Title: Tobacco smoking and survival after a prostate cancer diagnosis: A systematic review and meta-analysis

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ABSTRACT

Background

While a number of studies indicating tobacco smoking has a detrimental impact on survival and recurrence after a prostate cancer diagnosis, there has been no quantitative review of this literature and it is unclear whether tobacco smoking affects clinical populations differentially. We conducted a systematic review and meta-analysis to investigate the associations between tobacco smoking and overall (OM) and prostate cancer-specific (PSM) mortality and recurrence after a prostate cancer diagnosis.

Methods

EMBASE and ISI Web of Science were searched for English-language studies, published up to August 17, 2017, which conducted a survival analysis to estimate the association between tobacco smoking and OM, PSM and/or recurrence. A random-effects meta-analysis was conducted to estimate the summary hazard ratios (HRs) for the associations between tobacco smoking and the three outcomes.

Results

A total of 28 studies met the inclusion criteria. The results of the primary meta-analysis indicate current smokers have significantly poorer overall survival (Summary HR=1.96, 95% CI=1.69, 2.28), prostate cancer-specific survival (Summary HR=1.79, 95%CI=1.47, 2.20) and recurrence-free survival (Summary HR =1.48, 95%CI=1.28, 1.72) than never smokers. Similar results were found in population-based studies and in studies conducted in specific clinical populations.

Conclusions

The results of this systematic review and meta-analysis indicate that tobacco smoking at prostate cancer diagnosis is associated with a significantly increased risk of overall mortality,

prostate-cancer specific mortality and recurrence. We recommend future studies collect more detailed information about tobacco smoking to further understanding of the association between tobacco smoking and PCa prognosis. In addition, further research should concentrate on the impact of smoking cessation post-diagnosis and post-treatment on prognosis, and the feasibility and effectiveness of smoking cessation programs.

Keywords: prostate cancer; tobacco smoking; mortality; prognosis; survival

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer among men worldwide, with an estimated 1.1 million new cases diagnosed in 2012.[1] PCa survival has improved significantly in the last few decades, and relative 5-year survival in most high income countries is now estimated to be above 90%.[2-4] Treatment and early detection have been recognized as the most likely reason for the observed increase in survival rates.[1] Despite the advancement in survival rates,[5] PCa is still the 3rd most common cause of cancer death among men in more developed countries.[1] Few non-clinicopathological prognostic factors for PCa have been identified, so it is important to identify potentially modifiable intervention targets which could further improve survival of PCa patients and prevent progression and recurrence of PCa,

While recent reviews report no association between tobacco smoking and PCa incidence [6, 7] a modest association has been reported between tobacco smoking and PCa mortality, suggesting tobacco smoking could potentially play a role in PCa progression.[6] A number of published papers have investigated the impact of tobacco smoking on survival and recurrence in males diagnosed with PCa, with the majority of these finding tobacco smoking is associated with higher overall mortality (OM), prostate-cancer specific mortality (PSM) and recurrence.[8] However these studies have been conducted in varied clinical populations and the reporting of results has been heterogeneous. To our knowledge, there has been no previous quantitative review of these studies.

We conducted a systematic review and meta-analysis of studies that have assessed the impact of tobacco smoking behaviors on overall mortality (OM), PCa-specific mortality (PSM) and recurrence among men diagnosed with PCa.

METHODS

Reporting guidelines and protocol registration

We followed the PRISMA guidelines whilst conducting this review.[9] Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at goo.gl/HZRX28.

Eligibility Criteria and Search Strategy

A systematic literature search of two electronic databases (EMBASE and ISI Web of Science) was conducted on December 12, 2016 to identify all studies up to that date which had investigated the association of tobacco smoking on survival in men diagnosed with PCa. In addition, reference lists of identified articles and relevant review articles were scanned for further articles that may not have been found in our electronic database search. The literature search was updated on August 17, 2017. Only studies in English were included. The search terms used for searches conducted in EMBASE and ISI Web of Science are available in Supplementary Table 1.

We included studies in which a survival analysis (i.e., a Cox proportional hazard regression model) was used to estimate the association between tobacco smoking and OM, PSM and/or recurrence. The removal of duplicates and assessment of articles eligibility based on title and abstract was completed by one author (ED). Full text assessment of eligibility was then performed independently by two authors (ED and TB) and any disagreements were resolved by consensus. Studies which provided an effect measure (i.e., a hazard ratio), quantifying the impact of smoking on one or more of the outcomes were eligible for inclusion in the meta-analysis. If the same patient sample appeared in more than one study the most informative article was kept in the review.

Data extraction

We developed a data extraction sheet which was pilot-tested in seven studies, and then modified accordingly. Data items were initially extracted by one author (ED) and included the following information on each study: (1) study participant characteristics (including age, stage and/or Gleason score, and treatment received), and the years and method of participant recruitment; (2) the type of exposure (including exposure timing, method of exposure measurement, and exposure status and/or dose); (3) type of outcome (including OM, PSM and recurrence), and outcome measurement quality and completeness; (4) prognostic factor adjustments (including measurement of prognostic factors); (5) effect estimates (i.e., hazard ratios) and corresponding 95% confidence intervals or p-values for the association of smoking with OM, PSM and/or recurrence. The extracted data were checked independently by a second author (TB) and any disagreements were discussed until a final decision was arrived at. Where a study reported inadequate data to include one or more outcomes in the meta-analysis, we requested the information from the corresponding author by email. Eleven authors were contacted for further information and we received information requested from two authors. Two articles were excluded from the meta-analysis at this point as insufficient information was available and no response was received from the authors. All extracted data are available from the authors by request.

Assessment of Risk of Bias in Individual Studies

Risk of bias in each included study was assessed independently by two authors (ED and TB) using the "Tool to Assess Risk of Bias in Cohort Studies", with disagreements resolved by consensus.[10] Three of the eight items were determined to be irrelevant for this review, so only the five following items were assessed: (1) "Can we be confident in the assessment of exposure?"; (2) "Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these

prognostic variables?"; (3) "Can we be confident in the assessment of the presence or absence of prognostic factors?"; (4) "Can we be confident in the assessment of outcome?"; and (5) "Was the follow up of cohorts adequate?". Each item was assessed as definitely yes, probably yes, probably no or definitely no for each outcome (i.e., OM, PSM and/or recurrence) in each study. In addition to the individual risk of bias items, studies were classified as having an overall lower risk of bias if all of the five items were assessed as definitely yes or probably yes, and as having a higher risk of bias if one or more of the five items was assessed as definitely no or probably no.

Statistical Analysis

We used random-effects meta-analysis to estimate the summary hazard ratios for the associations between tobacco smoking and OM, PSM and/or recurrence. For each outcome, we investigated the difference between the following pairs of exposure status definitions: (1) current smokers vs never smokers, (2) current smokers vs not current smokers, (3) ever smokers vs never smokers, and (4) former smokers vs never smokers. Heterogeneity was assessed using the I^2 and Q statistics. Publication bias and small study effects were assessed by visualising funnel plots and results of the Egger test.

Subgroup Analyses

Four pre-specified subgroup analyses were conducted: by clinical population (all patients, patients receiving Radical Prostatectomy (RP), or patients receiving Radiation Therapy (RT) (includes External Beam Radiation Therapy (EBRT) and Brachytherapy (BT))); by smoking measurement timing (Before/at diagnosis, or at treatment/post treatment); by study region (North America, Asia, or Europe) and by risk of bias (lower risk of bias or higher risk of bias). Meta-regression analysis was used to calculate ratios of risk estimates to test for statistically significant effect modification by clinical population, exposure timing, country region and risk of bias.

Smoking status was defined in several ways in the included studies, so a post-hoc subgroup analyses was performed to determine whether there were differences in the risk estimates obtained in studies which compared (1) current smokers vs never smokers, (2) current smokers vs not current smokers, and (3) ever smokers vs never smokers. The results of this subgroup analysis indicated the results from studies comparing ever smokers and never smokers were significantly different to those which compared current smokers and never smokers or current smokers with non-current smokers. As such, studies comparing ever smokers and never smokers were not included in the four pre-specified subgroup analyses outlined in the previous paragraph.

All statistical tests were two-sided, and a P-value less than .05 was considered statistically significant. All analyses were conducted with Stata software (version 14.2; StataCorp, College Station, Tx).

RESULTS

Study selection

We identified 4,144 articles in our literature search (Figure 1). Of those, 4,116 were excluded; 1,072 as duplicates, 2,960 by abstract review and 84 by full-text review. No further relevant articles were discovered upon reference list review. A total of 28 articles were included in this systematic review and meta-analysis [11-38].

Study characteristics

Detailed information on the characteristics of the 28 studies included in the primary meta-analysis is provided in Table 1. These 28 studies included a total of 70,737 patients diagnosed with PCa, with study population sizes ranging from 74 to 18,900. Included studies were published between 1997 and 2017. There were fourteen studies conducted in the US,[12, 15, 17-20, 29-32, 34, 35, 37, 38] two in Canada, [23, 25] two in South Korea, [22, 24] and one

each in The Netherlands,[11] Turkey,[13] Malaysia,[14] Germany,[16] Spain,[21] Italy,[26] Japan,[28] China,[33] and Sweden[36]. One study was conducted in the US and Austria[27]. Nineteen studies reported OM[11, 12, 15, 16, 19-21, 23-26, 31-38], 15 reported PSM [12, 14-17, 19-21, 23, 25, 26, 30, 34-36] and 12 reported recurrence[13, 15, 18-20, 22, 23, 25, 27-30]. Fifteen studies examined survival after a specific type of treatment, [13, 15, 16, 18, 20, 22, 23, 25, 27-32, 34], of which eight looked at survival after RP,[13, 15, 16, 18, 20, 22, 27, 28] and seven after RT [23, 25, 29-32, 34]. Tobacco smoking status was measured before or at time of diagnosis for 14 studies [11, 12, 14, 17, 19, 21, 24, 26, 27, 30, 35-38] and post diagnosis or at time of treatment for 13 studies.[13, 15, 16, 20, 22, 23, 25, 28, 29, 31-34] One study collected smoking status at both time points.[18] The prevalence of current smoking ranged from 5.2% to 48.6% (median = 16.1%). Four studies investigated survival in those with stage I-III PCa.[19, 21, 32, 35]

Risk of bias within studies

Of the 19 articles which investigated OM, we assessed 12 as having a lower risk of bias[11, 12, 15, 16, 19-21, 26, 31, 33, 36, 38] and seven as having a higher risk of bias.[23-25, 32, 34, 35, 37] Nine of the 15 articles investigating PSM were determined to have lower risk of bias[12, 15-17, 19-21, 26, 36] and six a higher risk of bias.[14, 23, 25, 30, 34, 35] Half of the twelve articles investigating recurrence were determined to have a lower risk of bias.[15, 19, 20, 22, 23, 25] The number of articles which adjusted for at least age and a clinical prognostic factor (e.g., Stage or Gleason score) were 15 (out of 19) for OM,[11, 12, 15, 16, 19-21, 23, 26, 31, 33, 35-38] 12 (out of 15) for PSM [12, 15-17, 19-21, 23, 26, 30, 35, 36] and 10 (out of 12) for recurrence.[13, 15, 18-20, 22, 23, 25, 27, 30]

Meta-analysis

Overall Mortality (OM)

The summary HR of the main results from the ten studies which compared current vs never smokers indicated an almost 2-fold greater risk of OM within the follow-up period for those who were current smokers compared to those who never smoked (HR=1.96, 95% CI=1.69, 2.28; Heterogeneity: I^2=30.1%, p=0.168) (Figure 2, Table 2). Similarly, the summary HR from the six studies which compared current smokers vs not current smokers indicated a 63% greater risk of OM for current smokers (HR: 1.63, 95%CI=1.37, 1.94). Heterogeneity across these studies was high (I^2=71.4%, P=0.004). From the three studies which compared ever smokers vs never smokers, the summary HR indicated a 17% greater risk for ever smokers (HR=1.17, 95%CI=1.05, 1.31; Heterogeneity: I^2=0.0%, p=0.481).

Eight studies compared former smokers with never smokers. The summary risk estimate from these studies indicates a 28% greater risk of OM for former smokers compared with never smokers (HR=1.28, 95%CI=1.14, 1.45; Heterogeneity: I^2=21.4%, p=0.260) (Figure 2, Table 3).

Very similar summary risk estimates for OM were found for the three different clinical populations when comparing current smokers with never or not current smokers (studies including all PCa patients: HR=1.80, 95%CI=1.47, 2.20; studies including only patients undergoing RP: HR=1.90, 95%CI=1.60, 2.25; studies only including patients undergoing RT: HR=1.75, 95%CI=1.31, 2.34) (Table 2). The meta-regression revealed no statistically significant difference between the HRs from studies which compared current smokers vs not current smokers with studies which compared current smokers vs never smokers (Ratio of HRs=0.82, 95%CI= 0.65, 1.04). However, results from studies which compared ever smokers vs never smokers were statistically significantly lower than those which compared current vs never smokers (Ratio of HRs=0.62, 95%CI= 0.46, 0.82) (Table 2). The summary risk

estimates for former vs never smokers were also similar in the different clinical populations (Table 3). The results of the other subgroup meta-analyses also revealed no differences in summary HRs by exposure timing, country or risk of bias (Table 2 and 3).

Prostate Cancer Specific Mortality (PSM)

The summary HR for the nine studies investigating the effect of current smoking vs never smoking on PSM revealed an 79% greater risk among current smokers (HR=1.79, 95%CI=1.47, 2.20; Heterogeneity: I^2=0.0%, p=0.712) (Figure 3, Table 2). A statistically significant summary HR was also observed for the four studies which compared current smokers with not current smokers, with a 37% greater risk among current smokers (HR=1.37, 95%CI=1.19, 1.58; Heterogeneity: I^2=0.0%, p=0.770). There was no evidence of an increased risk when comparing ever smokers with never smokers (HR=1.08, 95%CI= 0.90, 1.30; Heterogeneity: I^2=0.0%, p=0.594).

Meta-regression results revealed a statistically significantly lower HR among studies which compared ever vs never smokers than studies which compared current vs never smokers (Ratio of HRs=0.60, 95%CI= 0.45, 0.82) and a lower but non statistically significant difference between studies which compared current smokers vs not current smokers and studies comparing current vs never smokers (Ratio of HRs=0.76, 95%CI= 0.58, 1.00) (Table 2).

There was no evidence of a difference in PSM for the summary HR for the seven studies investigating difference between former and never smokers (HR=1.09, 95%CI=0.93, 1.27; Heterogeneity: I^2=0.0%, p=0.770) (Figure 3, Table 3).

As for OM, summary HRs were found to be similar among studies conducted in the different clinical populations when comparing current smokers to never or not current smokers (All patients: HR=1.50, 95%CI=1.30, 1.72; RP only: HR=1.34, 95%CI=0.87, 2.06; RT only:

HR=1.93, 95%CI=1.30, 2.87) and former vs never smokers (All patients: HR=1.10, 95%CI=0.92, 1.30; RT only: HR=1.10, 95%CI=0.62, 1.93). No differences in summary HRs were observed in exposure timing, country or risk of bias subgroup analysis (Table 2 and 3).

Recurrence

The summary HR for the eight studies which investigated differences in recurrence between current smokers and never smokers showed a 48% greater risk for those who were current smokers (HR=1.48, 95%CI=1.28, 1.72; Heterogeneity: I^2=29.3%, p=0.194) (Figure 4, Table 3). A small but non-statistically significant summary HR was found for the three studies comparing recurrence between current smokers and not current smokers (HR=1.22, 95%CI=0.94, 1.58; I^2=50.1, p=0.135). Only one study compared recurrence between ever smokers and never smokers, finding no evidence of a difference in recurrence (HR=0.88, 95%CI=0.70, 1.11).

Results from the meta-regression shows no evidence of a difference between the HRs for studies which compared current smokers and not current smokers and studies which compared current and never smokers (Ratio of HRs=0.81, 95%CI= 0.59, 1.12) however the HRs for the study which compared ever smokers and never smokers were statistically significantly lower than studies which compared current vs never smokers (Ratio of HRs=0.59, 95%CI= 0.38, 0.92) (Table 2).

The summary HR for the six studies examining recurrence for former vs never smokers found a 22% greater risk for former smokers compared to never smokers (HR=1.22, 95%CI=1.04, 1.42; Heterogeneity: I^2=50.5%, p=0.072) (Figure 2, Table 3).

For studies investigating recurrence among clinical subgroups, summary HRs were found to be similar for those comparing current and never or not current smokers (All patients: HR=1.61, 95%CI=1.16, 2.23; RP only: HR=1.32, 95%CI=1.06, 1.65; RT only: HR=1.50,

95%CI=1.22, 1.84) and former vs never smokers (All patients: HR=1.11, 95%CI=0.96, 1.29; RP only: HR=1.47, 95%CI=1.09, 1.96; RT only: HR=1.10, 95%CI=0.94, 1.28). No differences in summary HRs in results for subgroup meta-analysis for exposure timing, country region or risk of bias assessment were observed (Table 2 and 3).

Publication Bias

Visual inspection of funnel plots showed no evidence for publication bias or small study effects for any of the three outcome and exposure definition combinations. There were no statistically significant results for the Egger test (Supplementary Figures 1-3).

DISCUSSION

The results of this systematic review and meta-analysis indicate tobacco smoking status at diagnosis is associated with significantly poorer prognosis among men diagnosed with PCa. The summary HRs indicate a 96%, 79% and 48% higher risk of OM, PSM and recurrence respectively among current smokers at diagnosis when compared to those who have never smoked. Higher risks of OM (HR=1.63), PSM (HR=1.37) and recurrence (HR=1.22) were also observed in studies which compared current smokers with non-current smokers (i.e., never smokers and former smokers), although these summary risk estimates were attenuated when compared with those from studies comparing current smokers and never smokers. Similar summary results were obtained from studies of all PCa cases and from studies which only included cases receiving RP or RT, indicating tobacco smoking has a negative impact on prognosis regardless of which type of treatment is received.

The studies included in this systematic review and meta-analysis provide strong and consistent evidence of poorer prognosis after a PCa diagnosis for smokers than for non-smokers. This finding is in line with recent reviews investigating the impact of tobacco smoking on survival after a diagnosis of colorectal,[39] breast,[40] and urothelial cancer[41],

which have also found those who smoke at diagnosis have a poorer prognosis. Given the median prevalence of current tobacco smoking in the studies included in this review was 16%, it is likely that tobacco smoking is responsible for a substantial burden of premature mortality among people diagnosed with PCa. As such, and as has been previously suggested for other cancers,[41] the use of smoking cessation programs for men diagnosed with PCa cancer should be given high priority in disease management. Research indicates smokers who are diagnosed with PCa are more likely to quit smoking than smokers who have never received a cancer diagnosed,[42] suggesting a PCa diagnosis may be a 'teachable moment' and as such be an opportune time to promote smoking cessation. However, we are not aware of any studies that have investigated the effectiveness of different smoking cessation programs in PCa patients, so research in this area, as well as the effect of such programs on short and long-term outcomes, should also be given high priority.

In this meta-analysis we found former smokers had a greater risk of OM and recurrence than never smokers, however no significant association was found for PSM and the risk increases for OM and recurrence were substantially smaller than those seen for current smokers. These results indicate males who have quit smoking have better prognosis after a PCa diagnosis than those who continue to smoke. We also found significantly lower summary effect sizes for OM, PSM and recurrence in studies which compared ever smokers with never smokers than in studies which current smokers with either never smokers or non-smokers. The one study included in this review which investigated post-treatment smoking and outcomes found smoking one year after surgery was associated with a more than two-fold increased risk of recurrence compared to never smokers, but no evidence of an increased risk of recurrence among former smokers one-year post surgery.[18] Two other studies included in this review found poorer outcomes among those who quit smoking less than 10 years ago than among never smokers, with neither study observing a difference in survival outcomes between never

smokers and those who quit smoking more than ten years ago.[17, 19] Hence, it could conceivably be hypothesized that quitting smoking after a PCa diagnosis is associated with improved outcomes when compared to those who continue to smoke, as has been observed in studies conducted in lung,[43] urothelial[41] and breast[44] cancer patients. Future studies should directly examine whether smoking cessation post-diagnosis improves PCa prognosis.

In this meta-analysis we found the summary HRs for OM were greater than those for PSM. There are many common comorbidities associated with smoking which are likely to have contributed to the excess risk in all-cause mortality observed for current smokers. For example, previous studies have found men who are smokers at the time of PCa diagnosis have double the risk of both cardiovascular disease mortality and mortality from a second cancer compared with never smokers.[16, 19] However it is important to note our meta-analysis indicates current smoking is associated with higher risks of both PSM and recurrence, suggesting tobacco smoking has a specific effect on PCa progression. While the mechanism through which tobacco smoking may impact on PCa progression is not clear, many biologically plausible mechanisms have been suggested. These include: (1) deregulation of biological processes such as angiogenesis, proliferation and apoptosis from exposure to nicotine; (2) smoking-associated tumor DNA methylation promoting aggressive disease; (3) toxic substances in tobacco smoke such as cadmium and nitrosamines impacting on tumor promotion; and (4) testosterone level increases in plasma which is involved in PCa development and progression in current smokers.[19]

This study has some limitations which should be taken into account. Firstly, although we conducted a comprehensive literature search involving multiple databases and checking reference lists in relevant original and review articles, we may have missed relevant studies published in a language other than English. Secondly, we were unable to include all relevant studies identified in the literature search as insufficient data were reported in those papers and

we were unable to obtain the information from the authors. Thirdly, we were unable to investigate whether a dose response relationship existed between smoking intensity (e.g., pack-years) and survival after PCa diagnosis as few studies had information about pack-years, and the category definitions across the studies which did have pack-year data were too broad. For similar reasons we were unable to look at time since cessation among former smokers in this review. The lack of detailed information about smoking may have resulted in measurement error and/or exposure misclassification in the individual studies included in this review, so we recommend future studies collect more detailed information about tobacco smoking, including frequency and volume and time since quitting, to further understanding of the association between tobacco smoking and PCa prognosis. We also recommend all future studies collect information on current smoking status; in subgroup analysis we found the summary effect size for OM, PSM and recurrence were significantly lower in studies which compared ever smokers with never smokers than in studies which compared current smokers to never- or non-smokers, indicating that studies which do not have information about participants' current smoking status are likely to significantly underestimate the effect tobacco smoking has on PCa prognosis. In addition, previous research suggests the pattern of smoking over the lifetime may influence the association between tobacco smoking and prostate cancer risk [45], so this may also be an avenue for further research on smoking and prostate cancer survival.

The results of this systematic review and meta-analysis indicate that there is strong and consistent evidence of an increased risk of OM, PSM and recurrence among those who smoke tobacco at the time of PCa diagnosis. There was no evidence that the negative impact of tobacco smoking on survival differed across clinical populations. Further research should concentrate on the impact of smoking cessation post-diagnosis and treatment on prognosis, and the feasibility and effectiveness of smoking cessation programs.

Conflicts of Interest: None to declare

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Table 1: Characteristics of studies included in the review

First Author	Year	Country	Recruitment	Follow-up		Sample Size	Age		Smoking timing	Prevalence of Current Smoking (%)	Outcomes assessed	Risk of bias assessment[b] (Overall)
				End	Median		Range	Median[a]				
Aarts[11]	2013	NL	1991-2008	2009	NR	271	NR	70.1[c]	Dx	NR	OM	L
Antwi[12]	2013	US	2001-2010	2010	NR	18900	40-99	63.9-66.9[c]	Dx	41.7	OM/PSM	L/L
Arslan[13]	2017	TR	2009-2015	NR	NR	86	NR	62.2[c]	Tx	NR	R	H
Chemay[14]	2008	MY	1983-2004	2004	25.8 months[a]	74	56-87	NR	Dx	48.6	PSM	H
Curtis[15]	2017	US	1993-2014	2014	3.6 years	1924	NR	59-62	Tx	15.2	OM/PSM/R	L/L/L
Froehner[16]	2017	DE	1992-2007	NR	Censored~9.6 years	2630	NR	65	Tx	10.8	OM/PSM	L/L
Gong[17]	2008	US	1993-1996	2007	11.5 years	752	40-64	NR	Dx	16.4	PSM	L
Joshu[18]	2011	US	1993-2006	2009	7.3 years[a]	1416	NR	54.3-57.4[c]	Dx/Tx	6.7	R	H
Kenfield[19]	2011	US	1986-2006	2008	3.8-8.1 years	5366	NR	68-70.8[c]	Dx	5.2	OM/PSM/R	L/L/L
Moreira[20]	2014	US	1995-2010	NR	61-78 months	1670	NR	61	Tx	29.7	OM/PSM/R	L/L/L
Murta-Nascimento[21]	2015	ES	1992-2008	2011	Censored ~5.8 years	1109	44.3-90.2	70.6	Dx	NR	OM/PSM	L/L
Oh[22]	2012	KR	2004-2010	>2 years	NR	1165	NR	63.9-65.7[c]	Tx	16.1	R	L
Pantarotto[23]	2007	CA	1990-1999	NR	70.3 months	416	46-83	69.3	Tx	16.8	OM/PSM/R	H/H/L
Park[24]	2006	KR	1996-2002	2004	3.86 years	256	NR	NR	Dx	NR	OM	H
Pickles[25]	2004	CA	1994-1997	2003	53-64 months	601	NR	70-72	Tx	14.6	OM/PSM/R	H/H/L
Polesel[26]	2015	IT	1995-2002	2013	12.7 years	780	46-74	66	Dx	19.7	OM/PSM	L/L
Rieken[27]	2015	US/AT	2000-2011	NR	Censored~28 months	6538	NR	61	Dx	33.9	R	H
Sato[28]	2017	JP	2003-2013	NR	39 months	1165	NR	65-66	Tx	19.4	R	H
Solanki[29]	2013	US	1988-2008	NR	57 months	633	42-88	69	Tx	NR	R	H
Steinberger[30]	2015	US	1988-2005	NR	95 months	2095	NR	NR	Dx	7.6	PSM/R	H/H
Stone[31]	2014	US	1990-2007	>5 years	10 years[a]	1669	39-85	66	Tx	NR	OM	L
Taira[32]	2012	US	1995-2008	>3 years	7.5 years	2057	NR	66	Tx	16	OM	H
Tao[33]	2013	CN	1986-1989	2010	NR	132	NR	73.3	Tx	NR	OM	L
Tendulkar[34]	2013	US	1996-2009	NR	74 months	660	40-86	68	Tx	NR	OM/PSM	H/H
Warren[35]	2013	US	1982-1998	2010	NR	513	NR	65.6[c]	Dx	NR	OM/PSM	H/H
Wilson[36]	2016	SE	1971-1992	2007	4.5 years[a]	9582	NR	70.2[c]	Dx	NR	OM/PSM	L/L
Xiao[37]	2015	US	2001-2007	2012	NR	6457	40-95	66.45[c]	Dx	15.5	OM	H
Yu[38]	1997	US	1990-1995	NR	NR	1820	NR	NR	Dx	NR	OM	L

Abbreviations: *Country:* AT, Austria; CA, Canada; CN, China; DE, Germany; ES, Spain; IT, Italy; JP, Japan; KR, Republic of Korea (South Korea); MY, Malaysia; NL, The Netherlands; SE, Sweden; TR, Turkey; US, United States of America. *Follow-Up:* NR, Not reported. *Smoking Timing*: Dx, smoking exposure information was pre/at diagnosis; Tx, smoking exposure information collected after diagnosis or at/post treatment. *Outcomes Assessed*: OM, Overall Mortality; PSM, Prostate Cancer-Specific Mortality; R, Recurrence. *Risk of Bias*: H, Higher risk of bias; L, Lower risk of bias

a. Studies with a range of values either reported median/mean age for different levels of the exposure or different population subgroups
b. Risk of bias assessment was completed for each outcome within each study
c. Mean reported instead of median

Table 2. Summary of results from the primary and subgroup meta-analyses for current vs never smokers, current vs not current smokers, and ever vs never smokers for overall mortality, prostate-cancer specific mortality and recurrence.

	Overall mortality					Prostate cancer specific mortality					Recurrence				
	Meta-Analysis		Heterogeneity		Meta-Regression	Meta-Analysis		Heterogeneity		Meta-Regression	Meta-Analysis		Heterogeneity		Meta-Regression
	n	HR (95% CI)	I^2,%	*P*[a]	Ratio of HRs (95% CI)	*n*	HR (95% CI)	I^2,%	*P*[a]	Ratio of HRs (95% CI)	*n*	HR (95% CI)	I^2,%	*P*[a]	Ratio of HRs (95% CI)
Exposure definition															
Current vs Never	10	1.96 (1.69, 2.28)	30.1	0.168	1.00 (reference)	9	1.79 (1.47, 2.20)	0.0	0.712	1.00 (reference)	8	1.48 (1.28, 1.72)	29.3	0.194	1.00 (reference)
Current vs Not Current	6	1.63 (1.37, 1.94)	71.4	0.004	0.82 (0.65, 1.04)	4	1.37 (1.19, 1.58)	0.0	0.770	0.76 (0.58, 1.00)	3	1.22 (0.94, 1.58)	50.1	0.135	0.81 (0.59, 1.12)
Ever vs Never	3	1.17 (1.05, 1.31)	0.0	0.481	0.62 (0.46, 0.82)	2	1.08 (0.90, 1.30)	0.0	0.594	0.60 (0.45, 0.82)	1	0.88 (0.70, 1.11)	-	-	0.59 (0.38, 0.92)
Clinical population[b]															
All	9	1.80 (1.47, 2.20)	77.3	0.000	1.00 (reference)	7	1.50 (1.30, 1.72)	2.8	0.404	1.00 (reference)	1	1.61 (1.16, 2.23)	-	-	1.00 (reference)
RP only	3	1.90 (1.60, 2.25)	21.8	0.279	1.07 (0.76, 1.53)	3	1.34 (0.87, 2.06)	12.6	0.319	0.84 (0.50, 1.41)	6	1.32 (1.06, 1.65)	69.0	0.006	0.82 (0.45, 1.48)
RT only	4	1.75 (1.31, 2.34)	34.5	0.205	0.99 (0.68, 1.46)	3	1.93 (1.30, 2.87)	0.0	0.684	1.20 (0.71, 2.03)	4	1.50 (1.22, 1.84)	0.0	0.746	0.96 (0.50, 1.82)
Exposure timing[b]															
Dx	8	1.79 (1.45, 2.21)	80.0	0.000	1.00 (reference)	8	1.62 (1.37, 1.92)	16.1	0.303	1.00 (reference)	4	1.61 (1.38, 1.86)	0.0	0.419	1.00 (reference)
Tx	8	1.83 (1.60, 2.09)	12.0	0.336	1.05 (0.79, 1.39)	5	1.43 (1.04, 1.96)	0.0	0.604	0.85 (0.54, 1.33)	7	1.28 (1.09, 1.52)	35.8	0.155	0.79 (0.60, 1.05)
Country region[b]															
North America	10	1.79 (1.51, 2.12)	78.1	0.000	1.00 (reference)	9	1.59 (1.32, 1.91)	18.3	0.280	1.00 (reference)	9	1.41 (1.20, 1.65)	51.8	0.035	1.00 (reference)
Europe	4	1.93 (1.61, 2.31)	2.6	0.379	1.08 (0.77, 1.53)	3	1.62 (1.18, 2.22)	0.0	0.590	1.02 (0.65, 1.60)	0	-	-	-	-
Asia	2	1.69 (0.98, 2.90)	0.0	0.703	0.96 (0.48, 1.90)	1	1.65 (0.65, 4.20)	-	-	1.03 (0.34, 3.17)	2	1.48 (0.79, 2.78)	69.4	0.071	0.96 (0.60, 1.56)
Risk of bias assessment[b]															
Lower risk of bias	10	1.78 (1.49, 2.12)	76.5	0.000	1.00 (reference)	8	1.43 (1.27, 1.62)	0.0	0.443	1.00 (reference)	6	1.36 (1.12, 1.65)	49.7	0.077	1.00 (reference)
Higher risk of bias	6	1.91 (1.46, 2.49)	54.0	0.054	1.06 (0.78, 1.45)	5	1.96 (1.43, 2.67)	0.0	0.909	1.36 (0.94, 1.99)	5	1.45 (1.16, 1.81)	46.4	0.113	1.06 (0.75, 1.50)

Abbreviations*: n* = number of studies; HR= Hazard Ratio; CI=Confidence interval; - = not applicable; RP= Radical Prostatectomy; RT = Radiation Therapy; Dx = Before or at diagnosis; Tx = After diagnosis or at/after treatment; I^2, % = percentage heterogeneity between studies

a. P value for test for heterogeneity
b. Studies comparing ever smokers and never smokers were not included in subgroup analyses

Table 3. Summary of results from the primary meta-analysis and subgroup meta-analyses for former vs never smokers for overall mortality, prostate-cancer specific mortality and recurrence.

	Overall mortality					Prostate cancer specific mortality					Recurrence				
	Meta-Analysis		Heterogeneity		Meta-Regression	Meta-Analysis		Heterogeneity		Meta-Regression	Meta-Analysis		Heterogeneity		Meta-Regression
	n	HR (95% CI)	I^2,%	*P*[a]	Ratio of HRs (95% CI)	*n*	HR (95% CI)	I^2,%	*P*[a]	Ratio of HRs (95% CI)	*n*	HR (95% CI)	I^2,%	*P*[a]	Ratio of HRs (95% CI)
Primary Meta-Analysis															
Former vs Never	8	1.28 (1.14, 1.45)	21.4	0.260	-	7	1.09 (0.93, 1.27)	0.0	0.496	-	6	1.22 (1.04, 1.42)	50.5	0.072	-
Subgroup Meta-Analysis															
Clinical population															
All	5	1.25 (1.14, 1.38)	0.0	0.499	1.00 (reference)	4	1.10 (0.92, 1.30)	0.0	0.797	1.00 (reference)	1	1.11 (0.96, 1.29)	-	-	1.00 (reference)
RP only	0	-	-	-	-	0	-	-	-	-	2	1.47 (1.09, 1.96)	40.9	0.193	1.37 (0.92, 2.04)
RT only	3	1.28 (0.92, 1.78)	62.8	0.068	1.00 (0.69, 1.45)	3	1.10 (0.62, 1.93)	53.4	0.117	0.94 (0.53, 1.66)	3	1.10 (0.94, 1.28)	0.0	0.722	0.99 (0.70, 1.39)
Exposure timing															
Dx	5	1.25 (1.14, 1.38)	0.0	0.499	1.00 (reference)	5	1.11 (0.94, 1.31)	0.0	0.865	1.00 (reference)	4	1.22 (1.01, 1.48)	69.4	0.020	1.00 (reference)
Tx	3	1.28 (0.92, 1.78)	62.8	0.068	1.00 (0.69, 1.45)	2	1.04 (0.40, 2.68)	71.6	0.061	0.82 (0.43, 1.59)	2	1.20 (0.86, 1.67)	0.0	0.586	1.00 (0.52, 1.90)
Country region															
North America	4	1.26 (1.06, 1.50)	47.2	0.128	1.00 (reference)	5	1.07 (0.84, 1.35)	14.4	0.322	1.00 (reference)	6	1.22 (1.04, 1.42)	50.5	0.072	-
Europe	3	1.38 (1.05, 1.81)	25.3	0.262	1.09 (0.70, 1.70)	2	1.27 (0.85, 1.88)	0.0	0.876	1.20 (0.68, 2.11)	0	-	-	-	-
Asia	1	1.09 (0.43, 2.75)	-	-	0.86 (0.22, 3.33)	0	-	-	-	-	0	-	-	-	-
Risk of bias assessment															
Lower risk of bias	4	1.26 (1.12, 1.43)	8.5	0.351	1.00 (reference)	4	1.10 (0.92, 1.30)	0.0	0.797	1.00 (reference)	2	1.11 (0.97, 1.28)	0.0	0.898	1.00 (reference)
Higher risk of bias	4	1.27 (0.96, 1.68)	45.6	0.138	0.98 (0.68, 1.43)	3	1.10 (0.62, 1.93)	53.4	0.117	0.94 (0.53, 1.66)	4	1.29 (1.00, 1.68)	65.3	0.034	1.15 (0.70, 1.90)

Abbreviations*: n* = number of studies; HR= Hazard Ratio; CI=Confidence interval; - = not applicable; RP= Radical Prostatectomy; RT = Radiation Therapy; Dx = Before or at diagnosis; Tx = After diagnosis or at/after treatment ; I^2, %= percentage heterogeneity between studies.

a. P value for test for heterogeneity

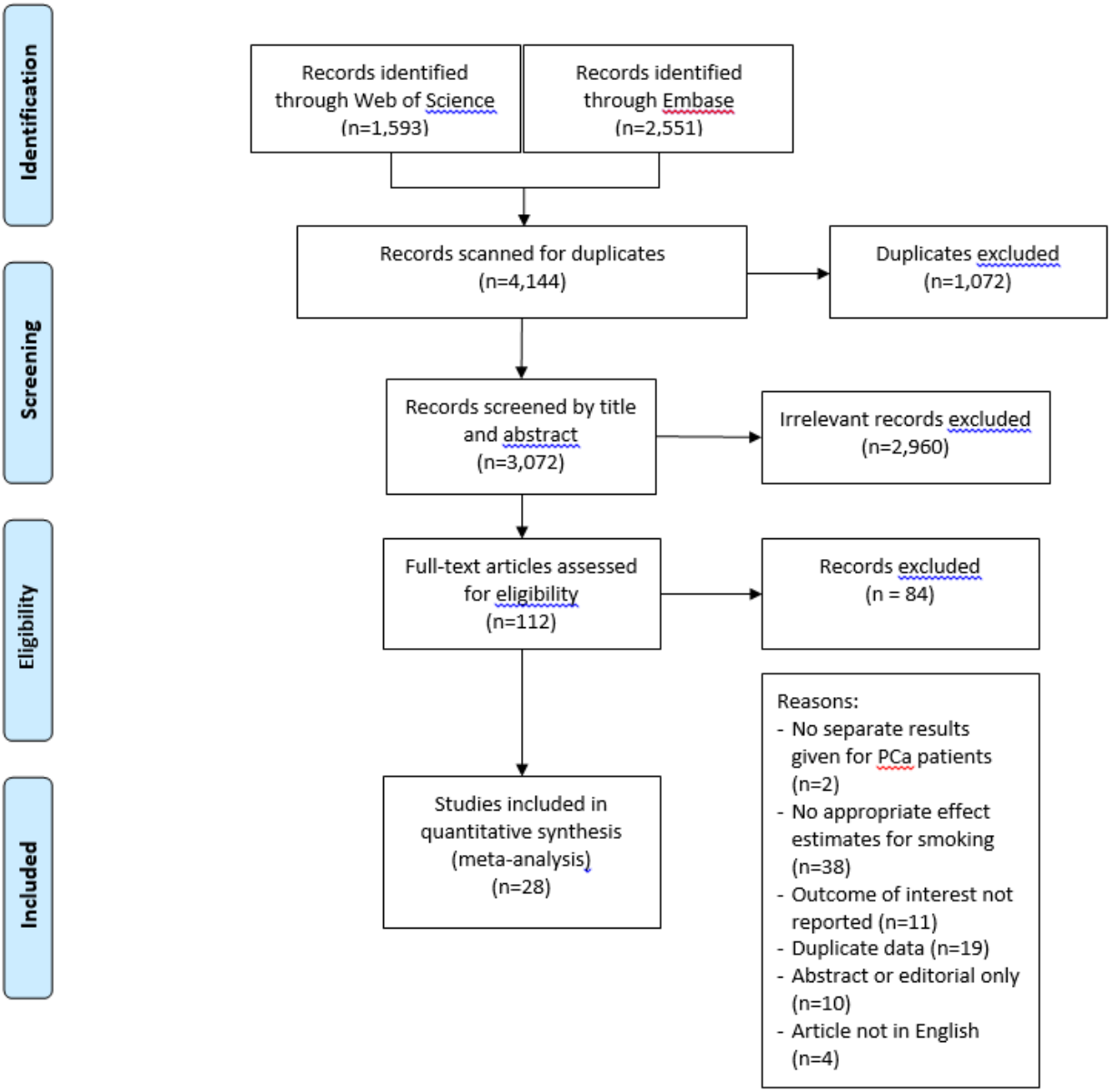


Figure 1. Flow chart of study selection

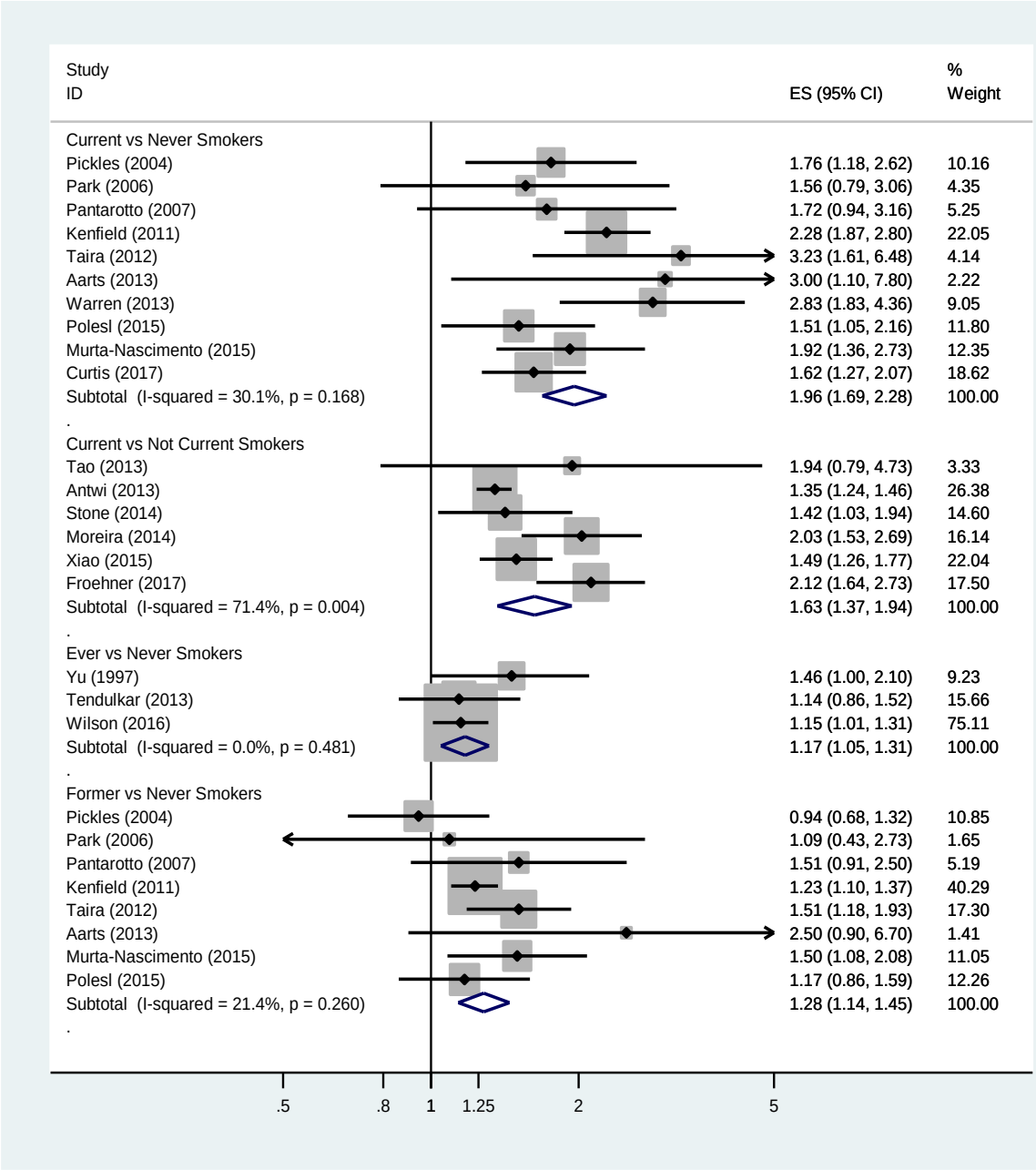


Figure 2. Random effects meta-analysis of the result of studies investigating associations between current smokers vs never smokers, current smokers vs not current smokers, ever smokers vs never smokers, and former smokers vs never smokers, and overall survival after a prostate cancer diagnosis. The black circles and horizontal lines represent the effect size and 95% confidence interval (CI) of each study. The relative size of the grey box around the effect estimate represents the weight that the study contributed to the summary hazard ratio. The diamonds represent the summary hazard ratio for each subgroup and associated 95% CI. ES=Effect size (Hazard Ratio). CI= Confidence Interval. I-squared=percentage heterogeneity between studies. p= test for heterogeneity

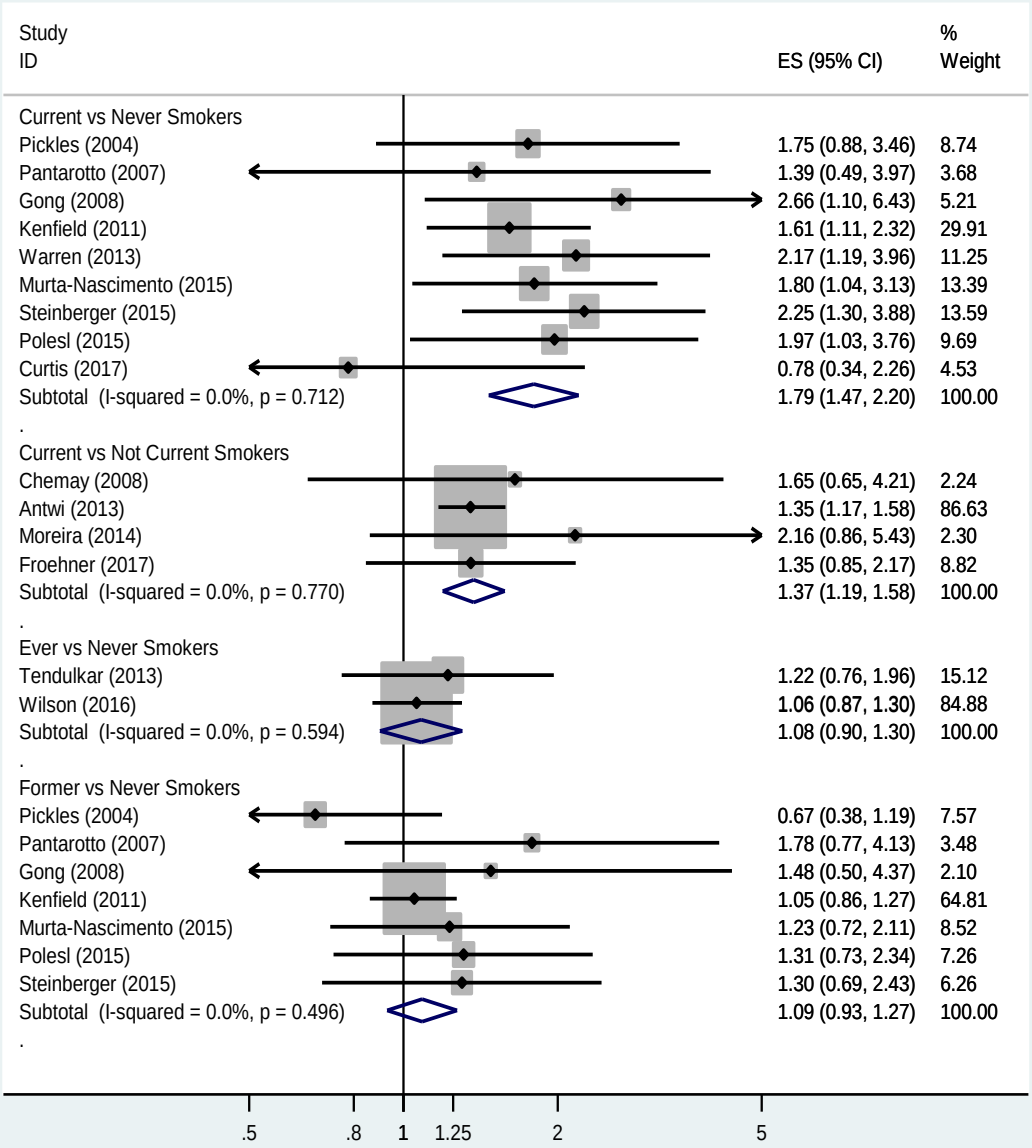


Figure 3. Random effects meta-analysis of the result of studies investigating associations between current smokers vs never smokers, current smokers vs non-smokers, ever smokers vs never smokers, and former smokers vs never smokers, and prostate cancer specific survival after a prostate cancer diagnosis. The black circles and horizontal lines represent the effect size and 95% confidence interval (CI) of each study. The relative size of the grey box around the effect estimate represents the weight that the study contributed to the summary hazard ratio. The diamonds represent the summary hazard ratio for each subgroup and associated 95% CI. ES=Effect size (hazard ratio). CI= Confidence Interval. I-squared= percentage heterogeneity between studies. p= test for heterogeneity

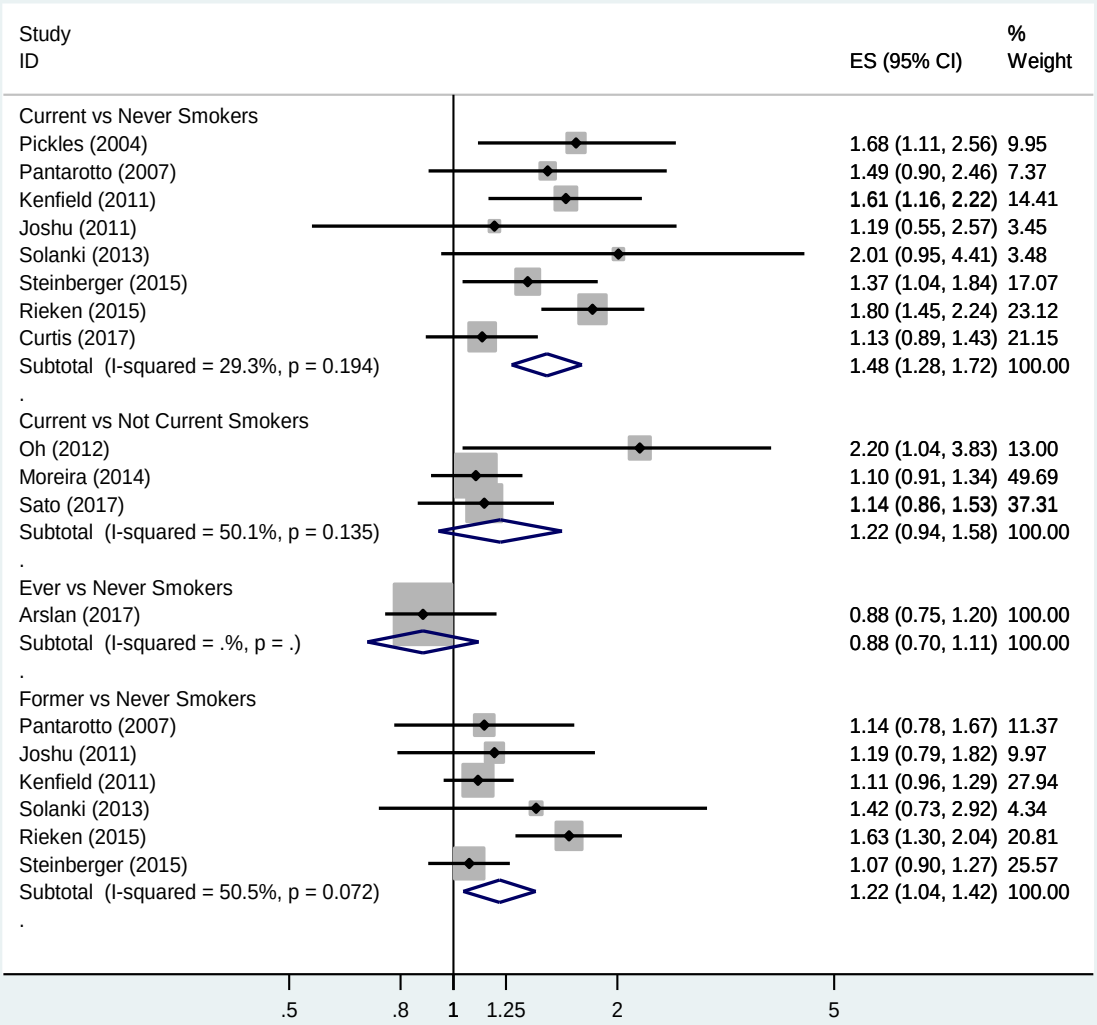
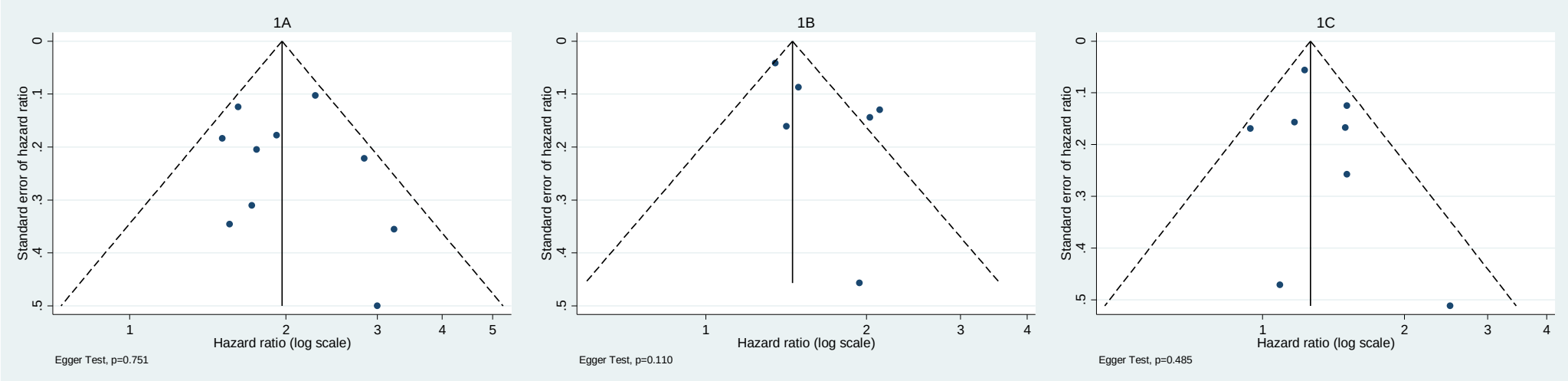


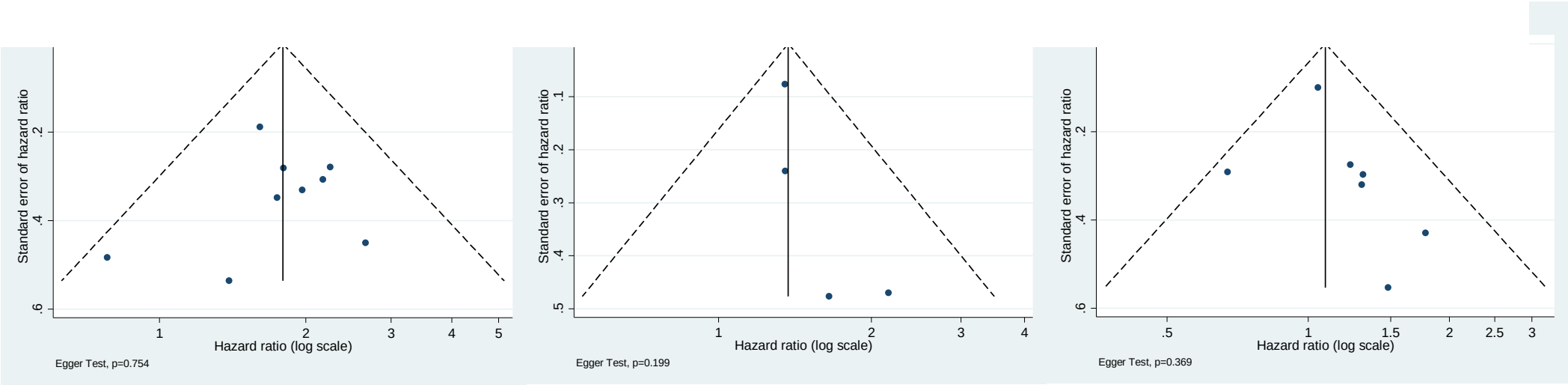
Figure 4. Random effects meta-analysis of the result of studies investigating associations between current smokers vs never smokers, current smokers vs not current smokers, ever smokers vs never smokers, and former smokers vs never smokers, and recurrence after a prostate cancer diagnosis. The black circles and horizontal lines represent the effect size and 95% confidence interval (CI) of each study. The relative size of the grey box around the effect estimate represents the weight that the study contributed to the summary hazard ratio. The diamonds represent the summary hazard ratio for each subgroup and associated 95% CI. ES=Effect size (Hazard Ratio). CI= Confidence Interval. I-squared= percentage heterogeneity between studies. p= test for heterogeneity

Supplementary Table 1: Search terms used for searches in EMBASE and ISI Web of Science

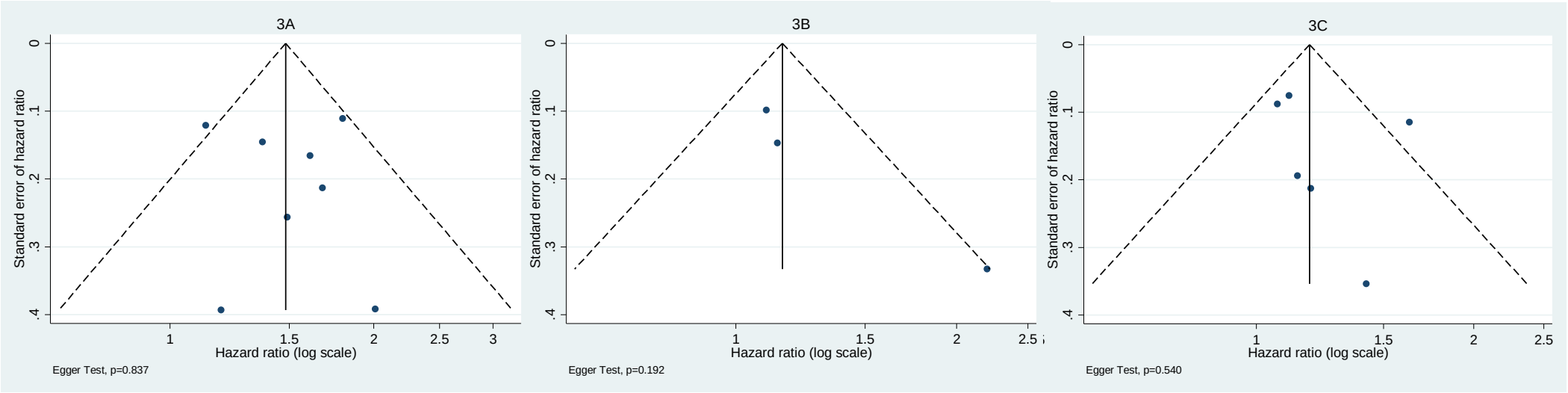
Databases	Search Terms
EMBASE	((((Prostat* neoplasm*) OR (prostat* cancer) OR ('prostate cancer' [MeSH Terms]) OR ('prostate tumor' [MeSH Terms]) OR (prostat* tumo?r) OR ((prostat*) AND (Cancer OR Neoplasm* OR Tumo?r*))) AND (Smok* OR Tobacco* OR Cigarette* OR 'Smoking' [MeSH Terms] OR 'tobacco use' [MeSH] OR 'Tobacco Dependence' [MeSH Terms]) AND (Surviv* OR Mortality* OR Prognosis OR (Period analysis) OR (Long term) OR 'Survival' [MeSH Terms] OR 'Mortality' [MeSH Terms] OR 'Survival Analysis' [MeSH Terms] OR 'Prognosis' [MeSH Terms] OR 'Survivors'[Mesh:NoExp] OR 'Time' [MeSH Terms] OR progress* OR outcome*)).
ISI Web of Science	((((Prostat* neoplasm*) OR (prostat* cancer) OR (prostat* tumo?r)) OR ((prostat*) AND (Cancer OR Neoplasm* OR Tumo?r*))) AND (Smok* OR Tobacco* OR Cigarette*) AND (Surviv* OR Mortality* OR Prognosis OR (Period analysis) OR (Long term) OR progress* OR outcome*)).



Supplementary Figure 1. Funnel plots and Egger tests for studies investigating overall mortality. 1A: Current vs never smokers. 1B: Current vs not current smokers. 1C: Former vs never smokers.



Supplementary Figure 2. Funnel plots and Egger tests for studies investigating prostate cancer specific mortality. 2A: Current vs never smokers. 2B: Current vs not current smokers. 2C: Former vs never smokers.



Supplementary Figure 3. Funnel plots and Egger tests for studies investigating recurrence. 3A: Current vs never smokers. 3B: Current vs not current smokers. 3C: Former vs never smokers.