Abstract
Cervical cancer develops through progression from normal cervical epithelium through squamous intraepithelial lesions (SIL) to invasive cancer. Cervical cancer is associated with oncogenic human papillomavirus (HPV). The HPV E6 oncoprotein binds to the tumor suppressor gene product p53, promoting its degradation; the Arg allele of p53 Arg72Pro polymorphism binds more ardently with HPV E6 than the Pro variant. Here we evaluate the role of p53 Arg72Pro polymorphism and HPV status on the initiation, progression, and development of cervical cancer. A systematic review and meta-analysis were conducted. Events of interest were the initiation of neoplasia (SIL vs. normal), progression to invasive cancer (cervical cancer vs. SIL), and risk of invasive cancer (cervical cancer vs. normal) by HPV status. OR were extracted from individual studies and pooled using generic inverse variance and random effects modeling. Forty-nine studies were included. In individuals showing HPV positivity, there was a significantly higher odds of progression from SIL to cervical cancer with the p53 Arg allele [OR 1.37; 95% confidence intervals (CI), 1.15–1.62; P < 0.001]. This association was not seen in HPV-negative individuals. p53 Arg72Pro was not associated with the risk of cervical cancer or initiation of SIL in either HPV-positive or HPV-negative patient subsets. The Arg variant of p53 Arg72Pro is associated with progression of SIL to cervical cancer only in the presence of HPV positivity. There were no associations of this variant with overall risk or initiation of cancer in either HPV-positive or HPV-negative patients. Clin Cancer Res; 18(23): 6407–15. ©2012 AACR.

Introduction
Human papillomavirus (HPV) is associated with cervical carcinogenesis. One host gene that interacts with HPV and promotes cancer development is TP53. The TP53 gene product, p53, functions as a tumor suppressor, arresting the cell cycle in G1 so that DNA damage can be repaired before DNA replication (1). Translation of the high-risk HPV E6 viral oncoprotein leads to the proteasomal degradation of p53 (2, 3). One specific single-nucleotide polymorphism in p53 is the nonsynonymous G-to-C variation in exon 4 (also known as rs1042522; Arg72Pro), which results in an arginine-to-proline change in codon 72. Evidence has shown that the Arg variant (Arg72) of Arg72Pro binds to the high-risk HPV E6 protein with greater efficiency than the Pro variant (4). There are also differences in the affinity between p53 and endogenous transcriptional elements with the Arg72Pro variant independent of HPV status (5, 6).

In patients with cervical cancer, the prevalence of cervical HPV infection is substantially higher than healthy women without cervical cancer (7, 8). Nonetheless, some women are not found to have HPV infection at the time of diagnosis. Although the reason for this is unknown, these women could have cleared a prior infection by the time of diagnosis, or have a substantially reduced HPV load that was missed by selective sampling. HPV-positive and HPV-negative subsets of patients may therefore represent biologically distinct entities, each involving a potentially different set of carcinogenic pathways because the viral oncoproteins E6 and E7 are only present in the subset of individuals positive for high-risk HPV infection (Fig. 1). As a result, the effect of host genetic factors on cervical cancer risk may also depend on HPV status. This host–virus interaction may occur during the initiation of cancer, when normal tissue transforms into squamous intraepithelial lesions (SIL), or during progression toward cancer after development of SIL.
Figure 1. Persistent high-risk HPV infection may promote the development of SIL. Low-grade and high-grade SIL seem to be part of a continuum of elevated E6 and E7 expression (24) in addition to an elevated ratio of integrated-to-episomal viral DNA (5, 26). The expression of oncogenic E6 and E7 in the basal epithelium is under stringent control, being expressed at low levels in SIL. Episomal production of E2 suppresses E6 and E7 expression from the integrated viral genome (41). The basal cells of low-grade SIL: (i) will spontaneously regress to normal tissue upon episomal clearance; (ii) will be recycled through HPV E2-induced apoptosis via a p53-dependent and p53-independent pathways (30); or (iii) will progress to high-grade SIL with continued E6 and E7 expression. Accumulation of chromosomal instability due to elevated and continued E6 and E7 expression causes the basal cells at this stage to lose transcriptional control of E6 and E7 (26). This results in further chromosomal instability, and more integration events associated with concomitant loss of the repressor protein E2 (5, 26). This will provide ideal conditions for unhampered E6-induced degradation of p53. Episomally expressed E2, E6, and E7 are shown in bubbles. Free E6 and E7 are integrant-expressed E6 and E7. Arrows indicate activation and blunt-ended lines indicate inhibition. Dark lines promote apoptosis, whereas light lines promote survival.

Data abstraction and categorization
Calculation of ORs from the raw data abstracted were independently corroborated by 2 reviewers (S. Habbous and V. Pang). When necessary, a third reviewer, G. Liu, acted as arbitrator and agreement was reached by consensus. Data were abstracted for cervical cancer, SIL, and healthy controls. SILs were categorized as high-grade (HSIL or CIN2/3), low-grade (atypical cells of undetermined significance, LSIL, CIN1), or SIL (when the grade was unspecified). Numbers of patients identified as Arg/Arg, Arg/Pro, or Pro/Pro were tabulated by HPV status. When data were available for different HPV subtypes (11 studies), high-risk HPV (typically, HPV subtypes 16 and 18) information was preferentially analyzed.

A number of sensitivity analyses were conducted. These included assessment of the effects of methodologic quality. Good methodologic quality was defined as: controls and cases being selected from the same base population, ages of cases and controls being known, the study not being a case series, cases and controls being histologically confirmed, and the TP53 genotyping of controls not deviating from Hardy–Weinberg equilibrium (HWE). Other sensitivity analyses included the assessment of studies focusing on high-risk HPV (rather than unspecified HPV infection), and selected for proper use of specimen source (i.e., where the material used for TP53 genotyping was blood or normal tissue instead of tumor tissue). Finally, common ethnicities including White and East Asian were also assessed in subgroups analyses.

Materials and Methods

Literature search and inclusion/exclusion criteria
MEDLINE (Host: PubMed) and EMBASE (Host: Ovid) were searched using the terms (“HPV” or “human papillomavirus”) and “p53” and “cancer.” Manual searches were also conducted by reviewing the references of publications. Eligible studies included those in which cases were either cervical cancer or SIL; the TP53 polymorphism Arg72Pro had been genotyped and HPV status had been determined in the same patients genotyped for TP53. Studies were excluded if they were reviews or case reports, were family-based genetic studies, published duplicate data, or in which relevant raw data (number of cases and controls for a given genotype and HPV status) could not be abstracted. This included studies in which cervical cancer and SIL were inseparable, or when raw data were not reported.

On the basis that the Arg72 variant confers greater affinity to high-risk HPV E6 than the Pro72 variant (4), we hypothesize that a greater risk of cervical cancer initiation, progression, and overall risk will be observed for this variant in the subset of individuals that are HPV-positive. As we expect the Arg72Pro polymorphism to be important only in the HPV-dependent pathway of cervical carcinogenesis, we further hypothesize that there is either no relationship, or a reduced relationship, with the Arg72 variant and the same outcomes in the subset of individuals who test negatively for HPV.

Habbous et al.
Statistical methods

Three comparisons were used in the meta-analyses: the recessive (Arg/Arg vs. Pro/–), dominant (Arg/– vs. Pro/Pro), and additive (number of Arg alleles) genetic models. The recessive comparison was selected as the primary genetic model because it was the most popular model evaluated in the literature and it was based on empirical phenotypic data (4, 6). The dominant genetic model was reported because of the allelic effect imparted on the HPV–p53 interaction by the Arg72 variant. The additive model was also reported because it is a robust screen of a variety of other genetic models (e.g., codominant, dominant), and assumes a dose–response association (Bradford–Hill criteria), which has biologic plausibility (9). Studies that did not separate the Pro/Pro genotype from the Arg/Pro genotype were limited to assessment by the recessive genetic model only (10–14). Deviations from HWE (P < 0.05) were evaluated using the Chi-squared test. Data were analyzed using RevMan 5.1 analysis software (The Cochrane Collaboration, Copenhagen, Denmark). Pooled estimates of OR were computed using generic inverse variance and a random-effects model (15, 16).

All statistical tests were 2-sided, and statistical significance was defined as P < 0.05. Heterogeneity between studies was assessed by the Cochran Q (P < 0.1) and I^2 (> 50%) tests. Differences between homozygous and heterozygous subgroups were assessed using methods described by Deeks and colleagues (17). With 6 meta-analyses (cancer initiation, progression, and overall risk were separately assessed for HPV-positive and HPV-negative subsets), the Bonferroni adjusted level of significance was α = 0.05/6 = 0.0083.

Results

Our database and manual search identified 1,494 studies. Duplicates, reviews, case reports, and studies including cancers not of cervical origin were excluded. An additional 206 studies were removed because the Arg72-Pro polymorphism was not assessed. A total of 49 publications were therefore included in this meta-analysis (Fig. 2). These included 4,292 patients with invasive cervical cancer, 1,519 with high-grade SIL, 810 with low-grade SIL, 648 with SIL of unspecified grade, and 5,326 healthy controls, all of whom had known HPV status. There were an additional 2,267 controls did not have HPV status available and were excluded from the analysis.

HPV positivity was found in 73% of cervical cancers, 75% of high-grade SIL, 56% of low-grade SIL, 55% of SIL of unspecified grade, and 21% of healthy controls. Studies were largely based on predominantly White (22/48, 46%) and East Asian (15/48, 31%) populations. The majority of studies evaluated overall risk as the primary outcome (41/48, 90%). Characteristics of the individual studies included in this meta-analysis are presented in Figure 2.
### Table 1. Initiation of carcinogenesis, progression to cervical cancer, and overall cancer risk in HPV-positive and HPV-negative subsets by genetic models

<table>
<thead>
<tr>
<th>Subset comparison</th>
<th>HPV-positive subset</th>
<th>HPV-negative subset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>N – number of studies (number of individuals)</td>
<td>Recessive</td>
<td>Dominant</td>
</tr>
<tr>
<td>Initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade SIL vs. control</td>
<td>N = 8 (1,370)</td>
<td>1.01 (0.68–1.49)</td>
</tr>
<tr>
<td>Low-grade SIL vs. control</td>
<td>N = 5 (465)</td>
<td>0.74 (0.49–1.15)</td>
</tr>
<tr>
<td>SIL (unspecified) vs. control</td>
<td>N = 5 (315)</td>
<td>1.45 (0.64–3.28)</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 5 (775)</td>
<td>0.37 (0.06–2.0)</td>
<td>P = 0.70</td>
</tr>
<tr>
<td>Any SIL vs. control</td>
<td>N = 14 (1,947)</td>
<td>0.96 (0.72–1.27)</td>
</tr>
<tr>
<td>Progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer vs. high-grade SIL</td>
<td>N = 11 (1,101)</td>
<td>1.42 (1.09–1.84)</td>
</tr>
<tr>
<td>Low-grade SIL vs. control</td>
<td>N = 10 (1,021)</td>
<td>1.63 (1.20–2.22)</td>
</tr>
<tr>
<td>SIL (unspecified) vs. control</td>
<td>N = 7 (704)</td>
<td>1.02 (0.72–1.44)</td>
</tr>
<tr>
<td>Cervical cancer vs. any SIL</td>
<td>N = 19 (2,339)</td>
<td>1.37 (1.15–1.62)</td>
</tr>
<tr>
<td>Overall risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-HPV only</td>
<td>N = 15 (7,111)</td>
<td>0.82 (0.55–1.23)</td>
</tr>
<tr>
<td>Methodologically sound</td>
<td>N = 11 (1,272)</td>
<td>0.70 (0.43–1.14)</td>
</tr>
<tr>
<td>Optimal tissue source</td>
<td>N = 9 (1,218)</td>
<td>0.96 (0.53–1.76)</td>
</tr>
<tr>
<td>Optimal genotyping method</td>
<td>N = 12 (1,255)</td>
<td>0.82 (0.47–1.41)</td>
</tr>
<tr>
<td>White</td>
<td>N = 6 (661)</td>
<td>1.05 (0.78–1.43)</td>
</tr>
<tr>
<td>East Asian</td>
<td>N = 6 (765)</td>
<td>1.00 (0.31–3.23)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Initiation of carcinogenesis, progression to cervical cancer, and overall cancer risk in HPV-positive and HPV-negative subsets by genetic models (Cont’d)

<table>
<thead>
<tr>
<th>Subset comparison</th>
<th>HPV-positive subset</th>
<th>HPV-negative subset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recessive</td>
<td>Dominant</td>
</tr>
<tr>
<td>N = 60%</td>
<td>0.92 (0.63–1.33)</td>
<td>0.94 (0.68–1.30)</td>
</tr>
<tr>
<td>P = 0.64</td>
<td>P = 0.72</td>
<td>P = 0.37</td>
</tr>
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</table>

*Not significant upon consideration of the Bonferroni-corrected P value (P < 0.0083).*

Supplementary Table S1. There was no evidence of publication bias (Supplementary Fig. S1). Two publications reported results for 2 independent populations (18, 19). These were assessed as 2 separate studies. Two further reports contained data from the same underlying population; these data were considered as one study for the meta-analysis as the control population was the same (20, 21).

HPV-positive subset (HPV-positive cases and HPV-positive controls)

**Initiation of carcinogenesis.** In the HPV-positive subset of patients, the Arg72Pro polymorphism did not influence the initiation of carcinogenesis (Table 1; 14 studies; OR 0.96; 95% confidence intervals [CI], 0.72–1.27; P = 0.78). Similar findings were obtained when the comparison was limited to the 5 studies involving predominantly White patients, or when evaluating high grade, low grade, or unspecified grade of SILs separately (Table 1). There was no evidence of heterogeneity for this comparison in either the recessive (I² = 34%, P = 0.08) or additive (I² = 0%, P = 0.53) genetic model. Some heterogeneity was observed in the additive model (I² = 60%, P = 0.003).

**Disease progression.** In the primary analysis, there was a significant association of the Arg72 variant with the progression from any SIL to cervical cancer in individuals testing positive for HPV (Fig. 3; 19 studies; OR 1.37; 95% CI, 1.15–1.62; P < 0.001). This effect was maintained in the additive model (17 studies; OR 1.25; 95% CI, 1.04–1.51; P = 0.02; Table 1). Similar results were found when SIL was restricted to high-grade or low-grade lesions (Table 1). The Arg72 variant remained significantly associated with progression in all subgroups (Table 2). This association was primarily seen in the 9 studies of White-predominant individuals (OR = 1.59; 95% CI, 1.26–2.01; P < 0.00) with a nonsignificant effect of lower magnitude in the 7 East Asian studies (OR = 1.24; 95% CI, 0.92–1.67; P = 0.16). Funnel plots revealed no evidence of publication bias. Furthermore, heterogeneity among studies in either the recessive, dominant, or additive model was not seen in the overall comparison (I² < 3%, P > 0.4) or among any subset comparison (I² = 0%, P > 0.69).

**Overall risk.** The Arg72Pro polymorphism was not associated with risk of invasive cervical cancer in the subset of HPV-positive cases and controls under either a recessive (18 studies; OR 0.92; 95% CI, 0.63–1.33; P = 0.64; Supplementary Fig. S2A), dominant (14 studies; OR 0.94; 95% CI, 0.68–1.30; P = 0.72), or additive genetic model (14 studies; OR 0.90; 95% CI, 0.71–1.14; P = 0.37). Analysis of different subgroups did not alter the results in sensitivity analyses (Table 1). There was no evidence of publication bias as determined by funnel plots. Significant heterogeneity among studies was observed only for the recessive model (I² = 52%, P < 0.005) with the exception of the subset of studies based on predominantly White individuals (I² = 0%, P = 0.95).

HPV-negative subset (HPV-negative cases and HPV-negative controls)

**Initiation of carcinogenesis.** The Arg72Pro polymorphism did not influence initiation of carcinogenesis (Table 1) in the 16 studies of HPV-negative SIL and controls (OR = 1.11; 95% CI, 0.88–1.41; P = 0.39). When the comparison was restricted to the 6 studies involving predominantly White patients or studies involving only high grade, low grade, or unspecified grade of SIL, no significant associations were found (P > 0.15 for each comparison). There was no evidence of heterogeneity among studies in the recessive (I² = 25%, P = 0.15), dominant (I² = 0%, P = 0.9), or additive (I² = 0%, P = 0.93) genetic model.

**Progression of disease.** There was no association of the Arg72 variant with the progression from low- or high-grade SIL to cervical cancer in the HPV-negative subset (OR = 0.98; 95% CI, 0.67–1.42; P = 0.90, recessive model of 10 studies; OR = 1.21, 0.79–1.85, P = 0.39, additive model of 8 studies). Similarly, no associations were found in subsets of studies focused on high grade, low grade, or unspecified grade of SIL (Table 1). Heterogeneity among studies in any genetic model was not seen in the overall comparison (I² = 0%, P > 0.9) or any of the subset comparisons (I² = 0%, P > 0.71).

**Overall risk.** The Arg72Pro polymorphism was not associated with risk to cervical cancer in the subset of HPV-negative cervical cancers and controls, when considering the
recessive (OR = 1.07; 95% CI, 0.69–1.66; P = 0.76 in 18 studies; Supplementary Fig. S2B), dominant (OR = 1.12; 95% CI, 0.86–1.45; P = 0.41 in 15 studies), and additive (OR = 0.90; 95% CI, 0.73–1.10; P = 0.29 in 15 studies) genetic models. Similarly, no associations were identified in sensitivity analyses that restricted to methodologically sound studies, or when stratified by ethnicity (Table 1).

Our funnel plots, revealed no publication bias in this analysis. Heterogeneity was observed only in the recessive models (I² = 65%, P < 0.001), but not in the dominant or additive models (I² = 0%, P = 0.7) or in White-based studies (I² ≤ 42%, P > 0.14).

**Discussion**

Our meta-analysis suggests that the TP53 Arg72 variant confers an increased risk of cervical cancer development in patients with known SIL. This was seen in only the HPV-positive subset of individuals. These results were consistently significant across all sensitivity analyses and across all grades of SIL. In contrast, no significant associations were...
observed between the Arg72 variant and either overall risk (normal to invasive cancer) or initiation of carcinogenesis (normal to SIL) by HPV status, in either HPV-positive or HPV-negative patient subsets.

Cervical cancers in patients with HPV infection and in those without infection are likely biologically and genetically distinct entities. In HPV-positive patients, initiation of cervical carcinogenesis and progression through to invasive cancer is a complex process that may require persistence of HPV infection in the basal epithelium of the cervix (see Fig. 1). Thus, in HPV-negative subsets of patients, there may be little association between p53 Arg72Pro and initiation of, progression toward, or overall risk of cervical cancer. In the context of HPV positivity, however, initiation of carcinogenesis is dependent on persistent high-risk HPV infection with E6 and E7 expression in the basal cervical epithelium (Fig. 1). Although there is little data to support or refute the role of the Arg72Pro polymorphism with HPV persistence (22, 23), initiation of carcinogenesis is probably independent of this p53 polymorphism because the level of E6 and E7 expression in the basal cells of both SIL and healthy controls is relatively low (24). Moreover, most women who contract high-risk HPV will spontaneously clear the infection with no clinical sequelae (25).

In contrast, progression from SIL to cervical cancer is associated with an acceleration of integration of HPV viral episomes into the host genome (Fig. 1; refs. 5, 26). Successful integration results in greater expression of HPV E6/E7 and more stable transcripts. When viral episomes are integrated, the E2 gene is disrupted and E2 expression decreases (27, 28). When E2 levels decrease, expression of integrated E6/E7 becomes uninhibited and E2-mediated apoptosis also declines (29–31). Thus, greater E6/E7 production and inhibition of apoptosis promotes the progression from SIL to invasive cervical cancer. In individuals who carry the Arg72 variant, E6 has been shown to have increased binding affinity and degradation of the p53 protein (4). These individuals may therefore be more likely to progress to cervical cancer than those harboring the Pro72 variant.

Five other meta-analyses have summarized the relationship between the Arg72Pro polymorphism and cervical cancer risk (32–36). Although 4 of these meta-analyses have addressed the issue of HPV infection to varying degrees, none has focused on the association between the TP53 genotype and cervical cancer risk as a function of HPV status (33–36). Koushik and colleagues considered HPV status only in the context of a comparison of high-risk HPV-positive cases to any HPV-positive case (34). The HPV status of controls was not mentioned by Lee and colleagues, and none of the genetic models included all possible Arg72Pro genotypes (33). Klug and colleagues combined cervical cancers and high-grade SIL in the HPV-positive subset.
Finalmente, Francisco y colegas no se centraron en el cáncer cervical solo, encontraron asociaciones con riesgo moderado con HPV status, pero no mostraron los datos en detalle (36). Aunque 3 de los 5 meta-analizas incluyeron SIL (análisis de infección por HPV de origen), se limitaron en su aproximación a través de un análisis de distal evaluación del HPV status, o SIL fue combinada con cáncer cervical (32, 34, 35). Nuestra meta-análisis es el primero en resumir el efecto del Arg72Pro en un proceso de enfermedad de SIL a nivel cervical, y el primero para tratar HPV-positivo y HPV-negativo subconjuntos como entidades separadas.

Esta meta-análisis tiene limitaciones. Primero, variables demográficas que se conocen como asociadas con riesgo de cáncer cervical (como la edad) y variables clínicas (como el estado de los tumores) no se ajustaron para los análisis, como tales, los datos individuales de cada caso no fueron disponibles. Esta confusión puede haber llevado a algunas heterogeneidades, y los efectos secundarios de los modelos de los datos fueron usados para justificar este punto. Segundo, el método de detección para el HPV status fue suboptimal en todos los estudios. HPV testando a través de medición de la expresión E6 del virus del papiloma humano o a p16 sobreexpresión es ideal porque esto también puede identificar HPV positividad en mujeres con función activa HPV (37, 38). En cambio, todos los informes incluidos en este meta-análisis evaluaron HPV status utilizando métodos de base de ADN (es decir, PCR, captura híbrida), los cuales son más sensibles (39), pero no necesariamente muestran la presencia de función activa HPV. Porque de la alta sensibilidad de PCR, el HPV-positivo subconjunto de individuos puede incluir casos clínicamente irrelevantes de infección por HPV (40). A pesar de estas limitaciones, la relación entre la mutación Arg72Pro y el progreso de la enfermedad SIL hacia el cáncer cervical fue consistentemente superior en varios estudios.

En resumen, había una asociación consistente entre la mutación TP53 Arg72Pro y el cáncer cervical, probablemente modulada por la presencia de alto riesgo HPV durante el progreso de enfermedad de SIL a través del cáncer cervical. Este hallazgo se fortalece por una biológicamente plausible mecanismo, y ayuda a explicar por qué estudios previos y meta-análisis han fallado para encontrar relaciones consistentes con este polimorfismo. Últimamente, este polimorfismo podría tener relevancia clínica importante en el manejo de la enfermedad. En otras palabras, este polimorfismo podría mejorar la comprensión del mecanismo de HPV-associado enfermedad.

Disclosures of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: S. Habbous, L. Eng, W. Xu, G. Liu
Development of methodology: S. Habbous, L. Eng, E. Amir, G. Liu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Habbous, V. Pang, H.J. Mackay, E. Amir, G. Liu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Habbous, V. Pang, L. Eng, W. Xu, H.J. Mackay, E. Amir, G. Liu
Writing, review, and/or revision of the manuscript: S. Habbous, L. Eng, W. Xu, G. Kurtz, F.F. Liu, H.J. Mackay, E. Amir, G. Liu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Habbous, L. Eng, G. Liu
Study supervision: G. Liu

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p53 Arg72Pro Polymorphism, HPV Status and Initiation, Progression, and Development of Cervical Cancer: A Systematic Review and Meta-Analysis

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