# A Meta-Analysis of the Relationship between Testicular Microlithiasis and Incidence of Testicular Cancer

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**Purpose:** There are many recent observational studies on testicular microlithiasis (TM) and risk of testicular cancer. Whether TM increases the risk of testicular cancer is still inconclusive. The objective of this updated meta-analysis was to synthesize evidence from clinical observational studies that evaluated the association between TM and testicular cancer.

**Materials and Methods:** We identified eligible studies by searching the PubMed, Embase and Cochrane Library before March 2014. Adjusted relative risks (RR) with 95% confidence interval (CI) were calculated using random-or fixed-model.

**Results:** A total of 14 studies involving 35578 participants were included in the meta-analysis. On the basis of the Newcastle Ottawa Scale systematic review, eleven studies were identified as relatively high-quality. TM was strong association with an increased incidence of testicular cancer (RR = 12.70, 95% CI: 8.18-19.71, $P < .001$), with significant evidence of heterogeneity among these studies ($P$ for heterogeneity < .001, $I^2 = 82.1\%$). The subgroup and sensitivity analysis confirmed the stability of the results and no publication bias was detected.

**Conclusion:** The present meta-analysis suggests that TM is significantly associated with risk of testicular cancer. More researches are warranted to clarify an understanding of the association between TM and risk of testicular cancer.

**Keywords:** testicular diseases; complications; calculi; testicular neoplasms; carcinoma in situ; risk factors; testis; pathology.

## INTRODUCTION

In 1987 testicular microlithiasis (TM) was first described by Doherty as "innumerable tiny bright echoes diffusely and uniformly scattered throughout their substance of the testicle".[1] TM is a condition in which calcium deposits form in the lumen of seminiferous tubules,[2-4] or arise from the tubular basement membrane components.[5] It was categorized as limited testicular microlithiasis (LTM) if there was at least one image that showed fewer than five microliths, or as classic testicular microlithiasis (CTM) when five or more microliths existed. Hobarth and colleagues[6] reported that a prevalence of testicular microlithiasis of 0.6% in a population referred for symptomatic scrotal sonography. While Middleton and colleagues[7] reported incidence of 18.1% in referred patient. Yee and colleagues[8] reported incidence of TM of 6% in adults and children.

TM has been associated with male pseudohermaphroditism,[9] cryptorchidism,[9-11] subfertility,[12,13] infertility,[12,13] hypogonadism,[14] varicocele,[14] testicular torsion,[14] Klinefelter syndrome[14,15] and Down syndrome.[9]

Testicular malignancy has an annual incidence of three case per 100,000 men and is the most common cancer in young men.[16,17] Although a wide variety of factors have been studied for their connection with cancers, few are considered risk factors for the development of testicular cancer. Currently, there are different opinions as to the clinical importance of TM in association with testicular cancer. Many retrospective studies have reported a significant association between TM and risk of testicular cancer,[18-20] TM can no longer be regarded simply as a benign condition because of its association with testicular malignancy; however, some other studies failed to reach such associations.[21-23] Nowadays, the issue whether testicular microlithiasis has to be regarded as a premalignant lesion or not is still controversial.

Given the high prevalence of TM across the globe and inconsistent finding about the association between TM and risk of testicular cancer, this study aimed to conduct here a meta-analysis of published literature to investigate whether an epidemiologic relationship, if any, existed between TM and risk of testicular cancer.

## MATERIALS AND METHODS

### *Search Strategy*

Systematic literature search was conducted by two

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**Table 1.** Main characteristics of the included studies.

| Included Studies | Country of Origin | Study Period | Study Design | Age, years (Range) | No. of Participants | Definition of Microlithiasis | Follow-Up (Months) | Cancer Type |
|---|---|---|---|---|---|---|---|---|
| Cast et al. 2000[36] | UK | 1996-1998 | Cohort study | 37 (18-74) | 4892 | Classic | 9 | NR |
| Skyrme et al. 2001[31] | UK | 1995-1998 | Cohort study | 34 (23-78) | 2215 | Classic | 41 | 3 Seminoma |
| | | | | | | | | 2 Teratoma |
| Bach et al. 2001[19] | USA | 1992-1998 | Cohort study | 45 (18-87) | 528 | Classic | NR | 8 NSGCT |
| | | | | | | | | 4 Seminoma |
| Derogee et al. 2001[32] | The Netherlands | 1993-1999 | Cohort study | 35.4 (19-74) | 1535 | > 3mm | 61.8 | 11 Seminoma |
| | | | | | | | | 19 Non-seminoma |
| Middleton et al. 2002[7] | USA | 1996-1999 | Cohort study | 44.4 (15-92) | 1079 | Includes limited | 42 | 8 Seminoma |
| | | | | | | | | 1 MGCT |
| | | | | | | | | 2 Leydig cell tumor |
| | | | | | | | | 1 Embryonal cell carcinoma |
| Ahmad et al. 2007[35] | UK | 2000-2006 | Cohort study | 42.6 (17-82) | 4259 | Classic | 33.9 | NR |
| Lam et al. 2007[38] | USA | 1996-2005 | Case-control | 32 (0.01-75) | 274 | Includes limited | 19 | 4 Seminoma |
| | | | | | | | | 3 MGCT |
| | | | | | | | | 1 Choriocarcinoma |
| Miller et al. 2007[30] | UK | 1995-2000 | Cohort study | 40 (18-91) | 3279 | Includes limited | NR | NR |
| Sanli et al. 2008[29] | Turkey | NR(5-year) | Cohort study | 27.5 ± 10.1 (9–56) | 4310 | Classic | NR | 10 Seminomas |
| | | | | | | | | 3 MGCT |
| | | | | | | | | 2 Germ cell tumors |
| | | | | | | | | 1 Embryonal cell carcinoma |
| | | | | | | | | 1 Teratoma |
| Chen et al. 2010[34] | Taiwan | Jun-Dec 2007 | Cohort study | 54.32 (0.5-91) | 513 | Includes limited | NR | |
| | | | | | | | | 4 Seminoma |
| | | | | | | | | 3 MGCT |
| | | | | | | | | 1 Serous carcinoma |
| La Vignera et al. 2012[33] | Italy | 2005-2010 | Cohort study | 43.3 ± 7.0 (0.25-87) | 1056 | Includes limited | | NR |
| | | | | | | | | 10 Seminoma |
| | | | | | | | | 8 Leydig cell tumor |
| | | | | | | | | 7 Intratubular germ cell tumor |
| Cooper et al. 2014[18] | USA | 2003-2012 | Cohort study | 11 (0.6-17.9) | 3370 | Classic | 50.4 | 1 Seminoma |
| | | | | | | | | 1 MGCT |
| | | | | | | | | 1 Intratubular germ cell tumor |
| Heller et al. 2014[39] | USA | 1994-2011 | Case-control | 41.3 | 6002 | Classic | NR | |
| | | | | | | | | 52 seminoma |
| | | | | | | | | 1 Leydig cell tumor |
| Volokhina et al. 2014[37] | USA | 2000-2011 | Cohort study | 7.9 (0.01-19) | 2266 | Classic | 8.8 | 1 MGCT |

**Abbreviations:** NSGCT, Non-seminomatous germ cell tumor; MGCT, mixed germ cell tumor; NR, not reported.

**Table 2.** Newcastle-Ottawa Scale (NOS) assessment of the quality of the studies.

| Included Studies | Selection | | | | Comparability | | Outcome | | | Total Scores |
|---|---|---|---|---|---|---|---|---|---|---|
| | Ia | Ib | Ic | Id | IIa | IIb | IIIa | IIIb | IIIc | |
| Cast et al. 2000[36] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | 7 |
| Skyrme et al. 2001[31] | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 8 |
| Bach et al. 2001[19] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | 7 |
| Derogee et al. 2001[32] | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | 7 |
| Middleton et al. 2002[7] | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | 7 |
| Ahmad et al. 2007[35] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 8 |
| Lam et al. 2007[38] | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 8 |
| Miller et al. 2007[30] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | 7 |
| Sanli et al. 2008[29] | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 8 |
| Chen et al. 2010[34] | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | 6 |
| La Vignera et al. 2012[33] | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No | 6 |
| Cooper et al. 2014[18] | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Heller et al. 2014[39] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | 7 |
| Volokhina et al. 2014[37] | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | 6 |

For cohort studies; Ia: indicates that the exposed cohort was representative of the population; Ib: Indicates that the non-exposed cohort was drawn from the same population; Ic: Indicates that the exposure ascertainment was from secure records or a structured interview; Id: Indicates that testicular cancer was not present at start of study; IIa: Indicates that the cohorts were comparable for age and sex; IIb: Indicates that the cohorts were comparable on all additional factor(s) reported; IIIa: Indicates that testicular cancer was assessed from a secure record; IIIb: Indicates that follow-up was long enough for testicular cancer to occur; IIIc: Indicates that follow-up was complete.
For case-control studies; Ia: Indicates cases with independent validation; Ib: Indicates consecutive or representative cases; Ic: Indicates community controls; Id: Indicates controls with no history of testicular cancer; IIa: Indicates that study controls were comparable for age and sex; IIb: Indicates that study controls were comparable on all additional factor(s) reported; IIIa: Indicates that the same method of ascertainment was used for cases and controls; IIIb: Indicates that assessment of exposure was from a secure record; IIIc: Indicates that the non-response rate was similar in both groups.

independent reviewers (Tao Wang and Luhao Liu) in PubMed, The Cochrane Library and Embase database for papers published before March 2014. The following keywords were used in our search strategy: microlithiasis, testicular microlithiasis, testicular calcification, testicular cancer, testicular neoplasms, testicular tumor, germ cell tumors, germ cell neoplasms, nonseminoma, and seminoma. Duplicate citations were then removed. In addition, the reference lists of selected articles were also manually examined to find relevant studies not discovered in the databases. The language was limited to English.

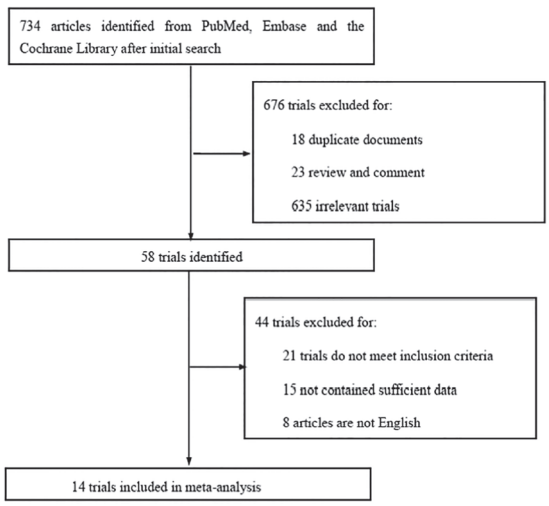


**Figure 1.** Flow chart of study selection.

### *Study Selection Criteria*

The studies included in the meta-analysis must have met all the following inclusion criteria:[(1)] all available retrospective comparative studies (cohort or case-control studies) that had comparative data of the association between TM and testicular cancer; [(2)] one of the exposure of interest was TM; [(3)] one of the outcome interest was testicular cancer;[(4)] reported rate ratio, hazard ratio, or standardized incidence/mortality rate (SIR/SMR) with their 95% confidence intervals (CIs), or provided sufficient information to calculate them and[(5)] the identified studies were reported in English.
Following studies were excluded:[(1)] case reports, editorials, review articles and animal experimental studies; [(2)] articles about association of TM and testicular cancer were excluded for which TM were included in both case and control groups without non-TM to compare; [(3)] duplicate data and [(4)] if they provided only an effect estimate with no means to calculate a CI. When multiple reports describing the same population were published, the most recent or complete report was used.

### *Data Extraction*

Two collaborators (Tao Wang and LuHao Liu) independently reviewed all of the articles and data

**Table 3.** Subgroup analysis of the association between testicular microlithiasis and testicular cancer.

| Subgroups | No. of Studies | RR (95% CI) | $I^2$ (%) | *P*-Value Heterogeneity |
|---|---|---|---|---|
| Geographical region | | | | |
| North America (USA) | 6 | 9.43 (4.58-19.44) | 83.4 | .000 |
| European countries | 6 | 16.31 (11.12-23.94) | 40.2 | .137 |
| Asia | 2 | 16.06 (10.04-25.69) | 0.0 | .882 |
| Study design | | | | |
| Cohort study | 12 | 13.62 (8.08-22.96) | 84.0 | .000 |
| Case-control study | 2 | 7.68 (5.54-10.64) | 0.0 | .967 |
| Age | | | | |
| <18 | 2 | 13.04 (0.92-184.64) | 82.5 | .017 |
| >18 | 12 | 12.11 (7.76-18.89) | 82 | .000 |
| No. of participants | | | | |
| ≤ 1000 | 3 | 6.58 (2.32-18.68) | 52.1 | .124 |
| > 1000 | 11 | 14.80 (10.07-21.76) | 69.8 | .000 |

**Abbreviations:** RR, relative risks; CI, confidence interval.

disagreement was resolved by a third review or by consensus. The following information was extracted from each study: the first author, publication year, country of origin, study design, age of study population, number of patients in each group, duration of follow-up and tumor histology. When such data were not explicitly reported, they were derived from data provided in the articles or requested from the authors through personal contacts, wherever possible.

### *Statistical Analysis*

The association of TM and testicular cancer was estimated by calculating pooled relative risk (RR) and 95% CI. The significant of pooled RR was determined by Z test ($P < .05$ was considered statically significant). Statistical heterogeneity between studies was assessed by using Q-test with significance set at $P < .10$, and heterogeneity was quantified using the I2 statistic (significance level at $I^2 > 50\%$). The random-effects model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was used.[24,25]

We conducted subgroup analysis to explore heterogeneity across studies and the difference between subgroups was tested by meta-regression analysis. The methodological quality of observational studies was assessed by using the Newcastle-Ottawa Scale (NOS) systematic review method, with some modifications to match the needs of the present study.[26] The quality of studies was evaluated by examining three aspects of the study design: patient

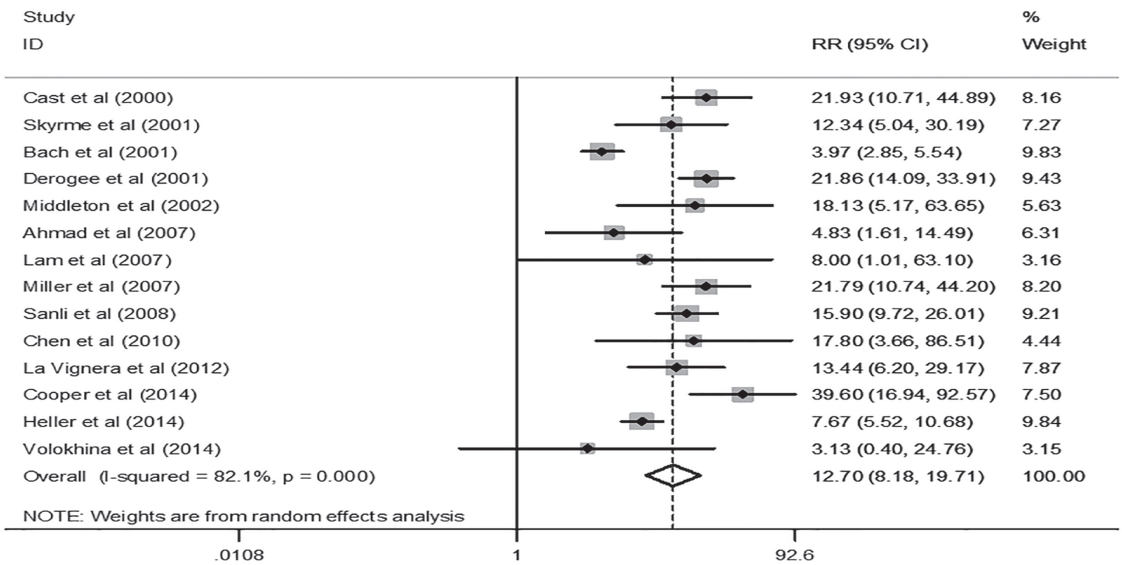


**Figure 2.** Forest plot of testicular microlithiasis and risk of testicular cancer.
**Abbreviation:** CI, confidence interval.

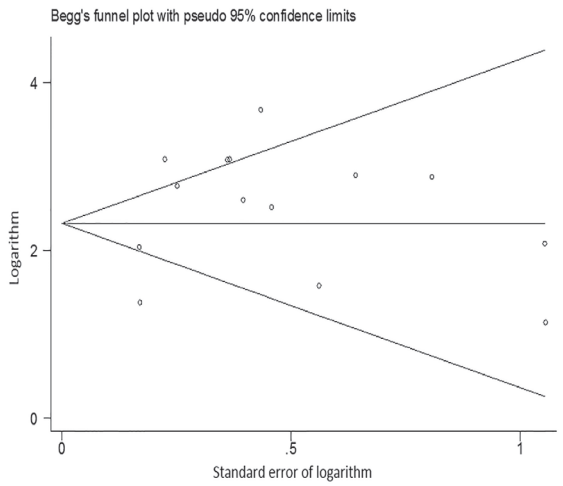


**Figure 3.** Begg's funnel plot for publication bias evaluating the association between testicular microlithiasis and testicular cancer.

selection, comparability of the groups, and assessment of outcomes. In this 9 scores system, studies scored greater than or equal to 7 were considered to be of high quality. Sensitivity analysis was performed by sequential omission of individual studies under various contrasts to reflect the influence of the individual data to the pooled RRs and evaluate the stability of the results.

We used the Begg adjusted rank correlation test, and the Egger regression asymmetry test to detect publication bias and $P > .05$ for both tests was considered to be no significant publication bias.[27,28] The STATA 12.0 statistical software (Stata Corporation, College Station, Texas, USA) was used for all the statistical analyses. $P$ values < .05 were considered statistically significant, and All the $P$ values were two-sided.

# RESULTS

### *Search Results*

Our initial search identified 734 articles, and 676 articles were excluded by examining the titles and abstracts. By examining the full-texts of these articles, we excluded 44 studies because association of interest was not evaluated, requested data were not reported, or articles were not published in English. Finally, a total of 14 articles were selected for our meta-analysis, including 12 cohort[7,18,19,29-37] and 2 case-control studies.[38,39] Examination of the reference lists of these studies did not detect any further studies for evaluation. Our search flow diagram was shown in **Figure 1**.

### *Study Characteristics and Quality Assessment*

The characteristics and information of the included studies were shown in **Table 1**. The 14 selected studies contained 35578 participants (ranging from 274 to 6002) with 1493 cases of TM from different populations (6 studies originated from the United States and 2 studies from Asia). The remaining 6 studies were from European countries, including: 4 from UK, 1 from Italy and 1 from Netherlands, with varied length of the follow-up period (ranging from 8.8 to 61.8 months). The results of quality assessment according to NOS for included studies were shown in **Table 2**. In this total 9 points evaluation system, the scores of included studies ranged from six to eight, while eleven of them were defined high-quality.

### *Results of Meta-analyses*

We identified 14 observational studies that reported results on TM and testicular cancer incidence. As shown in **Figure 2**, the summary RR was 12.70 (95% CI: 8.18-19.71) in a random-effects model for TM patients, compared with individuals without TM. There was significant heterogeneity among these studies ($P < .001$, $I2 = 82.1\%$). To further elicit the association between TM and the risk of testicular cancer, subgroup analyses were adopted, according to stratification on geographical region, study design, age and numbers of participants (**Table 3**). Our data supported the hypothesis that TM is association with an increased incidence of testicular cancer.

Sensitivity analysis was performed to assess the influence of individual studies on the overall risk of testicular cancer by excluding each individual study and recalculating the

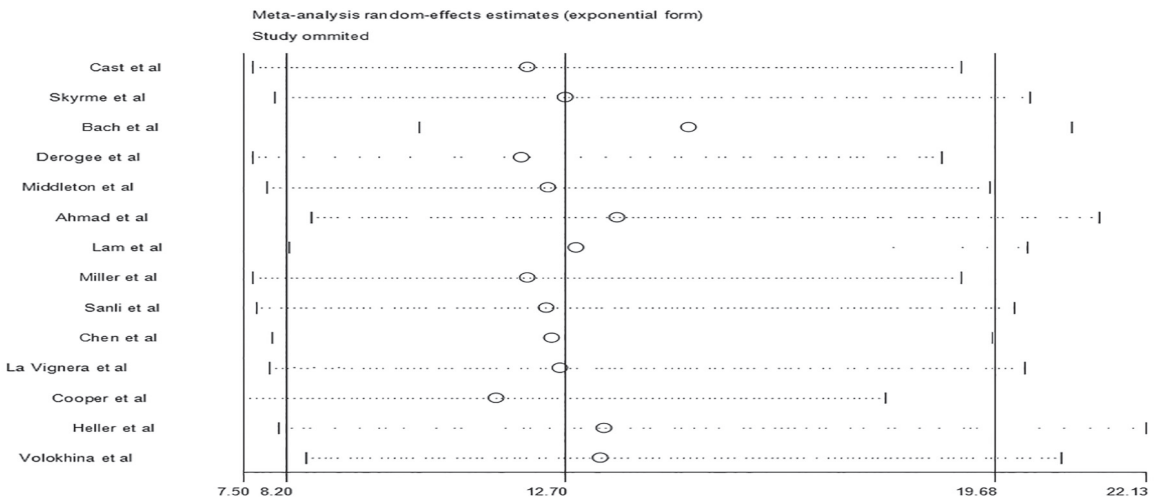


**Figure 4.** Influence of each individual study on the relative risks of testicular cancer in testicular microlithiasis patients as compared with individuals without testicular microlithiasis.

pooled RR. Similar RR and 95% CI were generated with the exclusion of each study, indicating the high degree of stability of the results (**Figure 4**).

***Publication Bias***

There was no funnel plot asymmetry for the association between TM and risk of testicular cancer (**Figure 3**). *P* values for Begg adjusted rank correlation test was 0.381 and the Egger regression asymmetry test was 0.231, suggesting a low probability of publication bias.

## DISCUSSION

In the last decade, several epidemiological studies have examined the association between TM and risk of testicular cancer but provided inconsistent results. Based on data from 12 cohort studies and 2 case-control studies, the present study represents the meta-analysis quantitatively investigating the association between TM and risk of testicular cancer. We found that compared with non-TM or general population, individuals with TM might have more than 12-fold increased incidence of testicular cancer. Further stratification for age demonstrated similar trends. Our study recruited a total of 1493 TM cases and 34085 controls, which greatly improved the statistical power and the conclusions were more credible than those of individual studies. Subgroup analyses were performed to explore the degree to which potential confounders might have influenced the findings, according to stratification on geographic location, study design and age. The sensitivity analysis further confirmed the stability of the conclusions.

The mechanisms by which TM could affect the pathogenesis of testicular cancer remain largely unknown. TM is an incidental finding detected during ultrasonographic examination of the scrotum. Owing to the use of higher-frequency ultrasound transducers resulting in enhanced spatial resolution and thus improved sensitivity, exquisite detail of testicular pathology can be demonstrated. Moreover, an increased general knowledge of the association of TM with testicular cancer, more cases of TM have recently been reported. It is unclear if the high prevalence rate is a result of a true high incidence, because of a wide variety of ultrasound transducers used and different methods for identifying patients with TM.[14] Although originally thought to be a rare abnormality, the reported frequency of detection of TM in relationship to the racial background of a healthy population was 4.2% white, 14.1% African American, 8.5% Hispanic, 5.6% Asian or Pacific Islander and 5.2% who did not claim a race affiliation.[21] In addition, testicular microlithiasis can be seen at all ages but is reported to be more common in childhood.[6] Its relative prevalence has been reported in previous literature as 1/2100 for adults, 1/618 for boys and 1/15 for boys with cryptorchidism.[40]

It is generally accepted that TM consists of calcified cores surrounded by concentric layers of collagen fibers located in the lumen of the seminiferous tubules.[41] However, some author believe that the microliths are located outside the tubules and have been present since early stage of testicular development.[5] The microcalcification may be initiated by sloughing of degenerated cells into the tubule. The major defect is believed to be in the breakage of the basement membrane of the seminiferous tubule.[10] Almost all of the patients examined had tubular hyalinization in the tissue surround the testicular cancer, the same as reported by previous studies,[42,43] as a result not only of autoimmune processes but also of ischemic or obstructive events that may account for the development of a cancer in a predisposing environment. This is also supported by the fact microlithiasis and tubular hyalinization are absent in the only benign neoplasm,[44] while not excluding an environmental component. Coffey and colleagues[45] noted that a higher degree of concordance for TM among testicular germ cell tumors cases and matched relative pairs than was expected by chance. Therefore TM may be, at least in part, genetically determined and may have a joint etiology.

Given the current literature and our data, we can prove the hypothesis that TM is associated with an increased incidence of testicular cancer; but we cannot assess whether TM is a cause or risk factor for development of testicular cancer. As noted in the literature, because the clinical importance of TM is still in debate, the role of ultrasound and the recommendations for follow-up studies in patients with TM vary among different authors. Some authors recommend annual physical examination and periodic self-examination, but no regular ultrasound follow-up.[7] Decastro and colleagues[46] suggested that testicular cancer will not develop in the majority of men with TM (98.4%) during a 5-year follow-up. It is unlikely that an extensive screening program would benefit men at risk with any decreased burden of treatment or improved cure rate. Because of a high prevalence of testicular cancer in infertile men, some authors recommend biopsy or follow-up ultrasound when TM is seen in an atrophic testis.[46] Most studies had not found elevated tumor markers in those with incidental TM, monitoring of serum tumor marker was not appropriate. We advocate that the most prudent approach will be to instruct patients with incidental TM to perform testicular self-examination and annual physical exams by a primary care provider, while TM in patients with risk factors for developing testicular cancer to rely on monthly testicular self-exams, annual physical exams by a urologist and ultrasound follow-up.[22]

The present meta-analysis has the following limitations that must be taken into account. First, the main limitation was that all the included studies were retrospective studies, which might not be prone to recall bias but were prone to selection bias. In the future, longitudinal prospective studies are required to validate the evidence of a parenchymal environment predisposing to the development of testicular cancer. Second, we did not uncover unpublished studies and chose to collect only published articles in English, which could bring publication bias, despite there being no significant evidence of publication bias observed in Egger's test. Third, great heterogeneity existed in terms of ethnicity, study design, age and definition of microlithiasis. Use of the random-effect model for pooled data might minimize the effects of heterogeneity, but did not abolish them. The degree of heterogeneity fell for most outcomes with sensitivity analysis, but this difference was not significant.

## CONCLUSION

In conclusion, results of this meta-analysis suggest a potential hazardous effect of TM for developing testicular cancer. Given its association with testicular cancer, we advocate that all TM patients are well informed and educated to practice regular self-examination of testes and annual physical exams. In future, large-scale and well-designed prospective studies are necessary to be

conducted to further elucidate the association between TM and risk of testicular cancer.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

None declared.

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