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Exogenous hormone use and cutaneous melanoma risk in women: The European Prospective Investigation into Cancer and Nutrition

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Abbreviations: 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; MHT: menopausal hormone therapy; OC: oral contraceptive; UV: ultraviolet radiation

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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 nonsignificant 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.

What's new?

Evidence suggests that sex hormones may influence melanoma risk. As part of a prospective study, the authors of this report found that women who had used oral contraceptives at any time had a moderately increased risk of melanoma, which increased linearly with longer usage. Menopausal hormone therapy (MHT), also increased risk somewhat. Further research is needed, in order to investigate potential confounding or effect-modification of melanoma risk, for various types and formulations of hormones, and for UV exposure.

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 to 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 to 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 *Etude Epidemiologique auprès de femmes de l'Education*

Nationale [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 after 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 European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (breast,[18–20] cervical,[21] 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 regard 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 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 International Classification of Diseases for Oncology-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, 13–14, ≥15 years, missing), mean length of menstrual cycles (<30, 30–33, 34–36, ≥37 days, missing), number of full-

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	United Kingdom (%) *n* = 54,491	The 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
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

(Continues)

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

	ALL (%) *n* = 334,483	France (%) *n* = 68,612	Italy (%) n = 31,072	Spain (%) *n* = 25,321	United Kingdom (%) *n* = 54,491	The Netherlands (%) *n* = 27,409	Greece (%) *n* = 15,531	Germany (%) *n* = 27,877	Sweden (%) *n* = 20,494	Denmark (%) *n* = 29,010	Norway (%) *n* = 34,666
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
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]Cutoff 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)

Among ever users of OCs	**All** *n* = 195,437	**France** *n* = 41,788	**Italy** *n* = 12,751	**Spain** *n* = 10,679	**United Kingdom** *n* = 36,481	**The Netherlands** *n* = 20,021	**Germany** *n* = 22,615	**Denmark** *n* = 16,900	**Norway** *n* = 22,116	**Greece** *n* = 1,482	**Sweden** *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		
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		

(Continues)

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

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**
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	
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.

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 hr], 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 our 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 (superficial spreading melanoma, 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 ($p_{\text{homogeneity}}$ = 0.42) (Supplementary Table S1). 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

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)

(Continues)

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) (Continued)

	Cases	Model 1 HR (95% CI)[1] n = 134,758	Model 2 HR (95% CI)[2] n = 134,758
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.

(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 S2).

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 S1). 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 S3).

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 S3). 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

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.

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 to 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 S4).

In type- and site-specific analyses, the positive association between OC use and melanoma risk was restricted to the acrolentiginous melanoma subtype (ALM: HR = 3.24, 95% CI = 1.24–8.48; $p_{\text{homogeneity}}$ = 0.05; Supplementary Table S5). 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 ($p_{\text{homogeneity}}$ = 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 ($p_{\text{interaction}}$ = 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 U.S. 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 U.S. studies reported no association with unopposed estrogens,[40,42] but it should be noted that the main type of estrogens prescribed in the United States 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 United Kingdom 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 and 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 to 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 to 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 socioeconomic 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.[26,27] 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 hyperandrogenism (irregular or heavy menses, acne, etc.) and androgens have been suspected to increase melanoma risk.[47,48] Lastly, 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.[49] 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.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–86.
2. Schadendorf D, van Akkooi ACJ, Berking C, et al. Melanoma. *Lancet Lond Engl* 2018;392:971–84.
3. Belbasis L, Stefanaki I, Stratigos AJ, et al. Non-genetic risk factors for cutaneous melanoma and keratinocyte skin cancers: an umbrella review of meta-analyses. *J Dermatol Sci* 2016;84: 330–9.
4. Kyrgidis A, Lallas A, Moscarella E, et al. Does pregnancy influence melanoma prognosis? A meta-analysis. *Melanoma Res* 2017;27:289–99.
5. Johansson ALV, Andersson TM-L, Plym A, et al. Mortality in women with pregnancy-associated malignant melanoma. *J Am Acad Dermatol* 2014; 71:1093–101.
6. Byrom L, Olsen C, Knight L, et al. Increased mortality for pregnancy-associated melanoma: systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2015;29:1457–66.
7. Wielowieyska-Szybińska DK, Spałkowska M, Wojas-Pelc A. Melanoma in pregnancy: a case report and review of the literature. *Adv Dermatol Allergol* 2015;32:483–7.
8. Mitkov M, Joseph R, Copland J. Steroid hormone influence on melanomagenesis. *Mol Cell Endocrinol* 2015;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, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer* 2008;112:1795–804.
11. Joosse A, de Vries E, Eckel R, et al. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. *J Invest Dermatol* 2011;131:719–26.
12. de Vries E, Nijsten TEC, Visser O, et al. Superior survival of females among 10,538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. *Ann Oncol* 2008;19:583–9.
13. Kvaskoff M, Bijon A, Mesrine S, et al. Cutaneous melanoma and endogenous hormonal factors: a large French prospective study. *Am J Epidemiol* 2011;173:1192–202.
14. Gandini S, Iodice S, Koomen E, et al. Hormonal and reproductive factors in relation to melanoma in women: current review and meta-analysis. *Eur J Cancer* 2011;47:2607–17.
15. IARC. Monographs - combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. CIRC; 2007. Report No.: vol 91. http://monographs.iarc.fr/ENG/Monographs/vol91/index.php
16. Ameye L, Antoine C, Paesmans M, et al. Menopausal hormone therapy use in 17 European countries during the last decade. *Maturitas* 2014; 79:287–91.
17. Ghazal S, Pal L. Perspective on hormone therapy 10 years after the WHI. *Maturitas* 2013;76: 208–12.
18. Bakken K, Fournier A, Lund E, 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;128:144–56.
19. James RE, Lukanova A, Dossus L, et al. Postmenopausal serum sex steroids and risk of hormone receptor-positive and -negative breast cancer: a

nested case-control study. *Cancer Prev Res* 2011;4: 1626–35.
20. Ritte R, Lukanova A, Berrino F, 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;14:R76.
21. Roura E, Travier N, Waterboer T, 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:e0147029.
22. Allen NE, Tsilidis KK, Key TJ, 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;172:1394–403.
23. Allen NE, Key TJ, Dossus L, 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;15:485–97.
24. Michaud DS, Gallo V, Schlehofer B, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. *Cancer Epidemiol Biomarkers* 2010;19:2562–9.
25. Hormonal contraception and post-menopausal hormonal therapy. CIRC; 1999. (IARC monographs of the evaluation of carcinogenic risks to humans). Report No.: 72. https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-49/
26. Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, et al. Postmenopausal hormone use and cutaneous melanoma risk: a French prospective cohort study. *Int J Cancer* 2019;145:1754–67.
27. Cervenka I, Mahamat-Saleh Y, Savoye I, et al. Oral contraceptive use and cutaneous melanoma risk : a French prospective cohort study. *Int J Cancer* 2018;143:2390–9.
28. Botteri E, Støer NC, Sakshaug S, et al. Menopausal hormone therapy and risk of melanoma: do estrogens and progestins have a different role? *Int J Cancer* 2017;141:1763–70.
29. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Exogenous hormone use: oral contraceptives, postmenopausal hormone therapy, and health outcomes in the nurses' health study. *Am J Public Health* 2016;106:1631–7.
30. Koomen ER, Joosse A, Herings RMC, et al. Estrogens, oral contraceptives and hormonal replacement therapy increase the incidence of cutaneous melanoma: a population-based case-control study. *Ann Oncol* 2009;20:358–64.
31. Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women: ovulatory life, menopause, and use of exogenous estrogens. *Cancer Epidemiol Biomark Prev* 1994;3:661–8.
32. Whiteman DC, Watt P, Purdie DM, et al. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* 2003;95:806–12.
33. Carli P, Palli D. Re: Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* 2003;95:1801 author reply 1801-1802.
34. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;5: 1113–24.
35. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007;26:2389–430.
36. Pintilie M. Analysing and interpreting competing risk data. *Stat Med* 2007;26:1360–7.
37. Gefeller O, Hassan K, Wille L. Cutaneous malignant melanoma in women and the role of oral contraceptives. *Br J Dermatol* 1998;138: 122–4.
38. Karagas MR, Stukel TA, Dykes J, et al. A pooled analysis of 10 case-control studies of melanoma and oral contraceptive use. *Br J Cancer* 2002;86: 1085–92.
39. Feskanich D, Hunter DJ, Willett WC, et al. Oral contraceptive use and risk of melanoma in premenopausal women. *Br J Cancer* 1999;81:918–23.
40. Donley GM, Liu WT, Pfeiffer RM, et al. Reproductive factors, exogenous hormone use and incidence of melanoma among women in the United States. *Br J Cancer* 2019;120:754–60.
41. Desai A, Ugorji R, Khachemoune A. Acral melanoma foot lesions. Part 1: epidemiology, aetiology, and molecular pathology. *Clin Exp Dermatol* 2017;42:845–8.
42. Tang JY, Spaunhurst KM, Chlebowski RT, et al. Menopausal hormone therapy and risks of melanoma and nonmelanoma skin cancers: women's health initiative randomized trials. *J Natl Cancer Inst* 2011;103:1469–75.
43. Simin J, Tamimi R, Lagergren J, et al. Menopausal hormone therapy and cancer risk: an overestimated risk? *Eur J Cancer* 2017;84:60–8.
44. Westerdahl J, Olsson H, Måsbäck A, et al. Risk of malignant melanoma in relation to drug intake, alcohol, smoking and hormonal factors. *Br J Cancer* 1996;73:1126–31.
45. Lea CS, Holly EA, Hartge P, et al. Reproductive risk factors for cutaneous melanoma in women: a case-control study. *Am J Epidemiol* 2007;165:505–13.
46. Richarz NA, Aguilera J, Castillo G, et al. Phototoxic reaction to a combined oral contraceptive (levonorgestrel/ethinylestradiol). *Photochem Photobiol Sci* 2017;16:1381–3.
47. Li W-Q, Qureshi AA, Ma J, et al. Personal history of prostate cancer and increased risk of incident melanoma in the United States. *J Clin Oncol* 2013;31: 4394–9.
48. Zhang M, Qureshi AA, Fortner RT, et al. Teenage acne and cancer risk in US women: a prospective cohort study. *Cancer* 2015;121:1681–7.
49. Liu-Smith F, Ziogas A. An age-dependent interaction between sex and geographical UV index in melanoma risk. *J Am Acad Dermatol* 2017. https://doi.org/10.1016/j.jaad.2017.11.049. [Epub ahead of print].