigate the association in different ethnic populations. Last but not least, although we used rigorous methods for study selection, data extraction, and data analysis, meta-analysis, as retrospective research, has inherent limitations.

## Conclusions

This meta-analysis suggests that the polymorphism rs678653 of CCND1 has no association with cancer risk when investigating the overall population. Furthermore, the subgroup analysis based on nationalities indicates that there is no association of CCND1 rs678653 with cancer risk for Taiwanese and Indian populations. The subgroup analysis based on cancer types showed no association of CCND1 rs678653 with the digestive tract cancer risk, head and neck cancer risk, and gynecological cancer risk. Our study suggests that CCND1 rs678653 is not an important functional polymorphism in predicting cancer risk.





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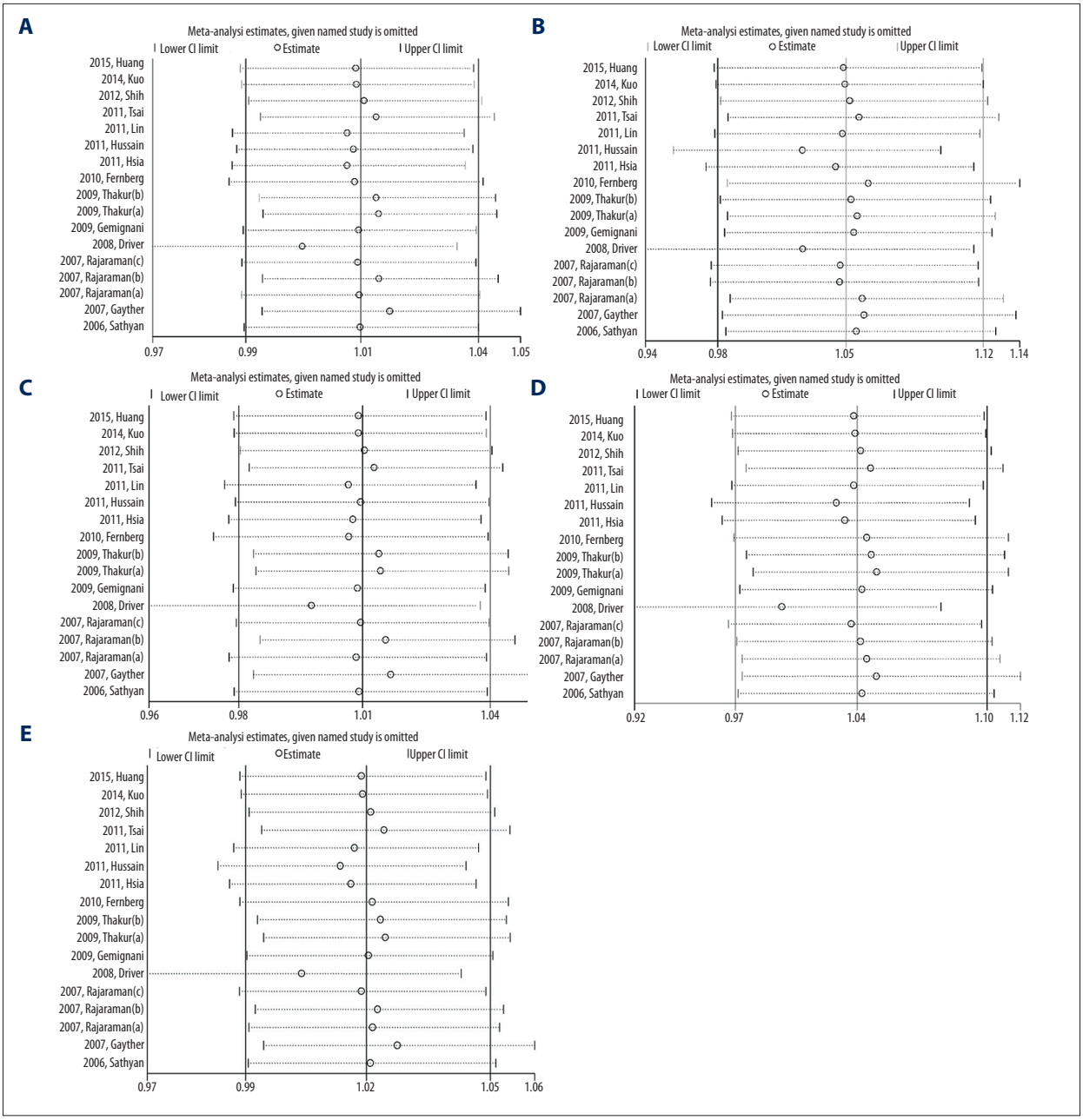


**Supplementary Figure 1.** Results of sensitivity analysis of the entire database under dominant model (**A**), recessive model (**B**), co-dominant heterozygote model (**C**), co-dominant homozygote model (**D**), and allelic model (**E**).

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