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*Original Article*

# Age at first birth and melanoma risk: a meta-analysis

Zhengyong Li[1*], Mingjin Gu[2*], Ying Cen[1]

*[1]Department of Burns and Plastic Surgery, [2]Mental Health Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China. [*]Equal contributors.*

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**Abstract:** Age at first birth has been shown to be correlated with melanoma risk, but the results were inconsistent. Thus, a meta-analysis was undertaken to evaluate the relationship between age at first birth and melanoma risk. Studies published up to September 6, 2014 were identified through searches of PubMed and EMBASE databases. Random-effect model was used to pool the study-specific risk estimates (RRs) with 95% confidence intervals (CIs). Three case-control, three nested case-control, and five cohort studies were found to be eligible. In a comparison of the oldest versus youngest age at first birth, the pooled RR for melanoma risk was 1.47 (95% CI: 1.07-2.02) in all studies, 1.37 (95% CI: 0.47-4.02) in population-based case-control studies, 2.69 (95% CI: 1.56-4.64) in hospital case-control studies, 1.38 (95% CI: 0.66-2.88) in nested case-control studies, and 1.39 (95% CI: 0.89-2.17) in cohort studies. In the subgroup analysis according to sites where studies were performed, the pooled RR was 1.44 (95% CI: 0.99-2.08), 1.18 (95% CI: 0.30-4.60), and 2.36 (95% CI: 1.42-3.93) for Europe, Americas, and Australia, respectively. In the subgroup stratified by whether the included study provided adjustment for specific potential confounders or important risk factors, the relationship between age at first birth and melanoma risk was significantly modified by age, naevi/pigmentation, sunlight exposure, and hair colour. This meta-analysis based on available observational data reveals that age at first birth is positively associated with melanoma risk. However, this finding should be interpreted cautiously, as residual confounding cannot be excluded. More investigations with well-designed are warranted to extend this finding.

**Keywords:** Melanoma, hormone, birth, reproductive history, meta-analysis

## Introduction

Melanoma is a proliferation of transformed melanocytes. The vast majority of melanoma (about 95%) originates from skin [1]. The incidence of melanoma has risen dramatically for the past 30 years. It has been estimated that an annual incidence increased approximately 3% in Caucasians since 2004 [2]. The etiology of melanoma is known to involve various physical and lifestyle characteristics, such as skin pigmentation, lifetime intermittent intense sun exposure, and eye and hair color [3, 4]. However, these factors listed above cannot account for prominent incidence differences in age-specific patterns of melanoma incidence or prognosis between women and men [5, 6]. Animal experiments have shown oestrogens and oestrogens/progesterone combinations could stimulate the melanocyte cells proliferation and increase melanin production [7]. Furthermore, women with a history of breast cancer seem to be associated with a higher risk of melanoma and proliferation of melanocytic nevi around puberty and reported changes in number and size of nevi during pregnancy and oral contraceptives were also found. All these biological events were related with to hormonal influence. A great number of epidemiologic studies from the 1970s have been undertaken to evaluate the effect of characteristics of female endocrine status on melanoma risk among different populations [3-5, 8-53], however, conflicting findings were shown. A previous meta-analysis has investigated the relationship between melanoma risk and exogenous hormone use and reproductive factors [7]. Gandini et al. found that exogenous female hormones do not contribute to an increased risk of melanoma, while significant associations of melanoma with parity and age at first pregnancy were detected. Unfortunately, they did not assess the link

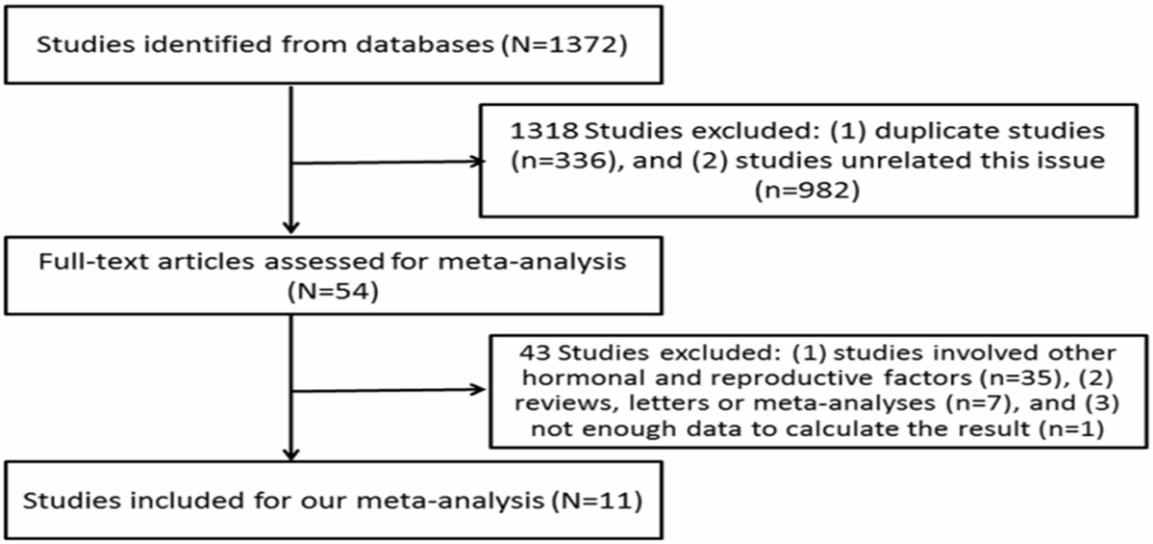


**Figure 1.** The flowchart for systematic literature search.

between melanoma risk and age at first birth, a more relevant exposure reflecting the level of endogenous hormones than age at first pregnancy. Therefore, a meta-analysis covering published case-control and cohort studies was performed to further elucidate this issue.

## Materials and methods

### *Literature search*

We identified epidemiologic studies of melanoma completed as of September 6, 2014. PubMed and Embase databases were searched with the following terms: (1) "Age at first birth", "birth", "reproductive history", "reproductive factors", "childbearing", "parity", "fertility", "hormone". (2) "Melanoma", "skin neoplasms", "skin cancer". (3) "Risk assessment", "risk", "risk factors".

Additional studies which were not found in electronic searches were ascertained through cross-referencing of reference lists of all relevant retrieved articles on the topic. No limitations were imposed during search.

### *Inclusion and exclusion criteria*

Studies included in the meta-analysis must fulfill the following criteria: (1) a case-control, nested case-control, or cohort study evaluated the relationship between age at first birth and melanoma risk; (2) RRs with corresponding 95% CI or the raw data were reported. The exclusion criteria were as follows: (1) studies were cross-sectional study, reviews, conference abstracts, case reports, letters, or editorial articles; (2) studies did provided the adjusted RRs with 95% CI or complete raw data; (3) when multiple studies concerning the same subjects, only the informative one was included.

### *Data extraction*

Data were extracted and cross-checked independently by two reviewers. The data included the first author's surname, publication year, sites where the study was undertaken, numbers of cases, controls, or cohorts, study type, years of study conducted, the highest vs. lowest classification of exposure, RRs with corresponding 95% CIs, and adjustment for potential confounding factors. When multiple risk estimates were available, only the maximally adjusted effect estimates were included in our study. However, the adjusted risk estimates were not reported, the raw data were used.

### *Statistical analysis*

Random-effect model was used to pool the study-specific risk estimates (RRs) with 95% confidence intervals (CIs) as the results from random-effect model were conservative and random-effect model takes both within and between-study variations into consideration [52]. Statistical heterogeneity of effects across studies was evaluated by Cochran's Q test sta-

tistic ($P_H$ < 0.05 was considered to be statistically significant heterogeneity) and $I^2$ statistic ($I^2$ < 25% no heterogeneity; $I^2$ = 25% to 50% low heterogeneity; $I^2$ = 50% to 75% moderate heterogeneity; $I^2$ > 75% large or extreme heterogeneity) [53, 54]. We also performed analyses stratified by study design, location where the study conducted, and adjustment status. Sensitivity analysis was performed to assess the robustness of overall results by excluding one study in each turn. An estimation of potential publication bias was evaluated by Egger's test (p < 0.05 was considered statistically significant) [55]. All statistical tests were done with the STATA software (version 12.0; Stata Corporation, College Station, TX).

## Results

*Literature search and study characteristics*

**Figure 1** shows the flowchart for systematic literature search. A total of 1372 articles were first identified. An overwhelming majority of them were not focused on the relationship between age at first birth and melanoma risk, and were not considered any more, while 54 publications with full-text were further assessed for our meta-analysis [1, 3-51, 56-59]. Thirty-five of these 54 studies evaluated the association between melanoma risk and oral contraceptives, hormonal replacement therapy, age at menarche/menopause, use of fertility drugs, age at first pregnancy, parity, and menopausal status [5, 8-10, 12, 13, 15-31, 33, 35, 36, 38, 39, 42-44, 46, 47, 49, 51], and were therefore excluded. In the rest of 19 studies, seven studies were reviews, letters or meta-analyses [1, 6, 7, 56-59] and one did not provide sufficient data [14]. Therefore, a final total of 11 studies including two population-based case-controls, one hospital-based case-control, three nested case-control, and five cohort studies, were eligible for our meta-analysis [3, 4, 11, 32, 34, 37, 40, 41, 45, 48, 50]. Characteristics of the 11 studies were shown in **Table 1**. These studies were published between 1983 and 2013. Many of the studies were performed in Europe [4, 32, 34, 40, 41, 45, 48], two in Americas [3, 11], and two in Australia [37, 50]. The number and type of potential confounders considered varied across studies, while three crude risk estimates were used in our meta-analysis [4, 11, 45].

*Data synthesis*

**Figure 2** shows the effect of age at first birth and melanoma risk. The pooled result showed that an increased risk of significance was associated with age at first birth (RR = 1.47, 95% CI: 1.07-2.02, $P_H$ < 0.001, $I^2$ = 84.0%). Simultaneously, sensitivity analyses were performed to evaluate the effect of one single study on the overall results by sequentially omitting each study in one turn. The results of sensitivity analyses indicated three studies could possibly affect the pooled of risk estimate (**Figure 3**). The pooled risk estimates were (RR = 1.38, 95% CI: 0.99-1.93), (RR = 1.49, 95% CI: 0.99-2.24), (RR = 1.40, 95% CI: 1.00-1.97) for the study by Naldi et al., 2005 [40], the study by Neale et al., 2005 [41], the study by Stewart et al., 2013 [50], respectively. Assessment of publication bias suggested no bias in all publications (P for Egger's test = 0.843).

**Table 2** shows the relationship between age at first birth and melanoma risk in subgroup analyses by study type, site, and adjustment status. When subgroup analyses were undertaken according to study type, the combined risk estimates were (RR = 1.37, 95% CI: 0.47-4.02, $P_H$ = 0.028, $I^2$ = 79.2%), (RR = 1.38, 95% CI: 0.66-2.88, $P_H$ = 0.107, $I^2$ = 55.3%), (RR = 1.39, 95% CI: 0.89-2.17, $P_H$ < 0.001, $I^2$ = 91.7%) for population-based case-controls studies, nested case-control studies, and cohort studies, respectively. Only one hospital-based case-control study has evaluated the association between age at first birth and melanoma risk. The risk estimate was (RR = 2.69, 95% CI: 1.56-4.64) [40]. In subgroup analysis by sites where the studies performed, the combined RRs were (RR = 1.18, 95% CI: 0.30-4.60; $P_H$ = 0.004, $I^2$ = 88.0%) for North Americas, and (RR = 1.44, 95% CI: 0.99-2.08; $P_H$ < 0.001, $I^2$ = 87.8%) for Europe. In adjusted group, no significant association were observed in studies which adjusted for age, naevi/pigmentation, sunlight exposure, or hair color, but significant positive associations were detected in those studies which provided risk unadjusted estimates for age, naevi/pigmentation, sunlight exposure, or hair color (**Table 2**).

## Discussion

To our best knowledge, this is the first meta-analysis which systematically assessed the relationship between age at first birth and mel-

**Table 1.** Characteristics of studies included in the meta-analysis

| Study | Country | No. cases | No. controls/ cohorts | Study type | Years of study conducted | Exposure (highest vs. lowest Y) | RR with 95% CI | Adjusted factors |
|---|---|---|---|---|---|---|---|---|
| Holly et al., 1983 [11] | US | 87 | 863 | Pop | 1976-1979 | ≥ 31 vs. ≤ 20 | 2.4 (1.16-4.95) | Unadjusted |
| Lambe et al., 1996 [32] | Sweden | 4779 | 23888 | NCC | 1958-1990 | > 40 vs. < 20 | 1.98 (1.03-3.81) | Parity |
| Westerdahl et al., 1996 [34] | Sweden | 400 | 640 | Pop | 1988-1990 | ≥ 31 vs. < 25 | 0.8 (0.4-1.5) | Hair color, raised naevi, sunlight exposure, and parity |
| Young et al., 2001 [37] | Australia | 14 | 3186 | NCC | 1980-1996 | ≥ 35 vs. < 25 | 3.43 (0.31-37.38) | Age, and cohort entry year |
| Freedman et al., 2003 [3] | US | 153 | 54045 | Cohort | 1983-1998 | ≥ 30 vs. < 25 | 0.6 (0.4-1.0) | Age, alcohol intake, smoked, skin pigmentation, hair color, personal history of non-melanoma skin cancer, decade began work as a technologist, education, and proxy measures for residential childhood and adult sunlight exposure. |
| Naldi et al., 2005 [40] | Italy | 316 | 308 | Hosp | 1992-1994 | ≥ 27 vs. < 23 | 2.69 (1.56-4.64) | Age, education, body mass index, number of melanocytic nevi, pigmentary traits, sunlight exposure, and reaction to sun exposure. |
| Neale et al., 2005 [41] | Sweden | 2285 | 1234967 | Cohort | 1958-1996 | ≥ 30 vs. < 20 | 1.37 (1.17-1.61) | Parity, twinning, and date of birth of the mother |
| Kaae et al., 2007 [4] | Denmark | 5688 | 1725627 | Cohort | 1968-2003 | ≥ 30 vs. < 12-19 | 2.59 (2.09-3.21) | Unadjusted |
| Hannibal et al., 2008 [45] | Denmark | 112 | 1226 | NCC | 1963-1998 | ≥ 35 vs. < 25 | 0.85 (0.49-1.47) | Unadjusted |
| Kvaskoff et al., 2011 [48] | France | 460 | 91,972 | Cohort | 1990-2005 | ≥ 27 vs. < 22 | 0.91 (0.67-1.23) | Age, hair color, skin complexion, number of nevi, number of freckles, skin sensitivity to sun exposure, physical activity, and mean ultraviolet radiation dose in regions of birth and of residence at baseline |
| Stewart et al., 2013 [50] | Australia | 149 | 21604 | Cohort | 1982-2010 | > 35 vs. < 25 | 2.32 (1.38-3.91) | Age |

Pop: population-based case-control study; Hosp: Hospital-based case-control study; NCC: nested case-control study.

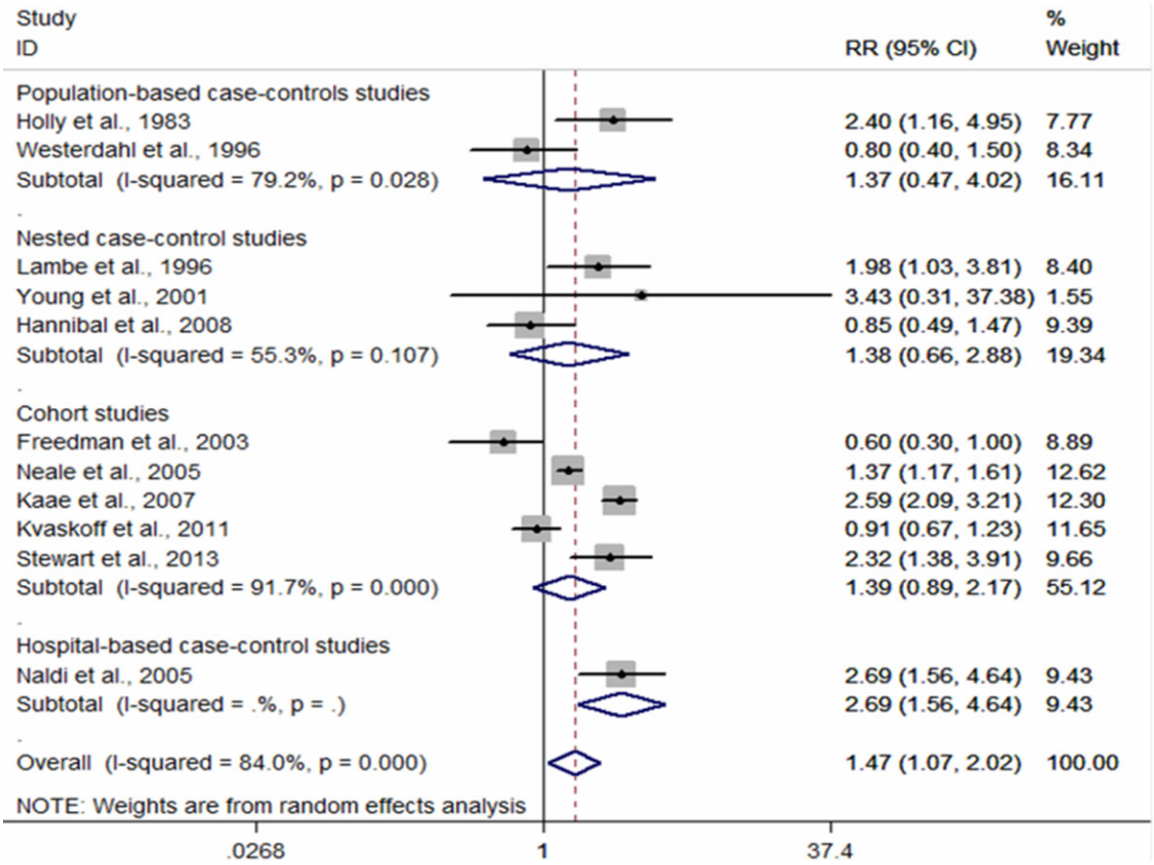


**Figure 2.** Forest plot of melanoma risk with age at first birth.

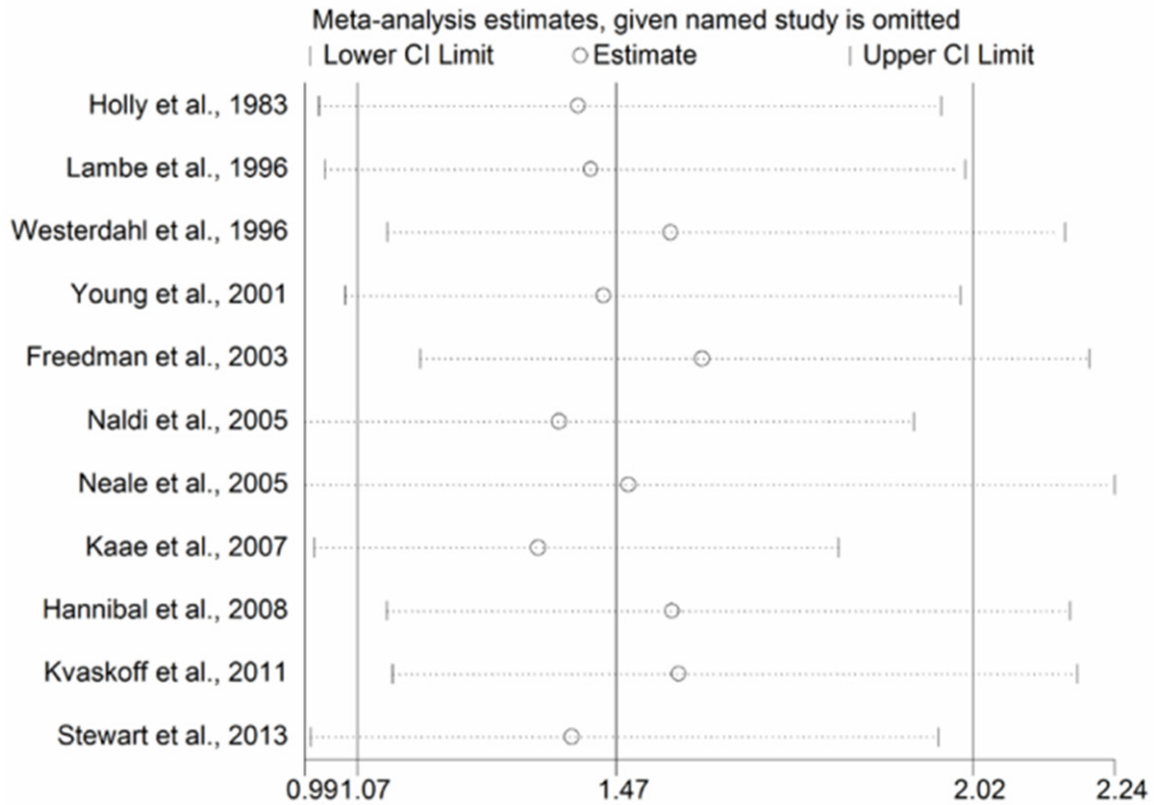


**Figure 3.** Sensitivity analyses for age at firth birth.

**Table 2.** Subgroup results of meta-analysis for melanoma

| | Subgroups | No. of studies | Summary Effect | | Study Heterogeneity | |
|---|---|---|---|---|---|---|
| | | | RR (95% CI) | *P* Value | $I^2$ | *P* Value |
| All studies | | 11 | 1.47 (1.07-2.02) | *0.018* | 84.0% | *< 0.001* |
| Study type | Pop | 2 | 1.37 (0.47-4.02) | 0.566 | 79.2% | 0.028 |
| | Hosp | 1 | 2.69 (1.56-4.64) | < 0.001 | -- | -- |
| | NCC | 3 | 1.38 (0.66-2.88) | 0.395 | 55.3% | 0.107 |
| | Cohort | 5 | 1.39 (0.89-2.17) | 0.153 | 91.7% | < 0.001 |
| Site | Europe | 7 | 1.44 (0.99-2.08) | 0.054 | 87.8% | < 0.001 |
| | North Americas | 2 | 1.18 (0.30-4.60) | 0.810 | 88.0% | 0.004 |
| | Australia | 2 | 2.36 (1.42-3.93) | 0.018 | 0.0% | 0.755 |
| Adjustment status | | | | | | |
| Age | Yes | 5 | 1.43 (0.76-2.68) | 0.271 | 83.0% | < 0.001 |
| | No | 6 | 1.15 (1.03-2.27) | 0.035 | 85.2% | < 0.001 |
| Naevi/pigmentation | Yes | 4 | 1.05 (0.58-1.89) | 0.877 | 81.5% | 0.001 |
| | No | 7 | 1.81 (1.26-2.58) | 0.001 | 80.4% | < 0.001 |
| Sunlight expsure | Yes | 4 | 1.05 (0.58-1.89) | 0.877 | 81.5% | 0.001 |
| | No | 7 | 1.81 (1.26-2.58) | 0.001 | 80.4% | < 0.001 |
| Hair color | Yes | 3 | 0.83 (0.65-1.07) | 0.148 | 0.0% | 0.477 |
| | No | 8 | 1.90 (1.37-2.64) | < 0.001 | 78.9% | < 0.001 |

anoma risk. This meta-analysis included three case-control, three nested case-control, and five cohort studies. The overall results showed that older age at first birth was correlated with a statistically significant increased risk of melanoma.

When we combined the results stratified by study type, no statistically significant associations were detected in population-based case-controls studies, nested case-control studies, or cohort studies. And there was only a hospital-based case-control study addressing this issue. In this study of 316 cases and 308 controls, Naldi and colleagues found that a 2.69-fold significantly increased risk of melanoma in women aged > 27 years at first birth compared with < 23 years [40]. In subgroup analysis stratified by sites where the studies performed, no statistically significant associations were observed in North Americas or Europe group, whereas an increased melanoma risk of statistical significance was associated with age at first birth in Australia studies.

Confounder is a main subject in meta-analysis of observational studies. In out meta-analysis, we performed subgroup analyses by adjusted status. In adjusted group for age, naevi/pigmentation, sunlight exposure, or hair color, we found that age at first birth was not significant correlated with melanoma risk. However, in unadjusted group, age at first birth play a positive role in the development of melanoma. Thus, this finding may be result out from confounder bias and should be explained cautiously.

Another problematic birth variable is age at lase birth. However, few studies have investigated the correlation between age at last birth and melanoma risk [40, 45, 48]. In Naldi and colleagues' study, women with older age at last birth were associated with an increased risk of melanoma (p for linear = 0.008) [40]. However, this trend did not emerge in two large prospective studies [45, 48]. In a Danish cohort study with 54,362 women, Hannibal et al found that an inverse association between age at last birth and risk of melanoma, although these results were not statistically significant (RR = 0.77, 95% CI: 0.43-1.36) [45]. In the latter cohort study of 91,972 French women aged 40-65 at inclusion into cohort, a similar trend with Danish cohort results was observed for melanoma (RR = 0.94, 95% CI: 0.70-1.26) [48]. In light of sparse data involved each individual study, these results may be chance findings. Therefore, this issue remains open to discussion.

One previous meta-analysis has assessed the relationship evaluated the association between melanoma risk and oral contraceptives, hormonal replacement therapy, age at menarche/menopause, use of fertility drugs, age at first pregnancy, parity, and menopausal status [7]. Gandini et al. 2011 concluded that oral contraceptives, hormonal replacement therapy, age at menarche/menopause, use of fertility drugs did not significantly contribute to risk of melanoma, while a significantly elevated melanoma risk emerged in women with late age at first pregnancy and women with more than one child may be at a lower risk for melanoma [7].

Several limitations in our meta-analysis should also be noticed. First, significant heterogeneity was observed in overall comparison and in the subgroup analysis. Therefore, the reliability of our results was questionable. In our study, the heterogeneity was partially owing to the following variations: study designs, characteristics of populations between studies, exposure ranges, and confounders. Second, our analysis was limited by the inconsistent categorization of the exposure variables, which may mask the true relationship between age at first birth and melanoma risk. Third, no data was involved Asians or Africans. Additional investigations about this issue are needed to confirm this finding. Finally, potential publication bias is a consideration in a meta-analysis as this kind of research was based on published studies. However, no evidence of publication bias was observed in current study.

In summary, findings of the present meta-analysis of eleven observational studies indicate that age at first birth is significantly associated with increased risk of melanoma. However, the potential effect of confounders on the relationship between age at first birth and melanoma should be clarified in future studies.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Ying Cen, Department of Burns and Plastic Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China. E-mail: ying_censichuan@hotmail.com

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