

1   **Title**

2   Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and  
3   Nutrition

5   **Short title**

6   Coffee, tea and melanoma risk.

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102 **List of abbreviations**

103 BMI            Body Mass Index

104	CI	Confidence Intervals
105	EPIC	European Prospective Investigation into Cancer and Nutrition
106	HR	Hazard Ratio
107	IARC	International Agency for Research on Cancer
108	ICD-O	International Classification of Diseases-Oncology
109	SES	Socio-economic status
110	UVB	Ultraviolet B

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## 112 **Novelty and Impact**

113       Laboratory studies suggest that coffee and tea may protect against melanoma; however,  
114 epidemiological findings are inconsistent. We found an inverse association between caffeinated  
115 coffee consumption and melanoma risk among men, but not among women, and no association with  
116 decaffeinated coffee or tea consumption, in the European Prospective Investigation into Cancer and  
117 Nutrition (EPIC). Melanoma has a high disease burden and coffee is a widely consumed beverage,  
118 therefore our findings may have important public health implications.

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123

124 **Abstract**

125         In vitro and animal studies suggest that bioactive constituents of coffee and tea may have  
126 anticarcinogenic effects against cutaneous melanoma, however epidemiological evidence is limited  
127 to date. We examined the relationships between coffee (total, caffeinated or decaffeinated) and tea  
128 consumption and risk of melanoma in the European Prospective Investigation into Cancer and  
129 Nutrition (EPIC). EPIC is a multi-centre prospective study that enrolled over 500,000 participants  
130 aged 25-70 years from ten European countries in 1992-2000. Information on coffee and tea drinking  
131 was collected at baseline using validated country-specific dietary questionnaires. We used adjusted  
132 Cox proportional hazards regression models to calculate hazard ratios (HR) and 95% confidence  
133 intervals (95% CI) for the associations between coffee and tea consumption and melanoma risk.  
134 Overall, 2,712 melanoma cases were identified during a median follow-up of 14.9 years among  
135 476,160 study participants. Consumption of caffeinated coffee was inversely associated with  
136 melanoma risk among men (HR for highest quartile of consumption vs. non-consumers 0.31, 95%  
137 CI 0.14-0.69) but not among women (HR 0.96, 95% CI 0.62-1.47). There were no statistically  
138 significant associations between consumption of decaffeinated coffee or tea and the risk of  
139 melanoma among both men and women. The consumption of caffeinated coffee was inversely  
140 associated with melanoma risk among men in this large cohort study. Further investigations are  
141 warranted to confirm our findings and clarify the possible role of caffeine and other coffee  
142 compounds in reducing the risk of melanoma.

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## 146 **Introduction**

147         The age-standardized incidence of cutaneous melanoma has been increasing for decades  
148 worldwide, although it has shown a tendency to stabilization in high-incidence countries in recent  
149 years [1]. In 2012, there were an estimated 232,000 new cases of cutaneous melanoma and 55,000  
150 related deaths globally [2]. The most affected world regions are those inhabited by white  
151 populations of European descent, with incidence being highest in Oceania, Northern America and  
152 Northern Europe and lowest in Africa, Southern America and Asia [2].

153         The main established risk factor for cutaneous melanoma is exposure to ultraviolet (UV)  
154 radiation. In particular, the risk of developing a cutaneous melanoma depends in a complex way on  
155 the interplay between the patterns of exposure to UV radiation (acute/intermittent or chronic  
156 exposure to sunlight, history of sunburns, use of sunbeds and sunlamps) and the individual  
157 susceptibility to disease (people with fair complexion, red or blonde hair, blue eyes, many naevi and  
158 freckles are at higher risk) [3-5]. Several other exposures have been investigated as possible risk or  
159 preventive factors for melanoma occurrence, and some evidence exists that overweight and obesity  
160 [6], adult height [7] and alcohol drinking [8] are positively associated with melanoma risk.

161         In vitro and animal studies have shown that caffeine and other constituents of coffee and tea  
162 influence several biological processes implicated in carcinogenesis, including DNA methylation,  
163 oxidative damage and apoptosis [9-12]. In particular, caffeine can inhibit UV-induced  
164 carcinogenesis through a number of complementary biological mechanisms [13], and black tea  
165 polyphenols can induce apoptosis of melanoma cell lines in vitro [14]. The hypothesis that coffee  
166 and tea consumption is protective against melanoma has been tested in several epidemiological  
167 studies, with conflicting results [15-20]. Despite some evidence of an inverse association between  
168 consumption of caffeinated coffee and melanoma risk, the question still remains unresolved as it  
169 has been examined in only a limited number of prospective studies with accurate collection of  
170 dietary habits and long enough follow-up. Hence, in the present study we aimed to examine the

relationships between consumption of coffee (total, caffeinated or decaffeinated) and tea and the risk of melanoma in the European Prospective Investigation into Cancer and Nutrition (EPIC).

173

## 174 **Materials and Methods**

### 175 Study population

176 EPIC is a multi-centre prospective cohort study that investigates the role of dietary, lifestyle,  
177 genetic and environmental factors in the aetiology of cancer and other chronic diseases. The  
178 methodology and rationale of the EPIC study have been described elsewhere [21-22]. Briefly,  
179 521,324 participants mostly aged 25-70 years were recruited during 1992-2000 in 23 centres from  
180 10 European countries (France, Italy, Spain, United Kingdom, the Netherlands, Greece, Germany,  
181 Sweden, Denmark and Norway). Most study participants were selected from the general population,  
182 with some exceptions: the French cohort recruited female members of a health insurance scheme for  
183 school and university employees; the Utrecht cohort in the Netherlands was based on women  
184 participating in the local breast cancer screening programme; the cohorts in Ragusa and Turin  
185 (Italy) and in the Spanish centres partly consist of blood donors; and the Oxford cohort in the  
186 United Kingdom consists predominantly of vegetarians and “health conscious” volunteers. Only  
187 female participants were recruited in Norway, France, Naples (Italy) and Utrecht (The Netherlands).  
188 Approval for the EPIC study was obtained from the Ethical Review Board of the International  
189 Agency for Research on Cancer (IARC) and the local Ethics Committees relevant for each study  
190 centre. All study participants provided signed informed consent before study entry.

191 For this study, we excluded study participants with prevalent cancers (n = 25,184); with  
192 missing or insufficient follow-up information (n = 4,148); with missing information on any of  
193 lifestyle factors, diet (including coffee and tea drinking) or anthropometry (n = 6,259); and those in  
194 the top or bottom 1% of the ratio of energy intake to energy expenditure (n = 9,573). Finally, the  
195 dataset for this analysis included 476,160 study participants.



196

197 Exposure assessment

198 Dietary intakes over the 12 months before recruitment were recorded at baseline by using  
199 validated country-specific dietary questionnaires. Questionnaires were usually self-administered,  
200 except in Spain, Greece and Ragusa (Italy), where the dietary questionnaire was filled in by a  
201 trained interviewer. In Malmö (Sweden), a short food-frequency questionnaire was combined with a  
202 7-day dietary diary. The structure of questions varied somewhat across centres: data on tea  
203 consumption was not available for Norway; data on consumption of caffeinated and decaffeinated  
204 coffee was not available in Naples and Ragusa (Italy), Umeå (Sweden), Denmark and (only for  
205 decaffeinated coffee) Norway and Malmö (Sweden). The recorded number of cups of coffee (any  
206 type, caffeinated or decaffeinated) and tea per month, week and day was translated into daily  
207 consumptions (mL/day).

208 Data on lifestyle factors were collected using gender-specific questionnaires common to all  
209 study centres, which included questions on smoking habits and alcohol consumption, education,  
210 occupation, medical history, occupational, household and leisure-time physical activity, and (for  
211 women) menstrual and reproductive history and use of exogenous sex hormones (oral  
212 contraceptives and hormone replacement therapy). More details on both questionnaires can be  
213 found elsewhere [22]. Height and weight were measured at recruitment by trained health  
214 professionals, except in France, Oxford (United Kingdom), and Norway, where self-reported  
215 measurements were obtained.

216

217 Follow-up and endpoints

218 The identification of incident cancers and vital status follow-up were conducted using a  
219 combination of methods including linkage with population cancer and pathology registries, health  
220 insurance and hospital discharge records, national and regional mortality registries, and active  
221 follow-up through study subjects and their next-of-kin. Incident cancers were coded according to

222 the International Classification of Diseases-Oncology (ICD-O), 3<sup>rd</sup> edition. The outcome of the  
223 present analysis was melanoma, which corresponds to the codes 8720-8790 for morphology (with 2  
224 or 3 as 5<sup>th</sup> digit for in situ and invasive malignancies, respectively); both cutaneous and extra-  
225 cutaneous melanomas were included in the analysis.

226

#### 227 Statistical analysis

228 We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) for the  
229 associations between the consumption of coffee (any type, caffeinated or decaffeinated) and tea and  
230 the risk of melanoma among male and female participants, by using Cox proportional hazards  
231 regression models with age as time scale and EPIC-participating centre and age at recruitment (in 1-  
232 year intervals) as stratifying variables. Person-time at risk was calculated from the date of  
233 recruitment until the date of first incident cancer (except for non-melanoma skin cancers), death,  
234 emigration, date of last contact, or end of follow-up (from June 2008 to December 2013, depending  
235 on centre), whichever occurred first. Participants diagnosed with melanoma after the censoring date  
236 (for instance, melanoma diagnosed as second primary malignancy) were considered non-cases. The  
237 proportional hazards assumption was checked by testing for a non-zero slope in a regression of the  
238 scaled Schoenfeld residuals on functions of time [23].

239 Previous research suggested that the association between coffee consumption and melanoma  
240 risk may vary with gender [16,19]. In addition, there is much diversity between countries regarding  
241 the patterns of consumption of coffee and tea [24-26]. Therefore, coffee and tea consumption were  
242 entered into the models using sex- and country-specific categories of intake: non-consumers were  
243 considered as the category of reference, and consumers were categorized into quartiles (for coffee,  
244 caffeinated coffee and tea) or tertiles (for decaffeinated coffee, due to the large number of non-  
245 consumers). Linear trends across categories of consumption were evaluated by entering the median  
246 value of each category of consumption as a continuous term in the model. Additional models were  
247 fitted using study-wide (instead of country- and sex-specific) categories of intake, or with the

consumption of each beverage entered as a continuous variable (HR calculated per 100 mL/day increase).

All models were adjusted for variables considered a priori to be potential confounders of the association between coffee consumption and melanoma risk, namely educational level (considered as a proxy of socioeconomic status; none, primary school, technical/professional school, secondary school, university or higher degree); body mass index (BMI; <25, 25-29.9,  $\geq$ 30 kg/m<sup>2</sup>); smoking status (never, former, current); alcohol drinking (non drinker; low intake: men >0-6 g/day, women >0-3 g/day; moderate intake: men >6-12 g/day, women >3-12 g/day; high intake: >12 g/day); and recreational physical activity levels (country- and sex-specific quartiles of metabolic equivalent [MET]-hours/week). In addition, we also adjusted for total energy intake (continuous), consumption of food groups (vegetables, fruits, red meat, poultry and fish; continuous) and estimated dietary intakes (estimated from food-frequency questionnaires) of beta-carotene, vitamin D (in  $\mu$ g) and vitamin C (in mg) (continuous). Models among women were adjusted for menopausal status at recruitment (premenopausal, perimenopausal, postmenopausal), age at menarche (continuous), age at first full-term pregnancy (continuous), and ever use of oral contraceptives (yes/no) or menopausal hormone therapy (yes/no) as well. Models for coffee (any type) and tea were adjusted for one another; models assessing caffeinated and decaffeinated coffee separately were adjusted for one another and for consumption of tea.

Additional analyses were conducted for melanoma belonging to different histological types (superficial spreading, nodular, and lentigo maligna melanoma) and occurring on different body sites (head and neck, trunk, upper limb, and lower limb). Heterogeneity of associations across categories of educational level, smoking status, alcohol drinking, and BMI were tested by adding multiplicative interaction terms to the models and using the likelihood ratio tests for interaction. We finally performed a range of sensitivity analyses by excluding extra-cutaneous melanomas, in situ melanomas, or incident cancers that were diagnosed during the first 12 months of follow-up (in order to evaluate whether preclinical disease may have influenced the results).

274 Statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, TX).  
275 All statistical tests were two-sided, and p-values of less than 0.05 were considered as statistically  
276 significant.

277

## 278 **Results**

279 Overall, 2,712 melanoma cases (including 221 in situ melanomas, 8.1%) were identified  
280 during a median follow-up of 14.9 years. The majority were cutaneous melanomas (n = 2,557,  
281 94.3%); the most frequent localizations were the lower limbs (30.8%) and the trunk (30.4%),  
282 followed by the upper limbs (20.4%) and the head and neck (13.2%); 1.4% were melanomas of  
283 overlapping sites of skin, and no information on skin site was available for 3.8% of cutaneous  
284 melanomas. Extra-cutaneous melanomas were 122 (4.5%), of which 77 were ocular melanomas; the  
285 primary melanoma site was unknown for 33 melanomas (1.2%). Information on morphology was  
286 available for 68.8% of cases: the superficial spreading histological type accounted for 69.4% of  
287 these, 12.3% were nodular melanomas, 11.4% were lentigo maligna melanomas, and 6.9%  
288 belonged to other histological types.

289 Numbers of study participants and melanoma cases, person-years, proportion of non-  
290 consumers, and the median and 10<sup>th</sup>-90<sup>th</sup> percentiles of consumption of coffee and tea by country  
291 are shown in Table 1. Melanoma incidence rate was highest in Denmark (58 cases per 100,000  
292 person-years) and lowest in Greece (10 cases per 100,000 person-years). Daily consumption of  
293 coffee and tea varied substantially across countries. The proportion of coffee non-consumers ranged  
294 between 3.7% (in Denmark and United Kingdom) and 14.7% (in France, only female participants).  
295 Among coffee drinkers, the lowest and highest reported consumption were in Italy (median 92  
296 mL/day) and Denmark (median 900 mL/day), respectively. Caffeinated coffee as a proportion of  
297 total coffee consumption ranged between 73.6% (in United Kingdom) and 95.8% (in Italy).  
298 Consumption of tea was lowest in Greece (median <1 mL/day) and highest in United Kingdom  
299 (median 475 mL/day).

300 Baseline characteristics of study participants according to consumption of coffee and tea are  
301 presented in Table 2. Study participants in the top quartile of coffee consumption were more  
302 frequently of male gender, slightly younger, more likely to be smokers and to drink alcohol, more  
303 physically active, and reported a higher energy intake, a lower consumption of fruit, vegetables and  
304 fish, and a higher consumption of red meat, compared to coffee non-consumers. Female participants  
305 in the top quartile of coffee consumption were also more likely to be pre-menopausal and have ever  
306 used oral contraceptives than coffee non-consumers. Tea consumers in the top quartile had a lower  
307 BMI, were more highly educated, less likely to be smokers but more likely to drink alcohol, were  
308 more physically active, reported a lower intake of fruit, red meat, poultry and fish, and a higher  
309 intake of  $\beta$ -carotene, compared to tea non-consumers. Female tea drinkers were more likely to have  
310 ever used oral contraceptives and menopausal hormone therapy than non-drinkers.

311 We found a statistically significant inverse association between consumption of coffee and  
312 melanoma risk among men (HR for study participants in the 4<sup>th</sup> quartile of consumption vs. non-  
313 consumers 0.47, 95% CI 0.23-0.94, p for trend = 0.001), but not among women (HR 1.10, 95% CI  
314 0.70-1.72, p for trend = 0.598) (p for heterogeneity <0.0001) (Table 3). The HR in linear models  
315 including coffee consumption by 100 mL/day was 0.95 (95% CI 0.92-0.98, p = 0.001) among men  
316 and 1.01 (95% CI 0.98-1.04, p = 0.471) among women. The inverse association between coffee and  
317 melanoma risk among men was driven by the consumption of caffeinated coffee (HR 0.31, 95% CI  
318 0.14-0.69, p for trend = 0.001); instead, the consumption of decaffeinated coffee was not  
319 statistically significantly associated with melanoma risk (Table 4). There were no statistically  
320 significant associations between consumption of tea and melanoma risk among neither men (HR  
321 1.18, 95% CI 0.72-1.94, p for trend = 0.940) nor women (HR 0.82, 95% CI 0.56-1.21, p for trend =  
322 0.401).

323 The association between the consumption of caffeinated coffee and melanoma risk varied  
324 somewhat across histological types among men: the HR for a 100 mL/day higher consumption of  
325 caffeinated coffee was 0.86 (95% CI 0.75-0.98, p = 0.021) for superficial spreading melanoma, 0.95

326 (95% CI 0.77-1.18,  $p = 0.651$ ) for nodular melanoma, and 0.83 (95% CI 0.69-1.01,  $p = 0.061$ ) for  
327 lentigo maligna melanoma. Concerning body sites, the corresponding HR was 0.56 (95% CI 0.34-  
328 0.91,  $p = 0.020$ ) for melanoma of head and neck, 0.85 (95% CI 0.76-0.96,  $p = 0.008$ ) for melanoma  
329 of the trunk, 1.01 (95% CI 0.86-1.19,  $p = 0.899$ ) for melanoma of the upper limb, and 0.73 (95% CI  
330 0.47-1.13,  $p = 0.154$ ) for melanoma of the lower limb. There was no association between  
331 consumption of caffeinated coffee and risk of melanoma of any histological type and at any body  
332 site among women.

333 The results were only marginally affected by the exclusion of in-situ and extra-cutaneous  
334 melanomas and melanomas of unknown primary site ( $n = 374$ ), or by the exclusion of melanomas  
335 diagnosed within the first 12 months of cohort inception ( $n = 146$ ). The use of study-wide instead of  
336 country- and sex-specific categories of beverages consumption did not alter the results either. We  
337 found no evidence that the relationship between consumption of caffeinated coffee and melanoma  
338 risk varied by educational level, smoking habits, alcohol intake, reproductive history, use of  
339 exogenous hormones, or BMI at study recruitment. We found no departures from the proportional  
340 hazards assumption of Cox models.

341

## 342 Discussion

343 In this large prospective multi-centre cohort study, the consumption of caffeinated coffee  
344 was inversely associated with melanoma risk among men, with some variability across different  
345 histological types and body sites. The reduction in melanoma risk among men was 10% for a linear  
346 increase in the consumption of caffeinated coffee by 100 mL/day, and 70% for those in the top  
347 country-specific quartile of consumption. We found no association between the consumption of  
348 caffeinated coffee and melanoma risk among women; likewise, the consumption of decaffeinated  
349 coffee or tea was not associated with melanoma risk among both male and female study  
350 participants. Results were robust with respect to model specifications and across a range of  
351 sensitivity analyses.

352 Our results point towards caffeine as the most plausible factor explaining the inverse  
353 association between coffee consumption and melanoma risk. This view is supported by  
354 experimental studies conducted on animal models and human tumour cells. In mice, the oral  
355 administration of caffeine has a sunscreen effect by inhibiting the dimerization of adjacent  
356 thymidine residues typically induced by UVB radiation [13,27], and may enhance apoptosis of  
357 damaged pre-cancerous cells through several complementary biological mechanisms, both p53-  
358 dependent and p53-independent [13,28-29]. In human melanoma cells, caffeine can inhibit the  
359 activation of transcription factors involved in the response to UVB exposure [30]; oppose cell  
360 growth and induce cell differentiation [31]; and prevent cell adhesion to the extracellular matrix,  
361 thereby reducing cell invasion and migration and ultimately the formation of distant metastasis [32-  
362 34].

363 The association between coffee drinking and melanoma risk had been investigated in only a  
364 few prospective cohorts prior to our study. No association between consumption of coffee (any  
365 type, filtered or boiled) and melanoma risk emerged in the Västerbotten Intervention Project cohort  
366 in Sweden [17]. Likewise, there was no evidence of an effect of coffee drinking on melanoma risk  
367 among women enrolled in the Women's Health Initiative Observational Study, except for a reduced  
368 risk among long-term coffee drinkers [18]. Instead, study participants in the highest category of  
369 coffee consumption in the US NIH-AARP (National Institutes of Health – American Association of  
370 Retired Persons) cohort had a lower melanoma risk compared to non-coffee drinkers [20]. Unlike  
371 our study, an inverse association between coffee consumption and melanoma risk was found among  
372 female members of a population-based cohort in Norway [16] and in the Nurses' Health Study,  
373 while no association emerged among male participants of the Health Professional Follow-up Study  
374 [19]. In the Norwegian Women and Cancer Study, melanoma risk was inversely associated with  
375 filtered coffee consumption, while no association was observed for consumption of instant or boiled  
376 coffee [35]. When consumption of caffeinated and decaffeinated coffee was separately investigated,  
377 the latter was not associated with melanoma risk in any of the above cohorts. Remarkably, and in

378 contrast to our findings, the inverse association between caffeinated coffee and melanoma risk was  
379 limited to malignancies arising on body sites with continuous sun exposure (head, neck, and  
380 extremities) in the Nurses' Health Study [19]. Finally, findings from prospective cohort studies are  
381 largely consistent with our finding of a null association between tea drinking and melanoma risk  
382 [15,18].

383 The geographical variability in factors that affect the content and concentration of caffeine  
384 and other biologically active compounds taken with coffee (including the roasting, brewing and  
385 preparation methods, and the average cup size) [24-26] and some methodological differences (for  
386 example the detail with which the information is collected on the consumption of coffee and tea)  
387 may help explain why the inverse relationship between coffee consumption and melanoma risk  
388 could not be seen in all prospective studies published to date. It is more challenging to explain the  
389 disagreement between our findings and the studies that found an inverse association only among  
390 women [16,19]. Previous studies reported that coffee consumption patterns and melanoma risk are  
391 associated with socio-economic status (SES) [36-37]. These associations may vary between  
392 genders, geographically and over time, which may partly explain the inconsistency of results from  
393 studies conducted in different countries and enrolling study populations of different age. We  
394 adjusted all our estimates by educational level, a commonly used surrogate variable for SES;  
395 however, SES is an elusive concept to define and measure in epidemiological studies, thus some  
396 residual confounding cannot be excluded.

397 Major strengths of our study are its prospective design, large sample size and long-term  
398 follow-up. The association between coffee and tea consumption and melanoma risk was associated  
399 in only a few European studies so far, while this study extends to a greater number of European  
400 populations. Exposure and covariates were assessed before melanoma diagnosis using validated  
401 questionnaires, thereby minimizing the likelihood of recall bias. The multicentre coverage of the  
402 EPIC study allowed examining a wide range of coffee and tea consumption patterns. Although no  
403 estimate of total caffeine intake (including sources other than coffee and tea) is available in the



EPIC study, coffee and tea are largely the predominant source of caffeine in all countries participating in the EPIC study [38]. We used country- and gender- specific quartiles (caffeinated coffee and tea) and tertiles (decaffeinated coffee) of consumption to reduce exposure misclassification, which might have diluted some of the associations; however, the use of cohort-wide categories of consumption did not substantially affect the results. Our study has several limitations as well. No information was available on study participants' phenotypic characteristics (like skin, hair and eye colour, freckling and naevus count). However, the use of models stratified by study centre should mitigate this limitation, as it is unlikely that there is a within-centre association between coffee and tea consumption and phenotypic risk factors for melanoma. We do not have any information on patterns of exposure to UV radiation either. However, in previous investigations, no association was reported between coffee consumption and behavioural risk factors for melanoma (except for sunscreen use) in the National Health and Nutrition Examination Survey (NHANES) in the US [20], and the adjustment for sunlight-related variables did not appreciably affect the association between coffee and tea consumption and the risk of melanoma in the Women's Health Initiative Observational Study [18] and in the Norwegian Women and Cancer Study [35]. We lack information on the concentration of bioactive compounds (such as caffeine, polyphenols and diterpens) in coffee and tea, and on the many factors affecting it, such as the coffee brewing methods and the type (black or green) and preferred drinking temperature of coffee and tea, all of which vary greatly across European countries (with Northern populations drinking large quantities of fairly diluted coffee, and Southern populations consuming a comparatively smaller amount of strong coffee, like espresso). Furthermore, we only had data on consumption of coffee and tea at cohort enrolment, which prevented us from examining the link between the lifetime consumption of these beverages and melanoma risk. Finally, participating centres vary in their ability to capture and report in situ melanoma; however, the exclusion of the latter did not substantially affect the risk estimates.

429           In conclusion, we found an inverse association between caffeinated coffee drinking and  
430 melanoma risk among men, but not women, enrolled into the EPIC study. As melanoma has a high  
431 burden of disease among populations of European descent [2], and coffee and tea are among the  
432 most widely consumed drinks in European countries [39], our results, if confirmed, may have  
433 important public health implications. Further investigations are warranted to confirm our findings  
434 and clarify the possible role of caffeine and other coffee compounds in reducing the risk of  
435 melanoma.

436

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549 **Table 1.** Distribution of study participants and melanoma cases, and consumption of coffee and tea, in countries participating to the European  
550 Prospective Investigation into Cancer and Nutrition (EPIC) study.

Country	Participants	Person-years	Melanoma cases	Coffee consumption (mL/day)			Tea consumption (mL/day)		
				Non consumers (%)	Median <sup>(a)</sup>	10 <sup>th</sup> -90 <sup>th</sup> percentile <sup>(a)</sup>	Non consumers (%)	Median <sup>(a)</sup>	10 <sup>th</sup> -90 <sup>th</sup> percentile <sup>(a)</sup>
<b>Denmark</b>	55,014	815,097	475	3.7	900	200-1600	16.1	200	3-900
<b>France</b>	67,403	869,372	383	14.7	280	70-657	40.8	214	15-721
<b>Germany</b>	48,557	504,479	192	4.3	400	103-870	24.0	53	2-450
<b>Greece</b>	26,048	281,284	28	6.3	140	48-380	46.3	<1	<1-34
<b>Italy</b>	44,545	630,951	160	8.9	92	37-189	45.0	43	5-150
<b>Norway <sup>(b)</sup></b>	33,975	452,171	219	9.0	420	120-780	-	-	-
<b>Spain</b>	39,989	637,947	131	11.6	102	4-289	96.0	114	29-306
<b>Sweden</b>	48,674	801,130	402	4.0	400	150-813	52.4	89	1-625
<b>The Netherlands</b>	36,539	524,671	248	4.9	500	250-1000	10.4	237	27-594
<b>United Kingdom</b>	75,416	1,122,765	474	3.7	380	4-857	2.7	475	2-1140
<b>Total</b>	476,160	6,639,867	2,712	7.1	310	50-900	38.6	179	3-855

551

552 <sup>(a)</sup> Medians and percentiles were calculated among consumers.

553 <sup>(b)</sup> No information on tea consumption was available for Norway.



554 **Table 2.** Baseline characteristics of study participants according to levels of coffee and tea consumption in the European Prospective Investigation into  
555 Cancer and Nutrition (EPIC) study.

	Total population	Coffee consumption		Tea consumption	
		Non-consumers	4 <sup>th</sup> quartile	Non-consumers	4 <sup>th</sup> quartile
<b>Participants (n)</b>	476,160	33,814	98,740	149,810	33,975
<b>Women (%)</b>	70.1	78.8	70.0	66.5	68.3
<b>Age (mean, SD)</b>	51.2 (9.9)	51.7 (9.6)	49.9 (8.9)	52.7 (8.8)	51.9 (9.9)
<b>Body Mass Index (kg/m<sup>2</sup>) <sup>(a)</sup></b>	24.8 (22.4-27.8)	24.4 (21.8-27.7)	25.1 (22.6-28.0)	25.8 (23.1-28.9)	24.2 (22.0-26.9)
<b>Education (%)</b>					
none/primary	31.1	33.4	31.7	48.5	19.1
technical/secondary school	44.2	43.8	44.2	33.8	45.9
university degree	24.7	22.8	24.1	17.7	35.0
<b>Smoking (%)</b>					
never smoker	50.0	65.0	38.1	49.9	51.4
former smoker	27.2	22.1	26.0	23.6	31.0
current smoker	22.8	12.9	35.9	26.5	17.6
<b>Alcohol drinking at recruitment (%)</b>					
- non drinker	13.4	31.0	12.6	21.7	10.2
>0-6 gr/d (M) / >0-3 gr/d (F)	30.0	29.0	28.6	22.3	29.9
>6-12 gr/d (M) / >3-12 gr/d (F)	26.0	19.9	26.4	21.5	27.2
>12 gr/d	30.6	20.1	32.4	34.5	32.7
<b>Recreational physical activity (MET-hours/week) <sup>(a)</sup></b>	24 (12-42)	21 (10-39)	24 (12-42)	21 (9-38)	28 (15-48)
<b>Age at menarche (mean, SD)</b>	13.1 (1.5)	13.1 (1.6)	13.0 (1.5)	13.0 (1.6)	13.1 (1.6)
<b>Age at first full-term pregnancy (mean, SD)</b>	24.9 (4.3)	25.0 (4.3)	24.4 (4.4)	24.7 (4.2)	25.2 (4.4)

**Menopausal status (%)**

premenopausal	34.8	32.3	38.1	31.0	32.6
perimenopausal	19.1	21.3	20.9	18.7	18.7
postmenopausal	46.1	46.4	41.0	50.3	48.7
<b>Ever use of oral contraceptives (%)</b>	58.6	52.1	61.2	47.4	64.9
<b>Ever use of hormones for menopause (%)</b>	25.9	24.7	25.6	22.6	30.5
<b>Total energy intake (kcal/day) <sup>(a)</sup></b>	1997 (1631-2436)	1973 (1590-2407)	2085 (1698-2549)	2077 (1691-2527)	2061 (1693-2500)
<b>Vegetables (g/day) <sup>(a)</sup></b>	175 (110-276)	199 (125-300)	179 (111-285)	188 (115-298)	184 (119-287)
<b>Fruit (g/day) <sup>(a)</sup></b>	201 (112-322)	235 (128-364)	193 (103-320)	232 (124-358)	198 (112-315)
<b>Red meat (g/day) <sup>(a)</sup></b>	35 (16-63)	34 (16-59)	39 (19-67)	41 (21-66)	37 (17-66)
<b>Poultry (g/day) <sup>(a)</sup></b>	15 (6-27)	16 (6-30)	16 (6-29)	18 (6-34)	13 (5-24)
<b>Fish (g/day) <sup>(a)</sup></b>	28 (14-50)	32 (16-55)	29 (15-51)	32 (16-54)	24 (12-41)
<b>β-carotene (μg/day) <sup>(a)</sup></b>	2864 (1817-4517)	3191 (1955-4924)	2854 (1784-4515)	2574 (1625-4102)	3378 (2126-5019)
<b>Vitamin D (μg/day) <sup>(a)</sup></b>	3.3 (2.2-5.0)	3.0 (2.0-4.6)	3.4 (2.3-5.2)	3.2 (2.0-5.1)	3.2 (2.2-4.6)
<b>Vitamin C (mg/day) <sup>(a)</sup></b>	114 (80-158)	120 (84-166)	112 (78-158)	119 (82-168)	117 (85-160)

<sup>(a)</sup> Median value (interquartile range)

SD: standard deviation

MET: metabolic equivalent of task

**Table 3.** Hazard ratios (HR) and 95% confidence intervals (CI) for consumption of coffee (any type) and tea and risk of melanoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Level of consumption	Men						Women					
	No. non-cases	No. cases	HR <sup>(a)</sup>	Lower 95% CI	Upper 95% CI	p-value <sup>(b)</sup>	No. non-cases	No. cases	HR <sup>(a)</sup>	Lower 95% CI	Upper 95% CI	p-value <sup>(b)</sup>
<b>Coffee</b>												
Non-consumers	7,119	46	1.00				26,521	128	1.00			
1 <sup>st</sup> quartile	38,657	270	0.99	0.51	1.93		95,026	547	0.98	0.64	1.50	
2 <sup>nd</sup> quartile	35,488	257	0.85	0.44	1.67		70,532	392	1.09	0.70	1.68	
3 <sup>rd</sup> quartile	30,545	187	0.83	0.41	1.67		71,325	380	0.95	0.59	1.51	
4 <sup>th</sup> quartile	29,524	148	0.47	0.23	0.94	0.001	68,711	357	1.10	0.70	1.72	0.598
Increase by 100 mL/d	141,333	908	0.95	0.92	0.98	0.001	332,115	1,804	1.01	0.98	1.04	0.471
<b>Tea <sup>(c)</sup></b>												
Non-consumers	49,835	319	1.00				99,173	483	1.00			
1 <sup>st</sup> quartile	30,322	167	1.06	0.68	1.64		58,681	293	0.88	0.62	1.26	
2 <sup>nd</sup> quartile	18,661	122	1.07	0.66	1.74		53,393	330	0.86	0.60	1.23	
3 <sup>rd</sup> quartile	25,969	179	0.92	0.59	1.43		51,385	283	1.08	0.75	1.53	
4 <sup>th</sup> quartile	16,546	121	1.18	0.72	1.94	0.940	35,727	196	0.82	0.56	1.21	0.401
Increase by 100 mL/d	141,333	908	1.00	0.96	1.04	0.978	298,359	1,585	0.99	0.95	1.02	0.365

<sup>(a)</sup> Country- and sex-specific quantiles of consumption. Proportional hazards regression models stratified on study centre and age at recruitment. Consumptions of coffee and tea were adjusted for one another and for education, body mass index, smoking, alcohol intake, recreational physical activity, energy intake, consumption of main food groups (vegetables, fruits, red meat, poultry and fish), dietary intakes of beta-carotene, vitamin C and vitamin D, and (for women) menopausal status, age at menarche, age at first full-term pregnancy, and ever use of oral contraceptives or menopausal hormone therapy.

<sup>(b)</sup> Evaluated by entering the median value of each category of consumption in the model.

<sup>(c)</sup> Information on tea consumption is not available in Norway.

**Table 4.** Hazard ratios (HR) and 95% confidence intervals (CI) for consumption of caffeinated and decaffeinated coffee and risk of melanoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Level of consumption	Men						Women					
	No. non-cases	No. cases	HR <sup>(a)</sup>	Lower 95% CI	Upper 95% CI	p-value <sup>(b)</sup>	No. non-cases	No. cases	HR <sup>(a)</sup>	Lower 95% CI	Upper 95% CI	p-value <sup>(b)</sup>
<b>Caffeinated coffee <sup>(c)</sup></b>												
Non-consumers	24,969	113	1.00				65,980	272	1.00			
1 <sup>st</sup> quartile	21,426	136	0.80	0.36	1.81		66,240	384	0.89	0.58	1.37	
2 <sup>nd</sup> quartile	19,068	128	0.72	0.32	1.61		54,778	315	0.85	0.56	1.27	
3 <sup>rd</sup> quartile	19,735	130	0.63	0.28	1.40		49,708	301	0.94	0.61	1.46	
4 <sup>th</sup> quartile	15,309	78	0.29	0.12	0.69	<0.001	46,647	247	0.93	0.60	1.43	0.988
Increase by 100 mL/d	100,507	585	0.89	0.83	0.85	0.001	283,353	1519	0.99	0.95	1.04	0.825
<b>Decaffeinated coffee <sup>(d)</sup></b>												
Non-consumers	57,430	260	1.00				141,725	608	1.00			
1 <sup>st</sup> tertile	15,949	75	0.80	0.25	2.59		45,961	262	1.13	0.68	1.88	
2 <sup>nd</sup> tertile	6,608	30	1.25	0.42	3.69		18,467	116	1.15	0.68	1.96	
3 <sup>rd</sup> tertile	10,406	70	0.84	0.35	2.05	0.940	29,481	168	1.05	0.63	1.74	0.835
Increase by 100 mL/d	90,393	435	0.88	0.75	1.04	0.133	235,634	1,154	0.99	0.91	1.08	0.853

<sup>(a)</sup> Country- and sex-specific quantiles of consumption. Proportional hazards regression models stratified on study centre and age at recruitment. Consumptions of caffeinated and decaffeinated coffee were adjusted for one another, for consumption of tea, and for education, body mass index, smoking, alcohol intake, recreational physical activity, energy intake, consumption of main food groups (vegetables, fruits, red meat, poultry and fish), dietary intakes of beta-carotene, vitamin C and vitamin D, and (for women) menopausal status, age at menarche, age at first full-term pregnancy, and ever use of oral contraceptives or menopausal hormone therapy.

<sup>(b)</sup> Evaluated by entering the median value of each category of consumption in the model.

<sup>(c)</sup> Information on consumption of caffeinated coffee is not available in Naples and Ragusa (Italy), Umeå (Sweden) and Denmark.

<sup>(d)</sup> Information on consumption of decaffeinated coffee is not available in Naples and Ragusa (Italy), Denmark, Norway and Sweden.