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Hormonal and reproductive factors in relation to melanoma in women: Current review and meta-analysis

Sara Gandini [a,*], *Simona Iodice* [a], *Els Koomen* [b], *Alessandra Di Pietro* [c], *Francesco Sera* [d], *Saverio Caini* [e]

[a] *Division of Epidemiology and Biostatistics, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy*
[b] *Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands*
[c] *Division of Sarcoma and Muscolo Cutaneous Melanoma, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy*
[d] *Medical Research Council Centre of Epidemiology for Child Health, University College London Institute of Child Health, London, UK*
[e] *Molecular and Nutritional Epidemiology Unit, ISPO, Scientific Institute of Tuscany, Via di San Salvi 12, 50135 Florence, Italy*

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ABSTRACT

A number of studies have focused on possible relationships between characteristics of female endocrine status and melanoma (CM) risk; however, the link between melanoma, oral contraceptive (OC) and hormonal replacement therapy (HRT) use, and reproductive factors remains controversial. A comprehensive, systematic bibliographic search of the medical literature was conducted to identify relevant studies. Random effects models were used to summarise results. Subgroup, meta-regression and sensitivity analyses have been carried out to explore sources of between-study variation and bias. We included thirty-six observational studies published in the last 30 years. Summarising a total of 5626 melanoma cases, we did not find any significant melanoma risk associated with OC and HRT use. Several reproductive factors were also investigated, summarising data on 16787 melanoma cases. We found a significantly increased melanoma risk for late age at first birth, and women with more than one child may be at a lower risk for melanoma; however, socio-economic confounders were found to play a significant role in explaining this association. This study confirmed no increased risk of CM with the use of oral contraceptives and hormone replacement therapy: exogenous female hormones do not contribute to an increased risk of CM. In contrast, significant associations of CM with parity and age at first pregnancy were observed in this meta-analysis finds and warrant further research.

1. Introduction

A number of epidemiological studies from the 1980s focused on possible relationships between characteristics of female endocrine status and melanoma (CM) but substantial controversy exists on potential hormonal effects on melanoma risk. The original concerns arose from some case reports of CM in pregnancy and the observation of hyperpigmentation during OC use and reports of nevi darkening and enlarging during pregnancy.[1–3]

Additionally, animal experiments have shown increases in melanin production or melanocyte number in association with oestrogens and oestrogens/progesterone combinations.[4,5]

Moreover, the influence of female sex steroids on melanoma is supported by several observational studies. Incidence

* *Corresponding author:* Tel.: +39 02 57489819; fax: +39 02 57489922.
E-mail address: sara.gandini@ieo.it (S. Gandini).
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trend studies have shown that until the age of 45 years, CM incidence rates in women exceeded those in men, after which the incidence rates in men rose markedly but levelled off in women, which may suggest hormonal or reproductive influences.[12–15]

Although the average age at diagnosis of CM is around 60 years, about one-third of all CM in women occurs during their childbearing age and, in women aged 25–29 years, CM is the most common malignancy.[16] Moreover, women with a history of breast cancer have been reported to be at higher risk for CM and vice versa.[14,17–20]

A number of studies from the 1980s focused on possible relationships between characteristics of female endocrine status and the risk of CM. [21,22,39,40,41] The studies included questions about the use of oral contraceptives (OC), hormone replacement therapy (HRT), parity and age at first child, age at menarche, menopausal status and age at menopause or infertility drugs that reflect influences of exogenous and endogenous hormones, respectively. However, the link between CM and pregnancy, hormonal and reproductive factors remains controversial.

Cancers sensitive to female sex steroids are associated with several risk factors, [6–11] such as low parity, infertility, early age at menarche, and late age at menopause. These factors frequently coexist in infertile patients and some studies suggested that different infertility causes could be involved in cancer risk development.[23] Furthermore, the influence of fertility drugs on malignant melanoma risk has not been widely studied despite the wide use of this group of exogenous hormones over the last 30 years and their recognised effect on ovulation and endogenous hormone production.[24] Given the increasing number of prescriptions of fertility drugs among infertile couples over the last 30 years, the question of whether fertility drugs may increase malignant melanoma risk is of great public health concern.

The aim of this paper is to review these issues using meta-analyses and evidence-based approaches. Dose–response models through meta-analytic approach allow investigation of different types of exposure: duration, age at exposure and time since first and last exposure.

Two meta-analyses and a pooled-analysis were published on OC use and a pooled-analysis on reproductive factors investigating the associations with CM risk.[25–27] Since these analyses, additional evidence has become available (include Refs. of studies not included in the above analyses). Moreover, previously published analyses did not include cohort studies, small studies and/or publications based on information from postal questionnaires.

To update previous meta-analyses and in order to also include cohort studies, small studies and/or publications based on information from postal questionnaires, we carried out an evidence-based systematic review and meta-analysis of all the literature to obtain an overall picture considering both exogenous and endogenous hormones, including evaluations on the effect of HRT use, menopausal status and menarche. Using dose–response models has allowed the investigation of different types of exposure: duration, age at exposure and time since first and last exposure. By including all possible studies we aim to avoid selection bias, publication bias and to quantitatively explore any possible similarities, inconsistencies and conflicting results due to imprecise estimation of risk (e.g. due to small sample size), inadequate study design or adjustments for potential confounding factors.

In this meta-analysis we will investigate associations between the incidence of cutaneous melanoma and the use of exogenous hormones, oral contraceptives (OC), hormonal replacement therapy (HRT), reproductive factors, including age at menarche, fertility, use of fertility drugs, parity, menopausal status and age at menopause.

2. Materials and methods

We planned, conducted and reported this systematic literature search and review following *MOOSE* guidelines regarding meta-analysis of observational studies.[28]

2.1. Data sources and search strategy

We reviewed published reports using validated search strategies[29,30] from these databases:

- PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi).
- Ovid MEDLINE® database (1950 to July 2009)
- ISI Web of Science® Science Citation Index Expanded™ (SCI Expanded)

The following keywords and/or corresponding MESH terms were used: melanoma, skin cancer, oral contraceptive, hormonal replacement therapy, oestrogens, pregnancy, parity, fertility, menarche and menopause. Additional studies were collected through cross-referencing of reference lists of the retrieved articles and preceding reviews and conference abstracts on the topic. The search was limited to human studies. No language or time restrictions were applied.

2.2. Data extraction

Data were extracted and cross-checked independently by two investigators (S.C. and S.G). Any disagreement was resolved by consensus among them. The following information from the published papers was extracted and coded: authors, year of publication, study period, type of study design, country, number of cases, number and sources of controls, features of included subjects or populations, use of matching in study design, definitions of exposure, and adjustments used for statistical analyses.

We used wide inclusion criteria in order to select studies with necessary information and to be able to investigate between-study variability:

(1) Study publications should contain the minimum information necessary to obtain comparable risk estimates and corresponding 95% confidence intervals (i.e. odds ratios or relative risks and a measure of uncertainty: standard errors, variance, confidence intervals or exact *P*-value of the significance of the estimates).
(2) The studies should be independent to avoid giving double weight to a single study. In case of multiple reports

of the same study, we considered the estimates from the most recent publication.

If multiple risk estimates were available for one item within a study, for example several estimates for different types of exposure measures or sources of data (e.g. types of drug fertility or data from questionnaires and from GPs), we included only one of those estimates, and chose to include the RR estimate showing the strongest association. In sensitivity analyses, we evaluated these choices.

2.3. *Definition of the outcome and exposures*

The main outcome of this systematic meta-analysis was risk estimates for incidence of histological confirmed CM.

We retrieved exposure data for: ever OC and HRT users but also dose–response estimates for duration of use, age and time since first use and since last use. We also retrieved data for parity, age at first child (or pregnancy), menopausal status, age at menopause, age at menarche, exams for fertility and use of fertility drugs. Finally, we reviewed and extracted risk estimates for the association between pregnancy and CM recurrence and mortality.

2.4. *Statistical analysis*

All measures of association and the corresponding confidence intervals, adjusted for the maximum number of confounding variables available, were translated into log relative risk, and corresponding variance, with the formula proposed by Greenland.[31]

We used random effects models, taking into account between-study and within study variability when more than one estimate from a single study was used. Summary relative risks (SRR) were obtained from maximum likelihood estimate: PROC MIXED in SAS.[32]

Homogeneity of effects across studies was assessed using the Chi-square statistic and quantified by I^2, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.[33,32]

Since the Chi-square test has limited power, we considered statistically significant heterogeneity at the $P = 0.10$ level of association. Between-study heterogeneity was investigated by sub-group analyses and meta-regressions.[34]

For dose–response, duration and time-dependent estimates we extracted RRs and frequencies for each category of exposure and we used linear models, within each study, taking into account correlation within RRs having the same reference category. We obtained the summary RR pooling the study-specific estimates by random effects models.[35]

Sensitivity analysis was carried out to evaluate whether results were influenced by a single study. A funnel-plot-based approach was used for assessing publication bias evaluating regression of log(RR) on the sample size, weighted by the inverse of the variance.[36]

We presented results exploring for any publication bias if heterogeneity (I^2) was not larger than 60% and if studies with significant results were present.

3. Results of meta-analysis

The analysis based on 36 independent publications between 1977 and 2009 was conducted on two main groups of risk factors: exogenous hormones use and reproductive factors. To evaluate the effect of oestrogens we considered OC and HRT use, time since first and last use, and age at first OC use. To assess the effect of reproductive factors we investigated parity, age at first pregnancy, age at menarche, menopausal status and age at menopause, and history of problems of fertility.

We retrieved 25 estimates:

- Twenty-two on OC and 10 on HRT 'ever use', time and age since first and last exposure and duration (two studies did not publish the estimate for 'ever use');
- Twenty-four on reproductive factors (18 on parity, 8 on age at first pregnancy, 7 on evaluation for infertility, 3 on fertility drugs, 6 on menopausal status and 3 on age at menopause, 7 on age at menarche).

We found 6 cohort studies for exogenous hormones use and 7 for reproductive factors. Among the remaining 16 case-control studies on oestrogens, 11 were population based; among the 17 case-control studies on reproductive factors, 12 were population based. From Europe, we retrieved 10 estimates for exogenous hormones use and 9 for reproductive factors (Tables 1 and 2).

Summary estimates for different types of exposure ('ever' versus 'never', 'highest' versus 'lowest' categories, dose–response and time-dependent evaluations) were presented in Table 3.

Forest plots are presented for the risk factors and comparisons with the highest number of studies: 'ever use' of OC and HRT and parity.

3.1. *Exogenous hormones' use*

This meta-analysis, evaluating a total of 5626 CM cases with information on exogenous hormones' use, confirmed that OC

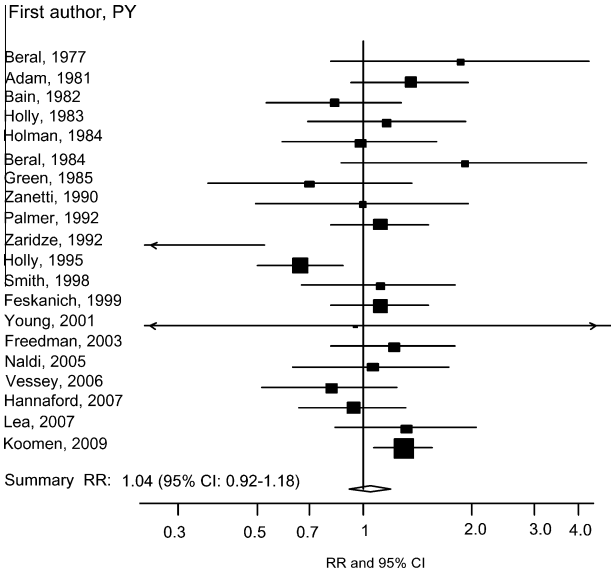

Fig. 1 – Forest plot of OC use and melanoma risk.

Table 1 – Included studies for oral contraceptive (OC) and hormone replacement therapy (HRT).

First author, PY	Study design	Country	N. cases	N. contr.[a]	Match	Source of controls	OC or HRT estimates[b]	Adjust. for pheno-photo types[c]	Adjust. for sun-exposure[d]
Beral, 1977[66]	CC	US	37	74	Yes	Hosp	OC		
Adam, 1981[67]	CC	UK	169	507	Yes	Pop	OC		
Bain, 1982[68]	NCC	US	141	2820		Pop.	OC		
Holly, 1983[69]	CC	US	87	863	Yes	Pop	OC, HRT		
Beral, 1984[70]	CC	Australia	287	574	Yes	Hosp	OC, HRT		
Holman, 1984[71]	CC	Australia	276	276	Yes	Pop	OC	Yes	Yes
Green, 1985[72]	CC	Australia	91	91	Yes	Pop	OC		
Osterlind, 1988[3]	CC	Denmark	280	536	Yes	Pop	HRT	Yes	Yes
Adami, 1989[73]	Cohort	Sweden	31	23244			HRT		
Zanetti, 1990[74]	CC	Italy	186	205	Yes	Pop	OC	Yes	Yes
Lê, 1992[75]	CC	France	91	149	Yes	Hosp	OC[e]	Yes	Yes
Palmer, 1992[76]	CC	US	615	2107	Yes	Hosp	OC	Yes	
Zaridze, 1992[77]	CC	Russia	96	96	Yes	Hosp	OC	Yes	
Holly, 1994[46]	CC	US	452	930	Yes	Pop	OC, HRT		
Persson, 1996[78]	Cohort	Sweden	60	22597			HRT		
Smith, 1998[79]	CC	US	308	233	Yes	Pop	OC	Yes	Yes
Westerdahl, 1996[80]	CC	Sweden	400	640	Yes	Pop	OC[e]	Yes	Yes
Feskanich, 199944	Cohort	US	146	183693			OC	Yes	Yes
Young, 2001[81]	NCC	Australia	14	93			OC		
Freedman, 2003[82]	Cohort	US	207	54045			OC, HRT	Yes	Yes
Naldi, 2005[83]	CC	Italy	316	308	Yes	Hosp	OC, HRT	Yes	Yes
Vessey, 2006[84]	Cohort	UK	94	17032			OC		
Hannaford, 2007[85]	Cohort	UK	146	28762			OC		
Lea, 2007[86]	CC	US	318	395	Yes	Hosp	OC, HRT	Yes	
Koomen, 2009[37]	CC	The Netherlands	778	4072	Yes	Pop	OC, HRT		

CC: case-control study. NCC: nested case-control study (case-cohort studies were codified as NCC). PY: publication year. Hosp: Hospital-based controls. Pop: population-based controls. Adjust. RRs adjusted for confounders.

[a] For cohort study we presented the overall study size.

[b] Including 'ever use', duration, age at first use and time since first and last use.

[c] Including naevi counts.

[d] Including sunburns.

[e] The authors reported estimates only for OC duration.

and HRT are not associated with a significant increase in CM risk (Table 3). SRR for 'ever use' was: 1.04 (95%CI: 0.92, 1.18; heterogeneity $P = 0.03$) for OC and 1.16 (95%CI: 0.93, 1.44; heterogeneity $P = 0.05$) for HRT. Dose–response models also indicated no significant increases in CM risk for OC or HRT use (for each 10 years of use of OC: 1.10, 95%CI: 0.88, 1.37; and for 5 years of use of HRT: 1.36, 95%CI: 0.65, 2.84). Furthermore, the summary estimates of age at first OC use and time since first and last OC confirmed no effect of OC on CM risk.

Only four studies, evaluating OC, presented mean age of cases: three out of four were below 40 years, and only one was 54 years.[37]

Forest plots for OC and HRT 'ever use' are presented in Figs. 1 and 2.

3.2. *Reproductive factors*

Several reproductive factors were also investigated, summarising data on 16787 CM. Summary estimates for menopausal status, age at menopause, age at menarche and exams for fertility showed that these factors were not associated with CM (Table 3).

The only factor that at a first look seemed significantly associated with CM risk is age at first pregnancy which showed an increase in risk of 10% for first pregnancy at 30 years of age, compared to pregnancy at 20 years of age or earlier.

Among reproductive factors the significant heterogeneity was found only for parity and age at first birth (Chi-square $P = 0.03$ and 0.06, respectively).

3.3. *Heterogeneity and sensitivity analyses*

Investigation of heterogeneity was carried out for factors with the highest number of studies that allowed subgroup and meta-regression analyses, looking at all the factors that could have an impact on the between-study variability.

In Table 4 we presented factors that explained some heterogeneity. Study design and country significantly explained heterogeneity for parity. Cohorts and population based case-control studies presented significantly lower estimates ($P = 0.004$) than hospital-based case-controls studies: for women with 2 children in population-based studies we obtained a reduction of 11% (95%CI: 6–16%) compared to nulliparous women, whereas hospital-based studies suggest a significant increase in risk. Furthermore, in European countries we observed significantly lower estimates than the other countries ($P < 0.001$); we estimated a significant 15% (95%CI:

Table 2 – Included studies for reproductive factors.

First author, PY	Study design	Country	N. cases	N. contr.	Match	Source controls	Age at menarche	Parity	Age at first pregnancy	Fertility exams[a]	Menop. [b]	Adjust. for pheno-photo types[c]	Adjust. for sun-exposure[d]	Adjust for educ.
Holly, 1983[69]	CC	US	87	863	Yes	Pop		X	X					Yes
Holman, 1984[71]	CC	Australia	276	276	Yes	Pop	X	X						
Gallagher, 1985[87]	CC	Canada	361	361	Yes	Pop		X				Yes		Yes
Green, 1985[72]	CC	Australia	91	91	Yes	Pop	X	X			X	Yes	Yes	
Osterlind, 1988[3]	CC	Denmark	280	536	Yes	Pop	X	X	X		X	Yes	Yes	
Brinton, 1989[88]	Cohort	US	4	2335						X				
Wyshak, 1989[89]	NCC	US	18	72		Pop				X				
Zanetti, 1990[74]	CC	Italy	186	205	Yes	Pop		X	X			Yes	Yes	
Lê, 1992[75]	CC	France	91	149	Yes	Hosp	X	X				Yes	Yes	
Holly, 1994[46]	CC	US	452	930	Yes	Pop	X				X			
Holly, 1995[90]	CC	US	452	930	Yes	Pop		X						Yes
Rossing, 1995[91]	NCC	US	12	135		Hosp				X				
Lambe, 1996[92]	CC	Sweden	4779	23888	Yes	Pop		X	X					
Westerdahl, 1996[80]	CC	Sweden	400	640	Yes	Pop		X				Yes	Yes	
Modan, 1998[93]	Cohort	Israel	8	2496						X				
Smith, 1998[79]	CC	US	308	233	Yes	Hosp		X	X		X	Yes	Yes	
Young, 2001[81]	Cohort	Australia	14	3186			X	X	X	X				
Freedman, 2003[82]	Cohort	US	153	54045			X	X			X	Yes	Yes	Yes
Neale, 2005[94]	Cohort	Sweden	2285	1234967				X	X					
Althuis, 2005[95]	Cohort	US	42	8422						X				
Naldi, 2005[83]	CC	Italy	316	308	Yes	Hosp		X	X		X	Yes	Yes	Yes
Kaae, 2007[96]	Cohort	Denmark	5688	1725627				X						
Lea, 2007[86]	CC	US	318	395	Yes	Hosp		X				Yes		Yes
Hannibal, 2008[97]	NCC	Denmark	112	1226		Pop		X		X				

CC: case-control study. NCC: nested case-control study (case-cohort studies were codified as NCC). Hosp: Hospital-based controls. Pop: population-based controls. Menop: Menopausal status. PY: publication year. Adjust. RRs adjusted for confounders. Ca. cases. Co. controls, but for cohort study we presented the overall study size. Educ. Educational factors.

[a] Including use of fertility drugs.

[b] Including age at menopause.

[c] Including nevi counts.

[d] Including sunburns.

Table 3 – Summary relative risks estimates for CM in women.

N. studies	Risk factors	SRR (95%CI)	I^2
Oral contraceptive (OC)			
20	Ever versus never	1.04 (0.92, 1.18)	42
17	Duration: (each year of use)	1.01 (0.99, 1.03)	45
3	Age at first use: ' ⩾ 25 y' versus never	1.03 (0.91, 1.17)	0
3	Age at first use (each year of older age)	1.01 (0.99, 1.02)	0
4	Time since first use: ' ⩾ 20' versus never	0.90 (0.46, 1.78)	74
4	Time since first use (each year since first use)	1.00 (0.97, 1.02)	74
6	Time since last use: ' ⩾ 10 y' versus never	0.85 (0.53, 1.38)	76
6	Times since last use: (each year since last use)	0.99 (0.97, 1.02)	76
Hormonal replacement therapy (HRT)			
10	'Ever use' versus never	1.16 (0.93, 1.44)	47
4	Duration: (each year of use)	1.06 (0.92, 1.23)	63
Reproductive factors			
7	Age at menarche: (each year of older age at menarche)	1.01 (0.99, 1.02)	19
7	Evaluation for fertility: ever versus never	1.23 (0.87, 1.75)	33
3	Use of fertility drugs	1.17 (0.57, 2.39)	17
8	Age at first pregnancy: (each year of older age at first pregnancy)	1.011 (1.008, 1.013)	51
18	Parity (one more child)	0.98 (0.91, 1.06)	55
6	Menopausal status: pre versus post	1.09 (0.78, 1.52)	0
3	Age at menopause: (each year of older age at menopause)	1.00 (0.97, 1.02)	34

RRs for +1 y are summary estimates from dose–response models. Median reference categories among studies were: 45 years for age at menopause; 20 years for age at I pregnancy; 12 for age at menarche.

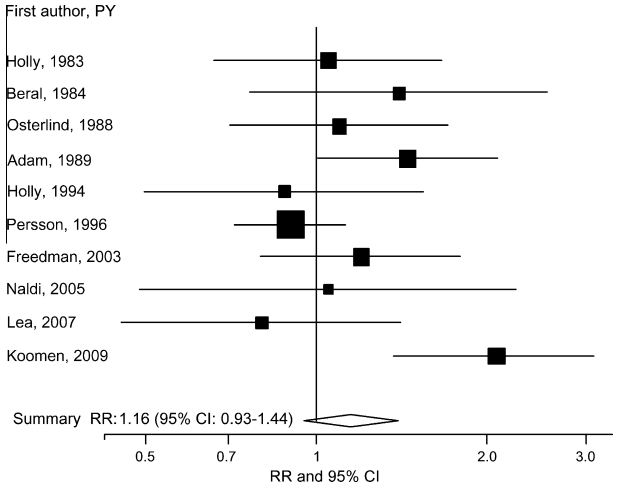

Fig. 2 – Forest plot of HRT use and melanoma risk.

11–18%) decrease in risk for women with 2 children in European countries compared to nulliparous women. No reduction was observed for the non-European countries.

Looking at the types of adjustments we found that estimates for parity, adjusted for education, one of the most important confounder for parity, were significantly greater ($P = 0.03$) suggesting no association with melanoma: the indication for an effect comes mainly from unadjusted estimates.

Forest plot for parity is presented by subgroups considering factors explaining between-study heterogeneity (Fig. 3).

None of the factors investigated significantly influenced risk estimates of age at first birth.

The only factor that explained some variability in the estimates for OC ('ever use') was adjustments for confounders: unadjusted relative risks were borderline significantly greater than adjusted estimates ($P = 0.09$): again the suggestion for an association comes mainly from unadjusted estimates.

Sensitivity analysis showed that heterogeneity for 'ever use' of OC is mainly due to a Russian hospital based case-control study[38] that published a highly significant protective effect for OC 'ever use': OR = 0.04 (95%CI: 0.003, 0.53). Excluding this publication, the summary estimate does not change: SRR = 1.05 (95%CI: 0.92, 1.19) and the heterogeneity decreased considerably (Chi-Square $P = 0.09$ and $I^2 = 33$).

If more than one estimate was presented by the authors, we carried out sensitivity analyses to include the available risk estimates. This did not change any of the conclusions. For example, for fertility drug use we did not observe an increased risk and no heterogeneity was present: SRR = 0.95 (95%CI: 0.43, 2.13) with $I^2 = 0$. For all end-points evaluated, none of the factors was associated with between-study heterogeneity; however, it is interesting to note that SRR for HRT 'ever use' adjusted for sun exposure and/or phenotypical factors were lower than estimates not adjusted for those factors: SRR = 1.05 (95%CI: 0.76, 1.44) for the 4 adjusted estimates and SRR = 1.22 (95%CI: 0.97, 1.52) for the unadjusted estimates, although this difference was not statistically significant ($P = 0.45$). On the other hand, the SRR for the 7 estimates on parity adjusted for sun exposure were virtually identical to the one summarising the unadjusted estimates: SRR = 0.94 (95%CI: 0.88, 1.01) and SRR = 0.97 (95%CI: 0.93, 1.00), respectively.

No indication for publication bias was found ($P = 0.25$ for OC 'ever use'; $P = 0.87$ for HRT use; $P = 0.72$ for age at first pregnancy and $P = 0.78$ for parity).

4. Conclusion

In this meta-analysis, we could not confirm an increased CM risk with the use of oral contraceptives and hormone replace-

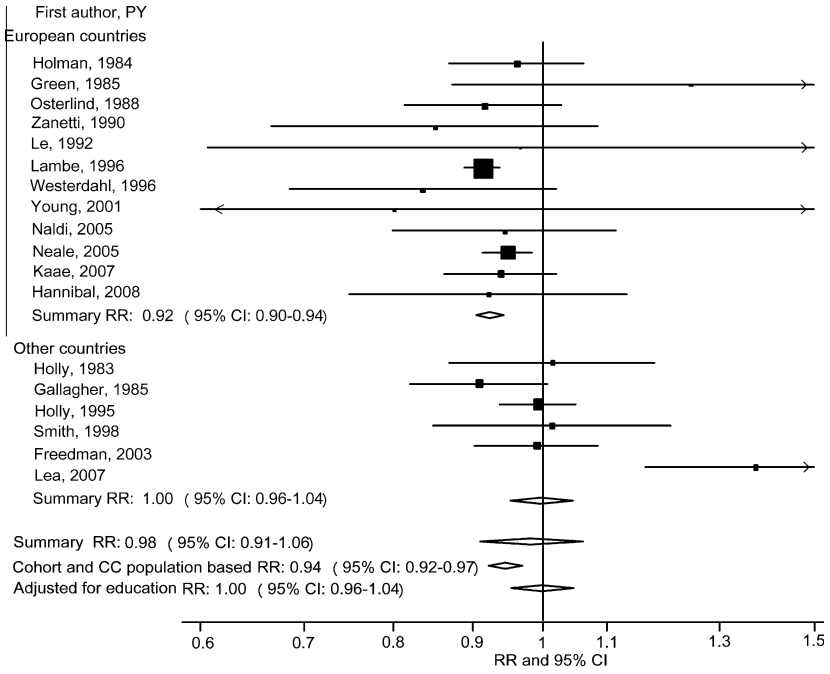

Fig. 3 – Forest plot of parity and melanoma risk.

Table 4 – Heterogeneity analyses: summary relative risks estimates by subgroup analyses.

N. studies	Subgroups	SRR 95%CI	P-value
Parity (+1 child)			
4	Hospital-based CC	1.10 (1.00, 1.22)	0.004
14	Pop. based CC or cohorts	0.94 (0.92, 0.97)	
9	In Europe	0.92 (0.90, 0.94)	<0.001
9	Other countries	1.00 (0.96, 1.04)	
12	RRs unadjusted for education	0.93 (0.91, 0.95)	0.003
6	Adjusted for education	1.00 (0.96, 1.04)	
Oral contraceptive ('ever use')			
15	Adjusted RRs[a]	1.00 (0.88, 1.14)	0.09
5	Crude RRs	1.32 (0.97, 1.79)	

CC: case-control study. P-values for the difference between groups obtained from meta-regression analysis.
[a] Adjustment for confounding factors.

ment therapy. To conclude: exogenous female hormones do not significantly contribute to the risk of developing CM. Simultaneously, this meta-analysis shows significant associations between CM risk and parity as well as age at first pregnancy. However, this may be caused by socio-economic differences.[65] Further research is required among women with more than one child and early pregnancy who may be at lower risk for CM either causally or due to confounding biases.

5. Discussion

A number of studies suggest a potential role of female hormones in the pathogenesis of melanoma among women. The studies included questions about the use of OC and postmenopausal oestrogen therapy, parity and age at menarche, menopause, and first childbirth, which reflect influences of exogenous and endogenous hormones. This analysis reviewed all the evidence using meta-analyses to summarise the estimates and understand variations in results. We wanted to update previous meta-analyses on OC and pooled-analysis on reproductive factors and present an overview of the evidence about the effects of endogenous and exogenous hormones on the development of CM.

Two previous meta-analyses and a pooled analysis of case-control studies concluded that OC use does not affect a woman's risk of CM.[25–27]

Our summary estimates, updating the previous meta-analyses, confirmed their conclusions: no increased risk of CM was found with ever-use of OC, duration of use, age at first use, and time since first and last use.

The main limitation of this analysis on CM and OC use is that we could not take into account oral contraceptive formulations used: during the 80s OCs deeply differed from the ones used later on, e.g. low oestrogen, triphasic. However, in the

Nurses Health Study[44] an elevated non-significant risk of melanoma was found in relation to the current but not past use of oral contraceptives and when we investigated the influence of publication year we did not find any significant trend.

In order to verify if an increased RR for use of OC could be identified for specific subgroups of patients, e.g. those diagnosed at a younger age, but mean age of cases in our meta-analysis was 41 years.

For HRT use we were able to obtain summary estimates for 'ever use' and duration of use, and we did not find significant associations; however, we were not able to obtain summary RRs for the time since menopause and age at start of therapy. Vandenbroucke[45] commented on the different results obtained from clinical trials and observational studies on HRT and breast cancer risk and suggested that the time since menopause should be the key point. In fact, shorter time since menopause increased the risk of HRT. The authors of a population-based study carried out in the San Francisco Bay Area did not find any trend effect on melanoma risk for time elapsed between menopause and first exogenous hormones use.[46]

Furthermore, if there is a risk it should be found in observational studies, summarised in this meta-analysis, because HRT is usually started close to menopause. Therefore, this should not be a major issue.

The previous pooled-analysis[47] summarising results of case-controls studies on pregnancy history showed that age at first birth and parity may play a role in risk of CM in women: they found a significant trend ($P = 0.02$) for number of live births (OR = 0.94, 95%CI: 0.89–0.99) and detected a significant reduced risk of melanoma among women with both earlier age at first birth (<20 years versus $\geqslant$25) and higher parity ($\geqslant$5 children), adjusting for socio-economic status.

For reproductive factors in the present work, we summarised information from eight studies that published data on age at pregnancy and we found that a 10-year increase in age at first pregnancy statistically increases the risk for CM by about 10%. Furthermore, investigating between-study heterogeneity of risk estimates among the eighteen studies presenting estimates for parity, this work shows that the studies with the best study design (cohort studies and population-based case-control studies) significantly differ from the others, suggesting a protective effect of parity. Similar differences were found when examining the country where the studies were conducted: studies carried out in Europe suggest a significant reduction in risk of about 15% for women with 2 children compared to nulliparous women. All these results are suggestive of an apparent protective effect of multiparity that could have an immunological background.[47] This negative association, however, may also reflect confounding by socio-economic status. In fact, heterogeneity analysis showed the significant effect of adjustment for education on estimates for parity. Residual confounding could also be due to sun exposure due to more modest sunbathing habits among mothers of many children; however, estimates adjusted for sun exposure were virtually identical to the unadjusted ones.

A previous pooled-analysis of case-controls[47] also investigated associations with fertility treatments and found no effect. Three studies published estimates on the effect of drugs for fertility and seven studies presented RRs for women with fertility problems, and possibly taking some treatments. Findings from the present meta-analysis confirmed previous results: fertility investigations/treatments were not found to be significantly associated with increased CM risk.

The issue of the relationship between hormones and cancer in humans is a rather wide field. Several publications have led to the hypothesis that reproductive events or hormonal exposures could explain gender differences in cancer susceptibility and mortality. Increasing parity is associated with reduced risks of breast and ovarian cancer, in the general female population and also in high-risk women.[48–50] A protective effect of parity for lung cancer has been observed in several countries.[51–54]

Prior studies have also reported inverse associations between increasing parity, younger age at first birth and older age at first birth and the risk of pancreatic cancer.[55–57]

Some clinical studies[58,59] showed that pigmentary and nevi changes occur during pregnancy, while experimental animal studies confirmed increased pigmentation, melanocytic proliferation, and tumour growth followed oestrogen administration.[25,47,60,61]

Observational studies suggest that the pattern of age-incidence rates of melanoma in women resembles that of breast cancer: they are higher in women than in men especially before age 45 years, and afterwards, differently from men, rates of increase slow down.[43] Furthermore, a higher risk of breast cancer among women with a history of melanoma and excess melanoma risk among breast cancer cases have been reported in several studies.[18–20,62–64]

This study confirmed no increased risk of CM for use of oral contraceptives and hormone replacement therapy: exogenous female hormones do not contribute significantly to increased risk of CM. On the other hand, this meta-analysis found significant associations of CM with parity and age at first pregnancy that requires further research.

Our findings supporting the hypotheses that pregnancy related factors could be causally linked with CM risk require further research.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.04.023.

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