Menopausal hormone therapy and risk of cutaneous melanoma: Do estrogens and progestins have a different role?

*Botteri E[1,2], Støer NC[1], Sakshaug S[3], Graff-Iversen S[3], Vangen S[1], Hofvind S[2,4], Ursin G[2, 5, 6], Weiderpass E [2, 7, 8, 9] * contact information: elisabete.weiderpass@kreftregisteret.no*

1 National Advisory Unit for Women´s Health, Oslo University Hospital, Oslo, Norway; 2 Cancer Registry of Norway, Oslo University Hospital, Norway; Norwegian Institute of Public Health, Oslo, Norway; 4 Faculty of Health Science, Oslo and Akershus University Collage of Applied Sciences, Oslo, Norway; 5 Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Norway; 6 Department of Preventive Medicine, University of Southern California, Los Angeles, CA, US; 7 Department of Community Medicine, University of Tromsø, The Arctic University of Norway, Tromsø, Norway; 8 Department of Medical Epidemiology an Biostatistics, Karolinska Institute, Stockholm, Sweden; 9 Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland

The association between use of menopausal hormone therapy and risk of skin malignant melanoma is controversial

Materials and Methods

We followed a nationwide cohort of 684 696 Norwegian women aged 45-79 at baseline from 2004 to 2008. The study was based on the linkage of Norwegian population registries. Multivariable Poisson regression models were used to estimate the effect of hormone therapy (HT) use, different HT types, routes of administration and doses of estrogen and progestin on the risk of skin malignant melanoma (SMM).

800 948 women born in Norway between 1925 and 1959; registered in the Norwegian National Registry; alive and residing in Norway by 1st of January 2004

52 074 women excluded: history of cancer before 2004
2 442 women with any cancer or censored before 1st of April 2004

746 432 women free of cancer by 1st of April 2004

33 299 women excluded: used sex hormones different from estrogens (ATC code G03C) or estrogen plus progestin (ATC code G03F)

713 133 women without prescription for other sex hormones

28 430 women excluded with first and only prescription dated after 1st of July 2004
7 women excluded with erroneous date of first birth

684 696 women without prescriptions for other sex hormones

Results

During the median follow-up of 4.8 years, 26% (178 307) women used HT and 1 476 women had a diagnosis of SMM. HT users were more educated, more likely to be married, less likely to be nulliparous, and more likely to have 2 children compared to non-users of HT. Estrogen therapy (ET) users were older, resided in areas with less sun exposure and had more children compared to users of estrogen-progestin therapy (EPT) and tibolone users.

Table 2. Current estrogen (ET) and estrogen-progestin therapy (EPT) use and risk of melanoma according to some population characteristics

	ET RR (95% CI)	EPT RR (95% CI)
Age		
45-53	1.83 (1.18-2.83)	1.30 (0.82-2.08)
54-62	1.62 (1.20-2.18)	0.89 (0.60-1.33)
63-79	1.34 (1.02-1.74)	0.68 (0.37-1.24)
Sun exposure		
Low	1.03 (0.64-1.66)	1.12 (0.62-2.01)
Medium	1.67 (1.31-2.13)	1.01 (0.70-1.44)
High	1.35 (097-1.88)	0.67 (0.39-2.84)
Age at first birth		
No child	1.46 (0.83-2.60)	0.79 (0.32-1.94)
< 21	1.67 (1.17-2.39)	1.04 (0.61-1.79)
22-25	1.44 (1.05-1.97)	1.07 (0.68-1.66)
> 25	1.32 (0.96-1.82)	0.61 (0.33-1.11)
Education		
Elementary school	1.40 (0.97-2.02)	1.07 (0.62-1.83)
High school	1.43 (1.11-1.84)	0.86 (0.59-1.25)
University or higher	1.54 (1.07-2.23)	0.90 (0.52-1.55)

Mutually adjusted in addition to adjustment for parity, marital status, use of antihypertensives, antidiabetics, statins and thyroid therapy;
ET – estrogen therapy, EPT – estrogen-progestin therapy, RR – incidence ratio, CI – confidence interval.

Table 1. Current use* of hormone therapy (HT) and risk of malignant melanoma of the skin

		All women		
		PY	Cases	RR (95% CI)
Status	Non-use	2 451 037	1 113	Ref
	Current use	450 912	248	1.19 (1.03-1.37)
	Past use	240 929	115	1.00 (0.82-1.21)
	Ever use	691 840	363	1.12 (0.99-1.26)
HT-type	Non-use	2 451 037	1 113	Ref
	Estradiol	152 488	107	1.48 (1.21-1.81)
	Estriol	38 309	28	1.33 (0.91-1.95)
	ET**	190 797	135	1.45 (1.21-1.73)
	Tibolone	29 705	19	1.39 (0.88-2.18)
	EPT	140 204	57	0.91 (0.70-1.19)
	Others	90 205	37	0.94 (0.68-1.31)
Type of combined regimen	Non-use	2 451 037	1 113	Ref
	Continuous EPT	119 981	44	0.80 (0.59-1.09)
	Sequential EPT	20 223	13	1.70 (0.98-2.94)
	Others	310 707	191	1.31 (1.12-1.52)
Route	Non-use	2 451 037	1 113	Ref
	ET** oral	68 848	49	1.45 (1.09-1.93)
	ET** vaginal	103 050	74	1.44 (1.14-1.84)
	Estradiol transdermal	11 267	5	1.01 (0.42-2.42)
	EPT oral	137 068	55	0.90 (0.69-1.18)
	EPT transdermal	2 232	2	2.00 (0.50-8.00)
	Others	128 447	63	1.11 (0.86-1.43)
Oral dose unit increase	Estrogen 1 mg/day			1.24 (1.00-1.53)
	Progestin 10 mg/month			0.71 (0.57-0.89)

*All RRs were adjusted for age, number of children, age at the first birth, , highest education, marital status, sun exposure, use of antihypertensives, antidiabetics, statins, thyroid therapy as ever use during follow-up; PY – person-years, RR – incidence rate ratio, CI – confidence interval, ET – estrogen therapy, EPT – estrogen-progestin therapy, *Except for past and ever use status, **Estradiol and estriol combined.*

Norwegian Prescription Database

We retrieved all prescriptions of sex hormones with anatomical therapeutic chemical (ATC) codes G03C and G03F prescribed between 2004-2008.
Total number of treatment days was calculated for each drug by multiplying package size by number of packages prescribed regarding the dosing intervals. Gaps between prescriptions shorter than 4 months were considered as continuous use.
All EPT use included estradiol and norethisterone acetate as other progestins are almost non-existing in Norway.

Sun exposure

Sun exposure on county-level in 16 of 19 Norwegian counties expressed as the yearly sum of erythemally weighted UV radiation (ERY), and was available from 1957 to 2005. The yearly ERY was quite stable and the value in 1980, the midpoint, was chosen. ERY in missing counties was estimated by the mean of exposures in the neighbouring counties.

Conclusion

Estrogens were associated with an increased risk of SMM, while combinations of estrogens and progestins were not. Oral estrogens increased, and oral progestins decreased the SMM risk in a dose-response analysis. Estrogens and progestins might affect the risk of SMM in opposite ways