Review Article
Height and risk of melanoma: a systematic review and meta-analysis

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Abstract: This systematic review and meta-analysis of prospective cohort studies aimed to comprehensively estimate the relationship between height and melanoma risk. Prospective cohort studies were identified through literature search in Pubmed and EMBASE. The summary relative risk (RR) with 95% confidence interval (95% CI) was calculated using random-effects meta-analysis. Twelve studies with a total of 4,723,739 participants and 20,049 melanoma cases were included. When compared with individuals with the lowest category of height, individuals with the top category of height had increased risk of melanoma (Random-effects RR = 1.46, 95% CI 1.24 to 1.73; P < 0.001). Per 10-cm increment in the height was positively correlated with increased melanoma risk (Random-effects RR = 1.27, 95% CI 1.19 to 1.35; P < 0.001). Subgroup analysis by gender showed that RRs of melanoma risk associated with per 10-cm increment in height in women and men were 1.27 (95% CI 1.18 to 1.36; P < 0.001) and 1.52 (95% CI 1.01 to 2.29; P = 0.04), respectively. There is strong evidence for the relationship between height and melanoma risk.

Keywords: Height, melanoma, association, risk factor

Introduction

Melanoma is a common malignant disease occurring in the melanocytes [1, 2]. Melanoma accounts for only about 2% of all skin cancers, but it the main cause of deaths associated with skin cancer [2, 3]. There is also an obvious increase in the incidence of melanoma in recent years [4]. There were more than 76,000 estimated newly diagnosed cases of melanoma and more than 10,000 estimated deaths caused by melanoma in United States in 2016 [3]. Ultraviolet light or sunlight exposure has been recognized as the main risk factor of melanoma, and several other risk factors are also reported, such as fair complexion, family history, and obesity [5-9]. However, the etiology of melanoma remains largely unknown, and more risk factors associated with melanoma need to be identified, which may be helpful for the prevention and screening of melanoma [6, 10-13].

Human height is considered to be determined by both genetic and environmental factors, and it is indeed associated with circulating insulin-like growth factor I (IGF-1) levels during childhood [14-16]. Both experimental and epidemiologic data have suggest that high IGF-1 level is intensively correlated with elevated risk of cancer [17-21]. Some studies demonstrated an association between height and risk of several types of cancer, such as breast cancer and colorectal cancer [22-27]. In contrast, the results of epidemiological studies investigating the relationship between height and melanoma were controversial and inconclusive. Some studies reported that higher height was a risk factor of melanoma, but other studies didn't. We therefore conducted this meta-analysis.

Materials and methods

Literature search and selection of eligible studies

Literature search was performed in Pubmed and EMBASE databases up to Oct 20, 2016. The following search strategy was used: (mela-

Table 1. Characteristics of prospective studies on height and melanoma risk

Study	Location (Study period)	Study design	Participants	Follow-up	Number of cases	Gender (female/male)	Age (median, range) years	Level of height	Adjustment for covariates	Study quality
Thune I 1993 [42]	Norway (1963-1975)	Prospective cohort study	1.3 million individuals	17.6 years	4958	2814/2144	NA	H vs L	Age, birth cohort, geographic region and BMI.	8
Veierod MB 1997 [43]	Norway (1977-1983)	Prospective cohort study	25,708 men and 25,049 women aged 16-56 years	12.4 years	108	61/47	52 (29 – 64)	H vs L	County of residence, gender, age at inclusion and attained age.	8
Freedman DM 2003 [34]	USA (1983-1989)	Prospective cohort study	68,588 white subjects	10 years	207	159/48	NA	H vs L	Age, weight, gender, alcohol intake, smoking, 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.	8
Batty GD 2010 [33]	Asia Pacific Cohort Studies Collaboration	Prospective cohort study	506648 study participants	6.5 years	88	25/63	NA	Per 6 cm increment	Age, study, and year of birth.	8
Green J 2011 [35]	UK (1996-2001)	Prospective cohort study	1297124 women	9.4 years	3583	NA	NA	Per 10 cm increment	Age, region, socioeconomic status, smoking, alcohol intake, body-mass index, strenuous exercise, age at menarche, parity, and age at first birth.	9
Kabat GC 2013 [37]	Canada (1980-1985)	Prospective cohort study	90,000 women	16.2 years	327	NA	NA	Per 10 cm increment	Age at entry, menopausal status, BMI, and years of education.	9
Kabat G 2013 [36]	USA (1993-1998)	Prospective cohort study	144,701 women participating in the Women's Health Initiative	12 years	1169	NA	NA	Per 10 cm increment	Age, alcohol, pack-years, hormone therapy, education, ethnicity, BMI, and randomization status.	9
Kvaskoff M 2014 [39]	France (1989-1991)	Prospective cohort study	98,995 women	18 years	589	0/589	NA	H vs L	Age, number of naevi, freckling, skin and hair colour, skin sensitivity to sun exposure, residential sun exposure, and physical activity.	9
Kabat GC 2014 [38]	USA (1995-1996)	Prospective cohort study	288,683 men and 192,514 women enrolled in the National Institutes of Health-AARP Diet and Health Study	10.5 years	4780	1224/3556	NA	Per 10 cm increment	Age at entry, education, race, smoking status, and body mass index.	9
Wiren S 2014 [44]	Austria, Norway, and Sweden	Prospective cohort study	585,928 participants from seven cohorts	12.7 years	1989	NA	NA	Per 5 cm increment	Date of birth and age at health examination, and stratified for sub-cohort within the model.	9

Is height a risk factor for melanoma?

Lahmann PH 2016 [40]	Australia (1992-1996)	Prospective cohort study	1171 Australian men and women	16 years	28	17/11	NA	Per 5 cm increment	Age, treatment allocation, skin cancer history, elastosis of the neck, and smoking status.	7
Meyle KD 2016 [41]	Denmark (1978)	Prospective cohort study	316,193 individuals from the Copenhagen School Health Records Register	29 years	2223	1205/1018	NA	Per height z-score	Birth cohort, age, and gender.	8

(BMI: body mass index; NA: not available).

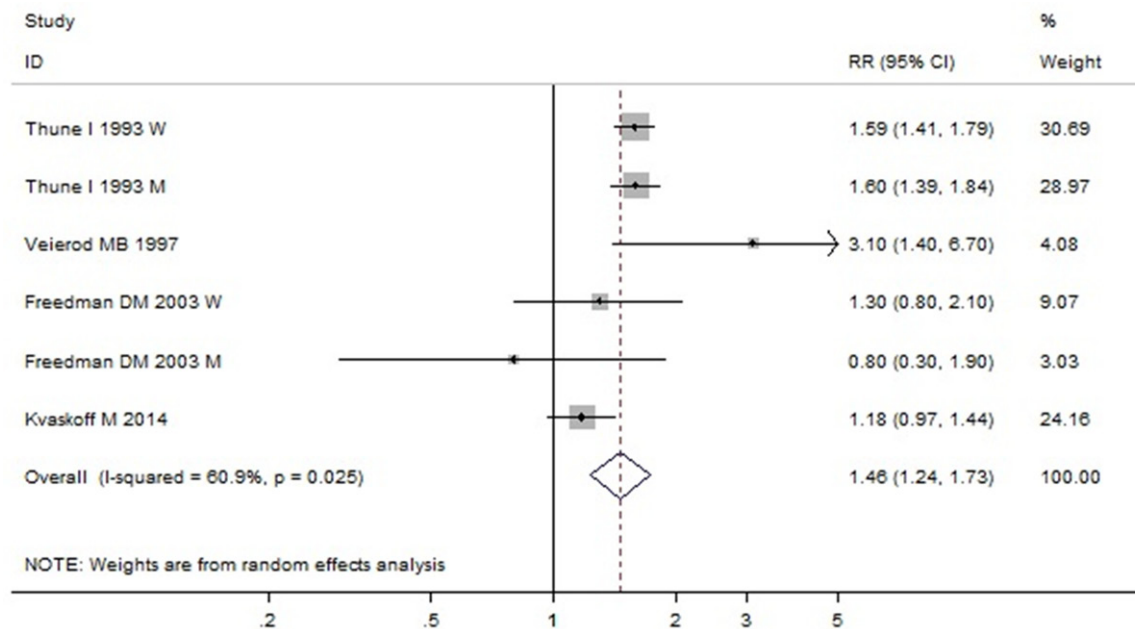# Is height a risk factor for melanoma?

Figure 1. Individuals with the top categories of height had increased risk of melanoma.

noma or skin cancer) AND (height OR body size) AND (prospective or cohort or longitudinal). No limitation in language was used. Additional studies were found by looking through the references of retrieved reviews or articles.

Prospective cohort study which evaluated the association between height and melanoma risk and reported risk estimates of melanoma risk were included. Studies which failed to meet any item of the selection criteria above were excluded.

Data extraction

Extracted information included first author, country, follow-up time, adjusted confounding factors, and adjusted RRs with 95% CIs. Any differences in extracted data were settled by consensus. RRs of melanoma associated with the top categories of height or per 10-cm increment in height were used in the meta-analysis. For studies reported RRs of melanoma associated with per 5-cm or per 6-cm increment in height, the RRs of melanoma associated with per 10-cm in height were calculated through the following formula [28]: $RR_{per\ 10\text{-}cm} = RR_{(original)}^{Increment\ (10)/Increment\ (original)}$. We assessed the studies' quality by Newcastle-Ottawa Scale (NOS) [29]. Studies with a quality score no less than 6 were considered as high-quality studies.

Statistical analysis

The RRs from included studies were pooled using random-effect model of DerSimonian-Lard method [30]. The RRs of melanoma associated with the top categories of height or per 10-cm increment in height were pooled separately. Heterogeneity was evaluated with the I^2 statistic, and I^2 more than 50% showed obvious heterogeneity between studies [31]. Sensitivity analysis was then performed by excluding single study by turns. Subgroup analysis was performed by gender. To qualitatively assess publication bias, both funnel plot and Egger's test was utilized [32].

Results

Characteristics of included studies

Of 359 abstracts identified from PubMed and EMBASE databases, 24 studies were firstly included and assessed for final inclusion by reading full-texts [33-44]. Twelve studies were then excluded [45-55], and the left 12 prospective studies were finally included in the current meta-analysis [33-44]. Batty et al's study reported a prospective study of participants from 38 cohort studies [33], and Wiren et al's study reported a prospective study of participants from seven cohort studies [44]. Either
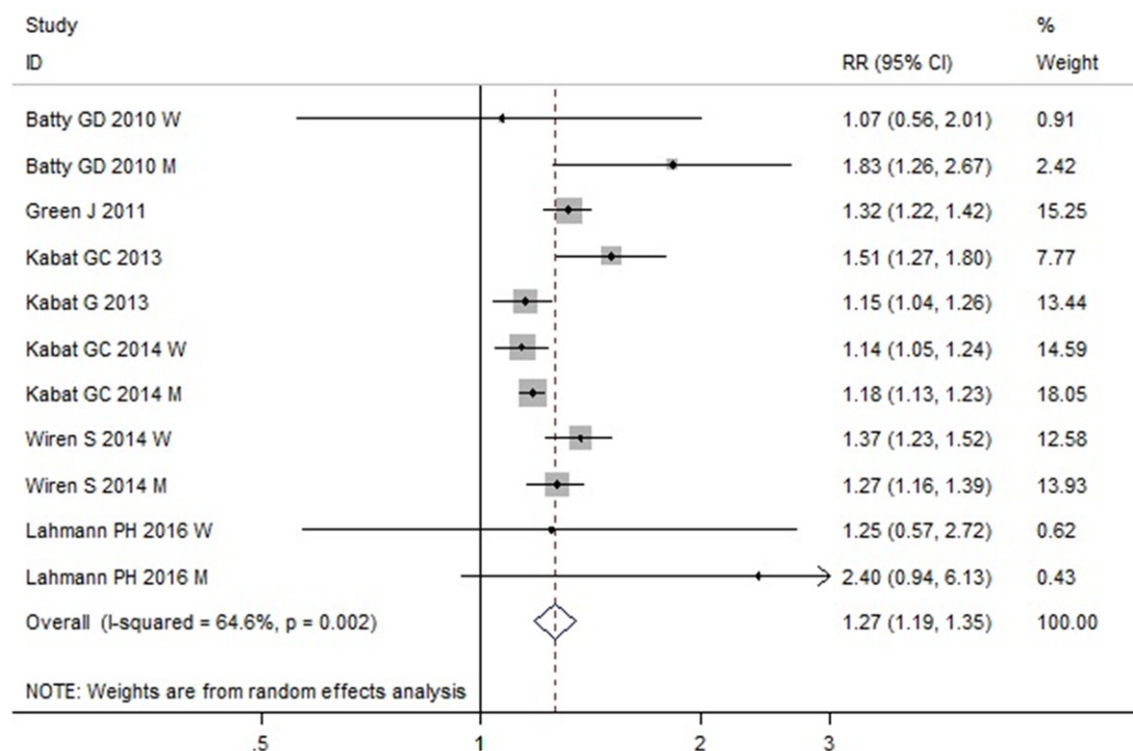
Is height a risk factor for melanoma?

Figure 2. Increased height (per 10-cm increment) was positively associated with an increased melanoma risk.

Batty et al's study or Wiren et al's study was regarded as one prospective study in the meta-analysis. Overall, 12 prospective cohort studies contained a total of 4,723,739 participants and 20,049 with cases melanoma [33-44].

Table 1 summarized the characteristics of included studies (**Table 1**). Most studies were performed in Caucasian populations, such as USA, UK, Canada, and Norway (**Table 1**). Four studies reported RRs of melanoma associated with the top categories of height compared with the lowest category of height, and the other 8 studies reported RRs of melanoma associated with per certain increment in height (**Table 1**). All included studies performed multivariate regression analyses by adjusting for potential confounding factors, but the factors varied obviously across different studies. The number of participants ranged from 1171 to 1.3 million, while the time of follow-up ranged from 6.5 years to 25 years (**Table 1**). All studies had a NOS score of more than 6 points, and thus had high-quality.

Meta-analysis

When compared with individuals with the lowest categories of height, individuals with the top categories of height had increased risk of melanoma (Random-effects model, $I^2 = 60.9\%$, $P = 0.029$; RR = 1.46, 95% CI 1.24 to 1.73; $P < 0.001$) (**Figure 1**). Increased height (per 10-cm increment) was positively associated with an increased melanoma risk (Random-effects model, $I^2 = 64.6\%$, $P = 0.002$; RR = 1.27, 95% CI 1.19 to 1.35; $P < 0.001$) (**Figure 2**). Subgroup analysis by gender showed that RRs of melanoma risk associated with per 10-cm increment in height were 1.27 (95% CI 1.18 to 1.36; $P < 0.001$; $I^2 = 59.5\%$, $P = 0.016$) in female and 1.52 (95% CI 1.01 to 2.29; $P = 0.04$; $I^2 = 72.8\%$, $P = 0.025$) in male, respectively (**Figure 3**).

There was also no obvious asymmetry in the funnel plot (**Figure 4**), and the *P* value of Egger's regression test was 0.27, which indicated lack of publication bias in the meta-analysis.

Discussion

The findings in the meta-analysis suggest an obvious association between height and melanoma risk. IGF-1 is a hormone which has key roles in childhood growth and many metabolic effects in adults [56, 57]. IGF-1 mainly produces its by binding to the insulin-like growth factor 1 receptor (IGF1R), which has been found on

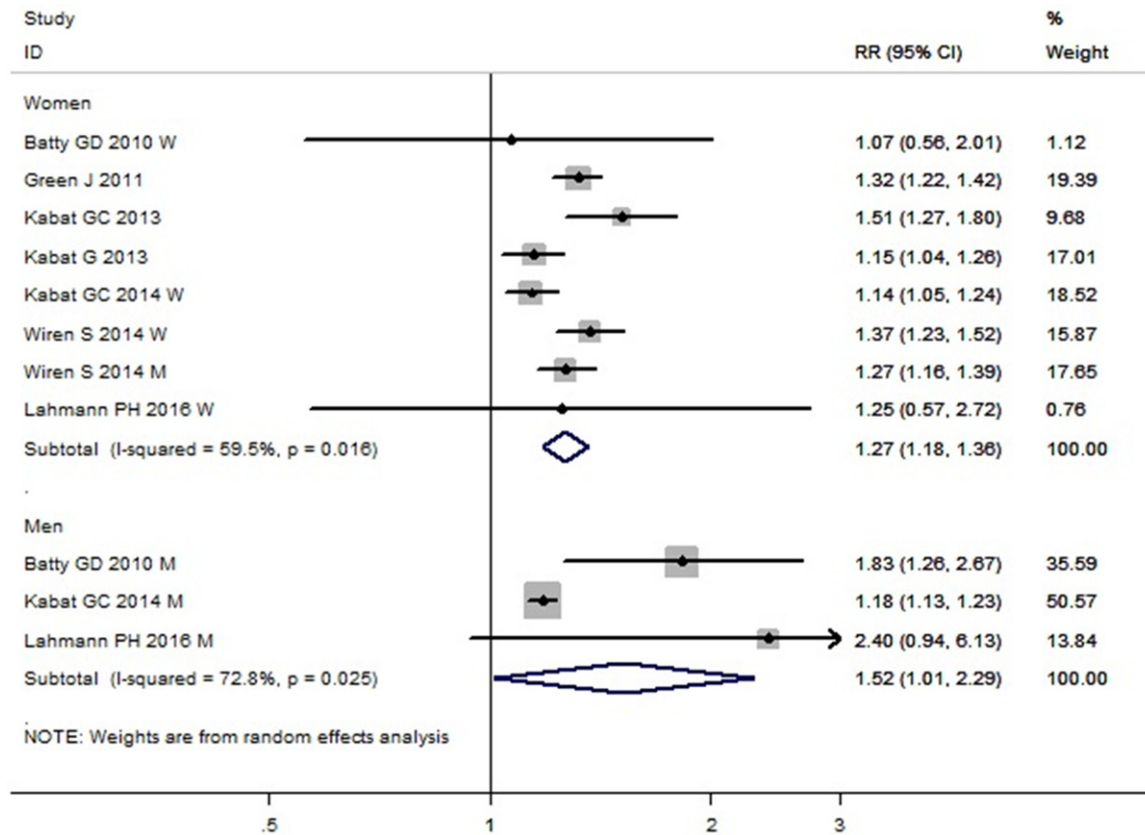# Is height a risk factor for melanoma?

Figure 3. Increased height (per 10-cm increment) was positively associated with an increased melanoma risk in both women and men.
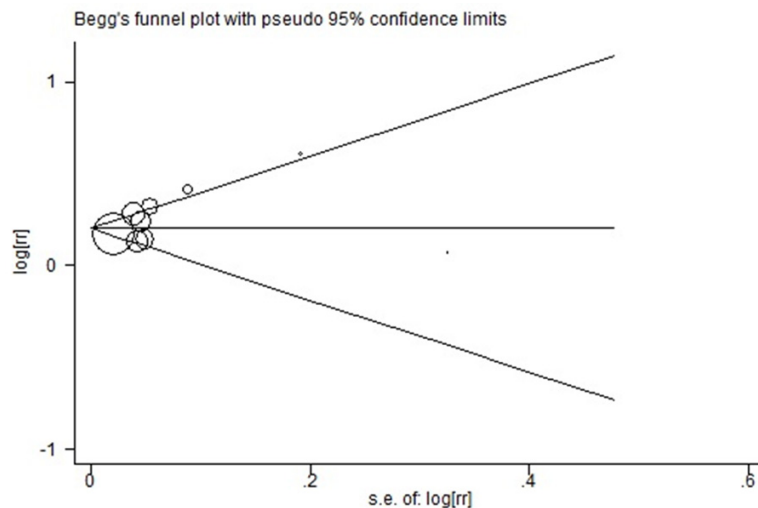

Figure 4. Funnel plot in the meta-analysis of studies reporting RRs of melanoma associated with per certain increment of height.

of many cancers [18, 59, 61]. Both experimental and epidemiologic data have suggest that high IGF-1 level is intensively correlated with elevated risk of cancer, and it has long been regarded as a tumor-promoting factor [18, 59, 61, 62]. Human height is intensively associated with circulating IGF-1 levels during childhood. Children with higher levels of circulating IGF-1 will grow taller than those with lower levels of circulating IGF-1 [63]. On the contrary, individuals with taller height would had higher levels of circulating IGF-1, and these individuals exposing to higher levels of circulating IGF-1 and therefore suffer from increased risk of diseases caused by higher levels of IGF-1 [63-65]. Therefore, there is

the cells of many tissues [56, 58-60]. Besides, IGF signaling pathway has been shown to have key roles in the development and progression

also a possible association between height and melanoma risk. However, the above association has not been directly supported by data from experimental studies. In addition, an epidemiologic study even reported an inverse relationship between IGF-1 concentration and melanoma risk [50]. Therefore, the exact biologic mechanisms underlying the association between height and melanoma risk is still largely unclear, and further studies exploring the mechanisms underlying the relationship between height and melanoma risk are also needed.

There were also several limitations in this study. There was obvious heterogeneity among those included studies. The heterogeneity may come from the different sample size, various adjusted confounding factors, and different demographic characteristics of participants. However, all included studies provided adjusted risk estimates, which could decrease the risk of bias caused by the difference in the design of included studies. Secondly, most studies were carried out in European countries and North America. The conclusion in the meta-analysis could not be generalized to Asians or Africans. More cohort studies from non-Caucasians are necessary to further elucidate the association. Thirdly, the present study only considered published literatures, and it's possible for the existence of publication bias which could affect the exact impact of height on melanoma risk. However, neither funnel plot nor Egger's test showed evidence of publication bias. Finally, IGF-1 has been considered as an important factor underling the biologic mechanism underling the association between height and melanoma risk. However, it's still unclear whether height can still increase the risk of melanoma after adjusting for IGF-1 levels in human bodies.

In summary, there is strong evidence for the relationship between height and melanoma risk.

Acknowledgements

Disclosure of conflict of interest

None.

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