

## **E-cigarettes and urologic health: a collaborative review of toxicology, epidemiology, and potential risks**

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49 **Abstract**

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

51 Smoking conventional cigarettes is a known risk factor for urological malignancy incidence,  
52 progression and mortality as well as for other urological health indicators. The potential  
53 impact of EC use on urological health is therefore of clinical interest to the urology  
54 community.

55 **Objective:** To review the available data on current EC use including potential benefits in  
56 urological patients, potential issues linked to toxicology of EC constituents and how this  
57 might translate into urological health risks.

58 **Evidence Acquisition:** A Medline search was carried out in August 2016 for studies reporting  
59 urological health outcomes and EC use. Snowballing techniques were also used to identify  
60 relevant studies from recent systematic reviews. A narrative synthesis of data around EC  
61 health outcomes, toxicology, potential use in smoking cessation and health policy was  
62 carried out.

63 **Evidence synthesis:** We found no studies to date that have been specifically designed to  
64 assess prospectively urological health risks, even in an observational setting. Generating  
65 such data would be an important contribution to the debate on the role of ECs in public  
66 health and clinical practice. There is evidence from a recent Cochrane review of RCTs that  
67 ECs can support smoking cessation. There are emerging data around potentially harmful  
68 components of ECs such as tobacco-specific nitrosamines, polyaromatic hydrocarbons and  
69 heavy metals could be linked to possible urological health risks.

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

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

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97 **1. Introduction**

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

103

104 *1.1 What are e-cigarettes?*

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

117

118 There are three main components of the e-liquid; propylene glycol or glycerol or a mix of  
119 these, nicotine, and flavouring. The propylene glycol/glycerol mix is important for user  
120 satisfaction (e.g. a high propylene glycol content gives a greater 'throat hit'), but may also

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

133

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

141

## 142 *1.2. Epidemiology/demographics around EC use*

143 Since being introduced, the prevalence of EC use has seen a relatively rapid increase in  
144 many high-income countries from which national longitudinal data are available, notably

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

158

159 On the other hand, prevalence of more regular use is higher in youth than older adults in  
160 North America. In 2013, 8.5% and 1.8% of Canadians reported ever and current (past 30-  
161 day) use of ECs, respectively.[15] The highest prevalence of current use was in age 20–24  
162 (3.9%), followed by age 15–19 (2.6%).[15] In the United States, the prevalence of current  
163 use among individuals aged  $\geq 18$  years in 2013–2014 was 3.3%.[16] However, there has been  
164 a substantial increase in ECs use among high-school students in the United States, with  
165 current use prevalence increasing from 1.5% in 2011 to 16.0% in 2015.[17] The recent US  
166 Surgeon General's report warned that in 2014, current use of ECs by young adults 18–24  
167 years of age surpassed that of adults 25 years of age and older. The report points to



168 potentially harmful constituents of ECs: particularly nicotine which can lead to addiction and  
169 can harm the developing adolescent brain.[18]

170

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

184

185 EC use has the potential to help smokers to quit cigarette smoking or reduce smoking  
186 intensity.[23] However, one of the primary concerns of EC use is the maintenance of  
187 tobacco use in current smokers (without any substantial decrease in smoking intensity), re-  
188 initiation in former smokers, and in particular, nicotine dependence in adolescents,[24-28]  
189 as EC user adolescents may show a higher intention to smoke traditional cigarettes.[25, 27]  
190 However, in many countries, the rate of EC use by never-smokers or smoking initiation  
191 following EC use has been relatively low, although there might be some variations across

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

206

207

## 208 **2. Evidence acquisition**

209 In order to identify any eligible trials addressing EC use and urological health outcomes, a search of  
210 the electronic databases MEDLINE was carried out from inception to August 2016. MEDLINE search  
211 terms were (e-cigarette or electronic-cigarette) AND (bladder or prostate or kidney or urol\*). In  
212 addition to database searches, recent systematic reviews of EC use were hand searched for any  
213 potentially eligible trials. To add context to the any available trials data, evidence around smoking  
214 cessation, available toxicology data and health policy around EC regulations are presented in this  
215 review. Quality appraisal was done subjectively according to expertise and clinical judgement of the

216 authors. Given that EC use and urological outcomes is an emerging clinical issue with a fragmentary  
217 evidence base and involves rapidly evolving technologies, a narrative synthesis of these data was  
218 undertaken.[30]

219

### 220 **3. Evidence synthesis**

#### 221 *3.1 Current urological health outcomes and trials of EC use*

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

226

#### 227 *3.2 Toxicity data and potential urological health impacts from ECs*

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

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

245

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

254

255 A recent review describes chemical profiles of EC solutions, cartridges, aerosols and  
256 environmental emissions.[43] Whilst ECs are designed to be devoid of tar, some ECs have  
257 been found to contain carcinogens such as tobacco-specific nitrosamines and formaldehyde.  
258 Other constituents such as polyaromatic hydrocarbons and heavy metals are known to  
259 cause cancer, and nicotine itself is thought by some to pose a urological cancer risk. [44, 45]  
260 For instance, polycyclic aromatic hydrocarbons (International Agency for Research on  
261 Cancer (IARC), Group 1 (human carcinogen)[46]), which has been associated with bladder  
262 cancer.[47] EC have also been found to contain certain heavy metals, such as lead.[48] Lead

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

271

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

282

283 Whilst there is a theoretic potential for adverse urological health outcomes from the use of  
284 ECs it should be stressed that robust data are currently absent to offer a convincing  
285 argument for either side of the debate. A recent systematic review of the health  
286 consequences of vaping/ECs highlighted frequent methodological problems with available

287 studies, problematic authorship conflicts of interest, small cohort size, selection bias,  
288 conflicting results and a paucity of long-term follow-up data.[48]

289

### 290 *3.3 Can ECs help stop tobacco smoking?*

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

294

295

#### 296 *3.3.1 Prospective cohort studies*

297 Five studies, with long-term outcomes, have looked at the use of ECs in people who were  
298 not ready to quit smoking. One followed 40 smokers over two years and reported that 13%  
299 achieved at least six months of CO validated abstinence from conventional cigarettes and  
300 28% had achieved a sustained  $\geq 50\%$  reduction from baseline cigarette consumption.[56, 57]

301 The second tested the same approach with 14 smokers with schizophrenia and reported  
302 14% 30-day CO validated abstinence rates at one-year.[58] The third followed a group of 34  
303 smokers for 8 months after discharge from hospital.[59] Over half (53%) reported no longer  
304 smoking. In the fourth, 50 smokers were provided with a second-generation device with  
305 9mg/ml concentration of e-liquid. At 6 month follow-up 36% were biochemically validated  
306 7-day point prevalence abstainers.[60] The fifth cohort study followed 71 smokers who  
307 purchased an EC from a vape shop. One year after their purchase 41% reported that they  
308 had not smoked at all for at least the last 30 days.[61]

309

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

318

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

325

### 326 *3.3.2 Randomised controlled trials*

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

332 Participants were provided with a referral to telephone quitline but with no face-to-face

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

342

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

349

### 350 *3.3.3 Systematic reviews*

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



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

365

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

372

373

#### 374 *3.4 European health policy and ECs*

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

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

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

399

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

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

414

#### 415 **4. Discussion**

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

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

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448 **Figure Legends:**

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

450

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452

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458 **Acquisition of data:** Bourke, Bauld, Bullen, Cumberbatch, Giovannucci, Islami, McRobbie,  
459 Silverman and Catto.

460 **Analysis and interpretation of data:** Bourke, Bauld, Bullen, Cumberbatch, Giovannucci,  
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476 **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, Malaysia, and Qatar, 2011–2013	≥15 years Greece (9,357), Indonesia (8,303), Malaysia	Current use ** Greece All 15–24 years 25–44	1.9 (F 1.8, M 7.8) 0.0 2.8	1.1 ¶

Reference; country, year	Age, no. of participants	Prevalence			
		E-cigarette use	Overall, %	Never tobacco smokers, %	
(4,244), Qatar (8,389)		45–64	2.7		
		≥ 65	0.8		
		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		
		≥ 65	0.0		
		Malaysia			
		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		
		Qatar			
		All	0.9 (F 1.8, M 7.8)	0.2 ¶	
15–24 years	0.5				
25–44	1.0				
45–64	1.3				
≥ 65	0.0				
Bunnell et al. [24]; USA, 2011–2013	Middle or high school students 61,932	Use in the past 30 days Ever use		0.3 0.9	

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

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

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

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

482 ¶ Among those with no current tobacco smoking.

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