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Triggers of Thyroid Cancer Diagnosis: A Systematic Review and Meta-analysis.

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Abstract:	<p>Background: Understanding the method of thyroid cancer detection has potential implications on interpreting incidence rates, the diagnosis and management of thyroid cancer. We conducted a systematic review of studies reporting methods of thyroid cancer detection to estimate the frequency of incidentally found cancers and classify triggers of incidental thyroid cancer diagnosis.</p> <p>Methods: We searched multiple bibliographic databases from inception to</p>

	<p>September 2018. A pair of reviewers, working independently and in duplicate selected studies for inclusion, extracted data, and evaluated each trial's risk of bias.</p> <p>Results: 16 cohorts and 1 cross-sectional study with a total of 4,470 patients with thyroid cancer were included: 89% had papillary thyroid cancer and 26% had micropapillary thyroid cancer. The proportion of patients with non-incidental and incidental thyroid cancer was the same: 50% [95% confidence interval (CI): 41-59%]. Subgroup analysis showed that most patients with incidental thyroid cancers had tumor size <10 mm (76%; 95% CI: 56-92%), age >45 (61%; 95% CI: 56-67%), and were detected through imaging (36%; 95% CI: 26-47%), of which ultrasound was the most common modality (31%; 95% CI: 17-48%). The heterogeneity for all the effect sizes was large and significant.</p> <p>Conclusions: About half of thyroid cancers were found incidentally through the use of imaging studies, in particular neck ultrasound. These incidentally found cancers were mostly small papillary thyroid cancer. These results highlight opportunities for interventions aimed at reducing drivers of over-diagnosis.</p>

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Manuscripts

1 **Triggers of Thyroid Cancer Diagnosis: A Systematic Review and Meta-analysis.**

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22 **Keywords:** Thyroid cancer, mechanism of detection, incidental diagnosis, systematic review,
23 meta-analysis.

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40 Abstract

41 **Background:** Understanding the method of thyroid cancer detection has potential implications
42 on interpreting incidence rates, the diagnosis and management of thyroid cancer. We
43 conducted a systematic review of studies reporting methods of thyroid cancer detection to
44 estimate the frequency of incidentally found cancers and classify triggers of incidental thyroid
45 cancer diagnosis.

46 **Methods:** We searched multiple bibliographic databases from inception to September 2018. A
47 pair of reviewers, working independently and in duplicate selected studies for inclusion,
48 extracted data, and evaluated each trial's risk of bias.

49 **Results:** 16 cohorts and 1 cross-sectional study with a total of 4,470 patients with thyroid
50 cancer were included: 89% had papillary thyroid cancer and 26% had micropapillary thyroid
51 cancer. The proportion of patients with non-incidental and incidental thyroid cancer was the
52 same: 50% [95% confidence interval (CI): 41-59%]. Subgroup analysis showed that most
53 patients with incidental thyroid cancers had tumor size <10 mm (76%; 95% CI: 56-92%), age >45
54 (61%; 95% CI: 56-67%), and were detected through imaging (36%; 95% CI: 26-47%), of which
55 ultrasound was the most common modality (31%; 95% CI: 17-48%). The heterogeneity for all
56 the effect sizes was large and significant.

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58 studies, in particular neck ultrasound. These incidentally found cancers were mostly small
59 papillary thyroid cancer. These results highlight opportunities for interventions aimed at
60 reducing drivers of over-diagnosis.

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79 Introduction

80 The incidence of thyroid cancer has increased worldwide(1, 2). In the United States, for
81 instance, it increased from a 4.9 to 14.2 per 100,000 person-years over the last two decades(3),
82 while in South Korea, thyroid cancer increased by more than seven fold, from 6.3 per 100,000
83 person year in 1999 to 47.5 per 100,000 population in 2009.

84 This difference in thyroid cancer trends reflects underlying different mechanisms of
85 thyroid cancer detection. In South Korea, 90% of the new thyroid cancers were detected by
86 screening with neck ultrasound. In other countries, however, the mechanism of detection of
87 thyroid cancer is unclear. Outside South Korea, some studies have suggested that the rise of
88 thyroid cancer incidence is driven by the incidental detection of small and asymptomatic thyroid
89 cancer lesion(1, 4–6) by increased use of imaging technologies(7), or detection of thyroid cancer
90 lesions found in the course of histologic review of thyroid glands removed for apparently benign
91 conditions(8, 9). Others have shown that the increased in incidence is also caused by larger, likely
92 palpable and symptomatic, advanced stage thyroid cancer(10).

93 Understanding the method of thyroid cancer detection has potential implications on
94 interpreting incidence rates, the diagnosis and management of thyroid cancer. The aim of this
95 study is to summarize the available evidence to assess the frequency of incidental thyroid cancer
96 and examine the triggers that lead to diagnosis with comparison across multiple cohorts.

97 Methods

98 A protocol was developed to perform this study. Additionally, preliminary results of this
99 study were presented previously as abstract in the 89th Annual Meeting of the American

100 Thyroid Association(11). Overall, this manuscript is reported according to the Preferred
101 Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines(12).

102 **Eligibility criteria and study selection**

103 We included original studies with patients older than 18 years with thyroid cancer
104 confirmed by histology and reporting at least two pathways of thyroid cancer detection, later
105 explained. Only manuscripts written in English, Spanish, or Portuguese were included. We
106 excluded studies in which the aim was only to assess the impact of thyroid cancer screening
107 (e.g. thyroid cancer screening in South Korea).

108 **Data sources and searches**

109 We applied a searched strategy developed in collaboration with an experienced librarian
110 to find potentially eligible studies in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process &
111 Other Non-Indexed Citations, and Daily, Ovid EMBASE, and Scopus from each database's
112 inception until September, 2018. Conference abstracts, literature reviews, case reports and
113 editorials we excluded. Reference lists of selected studies were searched to identify additional
114 publications. The actual strategy is in Appendix.

115 **Study selection**

116 Search results were uploaded into a systematic review software program (DistillerSR,
117 Ottawa, ON, Canada)(13). Reviewers, working independently and in duplicate, screened
118 abstracts and titles for eligibility using standardized instructions. Before initiating the abstract
119 screening phase, a pilot was performed with 20 articles to assess the clarity of the eligibility

120 criteria among reviewers and modifications were done accordingly. For abstract screening,
121 articles included by at least one reviewer were considered for full-text screening. A pilot was
122 performed with 10 articles before starting the full-text screening. At this stage, only articles
123 included by both reviewers were deemed eligible for this systematic review and in case of
124 disagreements, these were resolved by consensus between the 6 reviewers (E.L-N., P.S-P.,
125 O.J.P., B.A., T.L., T.L.). Full text screening agreement using Cohen's kappa was substantial
126 ($k=0.76$).

127 **Data collection and management**

128 For all included articles, one reviewer (E.L-N) extracted study data into a spreadsheet
129 sheet form and second reviewer (P.S-P) checked randomly 30% of data extracted for accuracy
130 and completeness. Variables extracted were: general characteristics of the studies (author, date
131 of publication, country, study design, data collection period), setting (single center, multicenter
132 and population based-study), participant characteristics (age, sex, mean tumor size, thyroid
133 cancer histological types), and pathway of thyroid cancer diagnosis into two categories:
134 incidental and non-incidental diagnosis. Incidental pathway including: i) cases when a thyroid
135 nodule harboring thyroid cancer was found during the use of imaging test requested for
136 reasons unrelated to a thyroid nodular disorder or symptoms, or ii) when thyroid cancer was
137 found incidentally in the histological examination of the thyroid gland removed for a benign
138 condition (e.g., goiter, Graves' disease). Non-incidental triggers included cases when a thyroid
139 nodule harboring thyroid cancer was found because a clinician or patient noted an abnormality
140 on physical examination possibly related to the thyroid mass, patient presented with neck

141 compression symptoms including dysphagia, dysphonia, and neck-pain. Additionally, we
142 extracted the type of imaging modality driving the detection of incidental thyroid cancer.

143 **Risk of bias in individual studies**

144 Study quality was assessed by two independent reviewers based on the nine-star
145 Newcastle Ottawa Scale (NOS) for cohort-studies(14)-(15) and an adapted form of the NOS for
146 cross-sectional studies(16), using three predefined domains, namely: selection of participants
147 (population representativeness), comparability (adjustment for confounders) and
148 ascertainment of outcomes of interests. For both tools, studies that received a score of nine to
149 eight were judged to be at low risk of bias; studies that scored five or seven were considered at
150 moderate risk, and those that scored four or less were considered at high risk of bias. Article
151 quality assessment was done independently by 2 authors (E.L-N. and P.S-P.) (Table2).

152 **Statistical analyses**

153 By using the number of people with an incidental diagnosis and the total number of
154 people in each study, we determined the overall proportion estimates and their confidence
155 intervals (95% CI). Every confidence interval was calculated by using the exact method for
156 binomial proportions(17)-(18) and the overall proportion was estimated with the Freeman-
157 Turkey double arcsine transformation to stabilize the variances(19). We chose the Freeman-
158 Turkey double arcsine as the main analyses method over others, because it depicts the weights
159 for individual studies and it seems to perform similar to other methods when the proportions
160 are not consistently close to 0 or 1(20). The random-effects model was performed with the
161 Dersimonian and Laird method (21). Since we estimated that we could encounter studies with

162 proportions close to 0 or 1. A sensitivity analysis was conducted by using generalized linear
163 mixed models (20). In such scenarios, this meta-analysis model seems to perform better than
164 other (e.g. less biased estimates)(20).

165 Heterogeneity across studies was assessed with the I^2 statistic and visually(22). We
166 considered that $I^2 < 25\%$ reflected low inconsistency and $I^2 > 75\%$ reflected high inconsistency.
167 In terms of subgroups analyses, predefined comparisons based on age, sex, and tumor size
168 were planned: > 45 years vs. ≤ 45 years, female vs. male, and tumor size $> 10\text{mm}$ vs. tumor size
169 $\leq 10\text{mm}$. Other post-hoc subgroup analyses were additionally executed and they include
170 studies performed in the United States vs. studies performed outside the United States and
171 population-based studies vs. non-population-based studies. The statistical program STATA v15
172 was employed to perform all types of analyses and forest plots. Coding scripts and excel files
173 with the extracted data are available online(23).

174 **Results**

175 Figure 1 describes the results of our search. We included 17 studies, conducted between
176 1991 and 2015, enrolling 4470 patients with thyroid cancer, age ranged from 18 to 89 years old,
177 most were female (76%) with papillary thyroid cancer (89%) and papillary microcarcinoma
178 (26%). Of 17 studies, 1 was cross-sectional(24) and 16 were cohort studies(8, 9, 32–37, 10, 25–
179 31), mostly performed in the United States (8, 9, 29–33) and Italy(25, 34–37) (Table 1). Overall,
180 in cohort studies, risk of bias seems to be low (11) to moderate (5), and low in the cross-
181 sectional study (Table 2).

182 The overall proportion of people whose thyroid cancer was found incidentally is 50%
183 [95% confidence interval (CI): 41-59%, heterogeneity (I^2): 97%] (Appendix). When the total
184 incidental diagnosis data was further analyzed by country, six out of the seven countries have
185 proportions above 40%, whereas the lowest number is seen in Canada with 17% (95%CI 11-
186 23%, I^2 95.79%) (Figure 2).

187 **Incidental thyroid cancer diagnosis by imaging techniques**

188 The proportion of people whose diagnosis of thyroid cancer was triggered by imaging
189 methods was 36% (95% CI: 26-47%, I^2 : 97%), and that of triggered by histological examination
190 was 23% (95% CI: 15-32%, I^2 : 97%). The specific imaging modalities for triggers of incidental
191 thyroid cancer was 31% (95% CI: 17-48%, I^2 : 98%) for ultrasound, 6% (95% CI: 4-9%, I^2 : 83%) for
192 computed tomography (CT), 3% (95% CI: 1-4%, I^2 : 71%) for positron emission tomography (PET),
193 and 2% (95% CI: 1-4%, I^2 : 77%) for magnetic resonance imaging (MRI) (Figure 3 and Appendix).

194 **Incidental thyroid cancer diagnosis by subgroups**

195 Incidental thyroid cancer subgroup analysis by tumor size showed that tumor \leq 10mm
196 was incidentally found in 76% (95% CI: 56-92%, I^2 : 97%), while tumors $>$ 10mm were 31% (95%
197 CI: 15-50%, I^2 : 97%), with a p value for interaction test of <0.01. Furthermore, the frequency of
198 incidental thyroid cancer was similar in women and men, 52% (95% CI: 39-64%, I^2 : 95%) vs. 55%
199 (95% CI: 43-66%, I^2 : 84%), respectively, with a p value for subgroup interaction of 0.74, and
200 different in age \leq 45 years 41% (95% CI: 34-49%) vs. $>$ 45 years 61% (95% CI: 56-67%), p value
201 for interaction test of <0.01. Similar findings were found when comparing studies performed in
202 the United States (42%; 95%CI: 32-53%, I^2 : 95%) vs. studies performed outside the United

203 States (56%; 95%CI: 42-69%, I^2 : 97%) with a p value for subgroup interaction of 0.12, and
204 population-based studies 53% (95% CI: 38-68%) vs. non-population-based studies (50%; 95%CI:
205 39-60%, I^2 : 97%) with a p value of 0.72 for interaction (Figure 3 and Appendix).

206 **Sensitivity analyses**

207 The overall estimates of studies with proportions different from 0% or 100%, including
208 those close to these numbers (e.g. 1-2%), were similar in both methods: generalized linear
209 mixed model and Freeman-Turkey double arcsine. Nonetheless, in estimates where one of the
210 studies had a proportion of 0% or 100%, the results were divergent. The Freeman-Turkey
211 double arcsine method in the incidental thyroid cancer subgroup analysis by tumor size showed
212 that for tumor \leq 10mm the proportion was 76% (95% CI: 56-92%, I^2 : 97%), while for tumors >
213 10mm it was 31% (95% CI: 15-50%, I^2 : 97%). In contrast, by using the generalized linear mixed
214 model, the estimate for the \leq 10mm group was 83% (95% CI: 53-95%), whereas for the > 10mm
215 the proportion was 17% (95% CI: 03-60%) (Figure 3 and Appendix).

216 **Discussion**

217 **Summary of evidence**

218 We found that a significant proportion of thyroid cancer (50%) was found incidentally in
219 asymptomatic people through the use of imaging studies, in particular neck ultrasound. These
220 incidentally found cancers were mostly small papillary thyroid cancer. This finding is consistent
221 with a recent study demonstrating that the use of thyroid ultrasound has increased at a rate of
222 20% per year from 2002 through 2013 among Medicare patients in the United States,
223 associating this with more thyroid cancer diagnosis(38).

224 Prior to the advent of neck sonography in the 1980s, thyroid cancer nodules had to
225 reach a large size prior to detection; however current neck ultrasonography technology has
226 revolutionized diagnosis and management of thyroid cancer detecting lesions as small as 2
227 mm(39). This increased sensitivity coupled with improved reimbursement and access to US has
228 led to increase in use by endocrinologists close to 80%(40). The increased use of thyroid
229 ultrasound raises question about whether or not its use is appropriate. Thyroid ultrasound is
230 indicated when there is a palpable thyroid nodule or in thyroid cancer screening of a high risk
231 population (e.g., head and neck radiation)(41). It is unlikely that the increased use of neck
232 ultrasound reflects a surge of new thyroid nodules found by palpation as more than half of
233 patients with thyroid cancer are asymptomatic(9). In fact, a study showed that many of the
234 thyroid cancers found by ultrasound were detected when clinicians erroneously believed that
235 they felt a nodule and consequently ordered an ultrasound. Interestingly this often revealed no
236 nodule in the palpated area but a small suspicious nodule in the contralateral lobe(9). Besides
237 ordering thyroid ultrasound due to thyroid nodule misdiagnosis, many thyroid ultrasounds are
238 ordered for the wrong indication. An audit of patients referred to an endocrine practice found
239 that 93% of ultrasounds were ordered without appropriate indication but rather for other
240 reasons such as thyroid dysfunction(42). This misuse of thyroid ultrasound, coupled with easy
241 access, increased sensitivity and the non-invasiveness nature of the test, make thyroid
242 ultrasound an important driver of thyroid cancer diagnosis(43)-(39)-(40).

243 Another significant driver of thyroid cancer diagnosis in our study was the histological
244 examination of thyroid glands, particularly when removed in the setting of a benign condition.
245 Parallel to the increased incidence of thyroid cancer, there has been a surge in the diagnosis of

246 thyroid nodules, which in turn has led to higher rates of thyroid surgery(44). Thyroid surgeries
247 are now more likely to involve the removal of the whole gland, rather than a part of the
248 thyroid(45). Several studies have demonstrated that about 10% of thyroid glands harbor small
249 incidental thyroid cancers(46); thus, the higher rates of thyroid surgery, in particular with
250 removal of the whole gland, will uncover this large reservoir of disease. Although factors
251 driving the increase in thyroid surgery for benign conditions remain unclear, it is possible that
252 collective awareness of the high incidence of thyroid cancer could play a factor. For example, as
253 many patients with benign autoimmune thyroid diseases are imaged, incidental thyroid nodules
254 are discovered, to which there may be a decision towards surgery due to reasons such as
255 provider or patient anxiety about the potential malignant nature of the nodule(s). This
256 approach has led to increased, unnecessary thyroid surgery (39% increase in recent years) and
257 its downstream associated risk- increasing rates of postoperative hypoparathyroidism. This is
258 best seen in South Korea following a rise in thyroid surgery driven by routine thyroid ultrasound
259 screening, now with reports of increasing postoperative hypoparathyroidism(47).

260 **Implications for research and practice**

261 Although efforts to reduce over treatment of these small thyroid cancer lesions with
262 strategies such as active surveillance are being implemented(48), approaches that address
263 avenues promoting thyroid cancer overdiagnosis are needed. Firstly, guidelines should provide
264 recommendations on low-yield diagnostic tests such as un-necessary ultrasound with focus on
265 high value meaningful use. As ultrasound use becomes adopted into training programs,
266 education on the indications and applicability is crucial. In one study, despite the recent uptake
267 in ultrasound use, 38% of practicing endocrine surgeons who perform it regularly reported no

268 formal training on its use or applicability(49). Although, ultrasound is an incredibly useful
269 diagnostic tool, its routine use needs to be re-examined in the context of thyroid cancer
270 overdiagnosis.

271 In the face of uncovering subclinical disease through histology, pathological
272 nomenclature of small incidental lesions needs to be re-examined. Referring to these lesions as
273 “thyroid cancer” may influence a more aggressive downstream course of otherwise non-
274 threatening subclinical lesions. Evidence suggests that changing nomenclature used in
275 describing small TC to terms such as “papillary lesion” reduced patient anxiety and influenced
276 management decision making towards a more conservative approach(50). We advocate to
277 rename low risk lesions such as has been done in cervical or breast cancers which may mitigate
278 overtreatment(51).

279 **Limitations**

280 The main limitation of this study lies in the retrospective nature of extraction of the initial
281 primary data. Significant heterogeneity among studies may exist in defining incidental and non-
282 incidental cancers. Consequently, patients could have been misclassified into wrong
283 categories. Likewise the variations in definitions, made some comparison between studies
284 difficult. Moreover, there is a risk of publication bias given the lack of inclusion of conference
285 abstracts or unpublished literature.

286 Despite these limitations, the strengths of this study remain notable. Firstly, this is the
287 first global perspective meta-analysis showing rates of incidental thyroid cancer across multiple
288 cohorts allowing for comparison and a summative perspective. Secondly, as we excluded cohorts
289 that were identified through screening programs, we offer a unique perspective into the avenues

290 leading to incidental thyroid cancer diagnosis other than screening. Finally, sensitivity analyses
291 comparing two analyses methods showed that results are consistent in almost all estimates,
292 except in the tumor size subgroup analysis ($\leq 10\text{mm}$ vs $>10\text{mm}$) as studies had proportions of 0%
293 or 100%.

294 **Conclusion**

295 Our study shows that frequency of incidental thyroid cancer is high across numerous
296 global geographic regions. Half of the thyroid cancers, and almost all micropapillary thyroid
297 cancers detected are found incidentally, illustrating that incidental thyroid cancer continues to
298 be a large driver of increasing overall thyroid cancer incidence. Subgroup analysis showed that
299 incidental thyroid cancer tends to represent small cancers likely with indolent course and are
300 primarily diagnosed by ultrasound, prompting a debate surrounding ultrasound misuse and
301 opportunities for interventions aimed at reducing this source of over-diagnosis.

302 **Disclosure Statement**

303 The authors declare have no disclosure statement.

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464

465

Figure legends**Main manuscript**

Table 1. General characteristics of included studies.

Table 2. Quality of evidence.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of studies selection process.

Figure 2. Frequency of incidental thyroid cancer diagnosis around the world.

Figure 3. Subgroup analysis of incidental diagnosis. *Sensitivity analysis: Imaging (35%, 95% CI: 26-46%), ultrasound (27%, 95% CI: 12-49%), histology (21%, 95% CI: 13%-32%), tumor size < 10 mm (83%, 95% CI: 53-95%), tumor size > 10 mm (17%, 95% CI: 3-60%) (Appendix).

Appendix

Figure 4. Overall frequency of incidental thyroid cancer diagnosis.

Figure 4.1. Overall frequency of incidental thyroid cancer diagnosis – sensitive analysis.

Figure 5. Frequency of incidental diagnosis by imaging.

Figure 5.1. Frequency of incidental diagnosis by imaging – sensitive analysis.

Figure 6. Frequency of incidental diagnosis by histology.

Figure 6.1 Frequency of incidental diagnosis by histology – sensitive analysis.

Figure 7. Frequency of incidental diagnosis by ultrasound.

Figure 7.1 Frequency of incidental diagnosis by ultrasound – sensitive analysis.

Figure 8. Frequency of incidental diagnosis by computed tomography.

Figure 8.1 Frequency of incidental diagnosis by computed tomography – sensitive analysis.

Figure 9. Frequency of incidental diagnosis by positron emission tomography.

Figure 9.1. Frequency of incidental diagnosis by positron emission tomography – sensitivity analysis.

Figure 10. Frequency of incidental diagnosis by magnetic resonance imaging.

Figure 10.1. Frequency of incidental diagnosis by magnetic resonance imaging – sensitive analysis.

Figure 11. Frequency of incidental diagnosis by tumor size.

Figure 11.1. Frequency of incidental diagnosis by tumor size – sensitive analyses.

Figure 12. Frequency of incidental diagnosis by sex.

Figure 12.1. Frequency of incidental diagnosis by sex – sensitive analysis.

Figure 13. Frequency of incidental diagnosis by age.

Figure 14. Frequency of Incidental diagnosis by country.

Figure 15. Frequency of incidental diagnosis in the United States and others.

Figure 15.1 Frequency of incidental diagnosis in the United States and others – sensitive analysis.

Figure 16. Frequency of incidental diagnosis by population-based studies vs non-population-based studies.

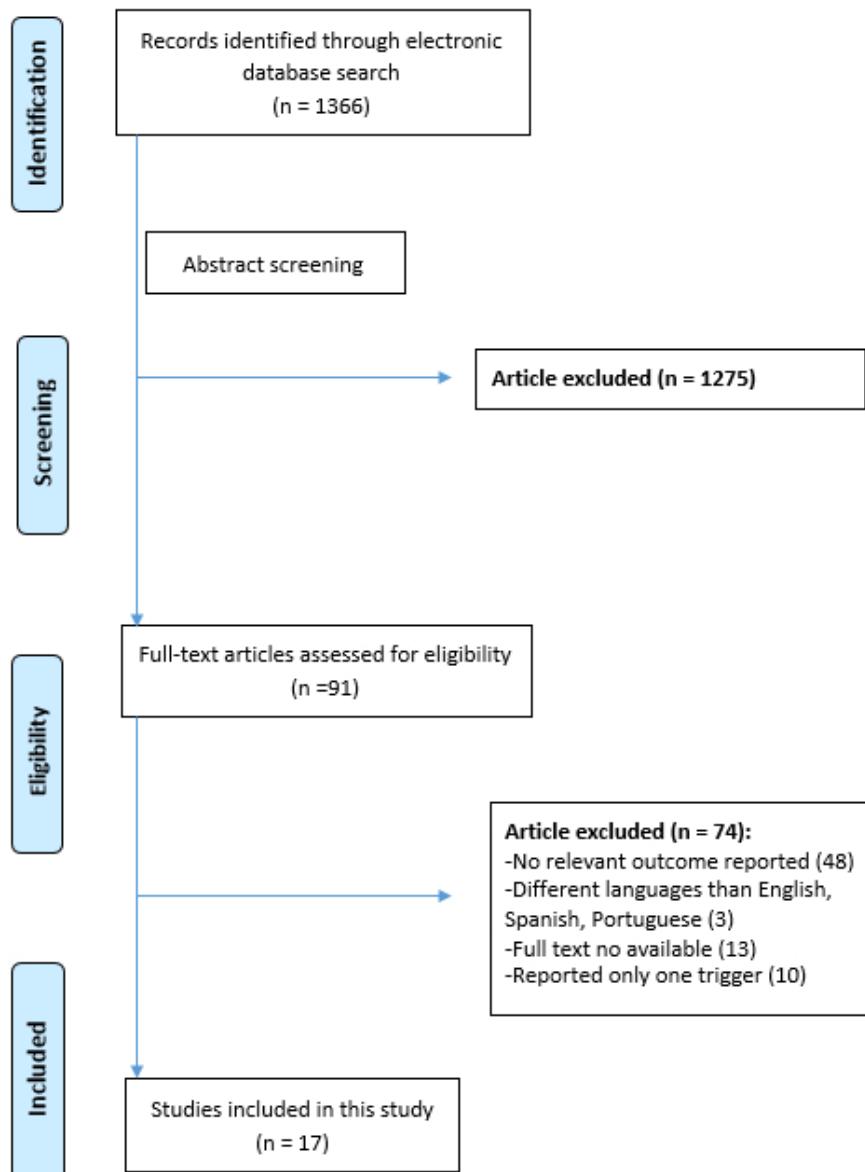
Figure 16.1. Frequency of incidental diagnosis by population-based studies vs non-population-based studies – sensitive analysis.

Table 1. General characteristics of included studies.

Lead author, Publication date	Country	Study design	Study period	Setting	Sample size	Female	Papillary thyroid cancer	Micropapillary thyroid cancer
Russo et al. 2018	Argentina	Retrospective cohort study	January 2003 to December 2012	Population-based study	176	158	166	Not reported
Iwata et al. 2018	United States	Retrospective cohort study	January 2006 to December 2010	Single center	128	Not reported	Not reported	Not reported
Seifert et al. 2017	Germany	Retrospective cohort study	October 2009 to September 2015	Single center	103	78	68	13
González-Sánchez-Migallón et al. 2016	Spain	Retrospective cohort study	2000 to 2014	Single center	259	208	225	92
Zagzag et al. 2017	United States	Retrospective cohort study	2004 to 2010	Multicenter in one country	473	352	427	100
Shakil et al. 2017	United States	Retrospective cohort study	2005 to 2014	Single center	172	131	160	54
Provenzale et al. 2016	Italy	Prospective cohort study	March 2013 to March 2014	Single center	374	Not reported	374	159
Brito et al. 2015	United States	Retrospective cohort study	2000 to 2012	Population-based study	213	149	199	Not reported
Choi et al. 2015	Canada	Retrospective cohort study	January 2000 to January 2013	Single center	168	126	168	Not included
Bahl et al. 2014	United States	Retrospective cohort study	January 2003 to December 2012	Single center	675	499	566	206
Malone et al. 2014	United States	Retrospective cohort study	January 2007 to August 2010	Single center	473	345	451	156
Kahn et al. 2012	Australia	Cross-sectional study	May 2006 to August 2008	Population-based study	419	321	359	Not reported
Davies et al. 2010	United States	Retrospective cohort study	2006 to 2007	Multicenter in one country	95	Not reported	86	Not reported
Ruggieri et al. 2001	Italy	Retrospective cohort study	1991 to 2000	Single center	30	Not reported	28	30
Marina et al. 2017	Italy	Retrospective cohort study	January 1998 to December 2015	Single center	281	220	259	Not reported
Minuto et al. 2013	Italy	Retrospective cohort study	February 2002 to November 2003	Single center	188	139	181	Not reported
Roti et al. 2006	Italy	Retrospective cohort study	1993 to 2002	Single center	243	197	243	243

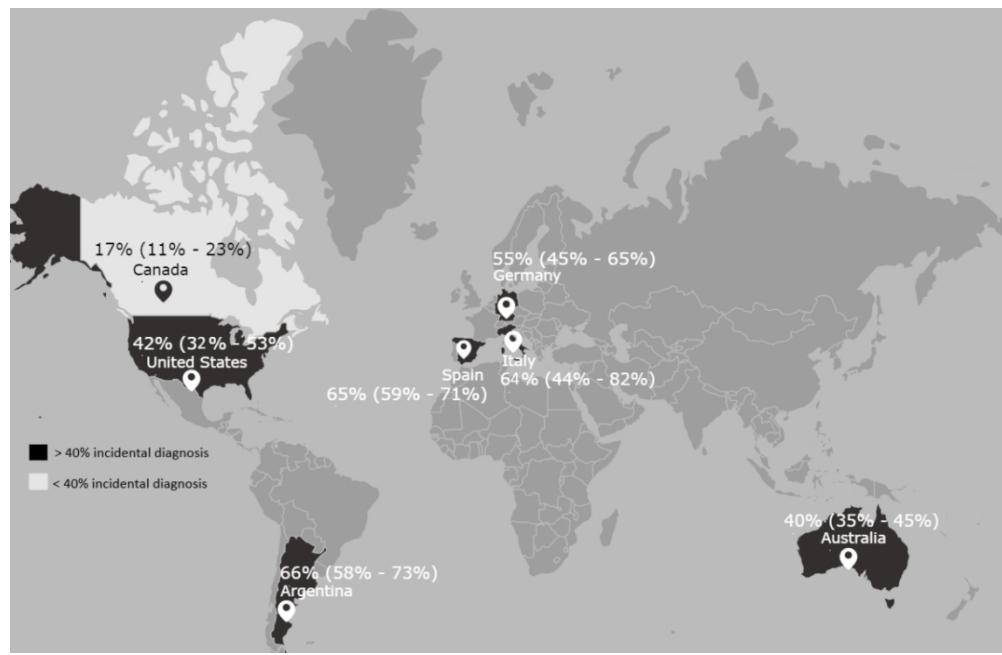
Table 2 Quality of evidence.

Authors/Publication Year	Design	Score				
		Selection/****	Comparability/**	Outcome/***	Total	Overall risk of bias
Newcastle-Ottawa Scale for Cohort Studies						
Russo et al. 2018	Retrospective cohort study	***	**	**	7	moderate risk
Iwata et al. 2018	Retrospective cohort study	***	**	**	7	moderate risk
Seifert et al. 2017	Retrospective cohort study	***	**	***	8	low risk
González-Sánchez-Migallón et al. 2016	Retrospective cohort study	***	**	***	8	low risk
Zagzag et al. 2017	Retrospective cohort study	***	**	***	8	low risk
Shakil et al. 2017	Retrospective cohort study	***	**	***	8	low risk
Provenzale et al. 2016	Prospective cohort study	***	**	**	7	moderate risk
Brito et al. 2015	Retrospective cohort study	***	**	***	8	low risk
Choi et al. 2015	Retrospective cohort study	***	**	***	8	low risk
Bahl et al. 2014	Retrospective cohort study	***	**	***	8	low risk
Malone et al. 2014	Retrospective cohort study	***	**	***	8	low risk
Davies et al. 2010	Retrospective cohort study	***	**	**	7	moderate risk
Ruggieri et al. 2001	Retrospective cohort study	***	**	***	8	low risk
Marina et al. 2017	Retrospective cohort study	***	**	***	8	low risk
Minuto et al. 2013	Retrospective cohort study	***	**	**	7	moderate risk
Roti et al. 2006	Retrospective cohort study	***	**	***	8	low risk
Newcastle-Ottawa Scale adapted for Cross-Sectional Studies		Selection/*****	Comparability/**	Outcome/***	Total	Overall risk of bias
Kahn et al. 2012	Cross-sectional study	*****	*	**	7	moderate risk



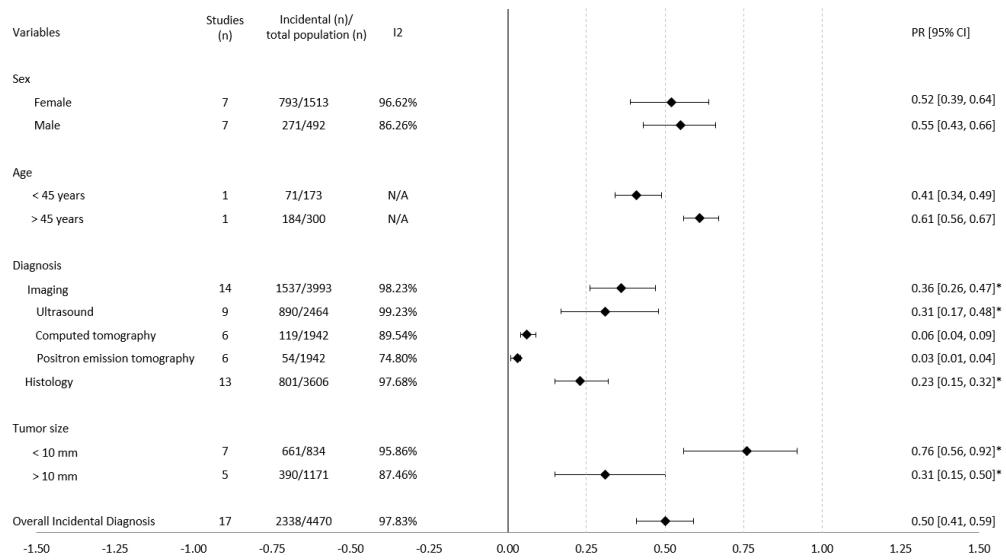
Main Manuscript-Figure 1.

139x170mm (96 x 96 DPI)



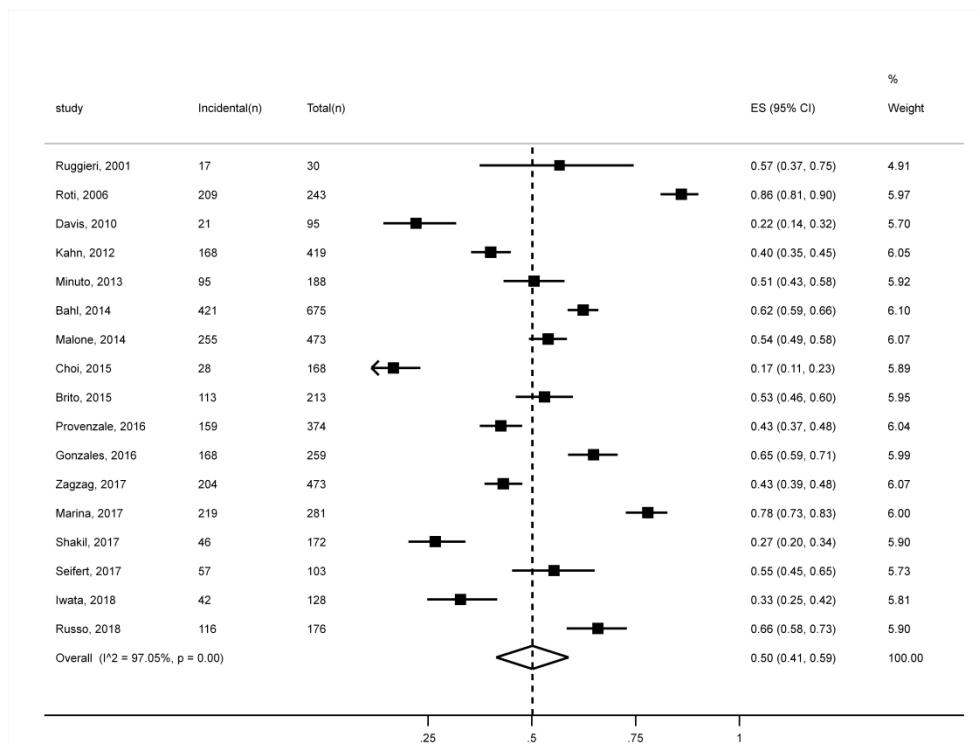
Main manuscript-Figure 2.

322x207mm (96 x 96 DPI)



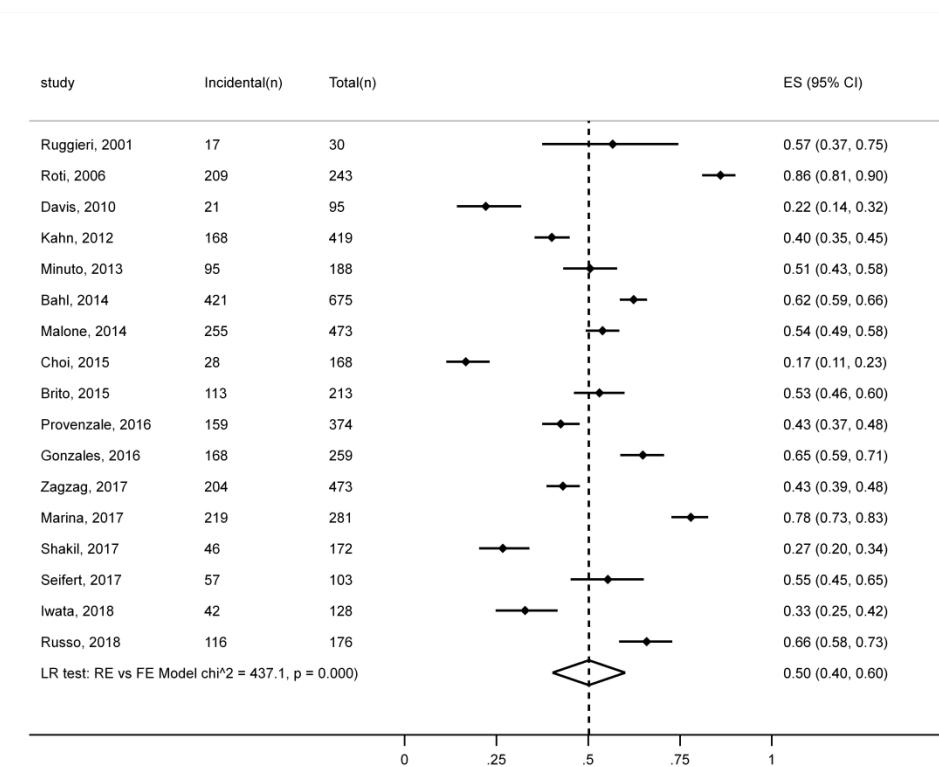
Main manuscript-Figure 3.

347x190mm (96 x 96 DPI)



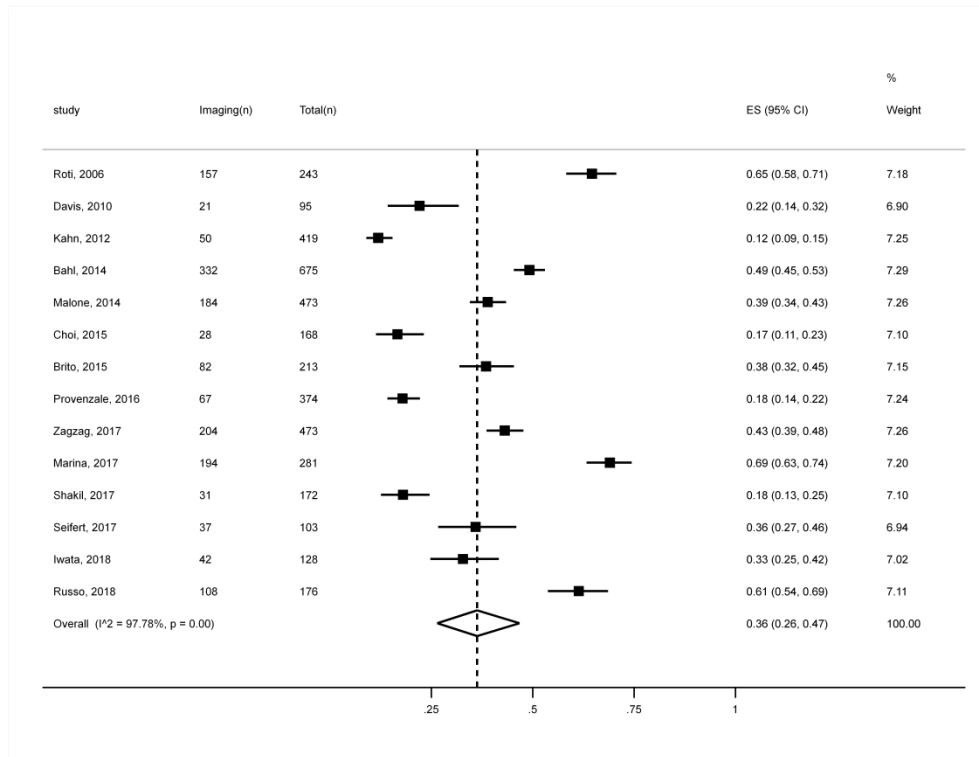
Appendix-Figure 4.

1414x1127mm (120 x 120 DPI)



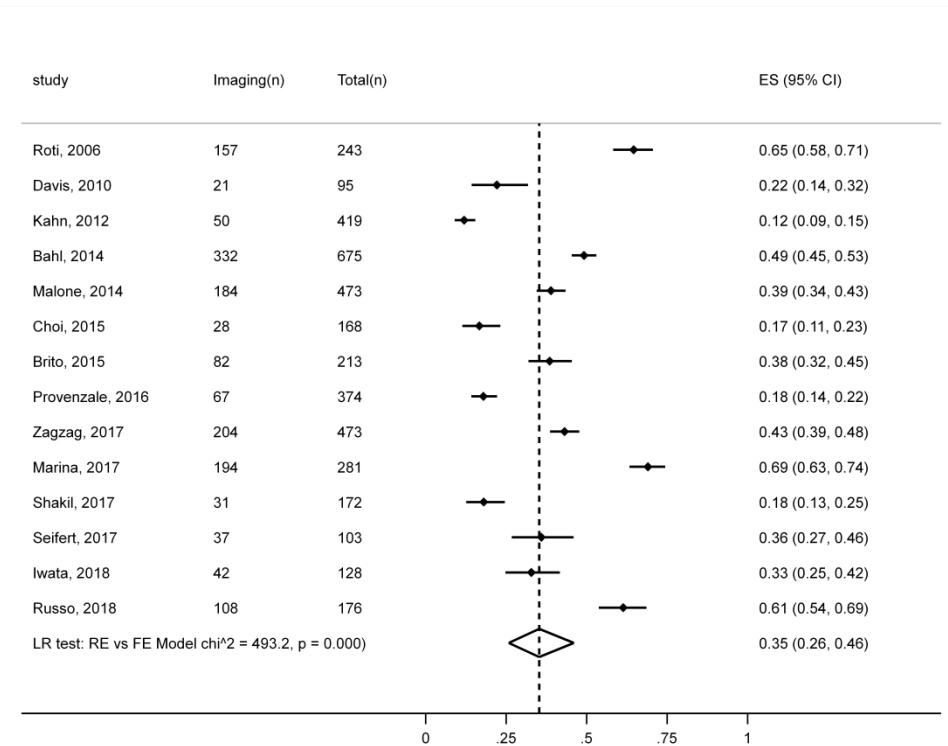
Appendix-Figure 4.1.

1419x1159mm (120 x 120 DPI)



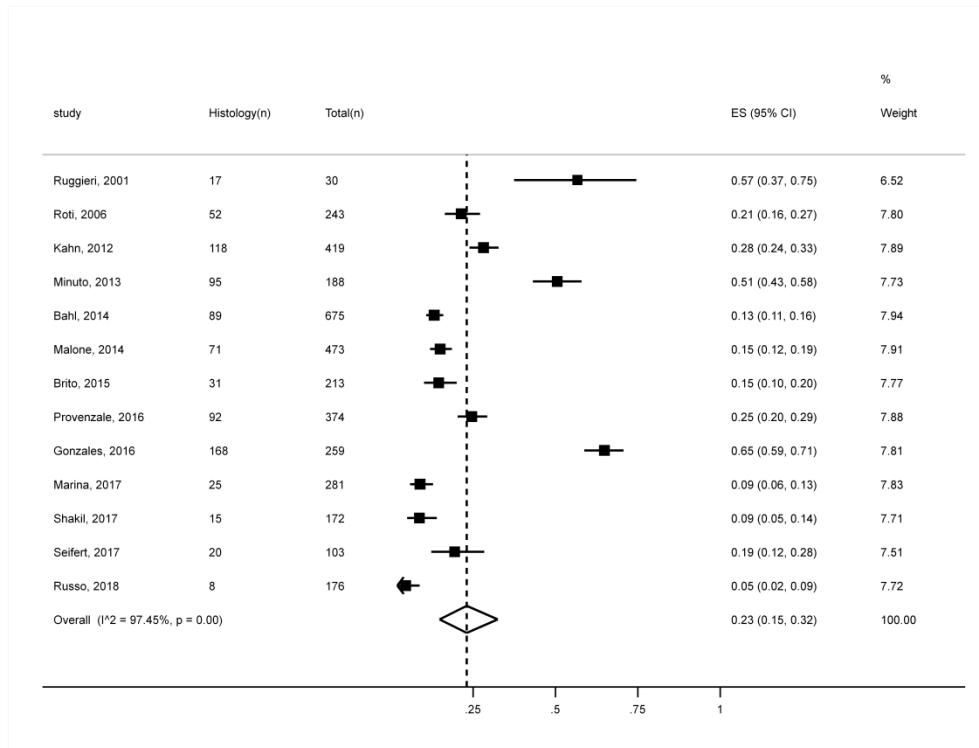
Appendix-Figure 5.

1405x1080mm (120 x 120 DPI)



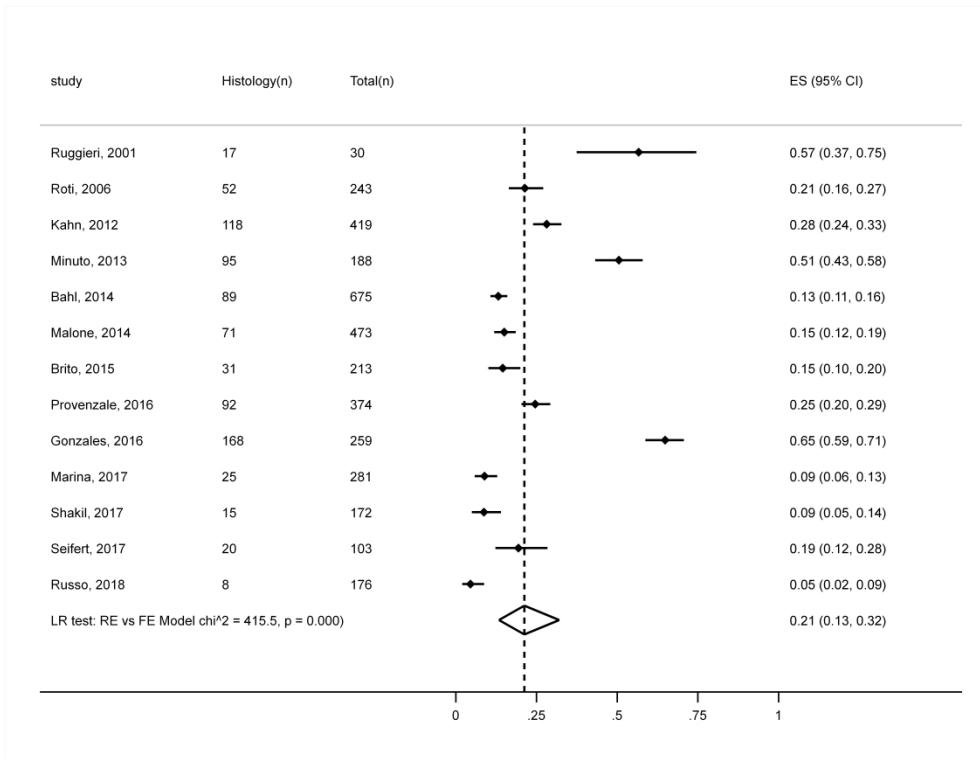
Appendix-Figure 5.1.

1414x1131mm (120 x 120 DPI)



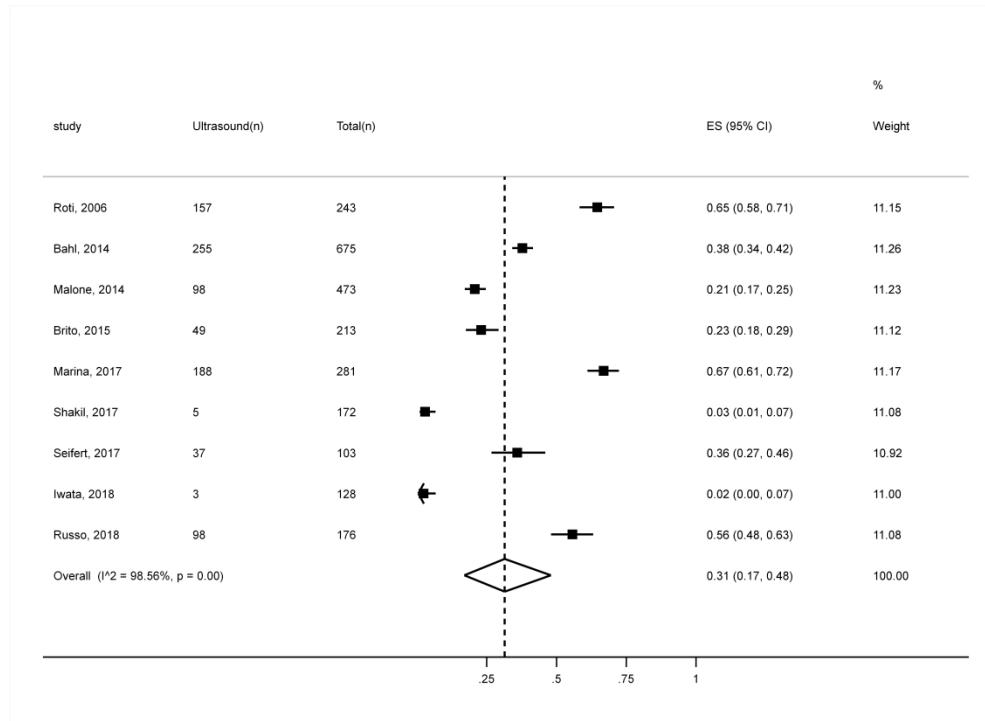
Appendix-Figure 6.

1405x1082mm (120 x 120 DPI)



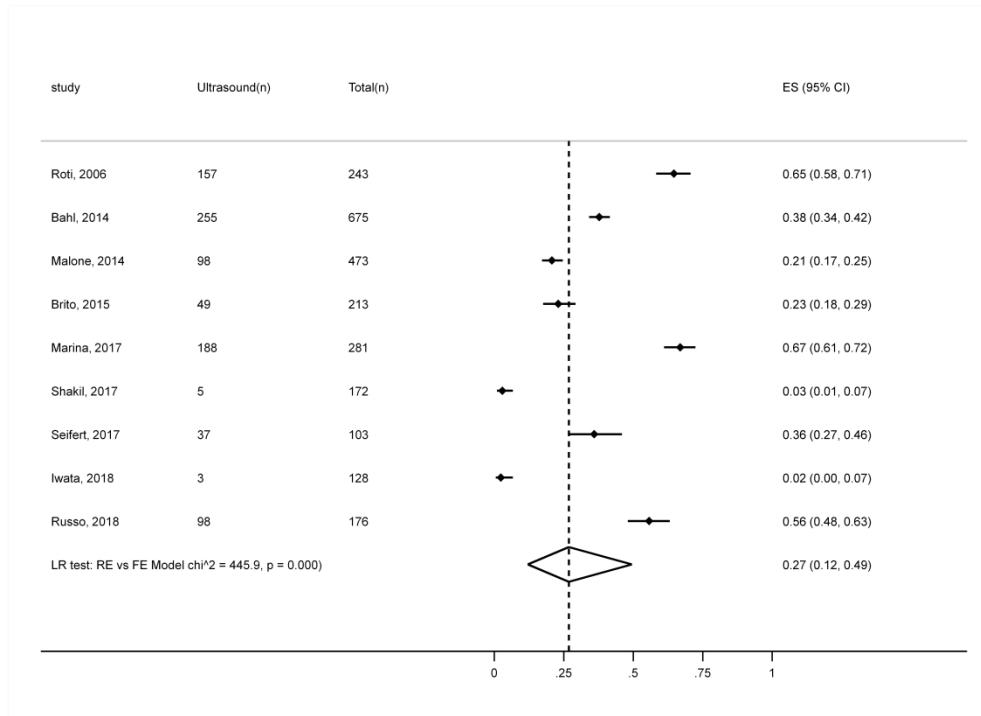
Appendix-Figure 6.1.

1407x1091mm (120 x 120 DPI)



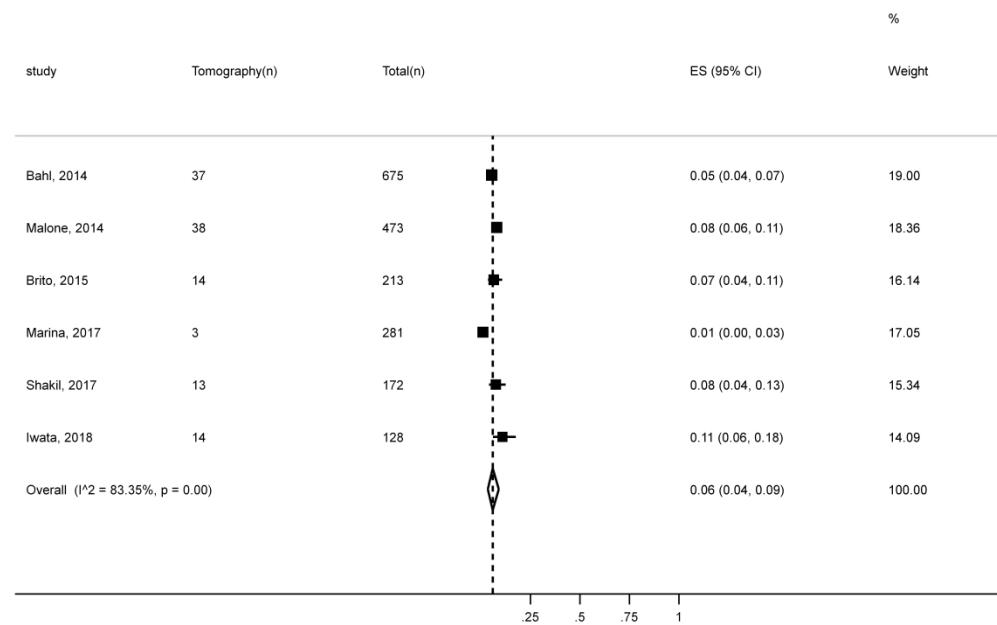
Appendix-Figure 7.

1396x1031mm (120 x 120 DPI)



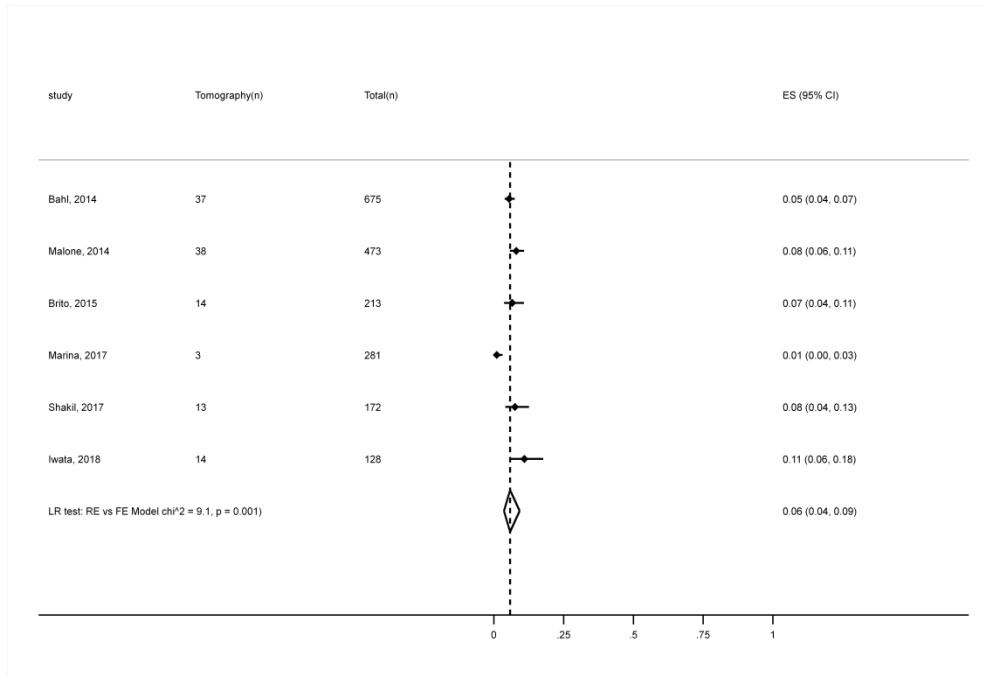
Appendix-Figure 7.1.

1394x1022mm (120 x 120 DPI)



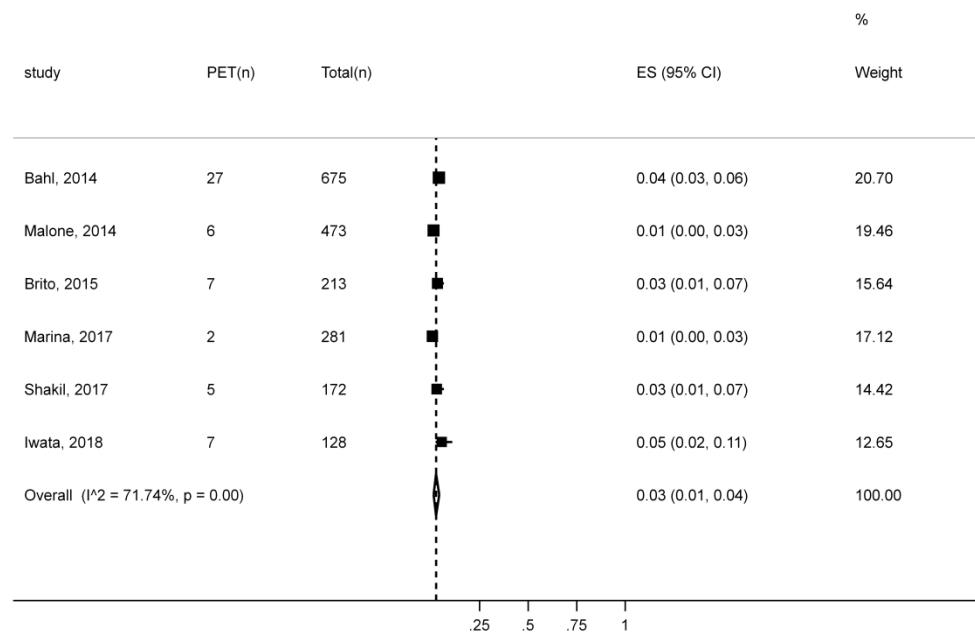
Appendix-Figure 8.

1278x863mm (120 x 120 DPI)



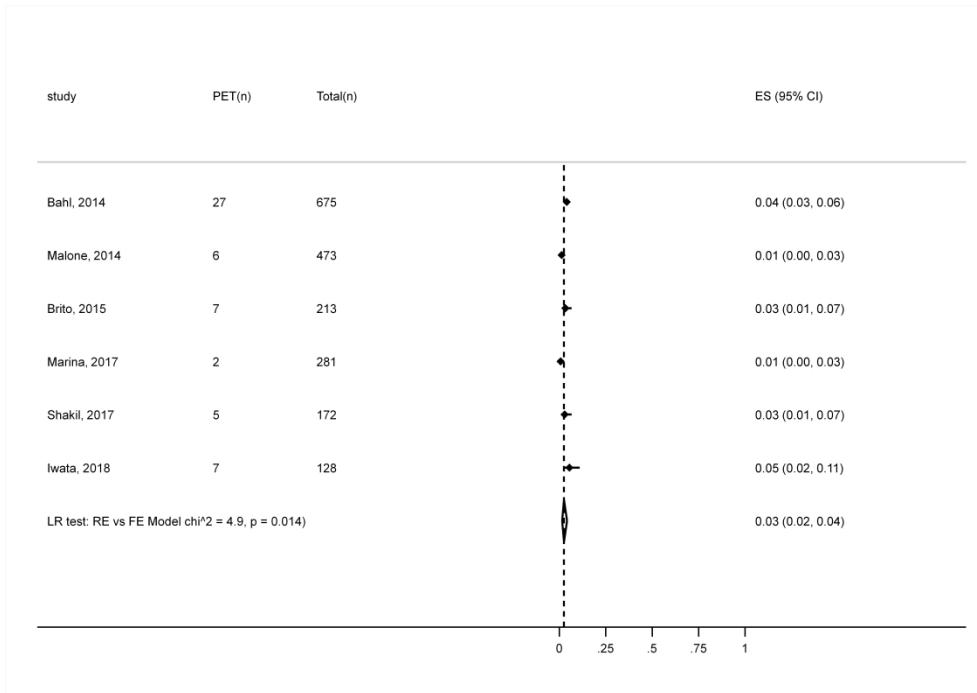
Appendix-Figure 8.1

1382x956mm (120 x 120 DPI)



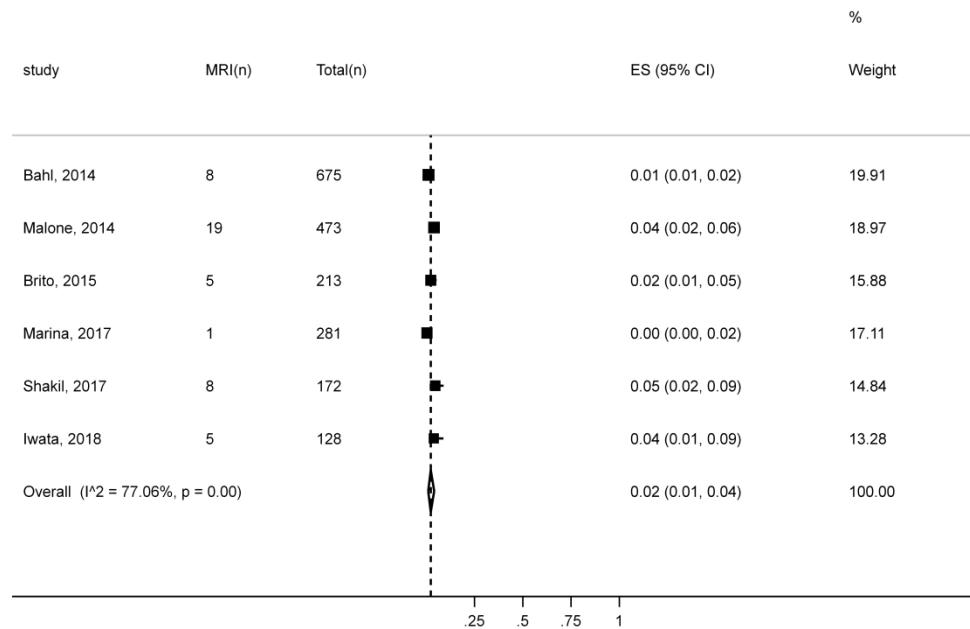
Appendix-Figure 9.

1295x833mm (120 x 120 DPI)



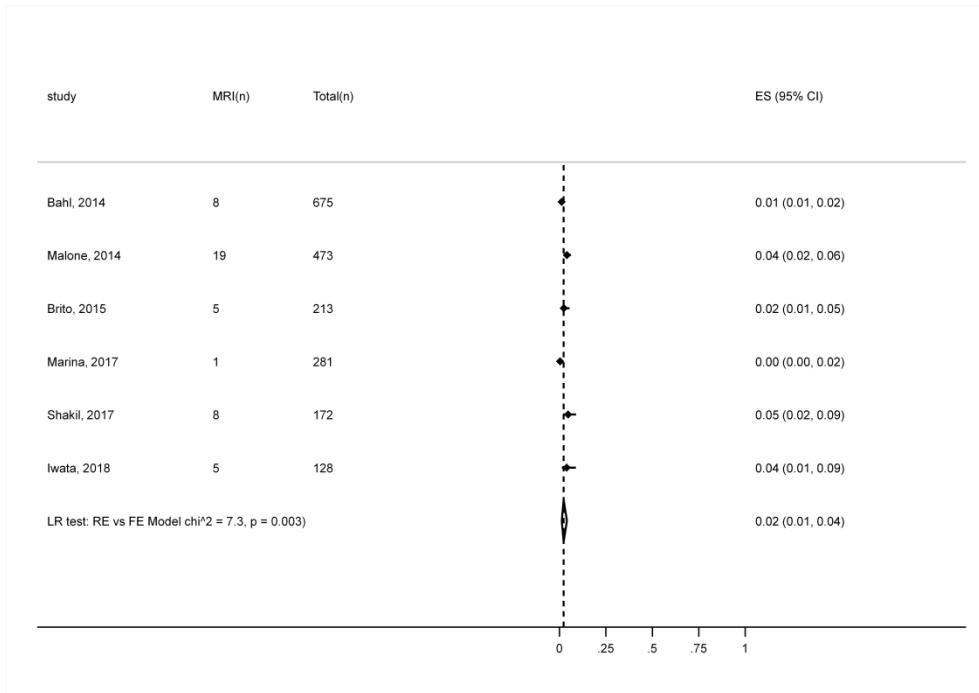
Appendix-Figure 9.1.

1387x979mm (120 x 120 DPI)



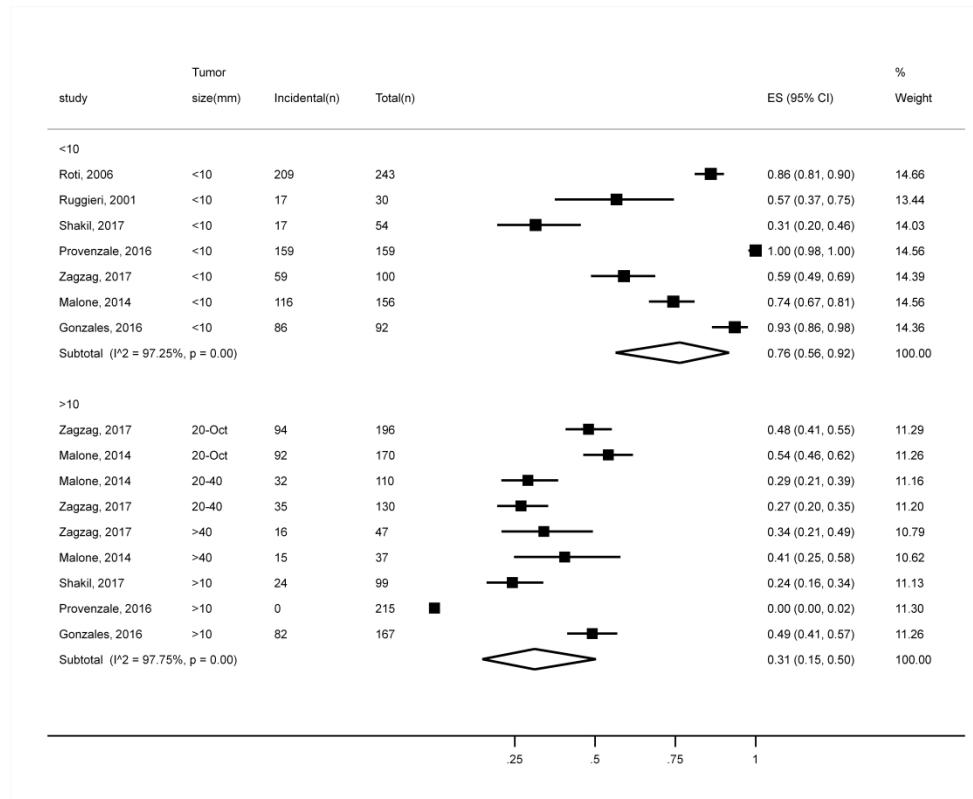
Appendix-Figure 10.

1302x846mm (120 x 120 DPI)



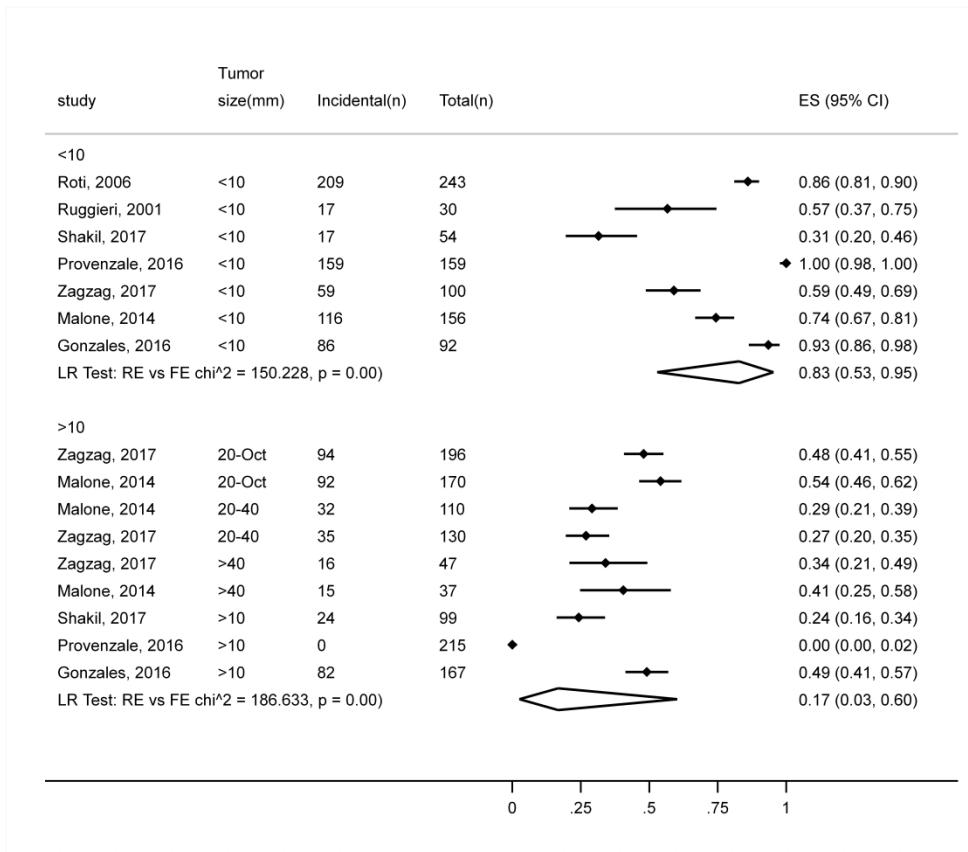
Appendix-Figure 10.1.

1387x979mm (120 x 120 DPI)



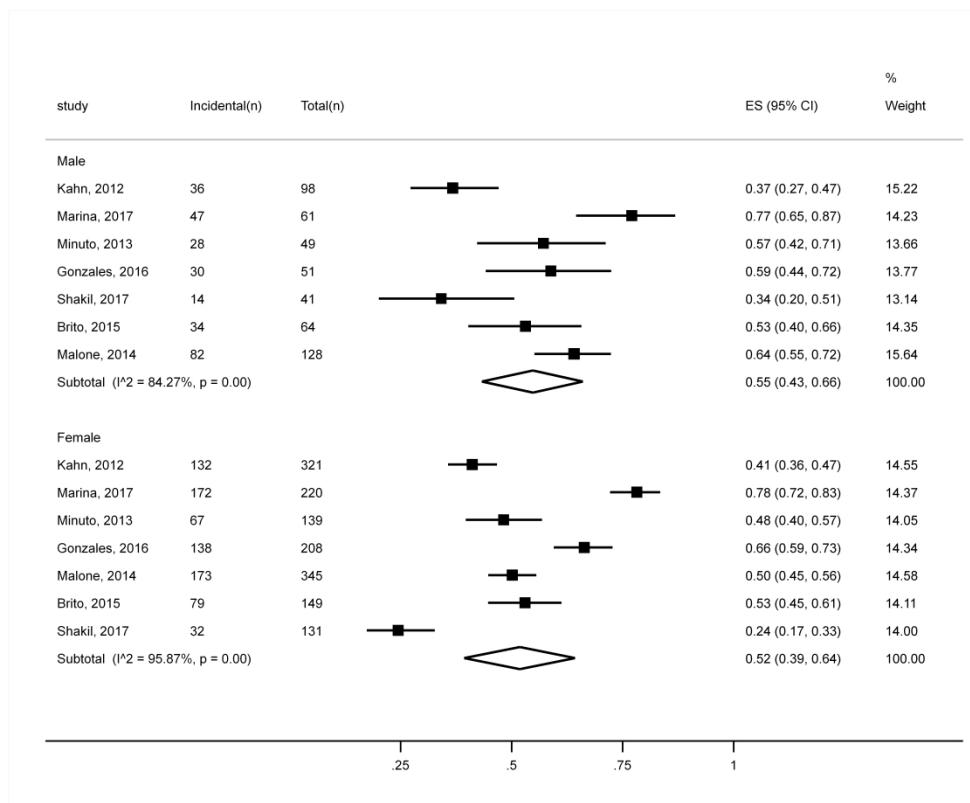
Appendix-Figure 11.

1421x1169mm (120 x 120 DPI)



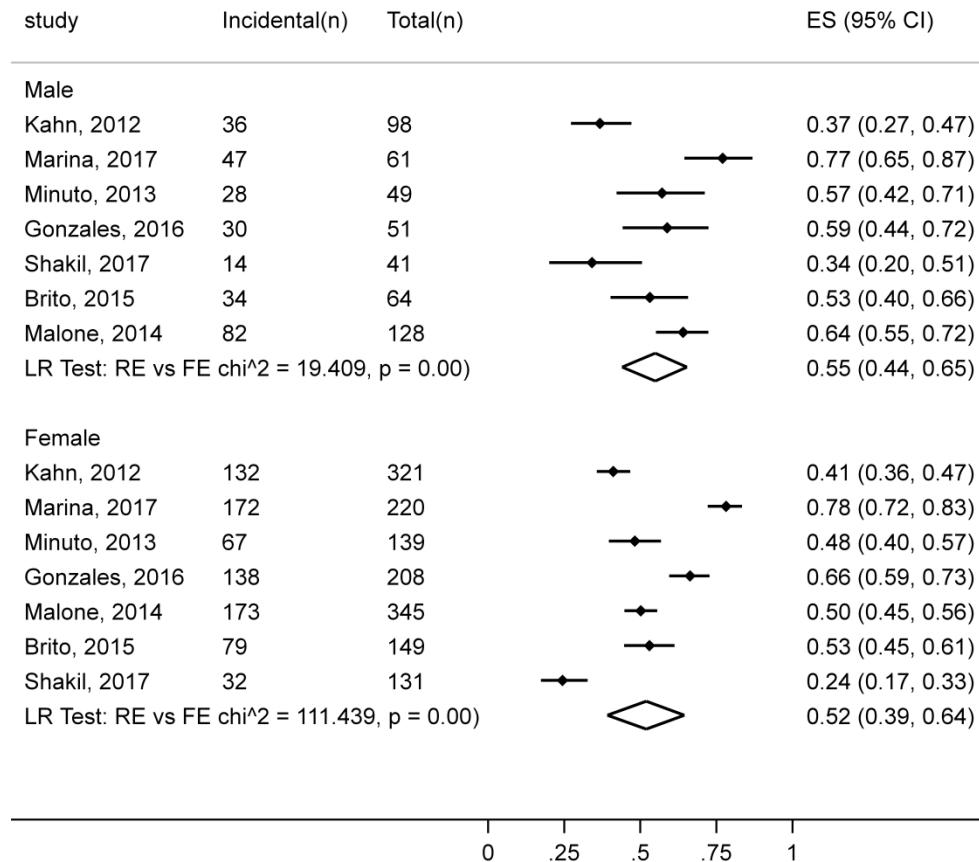
Appendix-Figure 11.1.

1436x1251mm (120 x 120 DPI)



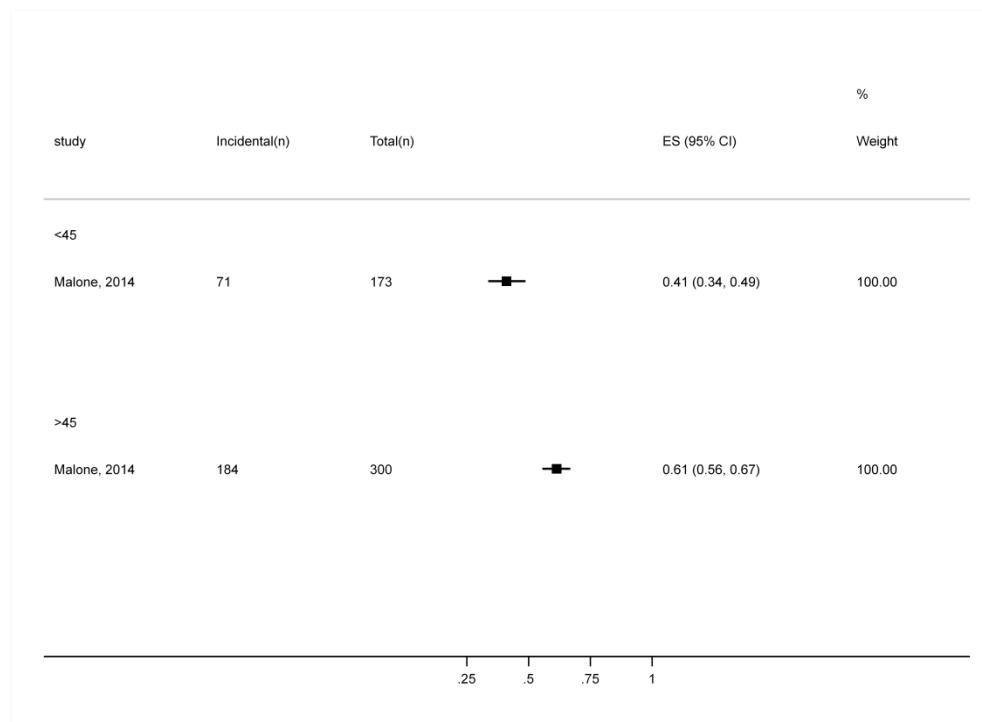
Appendix-Figure 12.

1421x1170mm (120 x 120 DPI)



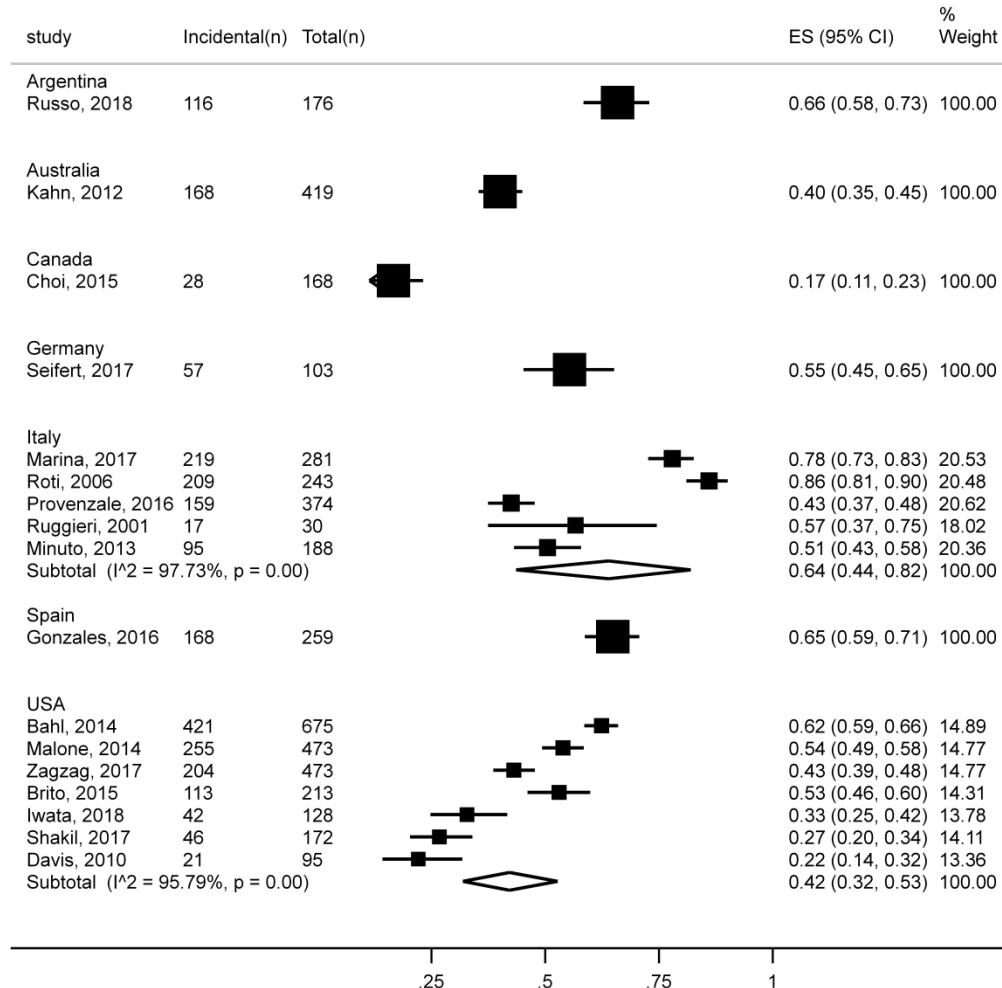
Appendix-Figure 12.1.

1295x1156mm (120 x 120 DPI)



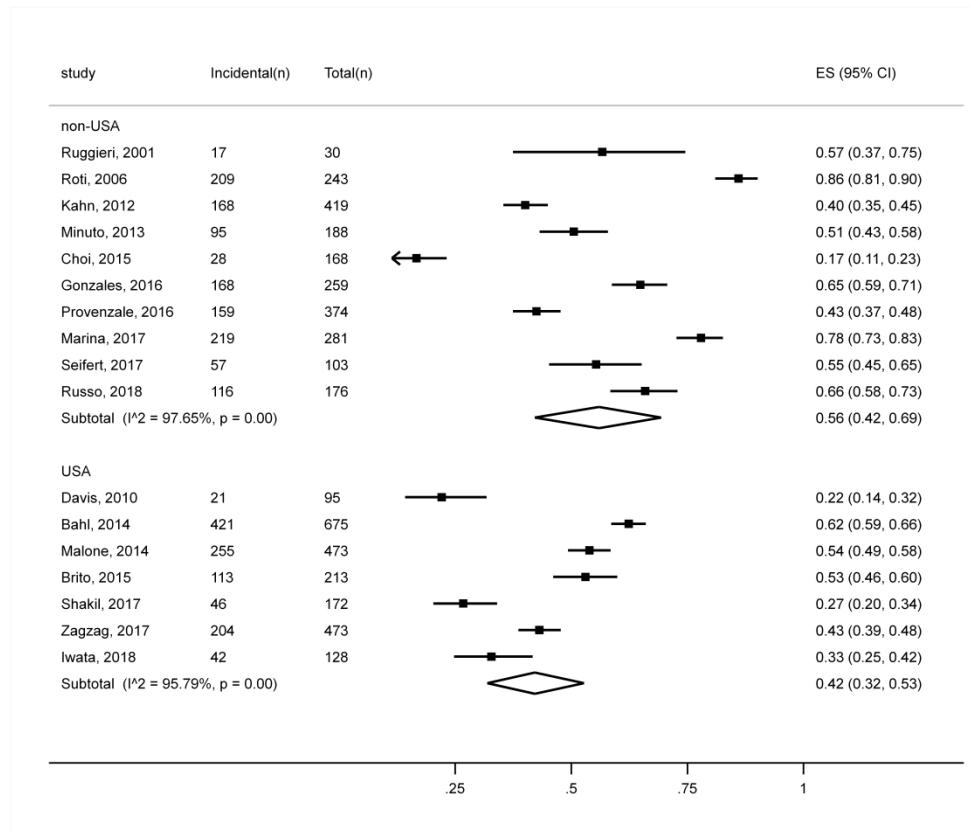
Appendix-Figure 13.

1395x1024mm (120 x 120 DPI)



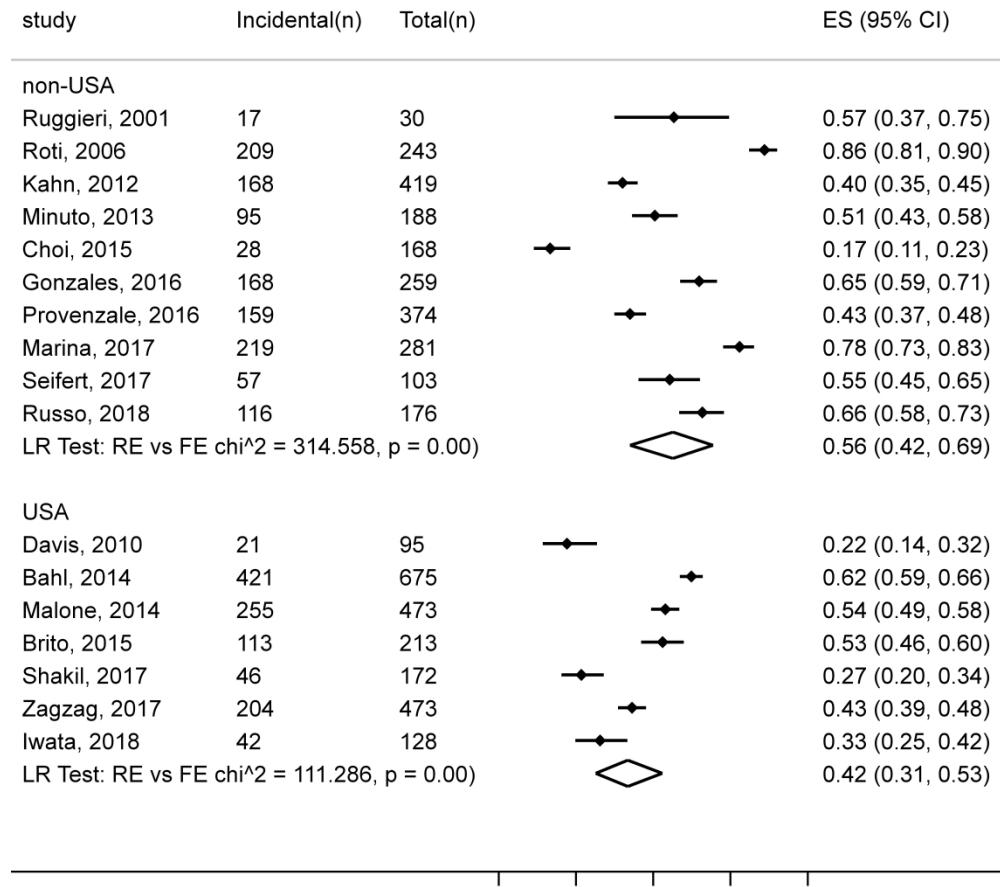
Appendix-Figure 14.

1319x1339mm (120 x 120 DPI)



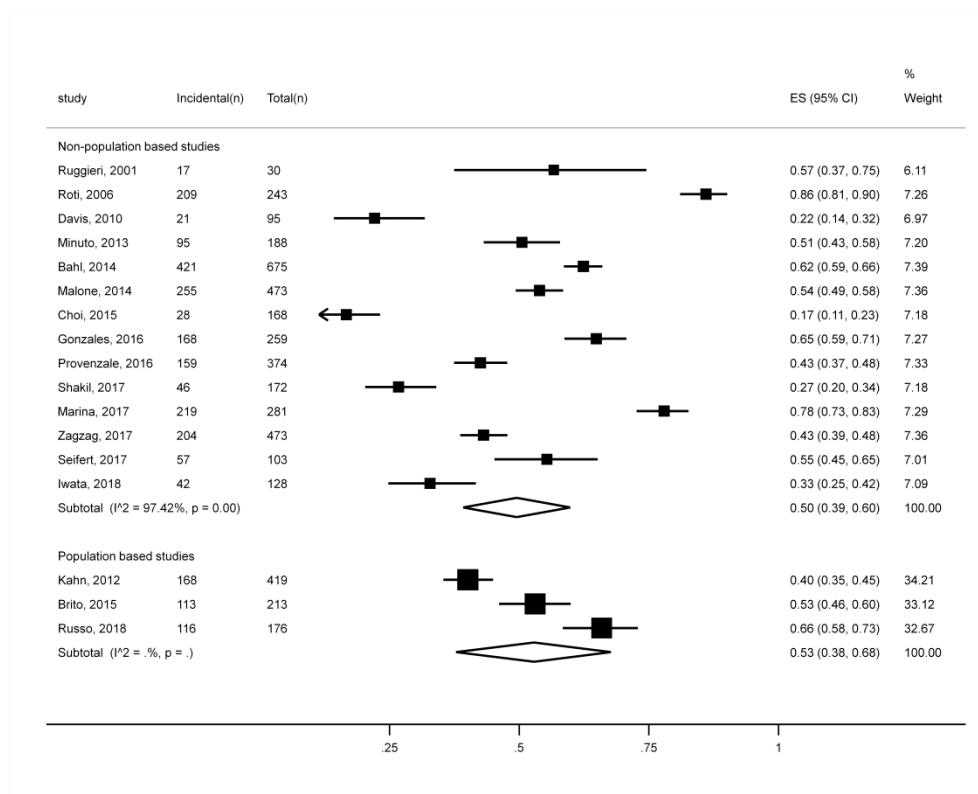
Appendix-Figure 15.

1430x1218mm (120 x 120 DPI)



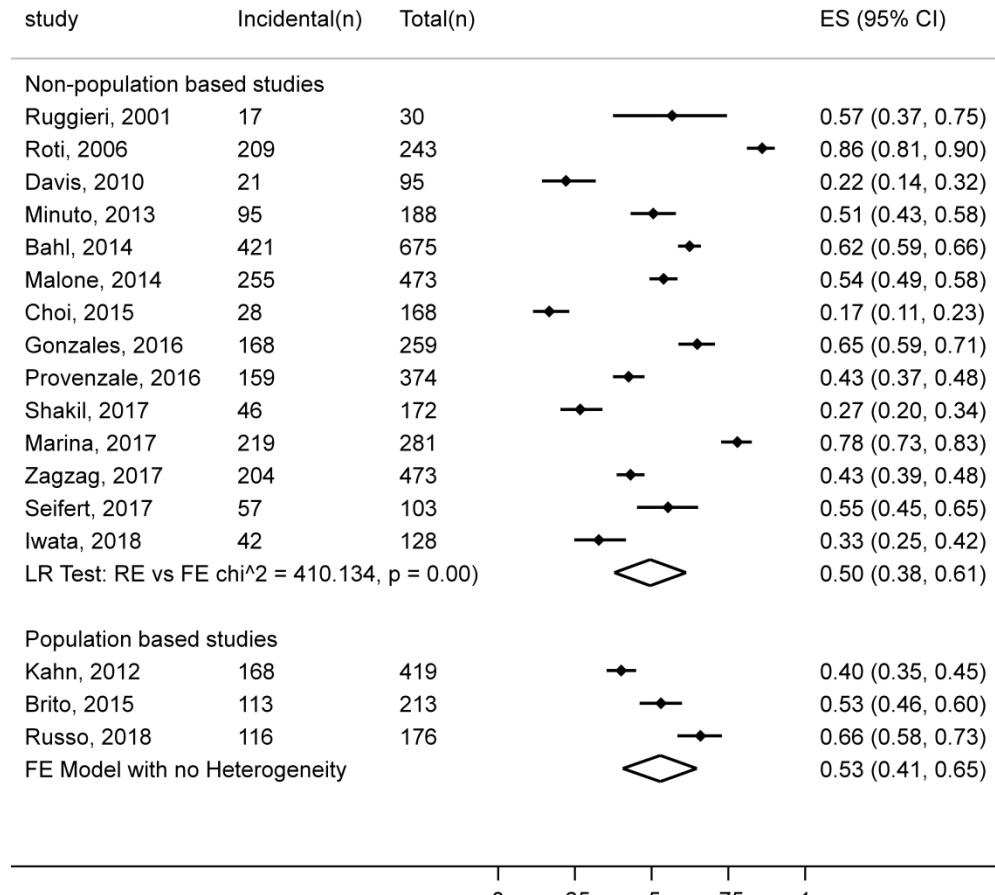
Appendix-Figure 15.1.

1280x1192mm (120 x 120 DPI)



Appendix-Figure 16.

1416x1141mm (120 x 120 DPI)



Appendix-Figure 16.1.

1288x1205mm (120 x 120 DPI)

1 Search strategies.

2 Ovid

3 Database(s): Embase 1988 to 2018 Week 39, Ovid MEDLINE(R) and Epub Ahead of Print, In-

4 Process & Other Non-Indexed Citations and Daily 1946 to September 21, 2018

5 Search Strategy:

#	Searches	Results
1	exp Thyroid Neoplasms/di, dg [Diagnosis, Diagnostic Imaging]	14676
2	exp thyroid cancer/di [Diagnosis]	22047
3	(thyroid* adj3 (cancer* or neoplasm* or carcinoma*)).ti,ab,hw,kw.	118062
4	(diagnos* or detect* or identify* or identified or identification*).ti,ab,hw,kw.	13979502
5	1 or 2 or (thyroid* adj3 (cancer* or neoplasm* or carcinoma*) adj3 (diagnos* or detect* or identify* or identified or identification*)).ti,ab,hw,kw.	32939
6	exp incidental findings/	23384
7	exp Mass Screening/	319779
8	exp Palpation/	22888
	((diagnos* or detect* or event or events or identify* or identified or identification*) adj5 (trigger* or chance)) or incidental or incidentally or palpabl*	2055424
9	or palpat* or screen* or serendipit* or subclinical).ti,ab,hw,kw.	
10	6 or 7 or 8 or 9	2064675
11	5 and 10	4308
12	exp comparative study/	2837337
13	exp Cohort Studies/	2178678

14 exp longitudinal study/	231767
15 exp retrospective study/	1384940
16 exp prospective study/	946632
17 exp population research/	92257
(cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective 18 study" or "prospective survey" or "prospective analysis" or prospectiv* or	12340709
(population adj3 (stud* or survey* or analys* or research)) or "incidence study" or "incidence survey" or "incidence analysis" or ((follow-up" or followup) adj (stud* or survey or analysis)) or (compar* and (study or trial)).mp,pt.	
19 or/12-18	12403274
20 11 and 19 limit 20 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or	1749
21 newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	8
22 20 not 21	1741
23 remove duplicates from 22	1366

Scopus

- 7
- 8 1 TITLE-ABS-KEY(thyroid* W/3 (cancer* or neoplasm* or carcinoma*) W/3 (diagnos* or detect* or
9 identify* or identified or identification*))
- 10 2 TITLE-ABS-KEY(((diagnos* or detect* or event or events or identify* or identified or
11 identification*) W/5 (trigger* or chance)) OR incidental OR incidentally OR palpabl* OR palpat*
12 OR screen* OR serendipit* OR subclinical)
- 13 3 TITLE-ABS-KEY(cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis"
14 or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or
15 survey or analysis or design)) or retrospective* or "prospective study" or "prospective survey" or
16 "prospective analysis" or prospective* or (population W/3 (stud* or survey* or analys* or
17 research)) or "incidence study" or "incidence survey" or "incidence analysis" or ((follow-up" or
18 followup) W/1 (stud* or survey or analysis)) or (compar* and (study or trial)))
- 19 4 1 and 2 and 3
- 20 5 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 21 6 4 and not 5
- 22 7 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7*
23 OR 8* OR 9*)
- 24 8 6 and not 7