Title

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

Short title

Coffee, tea and melanoma risk.

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List of abbreviations

BMI	Body Mass Index

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

Novelty and Impact

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

Abstract

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

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Introduction

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

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

In vitro and animal studies have shown that caffeine and other constituents of coffee and tea influence several biological processes implicated in carcinogenesis, including DNA methylation, oxidative damage and apoptosis [9-12]. In particular, caffeine can inhibit UV-induced carcinogenesis through a number of complementary biological mechanisms [13], and black tea polyphenols can induce apoptosis of melanoma cell lines in vitro [14]. The hypothesis that coffee and tea consumption is protective against melanoma has been tested in several epidemiological studies, with conflicting results [15-20]. Despite some evidence of an inverse association between consumption of caffeinated coffee and melanoma risk, the question still remains unresolved as it has been examined in only a limited number of prospective studies with accurate collection of 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).

Materials and Methods

Study population

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

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

Exposure assessment

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

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

Follow-up and endpoints

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

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

Statistical analysis

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

Previous research suggested that the association between coffee consumption and melanoma risk may vary with gender [16,19]. In addition, there is much diversity between countries regarding the patterns of consumption of coffee and tea [24-26]. Therefore, coffee and tea consumption were entered into the models using sex- and country-specific categories of intake: non-consumers were considered as the category of reference, and consumers were categorized into quartiles (for coffee, caffeinated coffee and tea) or tertiles (for decaffeinated coffee, due to the large number of non-consumers). Linear trends across categories of consumption were evaluated by entering the median value of each category of consumption as a continuous term in the model. Additional models were 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, ≥30 kg/m^2); 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 μg) 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).

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

Results

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

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

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

We found a statistically significant inverse association between consumption of coffee and melanoma risk among men (HR for study participants in the 4th quartile of consumption *vs.* non-consumers 0.47, 95% CI 0.23-0.94, p for trend = 0.001), but not among women (HR 1.10, 95% CI 0.70-1.72, p for trend = 0.598) (p for heterogeneity <0.0001) (Table 3). The HR in linear models including coffee consumption by 100 mL/day was 0.95 (95% CI 0.92-0.98, p = 0.001) among men and 1.01 (95% CI 0.98-1.04, p = 0.471) among women. The inverse association between coffee and melanoma risk among men was driven by the consumption of caffeinated coffee (HR 0.31, 95% CI 0.14-0.69, p for trend = 0.001); instead, the consumption of decaffeinated coffee was not statistically significantly associated with melanoma risk (Table 4). There were no statistically significant associations between consumption of tea and melanoma risk among neither men (HR 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 = 0.401).

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

(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 lentigo maligna melanoma. Concerning body sites, the corresponding HR was 0.56 (95% CI 0.34-0.91, p = 0.020) for melanoma of head and neck, 0.85 (95% CI 0.76-0.96, p = 0.008) for melanoma 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 0.47-1.13, p = 0.154) for melanoma of the lower limb. There was no association between consumption of caffeinated coffee and risk of melanoma of any histological type and at any body site among women.

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

Discussion

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

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

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

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

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

Major strengths of our study are its prospective design, large sample size and long-term follow-up. The association between coffee and tea consumption and melanoma risk was associated in only a few European studies so far, while this study extends to a greater number of European populations. Exposure and covariates were assessed before melanoma diagnosis using validated questionnaires, thereby minimizing the likelihood of recall bias. The multicentre coverage of the EPIC study allowed examining a wide range of coffee and tea consumption patterns. Although no 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.

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

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

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

[(a)] Medians and percentiles were calculated among consumers.

[(b)] No information on tea consumption was available for Norway.

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

		Coffee consumption		Tea consumption	
	Total population	**Non-consumers**	**4th quartile**	**Non-consumers**	**4th quartile**
Participants (n)	476,160	33,814	98,740	149,810	33,975
Women (%)	70.1	78.8	70.0	66.5	68.3
Age (mean, SD)	51.2 (9.9)	51.7 (9.6)	49.9 (8.9)	52.7 (8.8)	51.9 (9.9)
Body Mass Index (kg/m^2) [(a)]	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)
Education (%)					
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
Smoking (%)					
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
Alcohol drinking at recruitment (%)					
- 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
Recreational physical activity (MET-hours/week) [(a)]	24 (12-42)	21 (10-39)	24 (12-42)	21 (9-38)	28 (15-48)
Age at menarche (mean, SD)	13.1 (1.5)	13.1 (1.6)	13.0 (1.5)	13.0 (1.6)	13.1 (1.6)
Age at first full-term pregnancy (mean, SD)	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
Ever use of oral contraceptives (%)		58.6	52.1	61.2	47.4	64.9
Ever use of hormones for menopause (%)		25.9	24.7	25.6	22.6	30.5
Total energy intake (kcal/day) [(a)]		1997 (1631-2436)	1973 (1590-2407)	2085 (1698-2549)	2077 (1691-2527)	2061 (1693-2500)
Vegetables (g/day) [(a)]		175 (110-276)	199 (125-300)	179 (111-285)	188 (115-298)	184 (119-287)
Fruit (g/day) [(a)]		201 (112-322)	235 (128-364)	193 (103-320)	232 (124-358)	198 (112-315)
Red meat (g/day) [(a)]		35 (16-63)	34 (16-59)	39 (19-67)	41 (21-66)	37 (17-66)
Poultry (g/day) [(a)]		15 (6-27)	16 (6-30)	16 (6-29)	18 (6-34)	13 (5-24)
Fish (g/day) [(a)]		28 (14-50)	32 (16-55)	29 (15-51)	32 (16-54)	24 (12-41)
β-carotene (µg/day) [(a)]		2864 (1817-4517)	3191 (1955-4924)	2854 (1784-4515)	2574 (1625-4102)	3378 (2126-5019)
Vitamin D (µg/day) [(a)]		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)
Vitamin C (mg/day) [(a)]		114 (80-158)	120 (84-166)	112 (78-158)	119 (82-168)	117 (85-160)

[(a)] 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 [(a)]	Lower 95% CI	Upper 95% CI	p-value [(b)]	No. non-cases	No. cases	HR [(a)]	Lower 95% CI	Upper 95% CI	p-value [(b)]
Coffee												
Non-consumers	7,119	46	1.00				26,521	128	1.00			
1st quartile	38,657	270	0.99	0.51	1.93		95,026	547	0.98	0.64	1.50	
2nd quartile	35,488	257	0.85	0.44	1.67		70,532	392	1.09	0.70	1.68	
3rd quartile	30,545	187	0.83	0.41	1.67		71,325	380	0.95	0.59	1.51	
4th 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
Tea [(c)]												
Non-consumers	49,835	319	1.00				99,173	483	1.00			
1st quartile	30,322	167	1.06	0.68	1.64		58,681	293	0.88	0.62	1.26	
2nd quartile	18,661	122	1.07	0.66	1.74		53,393	330	0.86	0.60	1.23	
3rd quartile	25,969	179	0.92	0.59	1.43		51,385	283	1.08	0.75	1.53	
4th 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

[(a)] 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.

[(b)] Evaluated by entering the median value of each category of consumption in the model.

[(c)] 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 [a]	Lower 95% CI	Upper 95% CI	p-value [b]	No. non-cases	No. cases	HR [a]	Lower 95% CI	Upper 95% CI	p-value [b]
Caffeinated coffee [c]												
Non-consumers	24,969	113	1.00				65,980	272	1.00			
1st quartile	21,426	136	0.80	0.36	1.81		66,240	384	0.89	0.58	1.37	
2nd quartile	19,068	128	0.72	0.32	1.61		54,778	315	0.85	0.56	1.27	
3rd quartile	19,735	130	0.63	0.28	1.40		49,708	301	0.94	0.61	1.46	
4th 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
Decaffeinated coffee [d]												
Non-consumers	57,430	260	1.00				141,725	608	1.00			
1st tertile	15,949	75	0.80	0.25	2.59		45,961	262	1.13	0.68	1.88	
2nd tertile	6,608	30	1.25	0.42	3.69		18,467	116	1.15	0.68	1.96	
3rd 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

[a] 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.

[b] Evaluated by entering the median value of each category of consumption in the model.

[c] Information on consumption of caffeinated coffee is not available in Naples and Ragusa (Italy), Umeå (Sweden) and Denmark.

[d] Information on consumption of decaffeinated coffee is not available in Naples and Ragusa (Italy), Denmark, Norway and Sweden.