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2

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5

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51 **Abstract**

52 **Context:** Use of electronic cigarettes (ECs) is on the rise in most high income countries.

53 Smoking conventional cigarettes is a known risk factor for urological malignancy incidence,

54 progression and mortality as well as for other urological health indicators. The potential

55 impact of EC use on urological health is therefore of clinical interest to the urology

56 community.

57 **Objective:** To review the available data on current EC use including potential benefits in

58 urological patients, potential issues linked to toxicology of EC constituents and how this

59 might translate into urological health risks.

60 **Evidence Acquisition:** A Medline search was carried out in August 2016 for studies reporting

61 urological health outcomes and EC use. Snowballing techniques were also used to identify

62 relevant studies from recent systematic reviews. A narrative synthesis of data around EC

63 health outcomes, toxicology, potential use in smoking cessation and health policy was

64 carried out.

65 **Evidence synthesis:** We found no studies to date that have been specifically designed to

66 assess prospectively urological health risks, even in an observational setting. Generating

67 such data would be an important contribution to the debate on the role of ECs in public

68 health and clinical practice. There is evidence from a recent Cochrane review of RCTs that

69 ECs can support smoking cessation. There are emerging data around potentially harmful

70 components of ECs such as tobacco-specific nitrosamines, polyaromatic hydrocarbons and

71 heavy metals could be linked to possible urological health risks.

72 **Conclusions:** ECs might be a useful tool to encourage conventional cigarette smoking
73 cessation. However, data collection around EC specific impact on urological health is needed
74 to clarify the possible patient benefit, outcomes and adverse events.

75 **Patient summary:** Whilst ECs might help some people to stop smoking, their overall impact
76 on urological health is not clear.

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1. Introduction

Tobacco smoking is an established cause of bladder and kidney cancer (50% and 20% of incident cases, respectively [1]). For people who smoke, there are clear benefits of quitting. For people who don't smoke, or would never have started smoking in the absence of EC, there are potential risks. As such, it is important for urologists and urological health researchers to understand the possible implications of EC use in urology patients.[2]

1.1 What are e-cigarettes?

Electronic cigarettes (ECs) are battery-powered devices that all work by heating a liquid ('e-liquid') to create an aerosol that is then inhaled. The aerosol produced is more commonly referred to as vapour, and the use of the device as 'vaping'. Some are designed to resemble traditional cigarettes ('cigalikes' or first generation products), whereas newer generation (tank systems) are modular and can be personalised. The cigalike devices are closed systems and are, generally, not refillable. They may be made for single use (i.e. disposable) or they can have a rechargeable battery and replaceable cartridges that contain the heating coil (or atomizer) and liquid. The newer generation products are generally greater in size and consist of a high capacity lithium battery, sometimes with variable power, an atomizer, and a tank that the user fills with liquid. The atomizer is usually manually activated, which gives greater control over vapour production than the automated systems. Most people start out using a cigalike device, but regular vapers generally use tank system ECs [3].

120 There are three main components of the e-liquid; propylene glycol or glycerol or a mix of
121 these, nicotine, and flavouring. The propylene glycol/glycerol mix is important for user
122 satisfaction (e.g. a high propylene glycol content gives a greater 'throat hit'), but may also
123 be important for nicotine delivery.[4] Nicotine concentrations vary from 0 to 36mg/ml, with
124 18mg/ml being the most commonly used.[5, 6] However the European Tobacco Products
125 Directive, which came into effect on 20 May 2016, now limits the concentration to a
126 maximum of 20mg/ml. The directive also restricts the volume of bottles of e-liquid to 10ml
127 and volume of EC tanks to 2ml, as well as a number of other measures including restrictions
128 on advertising and promotions and packaging and labelling requirements. EC liquid (e-liquid)
129 is available in numerous flavours, which are important for user satisfaction. In Great Britain,
130 the most commonly used flavour by current vapers is tobacco, followed by fruit and
131 mint/menthol flavours.[3] The flavours used are considered safe for oral ingestion, but the
132 effects of heating these and then inhaling them are unknown. Some flavours appear to be
133 more cytotoxic than others (e.g. strawberry [7] and cinnamon [8]) and associated with
134 increased risk of respiratory disease (e.g. diacetyl, [9] which gives a buttery flavour).

135

136 Heating nicotine-containing e-liquid produces nicotine-containing vapour; however, the
137 association between the concentration of nicotine in the e-liquid and in vapour is
138 inconsistent. Other factors such as heating of the liquid, voltage and amperage resistance,
139 and how the user inhales on the EC also have a role to play. ECs also do not deliver as much
140 nicotine on a puff by puff basis as standard cigarettes.[10] Therefore, vapers typically take
141 longer puffs than with standard cigarettes (e.g. a mean of 2.4 seconds for conventional
142 cigarettes versus 4.3 seconds for ECs).[11]

143

144 **1.2. Epidemiology/demographics around EC use**

145 Since being introduced, the prevalence of EC use has seen a relatively rapid increase in
146 many high-income countries from which national longitudinal data are available, notably
147 North American and European countries. For example, the prevalence of ever-use among
148 individuals aged ≥ 15 years in 27 states of the European Union increased from 7.2% in 2012
149 to 11.9% in 2014 (Table 1).[12] On average, 15.3% of ever e-cigarette users became current
150 users in 2014. The greatest increases in the European Union occurred in Malta (5.5%
151 increase), Ireland (5.1%), Sweden (4.5%), and France (4.3%). In that survey, the lowest
152 prevalence in 2014 was reported from Portugal (5.7%), whereas the prevalence was 10% or
153 more in 15 countries, with the highest prevalence in France (21.3%).[12] Experimenting and
154 ever use of ECs is generally common among youth,[13] but in Europe, prevalence of regular
155 EC use is much higher in older adults who smoke. In 2014, prevalence of ever EC use in
156 individuals aged ≥ 15 years in the United Kingdom was 15.5%, and approximately one
157 quarter of them transitioned to current users.[12] Among adolescents aged 11–18 years in
158 Great Britain, prevalence of ever use of ECs in 2014 was 8.2%, while it was 1.7% for monthly
159 or more use.[14]

160

161 On the other hand, prevalence of more regular use is higher in youth than older adults in
162 North America. In 2013, 8.5% and 1.8% of Canadians reported ever and current (past 30-
163 day) use of ECs, respectively.[15] The highest prevalence of current use was in age 20–24
164 (3.9%), followed by age 15–19 (2.6%).[15] In the United States, the prevalence of current
165 use among individuals aged ≥ 18 years in 2013–2014 was 3.3%.[16] However, there has been
166 a substantial increase in ECs use among high-school students in the United States, with
167 current use prevalence increasing from 1.5% in 2011 to 16.0% in 2015.[17] The recent US

168 Surgeon General's report warned that in 2014, current use of ECs by young adults 18–24
169 years of age surpassed that of adults 25 years of age and older. The report points to
170 potentially harmful constituents of ECs: particularly nicotine which can lead to addiction and
171 can harm the developing adolescent brain.[18]

172

173 Information on EC use at the national level from countries in other regions is limited. In a
174 survey of Chinese adults (age 15–65 years) in Hong Kong in 2014, the prevalence of ever EC
175 use was 2.3%.[19] Among individuals aged ≥ 15 years in New Zealand in 2014, 13.1% had
176 ever used ECs and only 0.8% were current users. The highest prevalence of current use was
177 in age 22–44 years (1.2%), followed by age ≥ 45 (0.7%).[20] Prevalence of ever and current
178 use of ECs among students aged 13–18 years in South Korea in 2011 was 9.4% and 1.4%,
179 respectively.[21] Since 2011, questions on ECs use have been added to the Global Adult
180 Tobacco Survey (GATS), which is a nationally representative household survey of individuals
181 aged ≥ 15 years in a number of countries.[22] The prevalence of current EC use in four
182 countries with available data was 0.3% in Indonesia and 0.8% in Malaysia in 2011 and 0.9%
183 in Qatar and 1.9% in Greece in 2013.[22] It should be noted that due to rapid changes in
184 prevalence of EC use in some countries, prevalence of use across countries, especially
185 among youth, may not be comparable using results of surveys conducted in different years.

186

187 EC use has the potential to help smokers to quit cigarette smoking or reduce smoking
188 intensity.[23] However, one of the primary concerns of EC use is the maintenance of
189 tobacco use in current smokers (without any substantial decrease in smoking intensity), re-
190 initiation in former smokers, and in particular, nicotine dependence in adolescents,[24–28]
191 as EC user adolescents may show a higher intention to smoke traditional cigarettes.[25, 27]

192 However, in many countries, the rate of EC use by never-smokers or smoking initiation
193 following EC use has been relatively low, although there might be some variations across
194 countries. In a survey conducted in 2014 in the European Union, initiation of tobacco use by
195 using ECs was reported by 0.8% of participants who had used any tobacco product. Use of
196 nicotine-containing EC among never smokers was low (1.3%), with 0.09% reporting daily
197 use.[29] The prevalence of current EC use among never-smokers in 2013 was 0.3% in
198 Canada [15] and 1.4% in the United States.[26] Among adolescents, EC use at least monthly
199 was reported by only 0.2% of adolescents aged 11–18 years in Great Britain in 2014.[14]
200 Among middle and high school students in the United States in 2011–2013, prevalence of
201 current EC use was 0.3% among never smokers.[24] Prevalence of ever and current use of
202 ECs only (no other tobacco products) in age 13–18 years in South Korea in 2011 was 1.4%
203 and 1.1%, respectively.[21] Despite low rates of ECs use among never smoker adolescents,
204 this group could include a substantial number of children, as generally prevalence of
205 tobacco smoking in this age group is low. For example, the group of never smoker students
206 that were current ECs users (0.3% of never smokers) in the United States in 2013 included
207 263,000 children.[24]

208

209

210 **2. Evidence acquisition**

211 In order to identify any eligible trials addressing EC use and urological health outcomes, a search of
212 the electronic databases MEDLINE was carried out from inception to August 2016. MEDLINE search
213 terms were (e-cigarette or electronic-cigarette) AND (bladder or prostate or kidney or urol*). In
214 addition to database searches, recent systematic reviews of EC use were hand searched for any
215 potentially eligible trials. To add context to the any available trials data, evidence around smoking

216 cessation, available toxicology data and health policy around EC regulations are presented in this
217 review. Quality appraisal was done subjectively according to expertise and clinical judgement of the
218 authors. Given that EC use and urological outcomes is an emerging clinical issue with a fragmentary
219 evidence base and involves rapidly evolving technologies, a narrative synthesis of these data was
220 undertaken.[30]

221

222 **3. Evidence synthesis**

223 *3.1 Current urological health outcomes and trials of EC use*

224 We found no published clinical studies, which are *a priori* designed to evaluate the impact of
225 ECs on urological health outcomes. We were able to find only one published protocol for a
226 prospective observational study that will document hospitalizations and adverse events that
227 could report urological health outcomes (although not specifically designed to do this).[31]

228

229 *3.2 Toxicity data and potential urological health impacts from ECs*

230 ECs were introduced into the US and UK markets in 2007 [32] and so their long-term health
231 risks are not yet clear. Reducing the use of conventional cigarettes has numerous obvious
232 health benefits including links to incidence and progression of urological malignancies [33]
233 and complications after primary treatment for urological cancer.[34] EC operation does not
234 involve combustion and so no smoke or other harmful combustion products, such as tar and
235 carbon monoxide, are formed. Reduced excretion of tobacco-specific nitrosamines and
236 other carcinogens has been found in the urine of vapers compared with smokers. [35, 36]
237 ECs are thought to be much safer for long-term health by the public than traditional tobacco
238 cigarettes.[37] It is however, important to recognise that these devices are not entirely
239 benign. Due to the nature and components of these devices, ECs have a diverse hazard

240 profile. Operation of EC at high temperatures can generate relatively high levels of
241 aldehydes [38, 39], which have carcinogenic potential. However vapers naturally avoid this,
242 as it creates an unpleasant taste (commonly known as a 'dry puff')[39, 40]. A recent
243 systematic review highlighted adverse events linked between EC use and the respiratory,
244 gastrointestinal, cardiovascular, neurological and immune system; serious leg burns due to
245 exposure of the battery; serious oral burns, lacerations and fractures from an account of an
246 EC 'explosion'; both accidental and intentional nicotine overdoses (suicide attempts).[41]

247

248 Data regarding the constituents of ECs is evolving in the literature. Levels of each
249 component can be varied (e.g. Allen et al (2016) describe over 7000 flavours[42]) and there
250 is heterogeneity amongst manufacturers.[43] For example, nicotine levels were seen to vary
251 from 0 mg/ml to 87 mg/ml across studies, and there were reported deviations from the
252 device label of ingredients of up to 100%.[43] Furthermore, there is inconsistency in the
253 delivery of chemicals within each puff from the same device or brand. This may be due to
254 subtle differences in the size of particulate matter within each refill solution and the
255 delivery system that is used.

256

257 A recent review describes chemical profiles of EC solutions, cartridges, aerosols and
258 environmental emissions.[43] Whilst ECs are designed to be devoid of tar, some ECs have
259 been found to contain carcinogens such as tobacco-specific nitrosamines and formaldehyde.
260 Other constituents such as polyaromatic hydrocarbons and heavy metals are known to
261 cause cancer, and nicotine itself is thought by some to pose a urological cancer risk. [44, 45]
262 For instance, polycyclic aromatic hydrocarbons (International Agency for Research on
263 Cancer (IARC), Group 1 (human carcinogen)[46]), which has been associated with bladder

264 cancer.[47] EC have also been found to contain certain heavy metals, such as lead.[48] Lead
265 exposure has been linked to increased kidney cancer risk. [49, 50] The concentration of lead
266 in EC aerosol is variable but has been suggested in at least one analysis to be comparable to
267 that found in conventional cigarettes.[51] Other heavy metals in EC such as cadmium, nickel
268 and chromium are possible carcinogens (IARC 2b). Nickel, in particular, has been recorded at
269 levels present in ECs that are much higher than conventional cigarettes. [51] Although these
270 heavy metals are linked to an increase cancer risk, they have not yet been linked to
271 urological malignancies.[49] Cresol, which has been found in aerosols from EC cartridges is
272 also found in creosote, a suspect bladder carcinogen.[47]

273

274 In addition, in vitro data has demonstrated that EC vapour exposure, independent of
275 nicotine content induces increased cell death. In both normal epithelial cells and cancer cell
276 lines (head and neck squamous cell carcinoma) treated with nicotine free and nicotine-
277 containing vapour, up to a threefold increase in DNA double strand breaks has been
278 reported.[52] Nicotine is also negatively correlated with total sperm motility due to
279 metabolic breakdown products cotinine and trans-3'-hydroxycotinine levels in seminal
280 fluid.[53] Furthermore, cadmium (found in ECs) is associated with low sperm density.[54]
281 Preliminary evidence from a murine model has reported exposure to EC refill liquid can alter
282 anti-oxidant defence and induce histopathological changes reflecting renal collecting duct
283 cell apoptosis.[55]

284

285 Whilst there is a theoretic potential for adverse urological health outcomes from the use of
286 ECs it should be stressed that robust data are currently absent to offer a convincing
287 argument for either side of the debate. A recent systematic review of the health

288 consequences of vaping/ECs highlighted frequent methodological problems with available
289 studies, problematic authorship conflicts of interest, small cohort size, selection bias,
290 conflicting results and a paucity of long-term follow-up data.[48]

291

292 **3.3 Can ECs help stop tobacco smoking?**

293 The literature on the role ECs play in smoking cessation is growing very slowly, and the
294 messages are somewhat mixed. This section summarizes the current evidence from a range
295 of different study designs and levels of evidence.

296

297

298 **3.3.1 Prospective cohort studies**

299 Five studies, with long-term outcomes, have looked at the use of ECs in people who were
300 not ready to quit smoking. One followed 40 smokers over two years and reported that 13%
301 achieved at least six months of CO validated abstinence from conventional cigarettes and
302 28% had achieved a sustained $\geq 50\%$ reduction from baseline cigarette consumption.[56, 57]
303 The second tested the same approach with 14 smokers with schizophrenia and reported
304 14% 30-day CO validated abstinence rates at one-year.[58] The third followed a group of 34
305 smokers for 8 months after discharge from hospital.[59] Over half (53%) reported no longer
306 smoking. In the fourth, 50 smokers were provided with a second-generation device with
307 9mg/ml concentration of e-liquid. At 6 month follow-up 36% were biochemically validated
308 7-day point prevalence abstainers.[60] The fifth cohort study followed 71 smokers who
309 purchased an EC from a vape shop. One year after their purchase 41% reported that they
310 had not smoked at all for at least the last 30 days.[61]

311

312 Data are now being reported by the UK stop smoking services. A London-based stop
313 smoking service offered 100 clients, all of whom wanted to quit smoking, a choice of a first
314 or second generation EC.[62] In total, 67 accepted the offer and of these 45 (65%) were
315 recorded as biochemically validated abstainers at the end of treatment (4-weeks post-quit
316 date). The results from this study closely reflect the UK Stop Smoking Service monitoring
317 data from over 450,000 people that made a quit attempt, where 4-week self-reported quit
318 rates were 66% among people who used ECs (n=2221), compared to 48% among people
319 who used combination NRT (n=135,719).

320

321 Although there are data to support ECs as a potential aid to smoking cessation in the
322 general population, it is important to note that in those already diagnosed with cancer,
323 there is less certainty. Prospective cohort data from a major US cancer treatment centre
324 reported that significantly higher percentage of EC users were highly nicotine dependent
325 when compared with nonusers and were twice as likely to be smoking at the time of follow-
326 up as nonusers.[63]

327

328 **3.3.2 Randomised controlled trials**

329 To date only three randomised controlled trials that have examined the effects of EC in
330 helping people stop smoking have been published. One examined their use in people who
331 wanted to quit,[64] and two in those who did not.[65, 66] In a study of people who wanted
332 to quit from New Zealand [64], the investigators compared nicotine-containing ECs (n=289),
333 with 21mg nicotine patches (n=295), and with non-nicotine ECs (placebo ECs, n=73).

334 Participants were provided with a referral to telephone quitline but with no face-to-face
335 contact. In this minimal support context, there were no significant differences in validated
336 continuous abstinence at six months (7.3% nicotine EC, 5.8% nicotine patch, and 4.1% non-
337 nicotine EC). These findings were similar to an Italian study comparing EC use (two different
338 doses for 12 weeks) to non-nicotine ECs in 300 smokers who were not intending to quit. [65]
339 Biochemically validated six-month abstinence rates (at one-year follow-up) were not
340 significantly different; 13%, 9% and 4% in the three groups, respectively. Both of these
341 pioneering trials were underpowered and used first generation EC products with poor
342 nicotine delivery. These ECs often malfunctioned and neither is now available on the
343 market.

344

345 The third trial [66], from Belgium, randomised 48 smokers who did not want to quit to use
346 an EC (a tank system) or no intervention. At 8-week follow-up, 34% of those given an EC to
347 use had quit smoking compared to none in control group. From week 8, all participants
348 were provided with an EC and followed up at 8 months. Among this cohort 19% of early EC
349 users and 25% of the late starters (the control group) had stopped smoking. The results
350 from this study are difficult to interpret because of the small sample size and design.

351

352 **3.3.3 Systematic reviews**

353 There are now 16 published systematic reviews on ECs for smoking cessation. A recently
354 updated Cochrane review found that ECs with nicotine helped smokers quit for at least 6
355 months compared with no nicotine ECs (RR= 2.29, 95% CI: 1.05-4.96; 9% vs. 4%). [67] The
356 authors of the review gave these findings a 'low' confidence rating using GRADE standards,
357 not because of poor quality studies, but because there are only two studies. Crucially, the

358 'low' judgement also means that further research is very likely to have an important impact
359 on our confidence in the estimate of effect and is likely to change the estimate. The addition
360 of more trials to this review will further strengthen the conclusions made. Other systematic
361 reviews draw similar conclusions to the Cochrane review (e.g.[68, 69]), unsurprisingly
362 because they include the same studies. The review and meta-analysis by Kalkohern and
363 Glantz [70] came to the opposite conclusion (that EC use is associated with significantly
364 lower odds of achieving abstinence; OR 0.72; 95% CI: 0.57-0.91). The data in this review
365 included reports of many small surveys and cohort studies (all with serious limitations)
366 rendering the findings of this meta-analysis difficult to interpret.

367

368 Given that ECs now deliver nicotine to the user in similar quantities as NRT and even
369 cigarettes, there is little reason to doubt they could help people stop smoking. Some
370 estimates of the numbers who have stopped using ECs have been made. For example,
371 Farsalinos estimated 6.1 million European ever EC users have stopped smoking.[71] In
372 England this figure is thought to be around 0.56 million. Further research and monitoring
373 will strengthen confidence in these findings.[72]

374

375

376 **3.4 European health policy and ECs**

377 The use of ECs for smoking reduction or cessation is influenced by a range of factors that
378 extend beyond the safety and efficacy of these devices. Regulation also affects their use, in
379 particular policies that may result in changes to the price, availability or promotion of the
380 products.[73] The global context for EC regulation is highly variable.[74] In many countries
381 such as Argentina, Brazil, Indonesia, and Singapore, the import, distribution and sale of ECs

382 is banned. Other countries such as New Zealand, South Africa and Switzerland have
383 implemented a two tier system where ECs themselves and nicotine-free cartridges or e-
384 liquid can be sold sale of but nicotine-containing refills or e-liquid are prohibited. Other
385 countries permit their import and sale but certain restrictions on age of sale or marketing
386 are in place. Policies have evolved as use has become more prevalent and governments
387 have responded to a range of concerns often about youth uptake, addictiveness or safety.
388 Ironically, many jurisdictions now have more restrictive regulation on ECs than tobacco
389 products.

390 In the European Union (EU), EC use is prevalent and countries have taken a range of
391 approaches to regulation.[29] From May 2016 the revised EU Tobacco Products Directive
392 (TPD) was implemented and article 20 of the Directive applies to ECs and refill containers
393 that do not have a medicinal license.[75] Only one device, E-Voke (manufactured by British
394 American Tobacco) has been granted a medicinal license but is not yet available on
395 prescription or as an over the counter medication.[76] The EU TPD requires manufacturers
396 and importers of ECs to comply with a notification process that involves providing data on:
397 ingredients and emissions; nicotine delivery and uptake; health and addictive effects; the
398 product components and production process; and a declaration on safety and quality when
399 used as intended. It is anticipated that this process will remove some products from the
400 market that can't meet these requirements.

401

402 The TPD also places a limit on nicotine concentration with devices that do not have a
403 medicinal license limited to 20mg/ml and refill containers up to a maximum volume of 10ml.
404 The basis for this requirement is contested and some concerns have been expressed about
405 this limit in terms of delivering nicotine to smokers who are highly dependent.[77] ECs must

406 also be secure in terms of leakage and breakage, be child and tamper proof and contain a
407 leaflet with warnings, instructions and further information. Packaging must contain a
408 warning label about nicotine being a highly addictive substance and promotional elements
409 on packaging are also subject to regulation. Some forms of marketing are also restricted
410 under the TPD including the prohibition of all cross border advertising and sponsorship
411 although other forms of marketing such as billboards and point of sale are at the discretion
412 of member states. Finally, annual submissions on products are required to be submitted to
413 governments and a system for collecting information on adverse effects on health must be
414 in place. Other policy issues such as age of sale, use in public places and the regulation of
415 flavours are the responsibility of national governments.

416

417 **4. Discussion**

418 We were not able to find any clinical studies with prospective outcomes assessing EC use
419 and urological outcomes. We have presented data around toxicology of compounds found
420 in EC constituents and how this might impact urological health, but these must be viewed as
421 hypothesis generating and treated with caution. As such the use and potential outcomes
422 associated with EC use in urological patient populations is still to be determined. Some
423 international studies, such as the International Tobacco Control Survey,[78] are already
424 providing useful data allowing comparisons of the prevalence of EC use in adults and young
425 people, impact on smoking cessation, and harm perceptions to be examined across
426 countries. In the UK, Cancer Research UK and Public Health England have established the UK
427 Electronic Cigarette Research forum (UKECRF) which brings together researchers from a
428 range of disciplines three times a year to build new collaborations and pursue studies that
429 aim to address research gaps. The forum also produces a monthly evidence bulletin

430 summarising new studies. Networks of this type are needed in other countries to develop
431 high quality proposals for EC research and generate evidence to inform policy and practice
432 in this rapidly developing field. More research on patterns of tobacco use after e-cigarettes
433 use, in particular among youth, is needed.[79] Also, little information is available on
434 prevalence of use of nicotine-containing and non-nicotine e-cigarettes. Appropriate
435 regulations are needed to protect non-smokers especially adolescents, whilst granting
436 access to smokers to support cessation. In terms of urological health outcomes specifically,
437 data around vapour emission quantities and compositions would be helpful and to work
438 towards validated and standardised contents of ECs. This is an important public health
439 question because EC have been popularised as an aid to smoking cessation, particularly
440 among teenagers. Given the long latency of most cancers, it may take at least 15 years of
441 follow up to identify urological cancer risk among EC users. Analysis of the urine of EC users
442 for compounds such as nitrosamines, aldehydes, lead, arsenic, nickel, chromium and how
443 these are associated with the development of urological malignancies over time would also
444 be a valuable addition to the knowledge base. There is also the challenge of differentiating
445 between conventional cigarette and EC induced health problems, given that most EC users
446 also smoke conventional cigarettes. In this regard, methodologically robust prospective
447 studies looking at urological malignancies in EC users would be valuable data to add to this
448 debate.

449

450 **Figure Legends:**

451 Table 1: Selected representative prevalences of e-cigarette use

452

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454

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457 Liam Bourke had full access to all the data in the study and takes responsibility for the
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459 **Study concept and design:** Bourke, Catto

460 **Acquisition of data:** Bourke, Bauld, Bullen, Cumberbatch, Giovannucci, Islami, McRobbie,
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478 **Table 1.**

Reference; country, year	Age, no. of participants	Prevalence		
		E-cigarette use	Overall, %	Never tobacco smokers, %
Filippidis et al. [12];* European Union (27 countries), 2012–2014	≥15 years 2012: 26,751 2014: 26,792	Ever use, 2012 Ever use, 2014 Transition of ever to current users	7.2 11.9 15.3 (F 14.2; M 17.7)	
Eastwood et al. [14]; Great Britain, 2013–2014	11–18 years 2013: 2,062 2014: 1,952	< monthly, 2013 Monthly or more, 2013 < monthly, 2014 Monthly or more, 2014	3.7 0.9 † 6.5 1.7 †	0.6 0.1 1.5 0.2
Hu et al. [16]; USA, 2013–2014	≥18 years 75,233	Every or some days All 18–24 years 25–44 45–64 ≥ 65 Every/some days or rarely	3.3 (F 2.8, M 4.0) 5.5 4.4 2.8 0.9 6.6 (F 7.9, M 5.5)	
Czoli et al. [15]; Canada, 2013	≥15 years ~2.5 million	Use in the past 30 days All 15–19 years 25–44 45–64 ≥ 45 Ever use	1.8 (F 1.8, M 1.8) 2.6 (F 2.1, M 3.0) 3.9 (F 3.5, M 4.3) 2.4 (F NR, M 3.0) 1.0 (F 1.2, M 0.8) 8.5 (F 8.1, M 8.9)	0.5 (F 0.5, M 0.5) 3.6 (F 3.4, M 3.9)
Singh et al. [17]; USA, 2011–2015	Middle or high school students 2011: 18,866 2015: 17,711	Use in the past 30 days High school, 2015 Middle school, 2015 High school, 2011 Middle school, 2011	16.0 (F 12.8, M 19.0) 5.3 (F 4.8, M 5.9) 1.5 0.6	
Jiang et al. [19]; Hong Kong, 2014	15–65 years 809	Ever use All 15–29 years 30–49 50–65	2.3 (F 1.3, M 3.6) 5.2 1.8 1.0	1.0
Li et al. [20]; New Zealand, 2014	≥15 years 2,594	Monthly or more All 15–17 years 18–24 25–44 ≥ 45 Ever use	0.8 (F 1.0, M 0.5) 0.0 0.2 1.2 0.7 13.1 (F 12.8, M 13.7)	0.1
Lee et al. [21]; South Korea, 2011	13–18 years (students) 75,643	Use in the past 30 days All students Grade 7 8 9 10 11 12 Ever use	4.7 (F 1.8, M 7.8) 2.0 3.3 4.7 7.1 6.0 6.2 9.4	0.6
Palipudi et al. [22]; Greece, Indonesia,	≥15 years Greece (9,357),	Current use ** Greece		

Reference; country, year	Age, no. of participants	Prevalence			
		E-cigarette use	Overall, %	Never tobacco smokers, %	
Malaysia, and Qatar, 2011–2013	Indonesia (8,303)	All	1.9 (F 1.8, M 7.8)	1.1 ¶¶	
		15–24 years	0.0		
		25–44	2.8		
		45–64	2.7		
		≥ 65	0.8		
	Malaysia (4,244)	Qatar (8,389)	Indonesia		
			All	0.3 (F 1.8, M 7.8)	0.0 ¶¶
			15–24 years	0.2	
			25–44	0.3	
			45–64	0.3	
	Malaysia	Qatar	All	0.8 (F 1.8, M 7.8)	0.1 ¶¶
			15–24 years	4.4	
			25–44	5.0	
			45–64	0.0	
			≥ 65	0.0	
	Bunnell et al. [24]; USA, 2011–2013	Middle or high school students 61,932	Use in the past 30 days		0.3
			Ever use	6.1	0.9

479 F, female; M, male; NR, not-reported.

480 * Prevalences for individual countries are also presented in the article.

481 ** Those who responded “daily or less than daily” to the question “Do you currently use e-
482 cigarettes on a daily basis, less than daily, or not at all?”

483 † Males were 2.5-times more likely to be monthly or more users than females.

484 ¶¶ Among those with no current tobacco smoking.

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