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# Plasma fibrinogen levels towards cancer incidence: a systematic review and meta-analysis of epidemiological studies

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## Abstract

**Importance** Understanding the association between fibrinogen levels and cancer incidence is crucial for elucidating potential diagnostic and therapeutic implications in oncology.

**Objective** This meta-analysis aimed to comprehensively evaluate the relationship between circulating fibrinogen levels and various tumour types.

**Registration** This systematic review had been registered in PROSPERO (ID: CRD42024616015).

**Data sources** A systematic review search was performed on PUBMED, EMBASE and Cochrane databases until June 3, 2023.

**Study selection** Studies that fulfilled our pre-established inclusion criteria were incorporated into our analysis. These criteria encompassed prospective cohort, case–control, and nested case–control designs, all featuring histopathologically confirmed primary cancers. Furthermore, we included studies that had reported odds ratios (ORs), relative ratios (RRs) or hazard ratios (HRs) along with their corresponding 95% confidence intervals (95% CIs), ensuring the reliability and comparability of the data across studies.

**Data extraction and synthesis** Two independent authors meticulously extracted data from eligible studies, ensuring rigour and accuracy. Subsequently, we performed statistical analyses using the robust STATA version 12.0 software, guaranteeing the reliability of our findings. Moreover, we carried out in-depth subgroup analyses, categorizing studies based on tumour type, to meticulously explore and quantify the variations in the correlation between fibrinogen levels and tumour incidence. Through this approach, we have gained a nuanced understanding of the potential heterogeneity of this relationship across different cancer types.

**Main outcomes and measures** The major outcome of this study centred on elucidating the relationship between fibrinogen levels and cancer incidence, with subsequent subgroup analyses conducted to delve deeper into this relationship within specific tumour types. This approach aimed to provide a comprehensive understanding of how fibrinogen levels may varying influence different cancer types, thereby offering potential insights into the identification of novel risk factors or biomarkers for further clinical investigation.

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**Results** Twelve studies were meticulously incorporated into the meta-analysis. Notably, significant heterogeneity was observed across these studies, necessitating careful interpretation of the results. The meta-analysis demonstrated a compelling connection between elevated fibrinogen levels and an increased risk of cancer incidence, with an hazard ratio (HR) of 1.33 (95% CI: 1.16, 1.51; $p = 0.000$), demonstrating a statistically significant finding. Further subgroup analyses delved into specific cancer types and identified significant associations with smoking-related cancer (HR = 1.79; 95% CI: 1.54, 2.09; $p = 0.000$), lung cancer (HR = 1.98; 95% CI: 1.62, 2.43; $p = 0.000$) and colorectal cancer (HR = 1.27; 95% CI: 1.00, 1.62; $p = 0.048$). These findings underline the potential significance of fibrinogen levels as a potential biomarker or risk factor for these particular cancer types.

**Conclusions and relevance** Elevated plasma fibrinogen levels have been significantly associated with an increased incidence of cancer, particularly in the cases of lung and colorectal cancers. These compelling findings underscore the potential value of fibrinogen levels as a diagnostic or prognostic biomarker in cancer management. Accordingly, further studies and clinical validation are urgently needed to fully explore the role of fibrinogen in cancer and its potential application in clinical practice.

**Key points**

**Question** What is the relationship between plasma fibrinogen levels and cancer incidence across various tumor types?

**Findings** The meta-analysis included 12 studies with 11,834 cancer cases and 192,342 controls, revealing a significant association between elevated fibrinogen levels and increased cancer risk (HR = 1.21). Notably, strong correlations were found specifically for smoking-related cancer (HR = 1.79), lung cancer (HR = 1.98) and colorectal cancer (HR = 1.27).

**Meaning** These findings suggest that plasma fibrinogen levels may serve as potential biomarkers for cancer risk, particularly for lung and colorectal cancers, highlighting the need for further research to explore their clinical implications in cancer diagnostics and treatment.

**Keywords** Fibrinogen levels · Cancer incidence · Colorectal cancer · Lung cancer · Meta-analysis

## 1 Introduction

Cancer poses a critical challenge to global public health. In 2020, it accounts for 18% of all deaths globally and is the second leading cause of mrtality in the United States after heart disease [1]. In China, cancer contributed to two of the top five causes of years of life lost in 2017, with lung cancer ranking third and liver cancer fifth [2].

Fibrinogen is a 340 kDa dimeric glycoprotein synthesized by hepatocytes, traditionally recognized as a coagulation factor [3]. However, recent studies have demonstrated that fibrinogen plays a significant role in tumor development, progression, and metastasis [4]. Its abnormal deposition and expression in the tumor microenvironment interact with various cell receptors, regulate inflammatory processes, and promote tumor progression [5, 6].

In vivo studies have demonstrated that fibrinogen plays a multifaceted role in tumor progression through several interconnected mechanisms. First, fibrinogen deposition in the tumor microenvironment (TME) interacts with the extracellular matrix (ECM), creating a provisional matrix that promotes tumor cell adhesion, migration, and invasion [5]. This process is facilitated by fibrinogen's binding to integrin receptors on tumor cells, which activates downstream signaling pathways such as PI3K/AKT and FAK/ERK [7–9]. These pathways enhance cell cycle progression, inhibit apoptosis, and support anchorage-independent growth, all of which contribute to tumor survival and expansion [7, 8].

Furthermore, fibrinogen induce the epithelial-mesenchymal transition (EMT) in cancer cells, a critical process associated with increased invasiveness and metastatic potential [10]. Fibrinogen also interacts with matrix metalloproteinases (MMPs) and other proteases to degrade the ECM, thereby facilitating tumor cell dissemination and metastasis [5].

In addition to its direct effects on tumor cells, fibrinogen influences the TME by promoting angiogenesis and modulating immune responses. Fibrinogen stimulates endothelial cell proliferation, migration, and tube formation through its interaction with vascular endothelial growth factor (VEGF) and other pro-angiogenic factors, thereby supporting the formation of new blood vessels essential for tumor growth [11]. Simultaneously, fibrinogen contributes to immune evasion by inhibiting the cytotoxic activity of natural killer (NK) cells [4], as well as promoting the polarization of macrophages toward a pro-tumorigenic M2 phenotype [12].

In vitro studies have provided detailed insights into the direct effects of fibrinogen on tumor cells. Fibrinogen binds to integrins on the surface of tumor cells, activating downstream signaling pathways such as FAK and MAPK [13]. Additionally, fibrinogen activates the NF-κB signaling pathway, leading to the secretion of inflammatory cytokines such as IL-6 and TNF-α [14]. This enhances the inflammatory response within the TME, which not only promotes tumor cell proliferation but also recruits immune cells that further drive tumor progression. Together, these in vitro findings complement in vivo observations, providing a comprehensive understanding of fibrinogen's role in tumor biology.

Studies have shown that fibrinogen is closely associated with tumor incidence, but the results from different studies have not reached a consensus. Some studies suggest that elevated fibrinogen levels are linked to an increased tumor incidence [15, 16], while others have found no significant correlation between the two [17, 18]. Therefore, the specific role of fibrinogen in tumorigenesis remains inconclusive. We conducted a comprehensive meta-analysis, meticulously synthesising evidence from all available cohort studies and case–control trials. Our objective was to assess variations in fibrinogen levels among patients with distinct tumour types, as compared to healthy individuals, thus providing insights into the underlying role of fibrinogen in various cancer types.

## 2 Methods

### 2.1 Search Strategy

This systematic review adopts the stringent standards listed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) declaration criteria. We carried out a comprehensive search in three reputable online databases: EMBASE, PubMed, and the Cochrane Library. The search strategy ("Tumor" OR "Cancer" OR "Neoplasm" OR "Carcinoma") AND ("Fibrinogen") was used to search for all publications included up to June 3, 2023. To ensure maximum comprehensiveness in literature inclusion, the search was conducted without any filters or restrictions. Additionally, references from related articles were manually indexed.

### 2.2 Study selection

In this meta-analysis, two independent investigators assessed article eligibility according to predefined criteria. Disagreements were resolved through discussion or, if necessary, by consulting a third investigator. Duplicates were removed, and the titles and abstracts of remaining studies were screened to exclude unrelated articles. Full texts of the remaining articles were reviewed, and those meeting eligibility criteria were included in the final analysis.

Studies included in this meta-analysis were selected based on the following criteria: (1) Study Design: Observational studies, including prospective cohort studies, retrospective cohort studies, and case–control studies; (2) Research Focus: Studies that examined the association between serum fibrinogen levels and the incidence of tumour/cancer/neoplasm/carcinoma in human; (3) Outcome Measures: Studies reporting hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for the association between circulating fibrinogen levels and cancer outcomes. The exclusion criteria included: (1) non-English publications; (2) studies involving a general adult population that was diagnosed with cancer; (3) sample sizes smaller than 400. This systematic approach assures the integrity and reliability of our findings, eventually contributing to the advancement of knowledge in this important area of medical research.

### 2.3 Data extraction

Eligible studies were meticulously reviewed by two independent authors, who extracted the following key data points: author, year of publication, study design, country of origin, gender distribution, cancer type, the number of cancer cases and healthy controls, as well as ORs, RRs, or HRs with their corresponding 95% CI.

### 2.4 Quality assessment

The details of the study quality assessment are comprehensively outlined in Table 1. For this assessment, we adopted the renowned Newcastle–Ottawa Scale, a well-established tool that assigns a score ranging from 1 to 9 stars. This scale rigorously evaluates each study across three pivotal dimensions: the selection of study groups, ensuring their representativeness and appropriateness; the comparability of these groups, assessing potential biases and confounding factors; and the measurement of exposure, scrutinizing the accuracy and reliability of the data collected. By adhering to this comprehensive framework, we aimed to provide a nuanced and objective evaluation of the study quality.

### 2.5 Statistical analysis

Utilizing STATA version 12.0 software, we conducted rigorous statistical analyses to examine the data. To delve deeper into the potential differences in the relationship between fibrinogen levels and tumour incidence across various tumour types, we performed subgroup analyses, categorizing the studies based on the tumor type. In addition, sensitivity analyses were used to assess the robustness of the findings and to evaluate the impact of individual studies on the overall effect size. Additionally, to make sure of the integrity of our results, we conducted a formal Egger's test to detect any potential publication bias within our dataset. Analyzes asymmetry in the relationship between standardized effect sizes (SES) and precision (1/SE) via weighted regression.

## 3 Results

### 3.1 Study selection

The literature search and selection process is depicted in Fig. 1. Initially, a primary systematic search yielded a total of 20,771 records. After meticulously excluding duplicate entries, 18,112 articles remained for further consideration. Subsequently, a rigorous screening of titles and abstracts resulted in the elimination of 18,079 articles that failed to meet the established inclusion criteria. A comprehensive review of the full texts of the remaining 33 articles was then undertaken, during which a further 21 articles were excluded due to various reasons, including but not limited to, the absence of relevant data, being mere summaries of conference proceedings, responses to previous works, or repetitive research. Ultimately, a total of 12 studies were deemed suitable and included in this meta-analysis, ensuring the rigour and relevance of the analysis's underlying evidence base.

**Table 1** The Newcastle–Ottawa Scale (NOS) scores for included publications

| First author, Year | Selection | Comparability | Outcome | NOS |
|---|---|---|---|---|
| Toriola, 2013 | 3 | 2 | 3 | 8 |
| Chandler, 2016 | 3 | 2 | 3 | 8 |
| Han, 2021 | 3 | 1 | 3 | 7 |
| Parisi, 2022 | 4 | 2 | 2 | 8 |
| Allin, 2016 | 4 | 2 | 2 | 8 |
| Tobias, 2017 | 3 | 2 | 3 | 8 |
| Grafetstätter, 2019 | 4 | 2 | 2 | 8 |
| Hefler-Frischmuth, 2015 | 3 | 1 | 3 | 7 |
| Graf, 2018 | 3 | 2 | 3 | 8 |
| dos Santos Silva, 2010 | 3 | 1 | 3 | 7 |
| Kabat, 2016 | 3 | 1 | 3 | 7 |
| Prizment, 2011 | 4 | 2 | 3 | 9 |

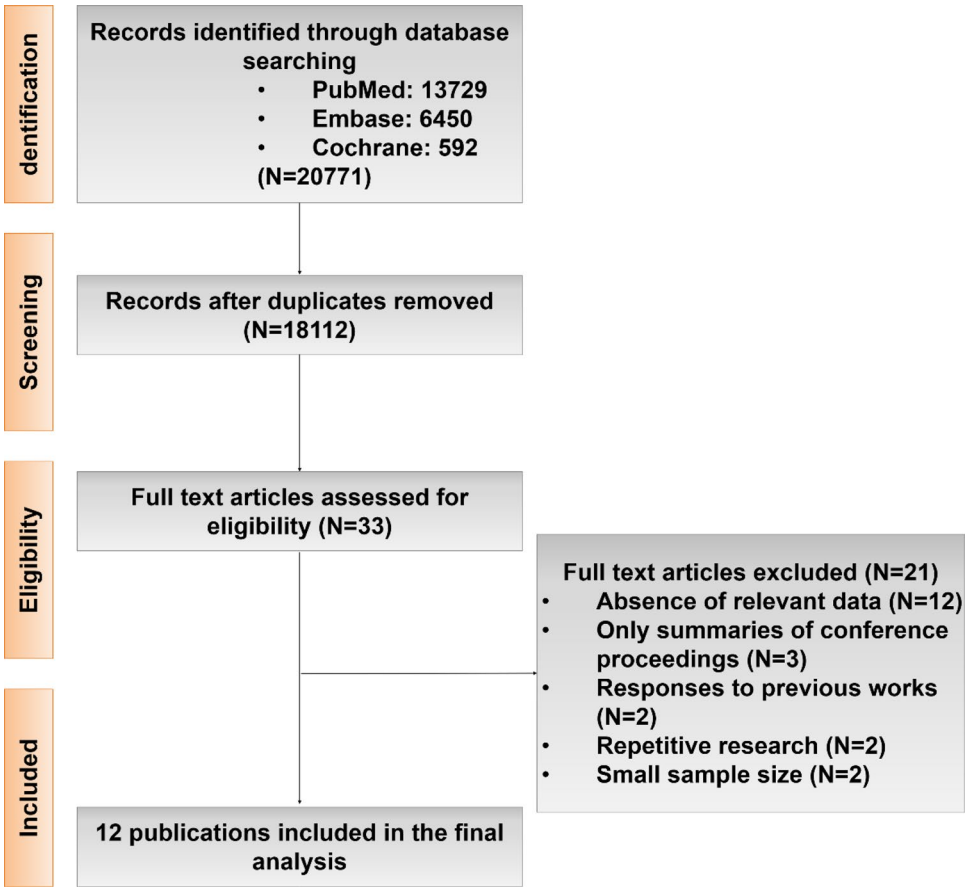


**Fig. 1** Flow diagram for the selection process of the included studies in the meta-analysis. The method followed in according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

### 3.2 Study characteristic

After integrating the studies, a comprehensive analysis encompassed a total of 11,834 cancer cases and 192,342 controls. Among the 12 publications reviewed, 4 were identified as case-cohort studies [15, 17–19]. Additionally, 6 publications were prospective cohort studies [16, 20–24], while 2 comprised case–control studies [25, 26]. Table 2 summarizes the salient features of these included publications.

We evaluated the quality of the publications using the Newcastle–Ottawa Scale (NOS) scores (Table 1). For the nested case–control study, the mean NOS score was 8, with a range spanning from 5 to 9 points. Similarly, the mean score for prospective cohort studies was 8, also within the range of 5 to 9 points. As for case–control and case-cohort studies combined, the mean score was 7.5, with a range of 5 to 9 points. Notably, four studies originated from the United States, Six from European. These studies were published between 2011 and 2022.

The analysis delved into the risks associated with various cancer types, with several studies examining multiple cancer sites as outcomes. In terms of prevalence, colorectal cancer topped the list with ten studies investigating it. The top five adjusted confounders considered in these studies were age, alcohol consumption, pack-years of smoking, gender, and energy intake.

The study participants, whose ages ranged from 45 to 75 years, demonstrated a body mass index (BMI) varying between 22.9 and 28.4 kg/m$^2$. Gender distribution among the subjects was nearly equal, with a balanced representation of males and females. Across the included studies, the HRs for various types of cancer among individuals with elevated fibrinogen levels ranged widely, from 0.61 to 6.452.

### 3.3 Meta-analysis

Table 2 provides a comprehensive summary of all the studies included in our analysis.

**Table 2** Detailed characteristics of the included publications

| First author, Year | Design type | Cancer type | Case/controls | Interpretation | Risk measure (HR/RR/OR with 95% CI) | Adjusted factors |
|---|---|---|---|---|---|---|
| Toriola, 2013 | Prospective | Prostate cancer | 203/2368 | Highest vs. lowest quartile | HR = 1.25 (95% CI 0.87–1.81) | Age, smoking, BMI, alcohol consumption, socioeconomic status, cardiorespiratory fitness, energy intake, vegetable and fruit intake, et al |
| Chandler, 2016 | Prospective | Colorectal cancer | 70/6784 | Highest vs. lowest quartile | HR = 1.31 (95% CI 0.92–1.85) | Age, sex, race, and study center, education, BMI, smoking status. et al |
| Han, 2021 | Case–control | Laryngeal squamous cell carcinoma | 218/207 | Cut-off 3.6 | OR = 2.138 (95% CI 1.615–2.831) | Age, sex, smoking history, drinking history, tumor site, and tumor size |
| Parisi, 2022 | Prospective nested case–control study | Colorectal cancer | 126/1290 | Cut-off 400 mg/dL | HR = 1.81 (95% CI 1.12–2.92) | Sex, age |
| Allin, 2016 | Prospective | All cancers | 4081/84,000 | Highest vs. lowest quartile | HR = 1.24 (95% CI 1.14–1.35) | Age, sex, body mass index, physical activity, smoking, and alcohol consumption |
| Tobias, 2017 | Prospective | Breast cancer | 1497/27,071 | Highest vs. lowest quartile | HR = 1.16 (95% CI 0.97–1.39) | Age, treatment group, breast cancer risk factors, family history, personal history of benign breast disease, alcohol consumption, smoking status, and BMI. et al |
| Grafetstätter, 2019 | Case-cohort | Lung cancer | 190/2480 | Highest vs. lowest quartile | OR = 2.03 (95% CI 1.16–3.55) | Age, sex, smoking, lifetime, alcohol intake, current aspirin use, CRP, physical activity BMI, height and education level |
| Hefler-Frischmuth, 2015 | Case–control | Ovarian tumors | 224/471 | Cut-off 390 mg/dL | HR = 2.40 (95% CI 1.40–4.00) | Age and serum CA 125 |
| Graf, 2018 | Case-cohort | Breast/prostate/colorectal cancer | 1397/2480 | Highest vs. lowest quartile | Breast cancer: HR = 1.20 (95% CI 0.87–1.67) Prostate cancer: HR = 1.05 (95% CI 0.75–1.48) Colorectal cancer HR = 0.83 (95% CI 0.55–1.24) | Age, smoking, lifetime, alcohol intake, current aspirin use, CRP, physical activity, BMI, height, education level, et al |
| dos Santos Silva, 2010 (NPHS-I) | Prospective | All cancers | 442/1606 | Highest vs. lowest quartile | RR = 1.00 (95% CI 0.75–1.34) | Age, smoking habits, and other confounders |
| dos Santos Silva, 2010 (NPHS-II) | Prospective | All cancers | 308/1747 | Highest vs. lowest quartile | RR = 1.39 (95% CI 1.01–1.91) | Age, smoking habits, and other confounders |

**Table 2** (continued)

| First author, Year | Design type | Cancer type | Case/controls | Interpretation | Risk measure (HR/RR/OR with 95% CI) | Adjusted factors |
|---|---|---|---|---|---|---|
| dos Santos Silva, 2010 (TPT low risk) | Prospective | All cancers | 1439/9265 | Highest vs. lowest quartile | RR = 1.27 (95% CI 1.06–1.52) | Age, smoking habits, and other confounders |
| dos Santos Silva, 2010 (TPT high risk) | Prospective | All cancers | 719/3559 | Highest vs. lowest quartile | RR = 1.21 (95% CI 0.83–1.76) | Age, smoking habits, and other confounders |
| Kabat, 2016 | Case-cohort study | Breast/colorectal/lung cancer | 275/5287 | Highest vs. lowest quartile | Breast: HR = 0.92 (95% CI 0.67–1.26) Colorectal: HR = 0.73 (95% CI 0.43–1.24) Lung: HR = 1.70 (95% CI 0.97–2.97) | Smoking status, BMI, physical activity, and other relevant covariates |
| Prizment, 2011 | Prospective | Colorectal cancer | 308/13,106 | Highest vs. lowest quartile | HR = 1.50 (95% CI 1.05–2.15) | Age, sex, race, education, smoking status, alcohol use, body mass index, physical activity, diabetes status, aspirin use, and hormone replacement therapy |

*OR*, odds ratio; *HR*, hazard ratio; *RR*, risk ratio, *BMI*, body mass index

Our meta-analysis, encompassing data from 15 studies, revealed a statistically significant association between fibrinogen levels and cancer incidence. Included studies analyzed data either through comparisons between extreme groups (e.g., highest vs. lowest quartiles) or by calculating risk estimates associated with incremental changes in inflammation parameters. Specifically, the pooled HR was found to be 1.33, with a 95% CI ranging from 1.16 to 1.51. This significant finding was supported by a z-score of 4.396, resulting in a *p*-value of < 0.001, indicating a highly robust relationship. Notably, significant heterogeneity was detected among the included studies, as evidenced by an $I^2$ value of 66.9% and a *p*-value of < 0.001 (Fig. 2).

The observed heterogeneity may stem from multiple sources. Methodological variations across studies, particularly in design types (prospective vs. cross-sectional), likely introduced confounding effects. Substantial population differences emerged in smoking status—a key modifier: among subjects with persistent fibrinogen elevation, current smokers constituted 61% versus 36% in transient elevation group (ex-smokers: 30% vs. 34%, respectively) [27]. Furthermore, demographic covariates including age and gender demonstrated significant associations in subgroup analyses [15]. In a pooled analysis of three UK male cohorts (n = 19,303), elevated fibrinogen demonstrated significant positive associations with overall cancer risk (HR = 1.24, 95% CI 1.12–1.38). Notably, this association was principally driven by smoking-related malignancies, particularly lung cancer. However, fibrinogen levels showed no significant correlation with non-smoking-related cancers, including digestive, genital, or hematological malignancies upon stratified analysis [23]. These findings collectively demonstrate that fibrinogen's association with cancer incidence exhibits marked etiological specificity across

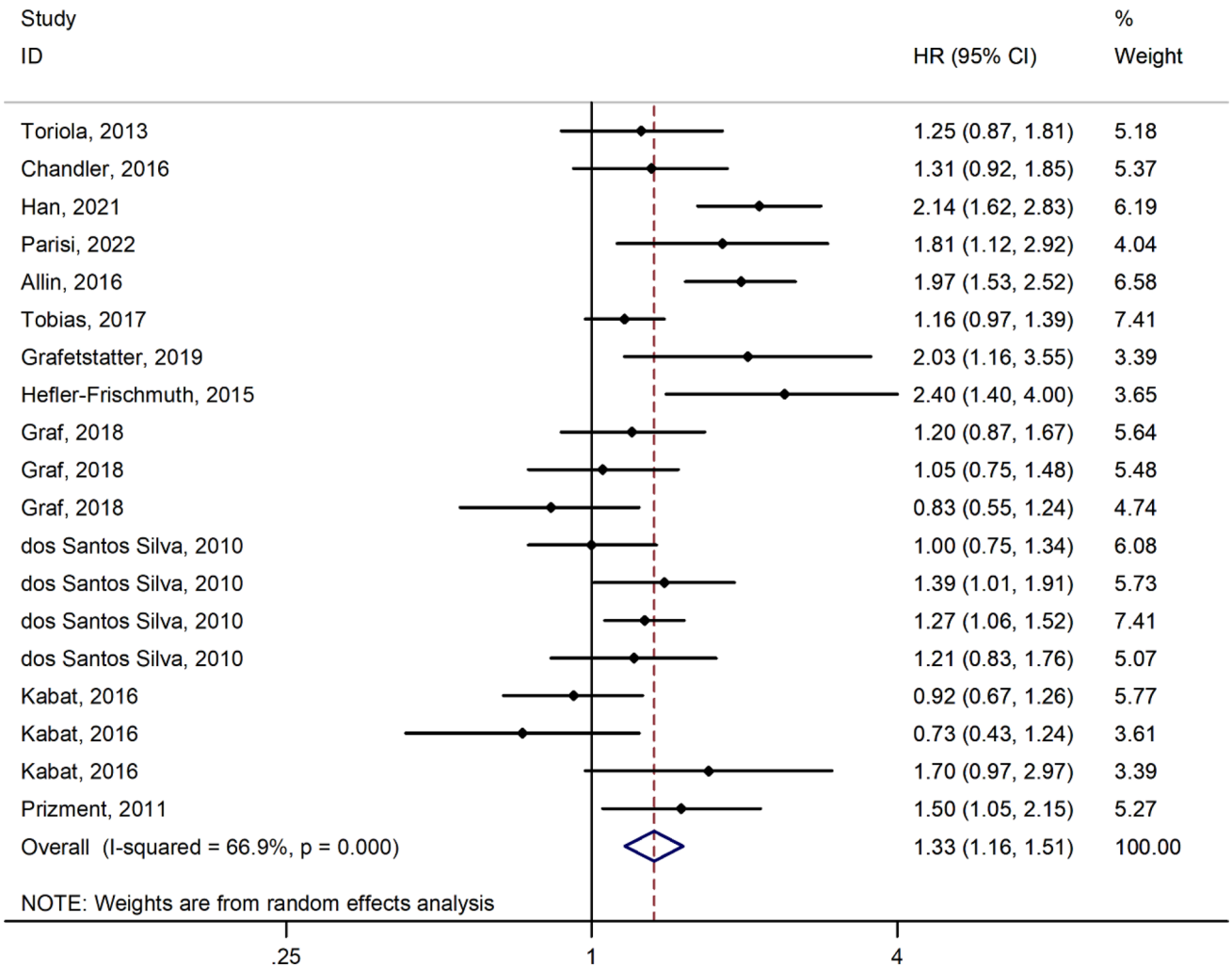


**Fig. 2** Forest plot for the plasma fibrinogen levels in the overall meta-analysis. Random-effects inverse-variance model was used to calculate the effect size. $I^2$ = proportion of total variation in effect estimate due to between-study heterogeneity

neoplastic subtypes. Notably, some studies exclusively enrolled female populations [17, 22], while some others [23] included only male participants, which may serve as a source of heterogeneity.

To delineate sources of heterogeneity, we implemented sensitivity analysis restricted to prospective studies. To further investigate this relationship and its potential variations across different cancer sites, we conducted subgroup analyses stratified by cancer type.

#### 3.3.1 Perspective studies on all types of cancer

Figure 3 presents the sensitivity analysis of the meta-analysis restricted to prospective studies investigating the association between fibrinogen and cancer, revealing an odds ratio of 1.21 (95% CI 1.11–1.31) with a z-score of 4.388 ($p < 0.001$). We observed moderate heterogeneity among the studies, with an $I^2$ value of 29.1%. However, this was not statistically significant ($p = 0.126$), indicating that the studies were relatively consistent despite potential methodological or population-specific differences.

#### 3.3.2 Smoking-related cancer

Smoking-related cancers, including lung, head and neck, esophageal, and gastric cancers, have been consistently linked to elevated fibrinogen levels in previous studies. We performed subgroup analyses specifically on

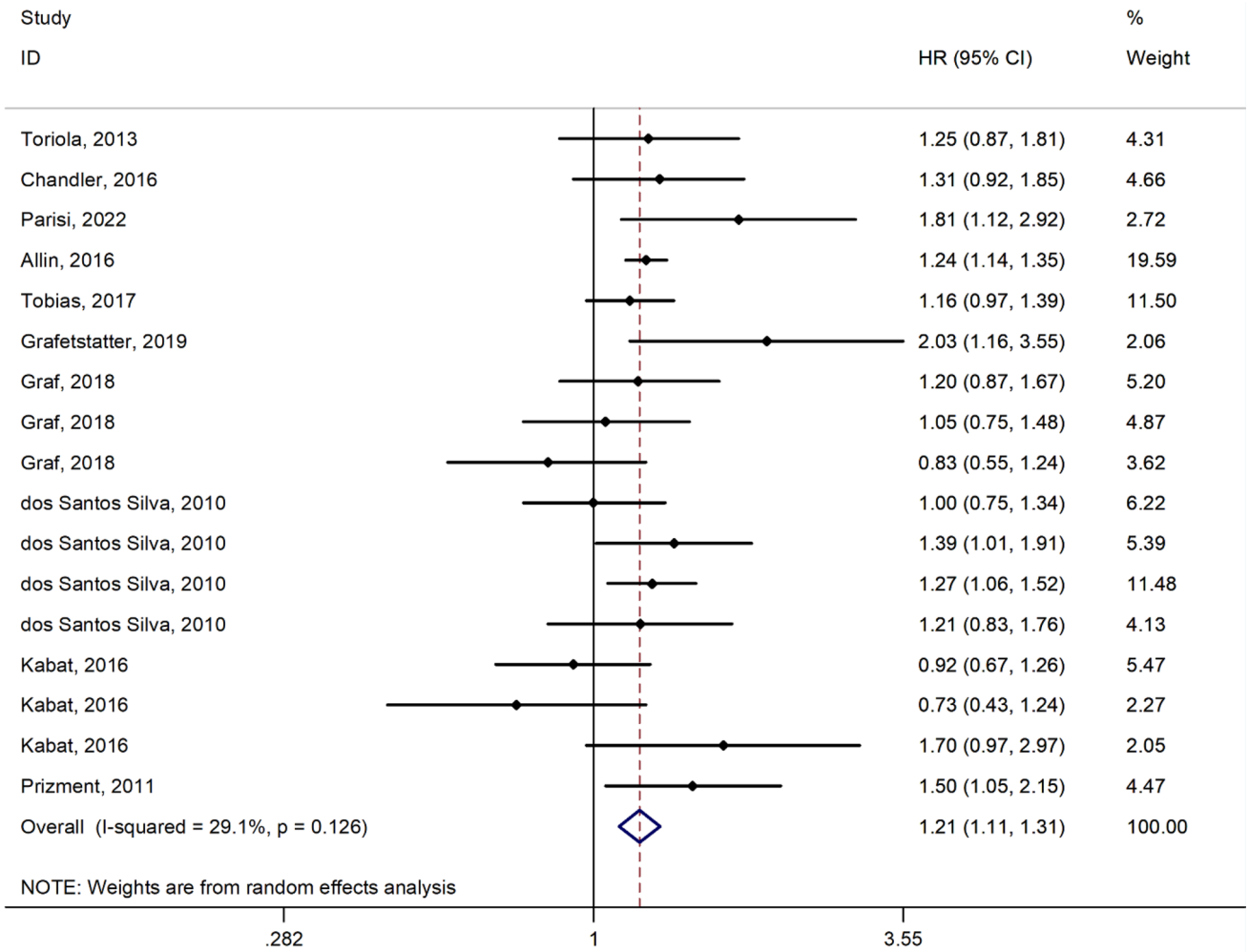


**Fig. 3** Forest plot for the plasma fibrinogen levels in the meta-analysis for perspective studies on all types of cancer. Random-effects inverse-variance model was used to calculate the effect size. $I^2$ = proportion of total variation in effect estimate due to between-study heterogeneity

smoking-related cancers (with lung cancer as the most prevalent subtype) to explore this association further. In a pooled analysis of seven prospective cohorts, including three studies focused on lung cancer, fibrinogen showed a strong association with smoking-related carcinogenesis (HR 1.79, 95% CI 1.54–2.09; z = 7.52, $p < 0.001$). The model exhibited minimal between-study heterogeneity ($I^2 = 0.00\%$, $p = 0.464$) (Fig. 4a).

### 3.3.3 Lung cancer

Additionally, we included data from seven studies (reported in four publications) investigating the relationship between fibrinogen levels and lung cancer risk. The analysis revealed an HR of 1.98 (95% CI 1.62–2.43), with a *p*-value of < 0.001, indicating a strong association. We observed low heterogeneity among the studies, with an $I^2$value of 9.0% ($p = 0.360$), suggesting consistency in methods and findings, contributing to the robustness of the overall result (Fig. 4b).

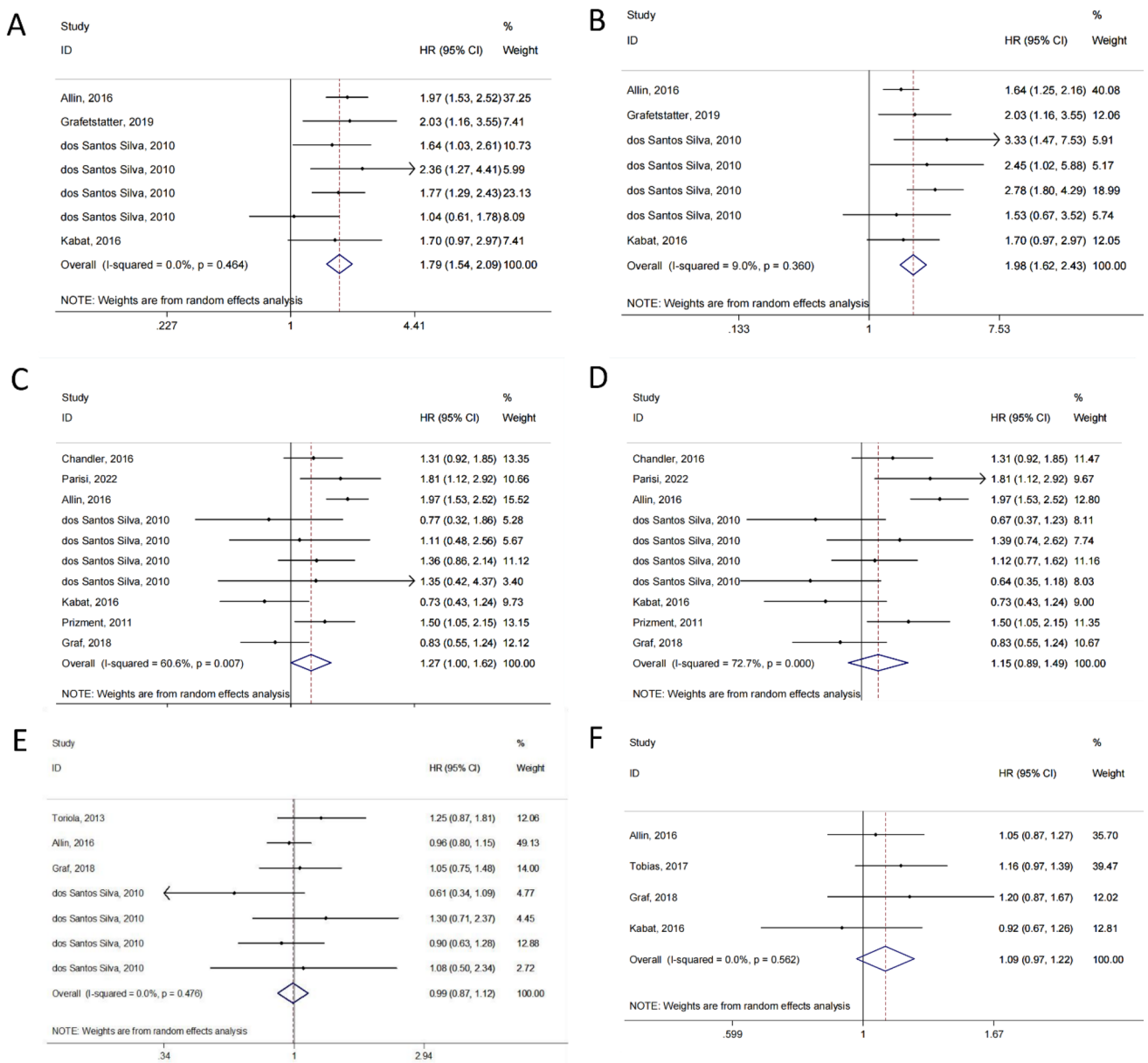


**Fig. 4** Forest plot for the plasma fibrinogen levels in the subgroup analyses. All the included studies have been sub grouped into smoking-related cancer (**a**), lung cancer (**b**), colorectal cancer (**c**), digestive system cancer (**d**), genitourinary system cancer (**e**), breast cancer (**f**)

#### 3.3.4 Colorectal cancer

Second, we included ten studies (from seven publications) investigating the relationship between fibrinogen levels and colorectal cancer incidence. The pooled analysis revealed an HR of 1.27 (95% CI 1.00–1.62), with a z-score of 1.98 and a *p*-value of 0.048. We observed relatively low heterogeneity among the studies, with an $I^2$ value of 60.6%. This was statistically significant ($p = 0.007$), indicating some inconsistencies, but the overall trend indicates a significant association between fibrinogen levels and colorectal cancer risk (Fig. 4c). To address within-group heterogeneity, we analyzed colorectal cancer risk stratified by sex. Both subgroups indicated no statistically significant association between fibrinogen levels and colorectal cancer risk ($p > 0.05$). Furthermore, the results showed no significant heterogeneity in this relationship for males ($I^2 = 0.00\%$, $p = 0.656$) (Supplementary Fig. 1).

#### 3.3.5 Digestive system cancer

Third, we synthesized data from ten studies (published in seven articles) examining the relationship between fibrinogen levels and the incidence of digestive system cancers. Six of these studies focused exclusively on CRC, resulting in findings largely consistent with those reported for CRC. The analysis yielded an HR of 1.15 (95% CI 0.89–1.49), indicating no statistical significance. We observed substantial heterogeneity among the studies, with an $I^2$ value of 72.7% ($p = 0.000$), indicating significant differences in methods, populations, or other factors (Fig. 4d).

#### 3.3.6 Genitourinary system cancer

Furthermore, we included seven studies (from four publications) examining the association between fibrinogen levels and genitourinary system cancers. The analysis yielded an HR of 0.99 (95% CI 0.87–1.12), with a z-score of − 0.149 and a *p*-value of 0.881, indicating no significant effect (Fig. 4e).

#### 3.3.7 Breast cancer

Finally, we included four studies (reported in four publications) examining the relationship between fibrinogen and breast cancer. The result was an HR of 1.09 (95% CI 0.97–1.22; $z = 1.513$; $p = 0.130$) with no heterogeneity ($I^2 = 0.0\%$; $p = 0.562$) (Fig. 4f).

In summary, when the analyses were confined to specific cancer types, namely smoking-related cancer, lung cancer, breast cancer, and cancers of the genitourinary system, as well as prospective studies encompassing all cancer types, the observed heterogeneity was notably diminished. This underscores the consistency of the findings within these subgroups.

Among these subgroups, statistical significance ($p < 0.05$) was achieved in the association between fibrinogen levels and cancer incidence for smoking-related cancers, lung cancer, colorectal cancer, and prospective studies across all cancer types. These findings highlight the potential role of fibrinogen in modulating the risk of these specific cancer types.

### 3.4 Publication bias

To evaluate the potential presence of publication bias, we employed funnel plots (Fig. 5a) and Egger's test (Fig. 5b). Our analysis revealed no discernible asymmetry in the funnel plot, indicative of an absence of significant publication bias. Egger's regression test indicated no statistically significant publication bias (intercept $p = 0.282$), suggesting symmetry in the funnel plot. However, results should be interpreted cautiously due to potential limitations in power and the need for complementary assessments.

## 4 Discussion

Fibrinogen has emerged as a pivotal factor in cancer pathogenesis [28]. Accumulating evidence highlights its dysregulation across multiple malignancies, including lung, colorectal, breast, and prostate cancers [29–31]. Fibrinogen also showed a positive association with cardiovascular disease (CVD) and cancer mortality, with HRs varying across quartiles of fibrinogen levels [32, 33]. Multiple meta-analyses have confirmed that elevated serum fibrinogen levels

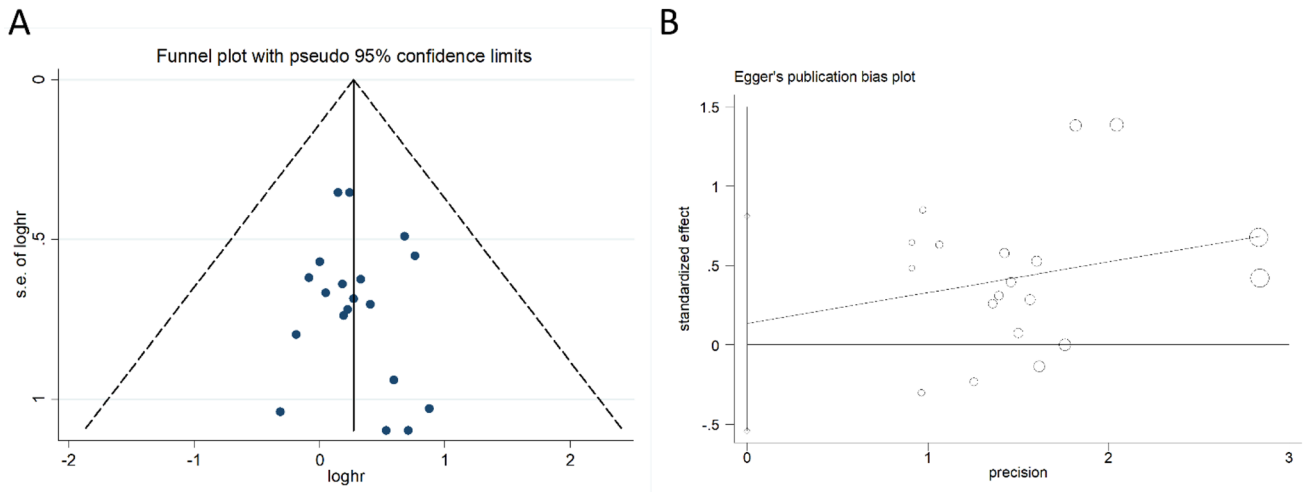


**Fig. 5** Funnel plot (**a**), and Egger's publication bias plot (**b**) for the included studies

are significantly associated with poor prognosis in various cancers, particularly in lung cancer and colorectal cancer [34–36]. However, relatively few studies have specifically focused on the association between fibrinogen and cancer incidence. Moreover, existing studies have reported inconsistent findings regarding this association. To the best of our knowledge, this is the first meta-analysis systematically evaluating fibrinogen's association with pan-cancer risk. Our findings are consistent with the meta-anakysis reported by Michels et al., which demonstrated a significant association between fibrinogen and the outcome (pooled OR = 1.22, 95% CI 1.07–1.39; $I^2 = 0\%$) [37]. Notably, this meta-analysis was limited in scope as it included only three studies with exclusively male populations, thereby introducing potential bias and limiting the generalizability of the findings. Pooling including diverse cancer types, we identified significantly elevated circulating fibrinogen levels in cancer patients compared to healthy individuals ($p < 0.001$). This finding highlights the potential significance of fibrinogen in tumour development, which aligns with existing fundamental research findings [6].

Our study has validated a significant association between serum fibrinogen levels and pan-cancer incidence. Notably, substantial heterogeneity ($I^2 = 66.9\%$) was observed in the pooled analysis. Subgroup analysis stratified by study design revealed methodological disparities, with the majority being prospective studies (n = 6) or case-cohort designs (n = 4), while a minority employed case–control methodology (n = 2). Crucially, sensitivity analysis excluding case–control studies demonstrated marked reduction in heterogeneity ($I^2 = 29.1\%$), confirming that research design constitutes a principal source of between-study variability.

Subgroup analyses further revealed tumor-specific associations. These results position fibrinogen as a potential biomarker for early detection of lung, colorectal, and smoking-related cancers, while underscoring its heterogeneous role across tumor types. Breast, genitourinary, and digestive tumors, aligning with Xu et al.'s report of fibrinogen's limited oncogenicity in breast cancer [38]. Similarly, elevated plasma fibrinogen emerged as a pan-tumor prognostic marker, with meta-analytic evidence showing progressively stronger OS detriment in renal, head/neck, lung, and colorectal cancers, but not in breast cancer [34]. The observed heterogeneity could be attributed to differential involvement of chronic inflammatory pathways in the development of distinct cancer subtypes. Chronic inflammatory responses exhibit a well-established association with tumorigenesis, particularly in malignancies such as lung and colorectal cancers, with their pathogenic roles being extensively documented in epidemiological and molecular studies [39–41]. As an acute-phase reactant, fibrinogen may mediate cancer risk through inflammation-driven mechanisms, potentially explaining the differential susceptibility across tumor types. Notably, fibrinogen exhibited pronounced associations with smoking-related malignancies. Stratification by smoking status revealed that inflammatory biomarkers, including fibrinogen, were significantly linked to lung cancer risk in former/current smokers, but not in never-smokers, aligning with prior evidence from the Fibrinogen Studies Collaboration [27]. This pattern suggests fibrinogen may partially mediate smoking's carcinogenic effects, as its oncogenic associations were confined to baseline smokers.

The robust association between fibrinogen and lung cancer is supported by preclinical evidence. Palumbo et al. demonstrated that fibrinogen deficiency reduces lung metastasis in mice, likely through restored NK cell-mediated tumoricidal activity [4]. Meanwhile, previous studies have demonstrated that elevated plasma fibrinogen levels are

associated with poor prognosis and adverse clinicopathological characteristics in lung cancer patients [42], suggesting that fibrinogen plays a pivotal role in the pathogenesis and progression of lung cancer.

For colorectal cancer, our findings contrast with previous meta-analysis conducted by Michaels et al. [37]. The observed heterogeneity could be attributed to methodological limitations in prior meta-analyses, specifically the paucity of male cohort investigations (n = 3), which substantially diminishes the statistical power and generalizability of the pooled estimates.

Apart from factors related to study design and differences in tumor types, there are other reasons that could lead to heterogeneity. As a nonspecific inflammation marker, fibrinogen levels are confounded by age, sex, ethnicity, and smoking status. While 85% of included studies adjusted for age/sex, residual confounding from unmeasured variables (e.g., estrogen-progesterone interplay in breast cancer, dietary patterns in colorectal cancer) likely persists. Significant sex disparities in cancer incidence have been well-documented across diverse populations. Men exhibit higher rates of fibrinogen-associated cancers (lung: male-to-female HR = 1.77; colorectal = 1.12) [43], whereas breast cancer, a hormonally driven malignancy with weak fibrinogen links, remains understudied in male populations. Paradoxically, the Moli-sani cohort reported stronger fibrinogen-colorectal cancer associations in women (HR = 2.24 vs. 1.84 in men), suggesting sex-dimorphic pathways [15]. Chronobiological variations in fibrinogen metabolism could potentially mediate its carcinogenic effects through time-dependent pathways. Hazard ratios attenuated with prolonged follow-up. Short-term studies (< 3 years) showed stronger associations, implying fibrinogen elevation may reflect paraneoplastic inflammation rather than initiate carcinogenesis [16].

## 5 Limitation

While this meta-analysis provides robust evidence for fibrinogen's association with tumorigenesis, several limitations necessitate cautious interpretation of the findings: The inclusion of studies with divergent designs (prospective vs. retrospective) introduces potential confounding. Prospective cohorts, though methodologically rigorous for establishing temporal relationships, may differ systematically from retrospective studies in exposure assessment and confounder adjustment. This heterogeneity complicates causal inference and increases susceptibility to selection bias. Most of participants were from Western populations, limiting generalizability to Asian/African cohorts where genetic variants differentially regulate fibrinogen metabolism. Certain studies enrolled only male participants, who typically exhibit higher smoking rates and higher incidences of lung and colorectal cancers compared to females. Covariates influencing fibrinogen-cancer relationships remain unaddressed: (1) Lifestyle: Smoking intensity (pack-years), alcohol intake, and processed meat consumption were inconsistently reported. (2) Comorbidities: Chronic inflammatory conditions (e.g., rheumatoid arthritis) and metabolic syndrome, which elevate both fibrinogen and cancer risk, were rarely adjusted. 3) Pharmacological Interventions: Statins (fibrinogen-lowering) and oral contraceptives (fibrinogen-elevating) may have introduced unmeasured confounding.

## 6 Conclusion

This meta-analysis establishes elevated plasma fibrinogen as a pan-cancer risk biomarker, showing strongest associations in smoking-related cancer (HR = 1.79), lung (HR = 1.98) and colorectal cancers (HR = 1.27). Current limitations in temporal dynamics assessment and confounding control necessitate: (1) Study designs: Longitudinal cohorts with serial fibrinogen measurements to disentangle acute/chronic inflammation effects. (2) Stratification: Sex-specific and molecular subtype analyses addressing population heterogeneity. (3) Mechanistic rigor: Multi-omics integration with preclinical models elucidating fibrinogen's dual roles in coagulation and tumor-stroma interactions. Causal inference approaches (Mendelian randomization) and mechanism-driven cancer classification will clarify fibrinogen's etiological role, advancing personalized risk prediction and anti-coagulation therapeutic strategies. International consortia pooling data from > 500,000 subjects are urgently needed to validate these associations in rare cancer subtypes.

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**Data availability** The datasets analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate** Not applicable.

**Patient consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.



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