EXOGENOUS HORMONE USE AND CUTANEOUS MELANOMA RISK IN WOMEN: THE EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION

Authors: I Cervenka[1,2], M Al Rahmoun[1,2], Y Mahamat-Saleh[1,2], A Fournier[1,2], MC Boutron-Ruault[1,2], G Severi[1,2], S Caini[3], D Palli[3], R Ghiasvand[4], MB Veierod[4], E Botteri[5,6], A Tjønneland[7,8], A Olsen[7], RT Fortner[9], R Kaaks[9], MB Schulze[10,11], S Panico[12], A Trichopoulou[13], C Dessinioti[13,14], K Niforou[13], S Sieri[15], R Tumino[16], C Sacerdote[17], B Bueno-de-Mesquita[18,19,20,21], TM Sandanger[22], S Colorado-Yohar[23,24,25], MJ Sánchez[24,26], L Gil Majuelo[27], L Lujan-Barroso[28], E Ardanaz[24,29,30], S Merino[31], K Isaksson[32], S Butt[32], I Ijuslinder[33], M Jansson[34], RC Travis[35], KT Khaw[36], E Weiderpass[37], L Dossus[38], S Rinaldi[38], M Kvaskoff*[1,2]

[1]CESP, Fac. de médecine - Univ. Paris-Sud, Fac. de médecine - UVSQ, INSERM, Université Paris-Saclay, 94805, Villejuif, France

[2]Gustave Roussy, F-94805, Villejuif, France

[3]Cancer Risk Factors and Lifestyle Epidemiology Unit, Cancer Research, Prevention and Oncology Network Institute (ISPRO), Florence, Italy

[4]Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Norway

[5]Department of Bowel Cancer Screening, Cancer Registry of Norway, Oslo University Hospital, Oslo, Norway

[6]Norwegian National Advisory Unit for Women's Health, Women's Clinic, Oslo University Hospital, Oslo, Norway

[7]Danish Cancer Society Research Center, Copenhagen, Denmark

[8]University of Copenhagen

[9]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, Heidelberg, Germany

[10]Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany

[11]Institute of Nutritional Sciences, University of Potsdam, Nuthetal, Germany

[12]Dipartimento di medicina clinica e chirurgia, Federico II University, Naples, Italy

[13]Hellenic Health Foundation, Athens, Greece

[14]1st Department of Dermatology Andreas Syggros Hospital University of Athens, Athens, Greece

[15]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano Via Venezian, 1, 20133 Milano-Italy

[16]Cancer Registry and Histopathology Department, Azienda Sanitaria Provinciale (ASP) Ragusa, Italy

[17]Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), Turin, Italy

[18]Former senior scientist, Dept. for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands

[19]Former associate professor, Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands

[20]Former Visiting professor, Dept. of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, St Mary's Campus, Norfolk Place, London, W2 1PG London, United Kingdom.

[21]Former Academic Icon / visiting professor, Dept. of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Pantai Valley, 50603, Kuala Lumpur, Malaysia

[22]Department of Community Medicine, UiT - The Arctic University of Norway, Tromsø, Norway

[23]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

[24]CIBER Epidemiología y Salud Pública (CIBERESP), Spain

[25]Research Group on Demography and Health, National Faculty of Public Health, University of Antioquia, Medellín, Colombia
[26]Andalusian School of Public Health, Biomedical Research Institute ibs.GRANADA, University of Granada, Granada, Spain
[27]Public Health Division of Gipuzkoa, Biodonostia Health Research Institute, Ministry of Health of the Basque Government, San Sebastian, Spain
[28]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO-IDIBELL), Gran Via de L'Hospitalet 199-203, 08908, L'Hospitalet de Llobregat, Barcelona, Spain
[29]Navarra Public Health Institute, Pamplona, Spain
[30]IdiSNA, Navarra Institute for Health Research, Pamplona, Spain
[31]Public Health Directorate, Asturias, Spain
[32]Department of Clinical Sciences Lund, Surgery, Lund University, Skåne University Hospital, Lund, Sweden
[33]Department of radiation sciences, Oncology, Norrlands University hospital, Umeå, Sweden
[34]Department of Surgery and Perioperative Sciences/Surgery, Umeå University, Sweden
[35]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK, OX3 7LF
[36]University of Cambridge School of Clinical Medicine
[37]International Agency for Research on Cancer, Lyon, France
[38]Nutrition and Metabolism Section, International Agency for Research on Cancer

[*]**Corresponding author**: Dr. Marina Kvaskoff, Inserm U1018, Health across Generations Team, Gustave Roussy, Espace Maurice Tubiana, 114 rue Edouard Vaillant, F-94805 Villejuif Cedex, France; Tel: +33 1 4211 5864; Fax: +33 1 4211 4000; Email: Marina.KVASKOFF@gustaveroussy.fr

Running head: Exogenous hormones and melanoma risk

Keywords: cohort studies; cutaneous melanoma; epidemiology; hormonal treatments; menopausal hormone therapy; oral contraceptives

Abbreviations used: ALM: acro-lentiginous melanoma; CEE: conjugated equine estradiol; CI: Confidence Interval; E3N: *Etude Epidemiologique auprès de femmes de l'Education Nationale*; EPIC: European prospective investigation into cancer and nutrition; HR: Hazard Ratio; IARC: International Agency for Research on Cancer; ICD-O: international classification of diseases for oncology; LMM: lentigo maligna melanoma; MHT: menopausal hormone therapy; NM: nodular melanoma; OC: oral contraceptive; SD: standard deviation; SSM: superficial spreading melanoma; UV: ultraviolet radiation.

Word count: Text: 3703; Abstract: 221

Conflict of Interest: None declared.

Novelty and impact

- Ever use of OCs was positively associated with melanoma risk, with no heterogeneity across European countries and a positive linear association with duration of use.
- Ever use of MHT was associated with a modest increase in melanoma risk overall. This association was heterogeneous across countries, which may reflect confounding by behavioral factors.
- More research is needed to investigate potential confounding or effect modification of sun exposure on these relations.

Abstract

Evidence suggests an influence of sex hormones on cutaneous melanoma risk, but epidemiologic findings are conflicting. We examined the associations between use of oral contraceptives (OCs) and menopausal hormone therapy (MHT) and melanoma risk in women participating in the European Prospective Investigation into Cancer and Nutrition (EPIC). EPIC is a prospective cohort study initiated in 1992 in 10 European countries. Information on exogenous hormone use at baseline was derived from country-specific self-administered questionnaires. We used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Over 1992-2015, 1,696 melanoma cases were identified among 334,483 women, whereof 770 cases among 134,758 postmenopausal women. There was a positive, borderline-significant association between OC use and melanoma risk (HR=1.12, 95% CI=1.00-1.26), with no detected heterogeneity across countries ($P_{homogeneity}$=0.42). This risk increased linearly with duration of use (P_{trend}=0.01). Among postmenopausal women, ever use of MHT was associated with a non-significant increase in melanoma risk overall (HR=1.14, 95% CI=0.97-1.43), which was heterogeneous across countries ($P_{homogeneity}$=0.05). Our findings do not support a strong and direct association between exogenous hormone use and melanoma risk. In order to better understand these relations, further research should be performed using prospectively collected data including detailed information on types of hormone, and on sun exposure, which may act as an important confounder or effect modifier on these relations.

Introduction

Cutaneous melanoma is the most lethal form of skin cancer, leading to more than 55,000 deaths annually worldwide (1,2). Established risk factors for this neoplasm include ultraviolet radiation (UV) exposure, pigmentary traits, and familial history of skin cancer (2,3). Among other factors under investigation, sex hormones have been suspected to influence melanoma risk. Case reports documented progression or worse prognosis of melanomas diagnosed during pregnancy (4–7), and sex steroids have been shown to influence cutaneous pigmentation (8). Epidemiologic trends show a higher melanoma incidence in females compared with males under age 55 (9), and women were consistently reported to have higher survival rates (10) and lower risks of mortality and metastasis (11) compared with men, regardless of tumor stage, histologic type, or anatomic site (10,12). Several epidemiologic studies reported associations between melanoma risk and reproductive and menstrual factors (including in the French E3N cohort (13)), some of which were confirmed in a 2011 meta-analysis (14).

Among hormonal exposures, oral contraceptives (OCs) and menopausal hormone therapy (MHT) represent a considerable source of exogenous hormone exposure. Various formulations have been developed over past decades, with different uses across countries. Overall, oral hormones remain the leading contraception method in industrialized countries (15), whereas MHT use decreased in the 2000s following the findings from the Women's Health Initiative trial, which showed increased breast cancer and cardiovascular risks in users of combined MHT (16,17).

The use of OCs and MHT has been associated with a higher risk of several cancers, including in the EPIC cohort (breast (18–20), cervical (21), and endometrial cancer (22,23), and meningioma (24)), and estrogen-only and combined estrogen-progestin hormonal therapy has been classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC)(15,25). With regards to melanoma, while several studies reported a higher melanoma risk associated with exogenous hormone use (26–31), findings are inconsistent to date. A meta-analysis concluded to no association between exogenous hormone use and melanoma risk (14); however, previous studies were heterogeneous, and

few were based on a prospective design. In addition, although melanoma has been shown to be a heterogeneous tumor (32,33), very few studies explored the associations between exogenous hormone use and melanoma risk according to tumor site or histologic type. Moreover, the cumulative use of both OC and MHT over time has been suggested to increase melanoma risk (30), but only one study examined this issue to date and it was based on a limited duration of use.

Our aim was to explore the use of OC and MHT in relation to melanoma risk in the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Materials and Methods

EPIC is a multicenter prospective cohort study involving 521,330 participants (367,903 women) who were recruited in 1992-2000 from 23 centers across 10 European countries (France, Italy, Spain, the United Kingdom, the Netherlands, Greece, Germany, Sweden, Denmark, and Norway). Complete descriptions of the cohort and data collection have been published previously (34). All participants gave written informed consent, and the Ethical Review Board of IARC and ethical committees from all participating centers approved the study.

Study population

We included only participants without a prevalent cancer at baseline (n=491,992). We then excluded men (n=148,007) and women with primary amenorrhea (n=43). For analyses on OCs, we further excluded women with missing information on OC use (n=9,459), leading to a study sample of 334,483 women. Analyses on MHT were restricted to women who were postmenopausal at baseline (n=160,025). Postmenopausal women from the Swedish (n=14,146) and Greek (n=8,838) cohorts were not included because of lack of data on MHT, and we further excluded 2,283 women who reported no information on MHT or OC use, leaving a final sample of 134,758 postmenopausal women for the MHT analyses.

Menopausal status was based on an algorithm previously used (18): women were considered postmenopausal if they reported 12 consecutive months of amenorrhea or bilateral oophorectomy. Women for whom menopause was obscured by hysterectomy, those who were still menstruating and using exogenous hormones, and women with no information on number of menses over the 12 months preceding baseline were considered postmenopausal if they were 55 years or older.

Identification of melanoma cases and follow-up

The identification of incident cancers and determination of vital status during 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 contacts with participants and their next-of-kin. The outcome was incident cutaneous melanoma (site codes ICD-O-2, code

C44), with no consideration of mucosal tumors. We considered both in situ and invasive tumors (morphology behavioral codes 2 and 3, respectively). Women were followed up from study entry until first diagnosis of incident cancer (except non-melanoma skin cancer), death, loss to follow-up, or end of follow-up period, whichever occurred first. The follow-up period ended between June 2008 and December 2013, depending on the center.

Exposure assessment

Information on hormone use was derived from country-specific questionnaire items, which covered questions on ever use of OC, age at first use, and duration of use. Information on MHT use included ever and current use, age at first use, duration of use, and brand name of MHT currently used at recruitment. From the MHT brand name, we could deduce the type of hormone and the route of administration, and for combined MHT, the regimen - defined as sequential (estrogen with added progestin 10-14 days a month) or fixed continuous (estrogen with added progestin daily).

Statistical analysis

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with age as time scale. Models were first stratified by center to control for different follow-up procedures and questionnaire design across centers, and by age at recruitment (in 1-year intervals) (Model 1), then further adjusted for potential confounders that were recorded in all countries: education (none/primary, technical/professional school, secondary school, longer education, missing), age at menarche (≤12 years, 13-14, ≥15 years, missing), mean length of menstrual cycles (<30 days, 30-33, 34-36, ≥37 days, missing), number of full-term pregnancies (none, one, two, three or more, missing), OC use (ever, never; for analyses on MHT), menopausal status (premenopausal, postmenopausal; for analyses on OCs), height (quartiles), body mass index (<18.5, 18.5-24, 25-29, ≥30 kg/m^2), and smoking status (never, former, current smoker, missing) (Model 2). Sensitivity analyses were performed with adjustment for additional factors, excluding countries for which covariates were not fully available (Norway, Denmark, Spain, Greece, Sweden, representing a total sample size of n=209,461 for analyses on OC, and n=92,489 for analyses on MHT). Model 3 was additionally adjusted for hours of recreational physical activity in summer (number of hours of walking, cycling, gardening, and

physical exercise in a typical week during the past year: below or above the median (10 hours), missing), which we used as a proxy for recreational sun exposure. Model 4 was based on Model 3, with additional adjustment for marital status (single, married/living together, divorced/separated, widowed, missing). For analyses on OCs, two additional models were built: Model 5 was based on Model 2 and additionally adjusted for MHT use (premenopausal, postmenopausal ever user of MHT, postmenopausal never user of MHT). In Model 6, all covariates were included (Model 2 additionally adjusted for physical activity during summer, marital status, and MHT use). Tests for homogeneity were performed using Wald chi-square tests to compare MHT formulations, and Q tests to compare estimates across countries. To address a potential reverse causality bias, ever use of exogenous hormones were also analyzed in relation to melanoma risk after excluding cases diagnosed within 1 year after baseline (n=108 for OC analysis and n=45 for MHT analysis).

We also tested for effect modification by factors associated with melanoma risk in our study sample (i.e. education, marital status, physical activity during summer, and height).

Melanoma risk was also analyzed according to histologic subtype and anatomic site using competing-risk models with the cause-specific hazards approach (35,36). Cases with missing information on anatomic site or histologic subtype were excluded from these analyses. We tested for heterogeneity between subtypes and sites using Q tests.

Analyses were performed using the SAS statistical software package (version 9.4).

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Results

A total of 1,696 incident cases of melanoma (including 136 in situ) were ascertained among 334,483 women for the OC analysis, and 770 incident cases (including 94 in situ) among 134,758 postmenopausal women for the MHT analysis. The incidence of melanoma was highest in Sweden and the Netherlands, with 48 and 46 cases per 100,000 person-years, respectively; and lowest in Greece, where the incidence was 8 per 100,000 person-years. Among melanomas with available information on histology, most were of the superficial spreading type (SSM, 73%). The most frequent body site of the tumor was the lower limbs (42%).

Table 1 presents the characteristics of participants at baseline. Most women reported to have ever used OCs or MHT, except in Italy, Spain, and Greece where OC or MHT use was markedly less common. Use of both treatments was highest in Germany (44%) and Norway (42%). Patterns of use varied across countries (**Table 2**). Among current MHT users, opposed estrogens were more frequent in France and Norway than in other countries; and while progesterone derivatives were mainly used to oppose estrogen in France, Italy, and Spain, other countries mainly used testosterone derivatives.

In Model 2, there was a modest positive association between ever use of OCs and melanoma risk (HR=1.12, 95% CI=1.00-1.26) (**Table 3**) and we observed no heterogeneity in estimates across countries ($P_{homogeneity}$=0.42) (**Supplementary table 1**). There was also a positive linear association with duration of use (≤5 years: HR=1.11, 95% CI=0.97-1.26; >5 years: HR=1.20, 95% CI=1.04-1.37 vs. never use, P_{trend}=0.01). However, there was no association with age at first OC use (P_{trend}=0.19). In sensitivity analyses using a restricted sample (n=209,461), associations remained stable across adjustment models, although statistical significance was lost with additional adjustment (**Supplementary table 2**).

There was a modest positive association between ever use of MHT and melanoma risk (HR=1.14, 95% CI=0.97-1.35 in Model 2) (**Table 4**). However, there was heterogeneity in estimates across countries ($P_{homogeneity}$=0.005): we observed increased risks for ever vs. never use in France (HR=1.69, 95% CI=1.18-2.42), Spain (HR=2.48, 95% CI=0.99-6.22), and Germany

(HR=2.75, 95% CI=1.22-6.21) but not in other countries (**Supplementary table 1**). In sensitivity analyses using a restricted sample (n=92,489), the association between ever use of MHT and melanoma risk was stronger and statistically significant (HR=1.32, 95% CI=1.08-1.62 in Model 2), but remained stable after adjustment for marital status and hours of physical activity in summer (**Supplementary table 3**).

We found no association between duration of MHT use or age at first use and melanoma risk (**Table 4**). Nevertheless, when considering MHT type, estradiol was positively associated with melanoma risk (HR=1.53, 95% CI=1.11-2.11), albeit with no heterogeneity across estrogen types ($P_{homogeneity}$=0.18). Unopposed estrogens administrated by cream (HR=2.20, 95% CI=1.12-4.29) were also associated with a higher risk. Also, while we found no heterogeneity across types of progestogens ($P_{homogeneity}$=0.16), among combined MHTs, those containing promegestone were positively associated with melanoma risk (HR=2.57, 95% CI=1.44-4.60 in Model 2). However, we found no association with type of regimen (sequential or fixed continuous). Of note, in sensitivity analyses, all these results remained stable across adjustment models (**Supplementary table 3**). Nevertheless, the association with MHT seemed stronger with higher durations of use (HR=1.32, 95% CI=0.94-1.85 for MHT use >5 years vs. no use in Model 2), and for norethindrone-containing MHTs (HR=1.88, 95% CI=1.16-3.06) and sequential regimens (HR=1.61, 95% CI=1.08-2.42).

We found no effect modification for ever use of exogenous hormones and melanoma risk by height, body mass index, marital status, hours of physical activity during summer, or education level on melanoma risk. Also, estimates were not substantially modified after exclusion of cases diagnosed within the first year of follow-up (ever use of OCs: HR=1.12, 95% CI=0.99-1.26; ever use of MHT: HR=1.12, 95% CI=0.95-1.33).

When exploring the cumulative use of OCs and MHT among postmenopausal women, we found no additional risk in women who have ever used OCs and not MHT, MHT and not OCs, or who used both treatments over their lifetime (**Table 5**). There was also no association between the combined duration of both treatments and melanoma risk. However, in sensitivity analyses, MHT users were at higher melanoma risk, with or without OC use, compared with women who never used hormonal therapies (never use of OCs: HR=1.30,

95% CI=1.00-1.70; ever use of OCs: HR=1.31, 95% CI=1.00-1.72, in Model 4) (**Supplementary table 4**).

In type- and site-specific analyses, the positive association between OC use and melanoma risk was restricted to the acro-lentiginous melanoma subtype (ALM: HR=3.24, 95% CI=1.24-8.48; $P_{homogeneity}$=0.05) (**Supplementary table 5**). The association between OC use and melanoma risk seemed stronger for tumors on the lower limbs, and the association between MHT use and melanoma seemed stronger for the ALM and lentigo maligna subtypes, and for head and neck tumors, albeit with no evidence for heterogeneity ($P_{homogeneity}$=0.98, 0.36, and 0.56, respectively).

Discussion

This prospective cohort study is one of the largest to date on the associations between exogenous hormone use and melanoma risk. Use of OCs was positively associated with melanoma risk, with no evidence of heterogeneity across countries and a linear association with increasing duration of use. A positive association was also found between ever use of MHT and melanoma risk, which was heterogeneous across countries.

Our finding of a modest positive association between OC use and melanoma risk is consistent with the results from the analysis of national data in France (27) and from a Dutch population-based case-control study (30), but contrasts with the results from previous meta-analyses (14,37) and a pooled-analysis of case-control studies (38) showing no association with OC use. These differences could be explained by the predominance of retrospective designs and small numbers of melanoma cases in most previous studies. Also, the women included in our study were generally older than in previous research (41 years old on average in Gandini et al.'s meta-analysis (14) and 61.5 years in our population). Of note, most studies reporting a positive association did not control for sun exposure in previous research (14). In a prospective study among premenopausal nurses, the association was positive with current use of OCs, and stronger in women reporting sunburns and skin sensitivity to sun exposure in childhood ($P_{interaction}$=0.07) (39). In Gandini's meta-analysis, summary estimates were slightly lower when adjusted for phenotype and sun exposure (14). In contrast, we did not observe any appreciable difference in the association after adjustment for hours of outdoor physical activity during summer in our study.

Regarding duration of OC use, we found a positive linear association with melanoma risk, while other studies reported no association overall (14,40). However, we found no association between age at first OC use and melanoma risk, consistent with previous studies (14).

OC use was associated with ALM risk in our study. However, this result could be due to chance given the small case numbers. Of note, ALM accounts for less than 5% of all melanoma cases worldwide, but this proportion increases up to 70% in darker skin types (41). The EPIC cohort lacked data on skin type or ethnicity, which might be important

confounders in this association. Nevertheless, the ALM tumor type has never been explored in relation to exogenous hormone use and should be further investigated in studies considering skin type or ethnicity.

In our main analyses, we found a modest positive association between MHT use and melanoma risk, which contrasts with the existing meta-analysis (14) and two recent US studies (40,42), but is consistent with three recent European cohort studies reporting positive associations (26,28,43). In addition, associations became stronger and statistically significant in our sensitivity analyses. This change in estimates likely reflects differences in population sample selection, since estimates were heterogeneous across countries and some countries were excluded from the sensitivity analyses.

We found no association between duration of MHT use or age at first use and melanoma risk, consistent with results from previous studies (14,40,44,45).

Several types of MHT were associated with melanoma risk in our study. We found positive associations with unopposed estradiol and unopposed estrogens administrated by cream. This is consistent with the results from the analyses of national data in France, Norway, and Sweden, showing a positive association with unopposed estrogens overall (mainly estradiol) (26,28,43). In contrast, previous US studies reported no association with unopposed estrogens (40,42), but it should be noted that the main type of estrogens prescribed in the US is conjugated equine estrogens (CEE), while the main type prescribed in European countries is estradiol, as reflected from the distribution in our population (except for Germany and the UK for which about half of opposed estrogens were CEE). This underlines the importance to consider the different types of estrogens in exploring the relation between exogenous hormone use and melanoma risk. However, it should be noted that the differences in type of hormones could be driven by differences across countries, although the three countries for which we found a stronger association (France, Spain, Germany) had marked differences in the type of hormone used. If confirmed, it could be hypothesized that the variations in these associations according to the type of hormone could be driven by a photosensitizing effect of some specific MHT components, as shown for ethinylestradiol (46).

MHTs containing promegestone were also positively associated with melanoma risk in our study, consistent with the findings from the French E3N cohort (26). In sensitivity analyses, MHTs containing norethindrone acetate also became positively associated with melanoma risk. This association was not reported in Norway, where norethindrone acetate is the only progestogen used in opposed formulations (28), and our sensitivity analyses excluded data from Norway. Another difference potentially contributing to this result is that the Norwegian study considered time-dependent MHT exposure, while there was a single baseline assessment of exposure in EPIC.

For combined MHT, sequential or continuous regimens reveal different levels of exposure to progestogens (continuous regimens involving daily exposure during treatment), and compared with sequential regimens, continuous ones have been shown to confer higher breast cancer risk (18). We used regimen of administration, which was seldom considered in previous research on melanoma risk, as an additional parameter to test whether melanoma could be influenced by exogenous hormones. We found no association with melanoma risk, except for a positive association with sequential regimens in sensitivity analyses. In the Norwegian cohort study, a similar association was found, although with no statistical significance. These results do not support the hypothesis of a strong relation between the progestogen component of hormonal treatments and melanoma risk. Of note, our findings on MHT formulations overall need cautious interpretation as no heterogeneity was found across estimates, and they rely on few cases.

We observed heterogeneity in estimates regarding MHT use across countries. Patterns of MHT use vary nationally, with for instance variability in age at first use or types of exogenous hormones prescribed in each European country, which is influenced by national recommendations (16). The profile of users might also vary, and importantly, sun exposure may be a confounder of the relations between exogenous hormones and melanoma risk, which is incompletely controlled for by stratifying by center in our analyses. While our results were not substantially modified after adjustment for hours of recreational physical activity in summer, we cannot rule out confounding or effect modification by sun exposure, as this was only a proxy.

In fully-adjusted models, MHT users were at higher risk of melanoma (with or without OC use) compared with women who never used hormonal therapies, and we found no association with cumulative duration of use. These results do not support a direct influence of cumulative hormonal exposure on melanoma risk.

Strengths of our study included the study design and availability of data on OC and MHT use in 10 European countries, spanning a wide diversity of hormonal formulations across Europe; information on melanoma site and type; and the large sample size of the EPIC cohort. However, one major limitation is the lack of information on risk factors for melanoma, such as sun exposure, pigmentary traits, family history of skin cancer, and socio-economic parameters such as income, hence compromising the study of a potential confounding effect by these factors. Although we used hours of recreational physical activity in summer as a proxy for time spent outdoors, the EPIC cohort did not evaluate behavioral sun exposure and there is high potential for residual confounding. It has indeed been suggested that exogenous hormone users are more prone to intentional UV exposure, with associations found between sunscreen use, sunburns, tanning bed use and melanoma risk (27,47). Another limitation is the single baseline assessment of exogenous hormone exposure from self-reports, which does not take into account variability in use over time and might procure recall bias, especially in case of past exogenous hormone use. While we had detailed data on MHT use, statistical power remained low in analyses over subcategories of MHT formulations. Data on OC use were less detailed, and did not enable a thorough analysis for OCs. Also, we lacked information on the reason for prescription. This could be important as OCs can be prescribed for conditions related to hyperandrogeny (irregular or heavy menses, acne, *etc.*) and androgens has been suspected to increase melanoma risk (48,49). Last, since EPIC participants were recruited at 51 years old on average, we were not able to study early-onset melanomas, which may be important to investigate in relation to hormonal exposures according to a recent study (50). However, this age range of recruitment allowed the study of long-term effects of exogenous hormones taken earlier in life, especially for OCs.

In conclusion, the findings from this large prospective study do not support a strong and direct association between exogenous hormone use and melanoma risk. If the hypothesis of

a hormonal influence on melanoma were true, it is likely modest and thus difficult to disentangle from the effects of other exposures, such as exposure to UV radiation, which has a major impact on melanoma risk. Further research performed in large prospective cohorts that include detailed information on types of hormone and UV exposure - which may act as an important confounder or effect modifier on these relations - will help further shed light on these relationships and their underlying mechanisms.

Acknowledgements

The authors thank all participants in the EPIC cohort for their invaluable contribution to the study. We thank the CERCA Program/Generalitat de Catalunya for their institutional support. We also thank the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands, for their contribution of the Prospect study to the International EPIC Study. Iris Cervenka was supported by a research scholarship from the French Ministry of Research. The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); German Cancer Aid, German Cancer Research Center, Federal Ministry of Education and Research (Germany); the Italian Association for Cancer Research (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports, Netherlands Cancer Registry, LK Research Funds, Dutch Prevention Funds, Dutch ZON, World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Health Research Fund (FIS) PI13/00061 and PI13/01162, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII Health Research Funds RD12/0036/0018 (Spain); Cancer Research UK, Medical Research Council (UK); the French National Institute of Health and Medical Research (Inserm), the Mutuelle Générale de l'Education Nationale, the Gustave Roussy Institute, and the French League against Cancer (France); and the Hellenic Health Foundation (Greece). Reza Ghiasvand was supported by a grant (project 6823329) from the Norwegian Cancer Society.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-386.

2. Schadendorf D, van Akkooi ACJ, Berking C, Griewank KG, Gutzmer R, Hauschild A, et al. Melanoma. Lancet Lond Engl. 2018 Sep 15;392(10151):971–84.

3. Belbasis L, Stefanaki I, Stratigos AJ, Evangelou E. Non-genetic risk factors for cutaneous melanoma and keratinocyte skin cancers: An umbrella review of meta-analyses. J Dermatol Sci. 2016 Sep 13;

4. Kyrgidis A, Lallas A, Moscarella E, Longo C, Alfano R, Argenziano G. Does pregnancy influence melanoma prognosis? A meta-analysis. Melanoma Res. 2017 Aug;27(4):289–99.

5. Johansson ALV, Andersson TM-L, Plym A, Ullenhag GJ, Møller H, Lambe M. Mortality in women with pregnancy-associated malignant melanoma. J Am Acad Dermatol. 2014 Dec;71(6):1093–101.

6. Byrom L, Olsen C, Knight L, Khosrotehrani K, Green AC. Increased mortality for pregnancy-associated melanoma: systematic review and meta-analysis. J Eur Acad Dermatol Venereol JEADV. 2015 Aug;29(8):1457–66.

7. Wielowieyska-Szybińska DK, Spałkowska M, Wojas-Pelc A. Melanoma in pregnancy: a case report and review of the literature. Adv Dermatol Allergol Dermatol Alergol. 2015 Dec;32(6):483–7.

8. Mitkov M, Joseph R, Copland J. Steroid hormone influence on melanomagenesis. Mol Cell Endocrinol. 2015 Dec 5;417:94–102.

9. ENHIS 2009 http://www.euro.who.int/__data/assets/pdf_file/0009/97029/4.2.-Incidence-of-melanoma-EDITED_layouted.pdf.

10. Lasithiotakis K, Leiter U, Meier F, Eigentler T, Metzler G, Moehrle M, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. Cancer. 2008 Apr 15;112(8):1795–804.

11. Joosse A, de Vries E, Eckel R, Nijsten T, Eggermont AMM, Hölzel D, et al. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. J Invest Dermatol. 2011 Mar;131(3):719–26.

12. de Vries E, Nijsten TEC, Visser O, Bastiaannet E, van Hattem S, Janssen-Heijnen ML, et al. Superior survival of females among 10,538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. Ann Oncol Off J Eur Soc Med Oncol. 2008 Mar;19(3):583–9.

13. Kvaskoff M, Bijon A, Mesrine S, Boutron-Ruault M-C, Clavel-Chapelon F. Cutaneous melanoma and endogenous hormonal factors: a large French prospective study. Am J Epidemiol. 2011 May 15;173(10):1192–202.

14. Gandini S, Iodice S, Koomen E, Di Pietro A, Sera F, Caini S. Hormonal and reproductive factors in relation to melanoma in women: current review and meta-analysis. Eur J Cancer Oxf Engl 1990. 2011 Nov;47(17):2607–17.

15. IARC Monographs - Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy [Internet]. CIRC; 2007 [cited 2017 Dec 5]. (Monograph). Report No.: vol 91. Available from: http://monographs.iarc.fr/ENG/Monographs/vol91/index.php

16. Ameye L, Antoine C, Paesmans M, de Azambuja E, Rozenberg S. Menopausal hormone therapy use in 17 European countries during the last decade. Maturitas. 2014 Nov 1;79(3):287–91.

17. Ghazal S, Pal L. Perspective on hormone therapy 10 years after the WHI. Maturitas. 2013 Nov;76(3):208–12.

18. Bakken K, Fournier A, Lund E, Waaseth M, Dumeaux V, Clavel-Chapelon F, et al. Menopausal hormone therapy and breast cancer risk: Impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2011 Jan 1;128(1):144–56.

19. James RE, Lukanova A, Dossus L, Becker S, Rinaldi S, Tjønneland A, et al. Postmenopausal serum sex steroids and risk of hormone receptor-positive and -negative breast cancer: a nested case-control study. Cancer Prev Res Phila Pa. 2011 Oct;4(10):1626–35.

20. Ritte R, Lukanova A, Berrino F, Dossus L, Tjønneland A, Olsen A, et al. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. Breast Cancer Res. 2012 May 14;14(3):R76.

21. Roura E, Travier N, Waterboer T, de Sanjosé S, Bosch FX, Pawlita M, et al. The Influence of Hormonal Factors on the Risk of Developing Cervical Cancer and Pre-Cancer: Results from the EPIC Cohort. PloS One. 2016;11(1):e0147029.

22. Allen NE, Tsilidis KK, Key TJ, Dossus L, Kaaks R, Lund E, et al. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. Am J Epidemiol. 2010 Dec 15;172(12):1394–403.

23. Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer. 2008 Jun;15(2):485–97.

24. Michaud DS, Gallo V, Schlehofer B, Tjønneland A, Olsen A, Overvad K, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2010 Oct;19(10):2562–9.

25. Hormonal contraception and post-menopausal hormonal therapy [Internet]. CIRC; 1999. (IARC monographs of the evaluation of carcinogenic risks to humans). Report No.: 72. Available from: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-49/

26. Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, Savoye I, Boutron Ruault M-C, Fournier A, et al. Postmenopausal hormone use and cutaneous melanoma risk: A French prospective cohort study. Int J Cancer. 2019;

27. Cervenka I, Mahamat-Saleh Y, Savoye I, Dartois L, Boutron Ruault M-C, Fournier A, et al. Oral contraceptive use and cutaneous melanoma risk : a French prospective cohort study. Int J Cancer. 2018;

28. Botteri E, Støer NC, Sakshaug S, Graff-Iversen S, Vangen S, Hofvind S, et al. Menopausal hormone therapy and risk of melanoma: Do estrogens and progestins have a different role? Int J Cancer. 2017 Jul 7;

29. Bhupathiraju SN, Grodstein F, Stampfer MJ, Willett WC, Hu FB, Manson JE. Exogenous Hormone Use: Oral Contraceptives, Postmenopausal Hormone Therapy, and Health Outcomes in the Nurses' Health Study. Am J Public Health. 2016 Sep;106(9):1631–7.

30. Koomen ER, Joosse A, Herings RMC, Casparie MK, Guchelaar HJ, Nijsten T. Estrogens, oral contraceptives and hormonal replacement therapy increase the incidence of cutaneous melanoma: a population-based case-control study. Ann Oncol Off J Eur Soc Med Oncol. 2009 Feb;20(2):358–64.

31. Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women: ovulatory life, menopause, and use of exogenous estrogens. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 1994 Dec;3(8):661–8.

32. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst. 2003 Jun 4;95(11):806–12.

33. Carli P, Palli D. Re: Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst. 2003 Dec 3;95(23):1801; author reply 1801-1802.

34. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr. 2002 Dec;5(6B):1113–24.

35. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007 May 20;26(11):2389–430.

36. Pintilie M. Analysing and interpreting competing risk data. Stat Med. 2007 Mar 15;26(6):1360–7.

37. Gefeller O, Hassan K, Wille L. Cutaneous malignant melanoma in women and the role of oral contraceptives. Br J Dermatol. 1998 Jan;138(1):122–4.

38. Karagas MR, Stukel TA, Dykes J, Miglionico J, Greene MA, Carey M, et al. A pooled analysis of 10 case-control studies of melanoma and oral contraceptive use. Br J Cancer. 2002 Apr 8;86(7):1085–92.

39. Feskanich D, Hunter DJ, Willett WC, Spiegelman D, Stampfer MJ, Speizer FE, et al. Oral contraceptive use and risk of melanoma in premenopausal women. Br J Cancer. 1999 Nov;81(5):918–23.

40. Donley GM, Liu WT, Pfeiffer RM, McDonald EC, Peters KO, Tucker MA, et al. Reproductive factors, exogenous hormone use and incidence of melanoma among women in the United States. Br J Cancer. 2019 Feb 28;

41. Desai A, Ugorji R, Khachemoune A. Acral melanoma foot lesions. Part 1: epidemiology, aetiology, and molecular pathology. Clin Exp Dermatol. 2017;42(8):845–8.

42. Tang JY, Spaunhurst KM, Chlebowski RT, Wactawski-Wende J, Keiser E, Thomas F, et al. Menopausal Hormone Therapy and Risks of Melanoma and Nonmelanoma Skin Cancers: Women's Health Initiative Randomized Trials. JNCI J Natl Cancer Inst. 2011 Oct 5;103(19):1469–75.

43. Simin J, Tamimi R, Lagergren J, Adami H-O, Brusselaers N. Menopausal hormone therapy and cancer risk: An overestimated risk? Eur J Cancer. 2017 Aug 4;84:60–8.

44. Westerdahl J, Olsson H, Måsbäck A, Ingvar C, Jonsson N. Risk of malignant melanoma in relation to drug intake, alcohol, smoking and hormonal factors. Br J Cancer. 1996 May;73(9):1126–31.

45. Lea CS, Holly EA, Hartge P, Lee JS, Guerry D, Elder DE, et al. Reproductive risk factors for cutaneous melanoma in women: a case-control study. Am J Epidemiol. 2007 Mar 1;165(5):505–13.

46. Richarz NA, Aguilera J, Castillo G, Fuente MJ, Ferrándiz C, Carrascosa JM. Phototoxic reaction to a combined oral contraceptive (levonorgestrel/ethinylestradiol). Photochem Photobiol Sci. 2017 Sep 13;16(9):1381–3.

47. Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, Savoye I, Boutron-Ruault MC, Fournier A, et al. Postmenopausal hormone use and cutaneous melanoma risk: A French prospective cohort study. Int J Cancer. 2019 Jan 22;

48. Li W-Q, Qureshi AA, Ma J, Goldstein AM, Giovannucci EL, Stampfer MJ, et al. Personal history of prostate cancer and increased risk of incident melanoma in the United States. J Clin Oncol Off J Am Soc Clin Oncol. 2013 Dec 10;31(35):4394–9.

49. Zhang M, Qureshi AA, Fortner RT, Hankinson SE, Wei Q, Wang L-E, et al. Teenage acne and cancer risk in US women: A prospective cohort study. Cancer. 2015 May 15;121(10):1681–7.

50. Liu-Smith F, Ziogas A. An age-dependent interaction between sex and geographical UV index in melanoma risk. J Am Acad Dermatol. 2017 Dec 1;

Table 1: Baseline characteristics of study participants by country, EPIC cohort (n = 334,483 women)

Table 2: Description of exogenous hormone use as assessed at baseline, EPIC cohort (n = 195,437 women)

Table 3: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for the associations between oral contraceptive (OC) use and melanoma risk, EPIC cohort (n = 334,483 women)

Table 4: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for the associations between MHT use and melanoma risk among postmenopausal women, EPIC cohort (n = 134,758 women)

Table 5: Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between exogenous hormone use and melanoma risk among postmenopausal women, EPIC cohort (n = 134,758 women)

Supplementary table 1: Country-specific and overall hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between exogenous hormone use and melanoma risk, EPIC cohort (n = 334,483 women)

Supplementary table 2: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for the associations between oral contraceptive (OC) use and melanoma risk, EPIC cohort (n = 209,461 women)

Supplementary table 3: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for the associations between MHT use and melanoma risk among postmenopausal women, EPIC cohort (n = 92,489 women)

Supplementary table 4: Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between exogenous hormone use and melanoma risk among postmenopausal women, EPIC cohort (n = 92,489 women)

Supplementary table 5: Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between exogenous hormone use and melanoma risk according to histologic type and body site of melanoma, EPIC cohort (n = 334,483 women)

Table 1: Baseline characteristics of study participants by country, EPIC cohort (n = 334,483 women)

	ALL (%) n=334,483	France (%) n=68,612	Italy (%) n=31,072	Spain (%) n=25,321	UK (%) n=54,491	Netherlands (%) n=27,409	Greece (%) n=15,531	Germany (%) n=27,877	Sweden (%) n=20,494	Denmark (%) n=29,010	Norway (%) n=34,666
Recruitment											
Mean age at recruitment (SD)	51.1 (9.7)	52.7 (6.6)	50.6 (8.1)	48.3 (8.4)	47.9 (14.3)	51.0 (11.6)	53.3 (12.5)	49.1 (9.0)	55.6 (8.1)	56.7 (4.4)	48.1 (4.3)
Recruitment period	1991-2000	1993-1997	1992-1998	1992-1996	1993-2000	1993-1997	1993-1999	1994-1998	1991-1996	1993-1997	1998
Mean length of follow-up (SD)	13.9 (3.8)	12.9 (3.4)	14.3 (3.0)	16.1 (2.9)	15.1 (3.6)	14.3 (3.4)	11.1 (3.5)	10.4 (3.0)	16.9 (4.9)	15.0 (3.9)	13.3 (2.5)
Incident cutaneous melanoma cases	1,696	381	96	67	295	181	13	86	167	204	206
Level of education											
None/primary	28.94	11.39	52.46	78.76	11.14	17.93	66.79	23.34	37.94	31.27	23.20
Technical/professional school	21.68	-	10.98	5.45	26.81	32.96	3.20	41.82	29.24	46.57	35.82
Secondary school	23.19	48.98	23.10	5.52	13.10	30.66	14.56	8.00	9.85	11.82	28.57
Longer education (incl. University degree)	22.46	35.59	13.30	9.49	32.11	18.14	15.21	26.79	22.57	10.19	12.41
Missing	3.72	4.04	0.15	0.77	16.84	0.31	0.24	0.05	0.40	0.14	-
Marital Status											
Single	9.00	16.57	6.29	-	15.00	13.96	4.18	9.27	7.55	-	-
Married/de facto	63.43	79.57	81.66	-	68.95	71.06	80.66	73.20	67.88	-	81.60
Divorced/Separated	4.79	-	4.89	-	9.34	8.15	2.98	12.49	15.80	-	-
Widowed	3.67	-	6.32	-	6.43	6.64	12.10	5.03	8.39	-	-
Missing	19.11	3.86	0.85	100.00	0.28	0.19	0.07	0.01	0.38	100.00	18.40
Age at menarche (years)											
≤12	36.01	41.62	50.11	40.02	39.05	32.01	35.02	34.09	23.69	22.48	28.32
13-14	47.02	46.62	41.73	45.59	44.84	46.12	46.03	48.73	52.31	47.77	53.02
≥15	15.77	11.18	8.14	14.28	13.79	20.48	18.38	17.15	22.72	26.23	17.07
Missing	1.20	0.58	0.02	0.10	2.32	1.39	0.57	0.04	1.27	3.53	1.59
Menstrual cycle length (days)											
<30	27.12	10.38	28.88	46.63	43.09	20.09	44.89	39.61	11.25	11.94	28.91
30-33	22.16	26.64	24.12	24.67	16.38	12.52	22.19	22.34	26.20	17.48	27.75

	ALL (%) n=334,483	France (%) n=68,612	Italy (%) n=31,072	Spain (%) n=25,321	UK (%) n=54,491	Netherlands (%) n=27,409	Greece (%) n=15,531	Germany (%) n=27,877	Sweden (%) n=20,494	Denmark (%) n=29,010	Norway (%) n=34,666
34-36	18.12	18.50	21.98	15.58	13.30	17.62	16.43	15.41	27.48	25.42	15.03
≥37	16.40	18.25	22.48	10.65	12.95	16.36	13.40	14.63	20.06	27.81	7.97
Missing	16.21	26.23	2.53	2.46	14.28	33.41	3.09	8.00	15.00	17.35	20.35
Number of full-term pregnancies											
None	14.43	8.93	13.17	10.51	30.00	20.30	10.12	14.38	11.06	11.58	6.50
1	14.89	15.38	22.05	9.90	13.55	4.86	11.00	25.56	17.65	15.51	12.18
2	39.26	41.36	43.87	36.40	32.53	22.12	48.54	43.15	38.87	45.38	45.01
≥3	26.27	27.02	20.90	42.34	21.51	23.48	30.08	16.67	23.67	27.26	34.31
Menopausal status											
Premenopause	34.01	26.09	39.18	53.47	49.27	32.45	36.40	46.16	7.89	7.25	35.06
Perimenopause	44.19	43.39	41.75	31.98	37.86	47.02	51.48	37.74	65.40	72.72	30.11
Postmenopause, natural	18.84	27.78	15.18	9.58	9.96	17.56	6.86	13.05	26.71	15.37	34.43
Postmenopause, artificial	2.96	2.74	3.88	4.96	2.90	2.97	5.25	3.05		4.66	0.40
Ever use of exogenous hormones											
Oral contraceptives	58.43	60.90	41.04	42.17	66.95	73.05	9.54	81.12	51.74	58.26	63.80
Menopausal hormone therapy[1]	45.72	59.34	25.34	19.00	40.43	26.34	-	60.10	-	49.55	68.75
OC use/MHT use[1]											
Never OC /Never MHT	34.49	27.79	58.64	65.47	42.51	32.93	-	18.58	-	25.22	16.63
Ever OC /Never MHT	19.79	12.87	16.02	15.53	17.07	40.73	-	21.33	-	25.24	14.62
Never OC /Ever MHT	19.61	29.55	15.74	12.73	15.53	8.1	-	15.93	-	20.29	27.08
Ever OC /Ever MHT	26.11	29.78	9.6	6.26	24.89	18.24	-	44.17	-	29.26	41.67
Height[2]											
Quartile 1	24.82	24.66	45.64	57.90	19.90	12.77	57.50	18.91	14.93	13.79	4.73
Quartile 2	21.92	26.54	25.01	23.32	22.62	18.22	20.95	22.18	20.55	20.80	12.73
Quartile 3	27.25	29.44	20.15	14.26	29.03	30.19	15.07	30.93	32.73	31.71	29.16
Quartile 4	26.02	19.36	9.20	4.51	28.45	38.81	6.48	27.98	31.79	33.71	53.38

	ALL (%) n=334,483	France (%) n=68,612	Italy (%) n=31,072	Spain (%) n=25,321	UK (%) n=54,491	Netherlands (%) n=27,409	Greece (%) n=15,531	Germany (%) n=27,877	Sweden (%) n=20,494	Denmark (%) n=29,010	Norway (%) n=34,666
BMI (kg/m^2)											
<18.5	2.02	3.79	1.18	0.13	2.97	1.65	0.35	1.18	1.99	1.25	1.50
18.5-24	56.12	73.85	48.68	27.18	63.00	53.62	25.97	51.57	54.14	50.36	63.19
25-29	29.03	18.03	35.57	42.00	24.95	32.93	37.27	31.26	31.74	34.35	27.25
≥30	12.83	4.32	14.57	30.70	9.08	11.80	36.41	16.00	12.14	14.03	8.06
Smoking at inclusion											
Never	55.70	66.60	53.66	71.30	60.43	40.87	73.07	55.90	50.36	43.73	34.09
Former smoker	22.70	19.09	20.13	9.86	27.96	31.36	5.40	25.56	24.66	24.61	29.08
Current smoker	19.48	8.67	26.20	18.79	10.95	27.71	17.07	18.37	24.69	31.44	31.15
Missing	2.12	5.64	0.01	0.05	0.66	0.06	4.46	0.18	0.30	0.21	5.68
Recreational physical activity during summer (hours/week)											
<10	37.12	46.48	60.76	61.02	27.01	21.33	45.47	28.00	46.96	44.45	-
≥10	43.57	44.53	28.85	38.98	55.15	65.23	54.53	71.09	21.74	54.01	-
Missing	19.31	9.00	10.39	-	17.84	13.44	-	0.90	31.30	1.54	100

[1] Among postmenopausal women (considering natural and artificial menopause)

[2] Cut- off points for quartiles were 157, 161, and 166 cm for height

Table 2: Description of exogenous hormone use as assessed at baseline, EPIC cohort (n = 195,437 women)

	All	France	Italy	Spain	UK	Netherlands	Germany	Denmark	Norway	Greece	Sweden
Among ever users of OCs	n=195,437	n=41,788	n=12,751	n=10,679	n=36,481	n=20,021	n=22,615	n=16,900	n=22,116	n=1,482	n=10,604
Mean age at first OC use (SD)	25.5 (6.8)	28.6 (6.6)	28.4 (6.8)	-	22.1 (5.8)	25.7 (7.4)	-	27.7 (5.7)	22.5 (4.1)	26.6 (6.0)	26.4 (7.3)
Mean duration of OC use (SD)	6.4 (5.0)	6.5 (4.9)	3.9 (3.9)	3.7 (3.4)	6.5 (4.5)	7.6 (5.1)	9.5 (5.1)	7.2 (5.3)	4.6 (4.1)	2.5 (2.6)	7.6 (5.3)
OC duration (%)											
≤ 5 years	45.55	38.50	74.71	76.10	44.35	20.44	28.37	45.85	69.28	86.37	40.02
>5 years	40.16	35.85	22.60	23.28	44.82	28.18	71.01	48.48	30.72	10.93	46.46
Missing	14.29	25.64	2.69	0.62	10.82	51.38	0.62	5.67	0.00	2.70	13.51
Age at first OC use (%)											
≤20 years	19.96	3.81	11.02	-	49.24	27.87	-	7.80	37.89	15.18	24.09
21-23 years	14.07	12.59	13.57	-	18.35	15.09	-	15.34	27.24	17.61	17.96
24-29 years	22.16	28.24	32.22	-	16.87	26.80	-	39.83	26.81	37.58	25.21
≥30 years	19.17	27.15	40.05	-	11.85	28.18	-	35.26	6.53	27.53	30.56
Missing	24.64	28.21	3.14	100.00	3.70	2.07	100.00	1.77	1.53	2.09	2.19
Among ever users of MHT	n=61,606	n=18,701	n=3,593	n=1,777	n=8,833	n=3,597	n=6,783	n=11,112	n=7,210		
Status of use (%)											
Current	66.77	62.57	47.31	55.26	69.42	51.38	77.69	66.12	85.40		
Past	30.57	31.76	50.82	44.74	26.88	46.04	22.29	33.53	13.95		
Unknown	2.65	5.67	1.86	-	3.70	2.59	0.01	0.35	0.65		
Mean age at first MHT use (SD)	49.7 (5.3)	51.7 (4.9)	48.4 (5.4)	48.4 (4.6)	50.0 (6.3)	48.7 (5.9)	50.0 (4.1)	48.4 (5.1)	47.1 (4.0)		
Mean duration of MHT use (SD)	4.1 (4.0)	3.6 (3.3)	2.2 (2.7)	1.8 (2.3)	4.1 (3.8)	4.2 (4.2)	4.4 (3.4)	6.0 (5.4)	3.6 (3.0)		
Duration of MHT use (%)											
<1 year	26.26	24.89	46.06	57.29	27.24	33.31	10.48	24.84	24.60		
2-3 years	23.63	29.04	20.99	27.01	24.93	23.49	13.34	18.01	26.93		
4-5 years	14.58	14.73	10.46	7.26	17.25	14.01	11.19	13.22	20.31		
6-10 years	15.87	14.42	5.93	4.05	17.68	15.21	13.62	24.06	15.09		
≥11 years	6.55	3.84	1.59	1.35	6.14	8.28	2.58	18.21	2.70		
Missing	13.12	13.08	14.97	3.04	6.76	5.70	48.78	1.66	10.36		

	All	France	Italy	Spain	UK	Netherlands	Germany	Denmark	Norway	Greece	Sweden
Among current users of MHT	n=41,137	n=11,701	n=1,700	n=982	n=6,132	n=1,848	n=5,270	n=7,347	n=6,157		
Type of MHT (%)											
Unopposed estrogens	21.81	12.38	30.82	30.86	29.62	39.61	25.12	25.90	14.99		
Opposed estrogens	64.57	87.04	32.41	46.03	51.13	20.67	59.43	51.82	79.88		
Tibolone	2.54	-	6.41	-	7.75	7.03	0.04	4.49	-		
Unknown	11.08	0.58	30.35	23.12	11.51	32.68	15.41	17.79	5.13		
Among current users of estrogen-only MHT	n=8,973	n=1,448	n=524	n=303	n=1,816	n=732	n=1,324	n=1,903	n=923		
Type of estrogens (%)											
Estradiol	61.58	60.64	71.18	50.17	43.83	60.52	37.39	82.24	89.27		
Conjugated equine estrogens (CEE)	21.60	3.66	8.59	7.26	47.36	28.96	55.06	0.89	-		
Low-potency estrogens	11.27	34.05	20.23	-	4.85	7.65	6.12	4.89	10.18		
Other/unknown	5.55	1.66	-	42.57	3.96	2.87	1.44	11.98	0.54		
Route of administration (%)											
Oral	40.08	9.81	6.11	10.89	48.95	38.66	53.47	57.23	45.50		
Cutaneous	30.22	55.39	14.12	64.36	23.79	37.16	21.53	16.29	37.05		
cream	8.78	33.84	4.01	5.28	3.47	0.27	0.08	10.25	-		
patch	21.44	21.55	10.11	59.08	20.32	36.89	21.45	6.04	37.05		
Other/unknown[1]	29.70	34.81	79.77	24.75	27.26	24.18	25.00	26.48	17.44		
Among current users of combined MHT	n=26,562	n=10,185	n=551	n=452	n=3,135	n=382	n=3,132	n=3,807	n=4,918		
Type of progestogen (%)											
Micronized progesterone	9.36	24.17	2.18	1.11	0.03	0.79	0.06	-	-		
Progesterone derivative	35.66	68.71	83.85	78.98	5.33	30.10	19.57	19.02	0.73		
Dydrogesterone	8.78	21.01	18.15	-	0.93	15.45	0.13	-	-		
Medroxyprogesterone acetate (MPA)	7.75	5.13	47.19	77.43	4.40	4.19	5.27	15.02	0.73		
Medrogestone	3.38	4.33	11.25	-	-	10.47	11.33	-	-		
Chlormadinone acetate	2.8	6.66	-	-	-	-	2.14	-	-		
Nomegestrol acetate	6.42	16.3	7.26	1.11	-	-	-	-	-		
Promegestone	5.24	13.64	-	0.44	-	-	-	-	-		
Cyproterone acetate	1.29	1.65	-	-	-	-	0.7	3.99	-		
Testosterone derivative	53.47	4.33	13.97	-	94.64	65.97	79.89	80.98	99.27		

	All	France	Italy	Spain	UK	Netherlands	Germany	Denmark	Norway	Greece	Sweden
Norethindrone	38.62	4.15	13.79	-	31.32	45.29	38.63	71.37	95.1		
Norgestimate	9.65	-	-	-	54.16	20.68	6.86	9.61	4.17		
Levonorgestrel	5.21	0.18	0.18	-	9.15	-	34.39	-	-		
Other/unknown	1.51	2.79	-	19.91	-	3.14	0.48	-	-		
Regimen (%)											
Sequential	44.38	7.06	18.51	2.88	89.82	68.06	69.28	70.92	61.18		
Fixed continuous	15.45	2.12	0.73		8.23	7.59	24.43	25.09	38.19		
Other/unknown	40.16	90.82	80.76	97.12	1.95	24.35	6.29	3.99	0.63		

[1] Including low-potency estrogens

Table 3: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for the associations between oral contraceptive (OC) use and melanoma risk, EPIC cohort (n = 334,483 women)

	Cases	Model 1 HR (95% CI)[1] n=334,483	Model 2 HR (95% CI)[2] n=334,483
OC use			
Never	658	ref	ref
Ever	1,038	1.12 (1.01 - 1.26)*	1.12 (1.00 - 1.26)*
Duration of OC use[3]			
Continuous (per year)		1.02 (1.01 – 1.03)*	1.02 (1.00 - 1.03)*
Never use	658	ref	ref
≤5 years	458	1.12 (0.98 - 1.28)	1.11 (0.97 - 1.26)
>5 years	448	1.21 (1.06 - 1.39)*	1.20 (1.04 - 1.37)*
p-trend		*0.005**	*0.01**
Age at first use[3]			
Continuous (per year)		1.01 (1.00 - 1.03)	1.01 (0.99 - 1.02)
≤20 years	172	ref	ref
21-23 years	158	1.14 (0.90 - 1.44)	1.12 (0.87 - 1.43)
24-29 years	279	1.22 (0.96 - 1.54)	1.20 (0.94 - 1.53)
≥30 years	253	1.26 (0.72 - 1.41)	1.24 (0.94 - 1.64)
p-trend		*0.15*	*0.19*

* Significant at P value ≤ 0.05

[1] Model 1: stratified for center and age at recruitment

[2] Model 2: model 1 with additional adjustments for education, age at menarche, length of menstrual cycles, number of full term pregnancies, menopausal status, height, body mass index, and tobacco use

[3] Totals may not add-up due to missing data: there were 27,933 (14.3%) missing values in duration of use, 48,147 (24.6%) in age at first use

Table 4: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for the associations between MHT use and melanoma risk among postmenopausal women, EPIC cohort (n = 134,758 women)

	Cases	Model 1 HR (95% CI)[1] n=134,758	Model 2 HR (95% CI)[2] n=134,758
MHT use			
Never	407	ref	ref
Ever	363	1.08 (0.93 - 1.27)	1.14 (0.97 - 1.35)
Status of MHT use			
Never	407	ref	ref
Current	244	1.10 (0.92 - 1.31)	1.18 (0.98 - 1.43)
Past	108	1.04 (0.84 - 1.29)	1.07 (0.86 - 1.34)
Unknown	11	1.34 (0.73 - 2.47)	1.36 (0.72 - 2.59)
Duration of MHT use[3]			
Never	407	ref	ref
≤5 years	228	1.06 (0.89 - 1.26)	1.12 (0.93 - 1.34)
>5 years	79	1.00 (0.78 - 1.28)	1.05 (0.80 - 1.36)
p-trend		*0.88*	*0.42*
Duration of use in ever users[3]			
Continuous (per year)		1.01 (0.98 - 1.04)	1.01 (0.98 - 1.05)
≤1 year	79	ref	ref
2-3 years	86	1.18 (0.87 - 1.61)	1.19 (0.87 - 1.63)
4-5 years	63	1.35 (0.97 - 1.90)	1.39 (0.99 - 1.96)
6-10 years	54	1.08 (0.76 - 1.54)	1.09 (0.76 - 1.57)
≥11 years	25	1.20 (0.75 - 1.94)	1.23 (0.76 - 2.01)
p-trend		*0.33*	*0.24*
Age at first use in ever users[3]			
Continuous (per year)		0.99 (0.97 - 1.02)	0.99 (0.97 - 1.02)
≤50 years	197	ref	ref
51-52 years	26	0.93 (0.61 - 1.43)	0.94 (0.62 - 1.45)
52-55 years	71	0.99 (0.73 - 1.33)	0.97 (0.71 - 1.32)
≥ 55 years	46	0.78 (0.54 - 1.14)	0.81 (0.55 - 1.19)
p-trend		*0.51*	*0.55*

Type of MHT currently used[4]			
Never	407	ref	ref
Unopposed estrogens	59	1.17 (0.89 - 1.55)	1.24 (0.93 - 1.64)
Estradiol	45	1.44 (1.05 - 1.97)*	1.53 (1.11 - 2.11)*
CEE	8	0.76 (0.37 - 1.55)	0.81 (0.39 - 1.65)
Weak	4	0.72 (0.27 - 1.93)	0.74 (0.27 - 1.99)
Other/unknown estrogen	2	0.69 (0.17 - 2.77)	0.70 (0.17 - 2.83)
Estrogens combined with a progestogen	155	1.09 (0.89 - 1.35)	1.18 (0.94 - 1.48)
Micronized progesterone	17	1.49 (0.88 - 2.51)	1.46 (0.85 - 2.51)
Progesterone derivative	50	1.13 (0.81 - 1.56)	1.21 (0.86 - 1.71)
Dydrogesterone	9	0.80 (0.41 - 1.60)	0.77 (0.37 - 1.59)
MPA	12	1.24 (0.69 - 2.22)	1.41 (0.78 - 2.57)
Medrogestone	2	0.46 (0.11 - 1.86)	0.48 (0.12 - 1.95)
Chlormadinone acetate	6	1.89 (0.82 - 4.35)	2.03 (0.88 - 4.69)
Nomegestrol acetate	5	0.63 (0.26 - 1.57)	0.70 (0.28 - 1.75)
Promegestone	14	2.34 (1.32 - 4.15)*	2.57 (1.44 - 4.60)*
Cyproterone acetate	2	1.13 (0.28 - 4.57)	1.31 (0.32 - 5.34)
Testosterone derivative	86	1.02 (0.78 - 1.33)	1.11 (0.84 - 1.48)
Norethindrone	61	0.96 (0.71 - 1.31)	1.05 (0.76 - 1.44)
Norgestimate	18	1.22 (0.74 - 2.01)	1.38 (0.82 - 2.31)
Levonorgestrel	7	1.08 (0.47 - 2.48)	1.22 (0.53 - 2.82)
Other/unknown progestogen	2	1.12 (0.27 - 4.55)	1.20 (0.29 - 4.93)
Other/unknown MHT type[5]	30	0.96 (0.66 - 1.40)	1.04 (0.71 - 1.53)
Route of administration[4,6]			
Never	407	ref	ref
Oral	29	1.38 (0.94 - 2.03)	1.46 (0.99 - 2.16)
Cutaneous	17	1.16 (0.71 - 1.89)	1.25 (0.76 - 2.04)
Cream	9	2.11 (1.08 - 4.12)*	2.20 (1.12 - 4.29)*
Patch	8	0.77 (0.38 - 1.56)	0.84 (0.41 - 1.70)
Other/unknown	13	0.88 (0.50 - 1.53)	0.91 (0.52 - 1.59)
Regimen[4,7]			
Never	407	ref	ref
Sequential	69	1.00 (0.75 - 1.32)	1.12 (0.82 - 1.53)
Fixed continuous	22	0.86 (0.55 - 1.36)	0.88 (0.55 - 1.41)

Unknown	64	1.36 (0.99 - 1.87)	1.43 (1.03 - 1.99)*

* Significant at P value ≤ 0.05

[1] Model 1: stratified for center and age at recruitment

[2] Model 2: model 1 with additional adjustments for education, age at menarche, length of menstrual cycles, number of full term pregnancies, oral contraceptive use, height, body mass index, and tobacco use

[3] Totals may not add-up due to missing data: there were 8,080 (13.1%) missing values in duration of use; 3,036 (5.0%) in age at first use

[4] Adjusted for past use

[5] Include tibolone

[6] Route of administration concerns unopposed estrogens, and analyses are additionally adjusted for use of other types of therapies

[7] Regimens concerns combined therapies, and analyses are additionally adjusted for use of other types of therapies

Table 5: Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between exogenous hormone use and melanoma risk among postmenopausal women, EPIC cohort (n = 134,758 women)

	Cases	%	Model 1 HR (95%CI)[1] n=134,758	Model 2 HR (95%CI)[2] n=134,758
OC use/MHT use				
Never OC /Never MHT	249	34.49	ref	ref
Ever OC /Never MHT	158	19.79	1.01 (0.81 - 1.24)	1.00 (0.80 - 1.24)
Never OC /Ever MHT	155	19.61	1.10 (0.89 - 1.36)	1.15 (0.93 - 1.43)
Ever OC /Ever MHT	208	26.11	1.08 (0.87 - 1.33)	1.13 (0.90 - 1.40)
Duration of OC/MHT use				
Never use of OC or MHT	249	34.49	ref	ref
≤ 5 years	302	39.35	1.02 (0.85 - 1.22)	1.13 (0.90 - 1.40)
6-10 years	45	5.11	1.18 (0.84 - 1.65)	1.40 (0.93 - 2.10)
>10 years	78	9.45	1.10 (0.83 - 1.45)	1.32 (0.93 - 1.89)
p-trend			*0.43*	*0.14*
Missing	96	11.60	1.15 (0.88 - 1.51)	1.38 (1.00 - 1.91)*

* Significant at P value ≤ 0.05

[1] Model 1: stratified for center and age at recruitment

[2] Model 2: model 1 with additional adjustments for education, age at menarche, length of menstrual cycles, number of full term pregnancies, height, body mass index, and tobacco use