REVIEW

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Global Incidence and Trend of Uveal Melanoma from 1943-2015: A Meta-Analysis

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Abstract

Background: Uveal melanoma (UM) is the most common primary intraocular malignancy in adults arising from uveal tissue melanocytes. Considering limited population based studies, we performed a meta-analysis of uveal melanoma incidence rate in worldwide. **Methods:** For this meta-analysis, the electronic database of PubMed, Scopus, Embase and Google Scholar were utilized. Qualified Cohort studies and registry system databases were included in the study. Trend analysis and the estimation of incidences were reported. Thereafter subgroup analysis on gender and diagnostic tests were performed. Analyses were done using random effect models. **Results:** A total of 22 publications were eligible to include in the meta-analysis. The incidence rates of uveal melanoma were 5.74 (95%CI: 4.37-7.11) and 7.30 (95%CI: 6.36-8.24) in North America and Europe respectively. The analysis showed a significant decreasing trend in North America. It was expected that the risk of UM decreased approximately 0.09 (SE=0.04) per million persons per year. No significant trend was detected in Europe. There was not any significant difference between the incidence rate in male and female (6.58, 95%CI: 5.42-7.75 vs. 5.44, 95%CI: 4.40-6.48). In addition, the reported incidence rates in different diagnostic approaches were similar (6.61, 95%CI: 5.63-7.58 in clinical vs. 6.67, 95%CI: 5.83-7.42 in histological). **Conclusion:** This analysis confirmed in recent decades, there has been a steady decline in the incidence in North America. However, in European countries where they still have the highest incidence worldwide, the trend was stable. It seems that international melanoma registration collaboration can conduct a unified, multicentral study to estimate the worldwide incidence of UM and impact of different factors on its rate.

Keywords: Incidence- trend- uveal melanoma- meta-analysis

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Introduction

Uveal melanoma (UM) is one of the common primary intraocular tumors with significant visual morbidity and metastatic disease related mortality. In spite of significant advancement in the treatment of this tumor and increased survival, no improvement in terms of a patient's survival has been reported during the last decades. Whereas both uveal and cutaneous melanomas initiate from the melanocytes, their genetic alteration and biological behavior are completely different. Approximately 85-90% of intraocular melanomas originate from uveal melanocytes distributed through the stroma of the choroid; only 10%–15% of uveal melanomas arise in the ciliary body and iris (Jovanovic et al., 2013, Aronow et al., 2018). History of prior malignancy, especially cutaneous melanoma has been reported in as high as 13.1% of UM patients (Mahendraraj et al., 2016).

The incidence of UM differs by sex, age, and country. Based on the Surveillance, Epidemiology and End Results database (SEER), the incidence of UM was 5.1 per million in USA (Mahendraraj et al., 2016, Singh et al., 2011). Both cancer registries from the USA (Singh et al., 2011) and Europe (Virgili et al., 2008) reported 1.2–1.3 fold higher age-adjusted incidence of UM in men compared with women. In Europe, as well as US, the incidence of UM varies between different states. For instance, published data from the European Cancer Registry-based study of survival and care of cancer patient (EUROCARE) revealed that the incidence rate in Europe ranged from 1.3 to 8.6 cases per million per year (Krantz et al., 2017, Damato, 2012, Damato and Damato, 2012, Chattopadhyay et al., 2016). It seems that the incidence diversity across the countries is related to several demographic and environmental risk factors. These include Caucasian ethnicity, light iris color, fair hair/skin complexion, family history of UM and coexistence of specific genetic predisposition (Regan et al., 1999, Singh and Damato,

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2013). It has been suggested that prolonged occupational exposure to the sun increase the risk of UM (Vajdic et al., 2003). For example, agricultural activities might be associated with more iris melanoma incidence (Ajani et al., 1992). Although some authors have disclosed the increased light exposure as a positive risk factor (Ajani et al., 1992, Vajdic et al., 2003, Lutz et al., 2005, Guénel et al., 2001) the others pointed out the darker eye and skin pigmentation, as a protective factor (Margo et al., 1998, Vajdic et al., 2003, Stang et al., 2005, Iscovich et al., 2001, Hu et al., 2005). There is a wide range of skin colors across Europe from high pigmentation in the south to low pigmentation in the north, which causes a broad spectrum of sensitivity to ultraviolet light - induced melanoma. While the mean age at diagnosis in US and Europe is 59 to 62 years, published results from Asian countries indicate lower age at diagnosis, ranging from 45 to 55 years (Singh et al., 2011, Kaliki and Shields, 2017, Virgili et al., 2008).

Different studies have been conducted on the incidence of UM with different results during the last decades. Estimating the pooled incidence and trend of UM will assist researchers in the elaboration of a comprehensive trend allowing clinicians to evaluate the impact of different risk factors on incidence of this deadly cancer. SEER (Aronow et al., 2018) and EUROCARE (Virgili et al., 2007) program have evaluated the trends of UM incidence during different time periods in Europe and North America showing a stable trend in recent years despite minor increase in Whites. However, a meta-analysis study is lacking in literature regarding the incidence and risk factors of UM worldwide. The current study aims to evaluate the epidemiological of UM in different populations and ethnicities. To the best of our knowledge this is the first meta-analysis of the incidence rate (IR) of UM that examined various published results over seven decades in different continents.

Materials and Methods

This meta-analysis included the registry systems as well as cohort studies. PRISMA protocol was considered as a guideline to perform the study.

Search Strategy and Eligibility criteria

The electronic database of PubMed, Scopus, Embase and Google Scholar were utilized to find relevant trials. The article search was restricted to English language. The mesh term key words to seek in electronic databases were "*incidence OR cohort OR epidemiology OR trend*" AND "*uveal melanoma OR choroidal melanoma OR iris melanoma*". Included studies were cohort studies in which incidence rate of UM were reported. Thus, all population –based registries and multi central studies that were the representative of a region were considered. Publications that were not demonstrative of such populations like hospital-based data were excluded. The publications with no information on sample sizes or total incidence rate, interventional studies as well as subgroup researches (limiting to a specific population) were excluded too. The studies without available full text were excluded unless the information of them was reported in at least two other studies with available full text. Study selection was done by two independent reviewers (FA and SCH). After reviewing the full-text articles, the relevant studies in accordance with eligibility criteria were selected.

Subgroup analysis and meta-regression

The primary outcome was the total incidence rate of UM in different regions. The wide ranges of differences were found between the studies in terms of research time interval. To consider if the outcome was affected by the length of the study, a meta-regression was done. In addition to assessing if there was any trend in the Incidence rate of UM, meta-regression was performed. For evaluating the trend, the mid-year of study duration was considered as study time. Duo to variation UM incidence rate, in different areas the estimates were calculated in North America and Europe. There were not enough studies to achieve an overall estimate for Asia. Subgroup analysis of gender was performed. For all analysis if the standard error (SE) or 95% confidence interval were not reported, SE was estimated from other information. In order to assess the effect of the diagnosis method on IR, the incidence rates in histological and clinical papers were compared and the studies with both methods of diagnosis were excluded from the diagnosis method comparison.

Data extraction

Most of the data were extracted by two independent researchers, from the primary publications. The type of study, UM Incidence rate, participants demographics, sample sizes, date of publication, method of diagnosis, source of outcome data and other relevant attributes were extracted.

Risk of bias

Risk of biased was evaluated using a modified checklist (De Jong et al., 2015) (Supplemental Table 1) that was developed for prevalence studies. Two independent authors (SCH and FA) were completed the check list and evaluated the bias.

Statistical analysis

Analysis was executed by STATA, version 14. P-value<0.05 was considered significant. Heterogeneity between studies was evaluated with the I2 heterogeneity statistic (I^2 >50 was regarded as considerable heterogeneity) (Higgins et al., 2003). The incidence rates with 95% confidence intervals were calculated by random effect models to control the heterogeneity and deriving more accurate estimates (DerSimonian and Laird, 1986, Barendregt et al., 2013). Incidences in each study were weighted by the inverse of variance. Forest plots were created for revealing confidence intervals for each study and total incidences). Sensitivity analysis was done in assessing the effect of outliers.

As the first step, a meta-regression with restricted maximum likelihood (RML) estimates was conducted to assess the effect of study durations. Second trend analysis was done and if it was significant, subgroup analysis in different time intervals were performed. Subgroup analysis was only done if two or more studies were available on

the subject of interest.

Results

Figure 1 illustrates the search results step by step. Finally a total of 22 publications were eligible to include in the meta-analysis. Table 1 shows the characteristics of included studies. The length of intervals were not similar, but it did not affect IR estimates significantly (p-value=0.774).

The Incidence Rate Estimate in North America

At last 9 Studies were included in the analysis, reporting the IR of UM from North America countries. We included the IRs studies which published from 1969 to 2015. Most of them (n=8, 89%) reported the IR for more than one year intervals. IRs were ranged from 3.75 to 6.9 per million, except one study with IR= 10.9 per million (Davidorf and Knupp, 1979). The most accurate studies based on standard errors were published by McLaughlin et al., Mahandaraj et al., (2016) and Aronow et al. (Aronow et al., 2018) from USA. The lowest IR was reported from Canada (IR=3.75 per million). Figure 2 illustrates the total risk of UM in northern America. The estimated IR was 5.74 per million with 95% CI: 4.37-7.11. Meta-regression was done to evaluate if there was any trend during the study period (Figure 3). A statistically significant decreasing trend was found from 1969 to 2015 (p-value=0.033). It was expected that the risk of UM decreased about 0.09 (SE=0.04) per million persons per year. Thus a decrease of 1 case per million would occur every 12 years. Sensitivity analysis showed a decreasing trend in all models; however, most of them were not significant. Although, most of obtained results were not significant, but the amount of shifting trend were quiet similar to each other (-0.1 to 0.08 expect two models) and p-values were at marginally significant level ($0.054 < \text{p-value} < 0.093$).

The Incidence Rate Estimate in Europe

In total 11 publications were eligible to include in the analysis. One study reported the IRs from Northern, Eastern and Western Europe, thus it was considered three times in the analysis. The included IRs of UM studies were taken into account from 1943 to 2015. Most of them (n=10, 91%) evaluated the IR during a period of more than one year. All of IRs were ranged from 4.6 from Western Europe reported by Gianni to 10 per million reported by Keenan et al. (Keenan et al., 2012) per million. Most of the studies were from northern Europe. Based on standard errors, the most accurate study considering standard errors was published by Mallone et al. (Mallone et al., 2012) The total IR of UM in Europe was 7.30 (95% CI: 6.36-8.24) (Figure 4). There was no statistically significant trend of

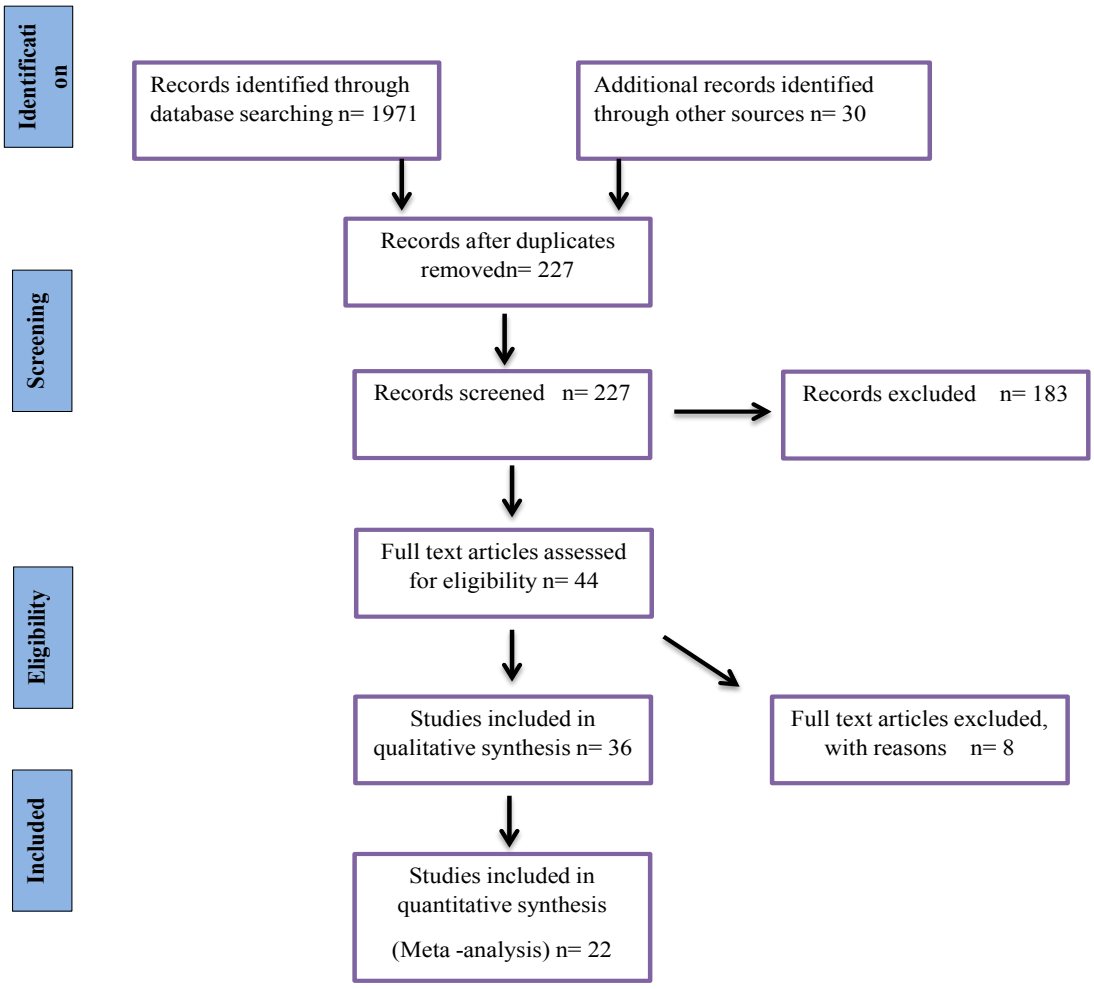

Figure 1. Flow Diagram Cligibility Criteria of Articles on UM Incidence.

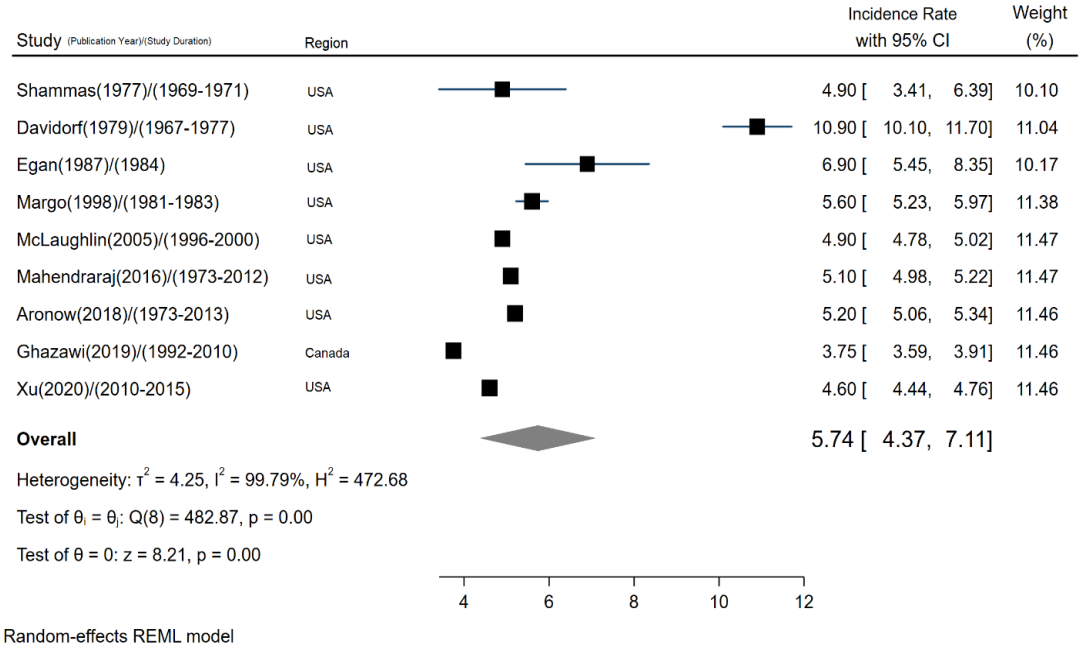

Figure 2A. Forest Plots from Meta-Analysis of Published Incidence Trends for North America UM.

IR for the period of1943-2015 (p-value=0.579) in Europe (Figure 5).

The Incidence rate Estimate in Asia

There were only three eligible studies reporting IR in Asia. One of them was by Iscovich et al., (1995) for Israel (IR=5.7, SE=0.37) and another ones were published by Park et al. (Park et al., 2015) for South Korea (IR=0.42, SE=0.02) and Tomizuka et al. (IR=0.64, SE=0.05) for Japan (Tomizuka et al., 2017). the article for Israeli is completely heterogeneous with the other two articles thus IRs of the studies cannot be merged with others. The total IR of UM in Asia was 0.53 (95% CI: 0.31-0.74).

The Incidence Rate Estimate by Gender, Method of Diagnosis and Age

Figure 6 shows the results of 12 publications assessing IR of UM by gender. The risk of UM in females and male were5.44 (95% CI: 4.40-6.48) and 6.58 (95% CI: 5.42-7.75) respectively. Gislason et al., (1985) (for Iceland), Aronow et al., (????) (for USA) and Baily et al., (????) (for Ireland) reported the highest difference in gender adjusted IR. Although the IR in males is higher than females, but the overlapping confidence intervals showed that the IR does not significantly differ between male and female. The merged IRs of UM for diagnostic methods (histological and clinical) were similar to each

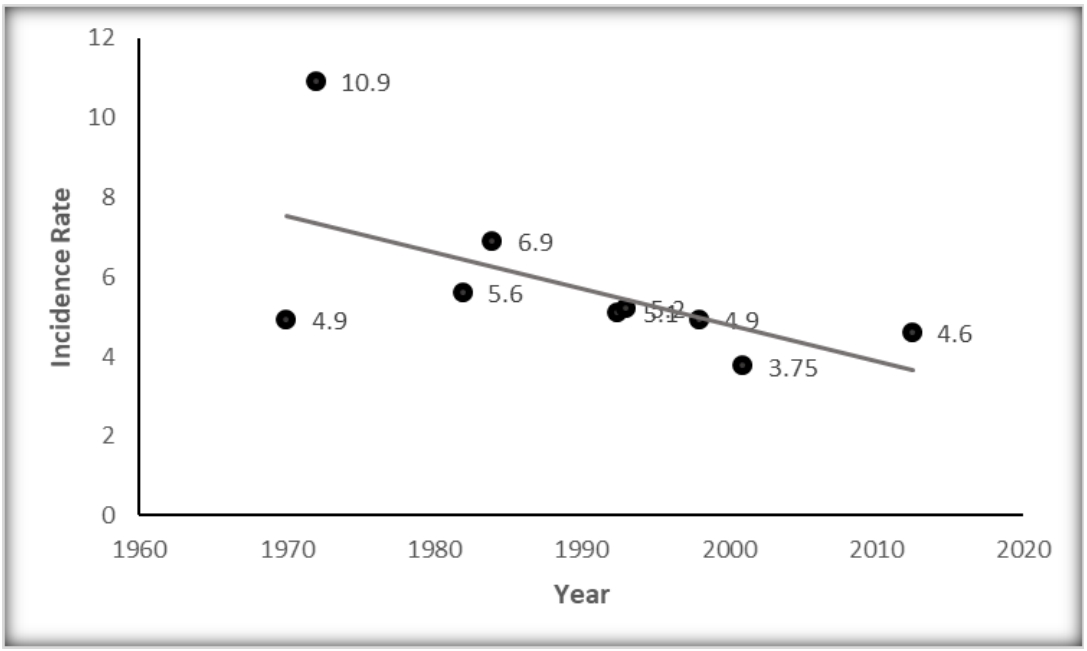

Figure 2B. UM Incidence Trend for North America

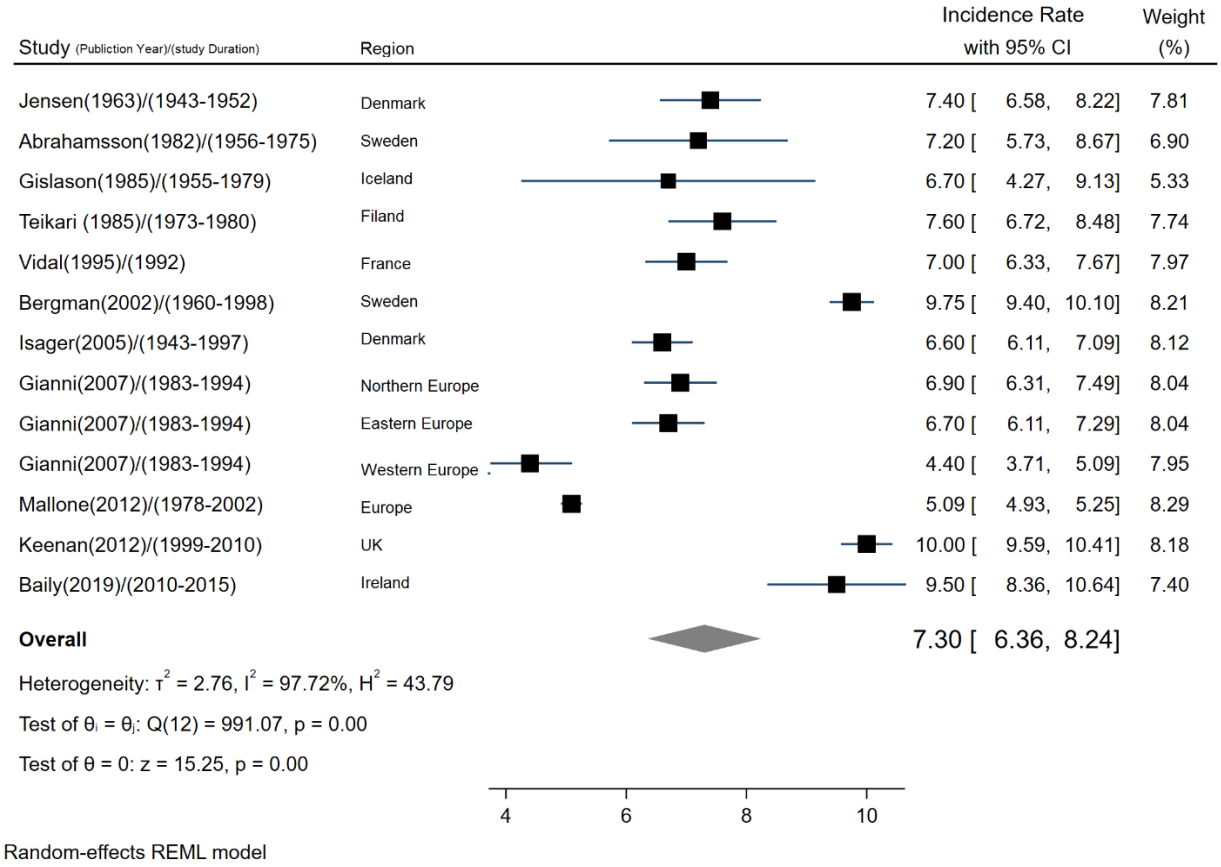

Figure 3A. Forest Plots from Meta-Analysis of Published Incidence Trends for Europe UM.

other (Figure 7).The range of the Time period using clinical and histological as the diagnosis methods were 1943-2000 and 1943-2013, respectively. The IR using the clinical diagnosis method was 6.61 (95%CI: 5.63-7.58) and IR in histological diagnosis method was 6.67 (95% CI: 5.83-7.42). Although, some papers reported the mean age of diagnosis UM, only 2 studies (Mahendraraj et al., (2016) from USA and Ghazawi et al., (2019) from Canada) reported the standard deviation. The mean age at diagnosis in these two studies were 61.4 (SD=15) and 61.12 (13.55). The merged results showed that the mean age at diagnosis was 61.32 (95% CI: 61.04-61.62).

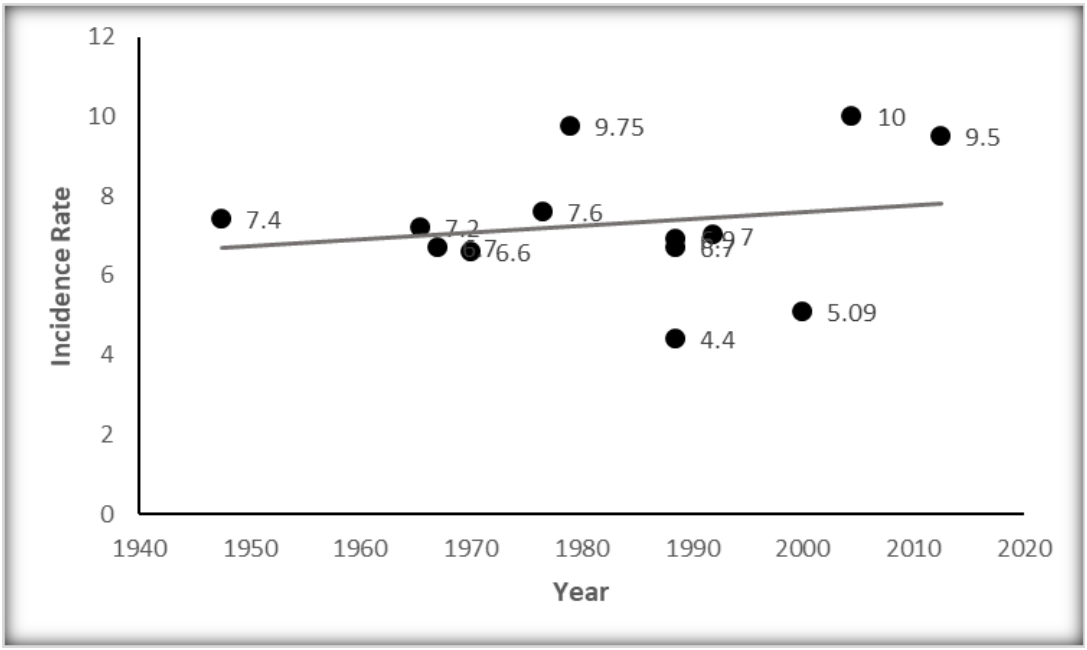

Figure 3B. UM Incidence Trend for Europe

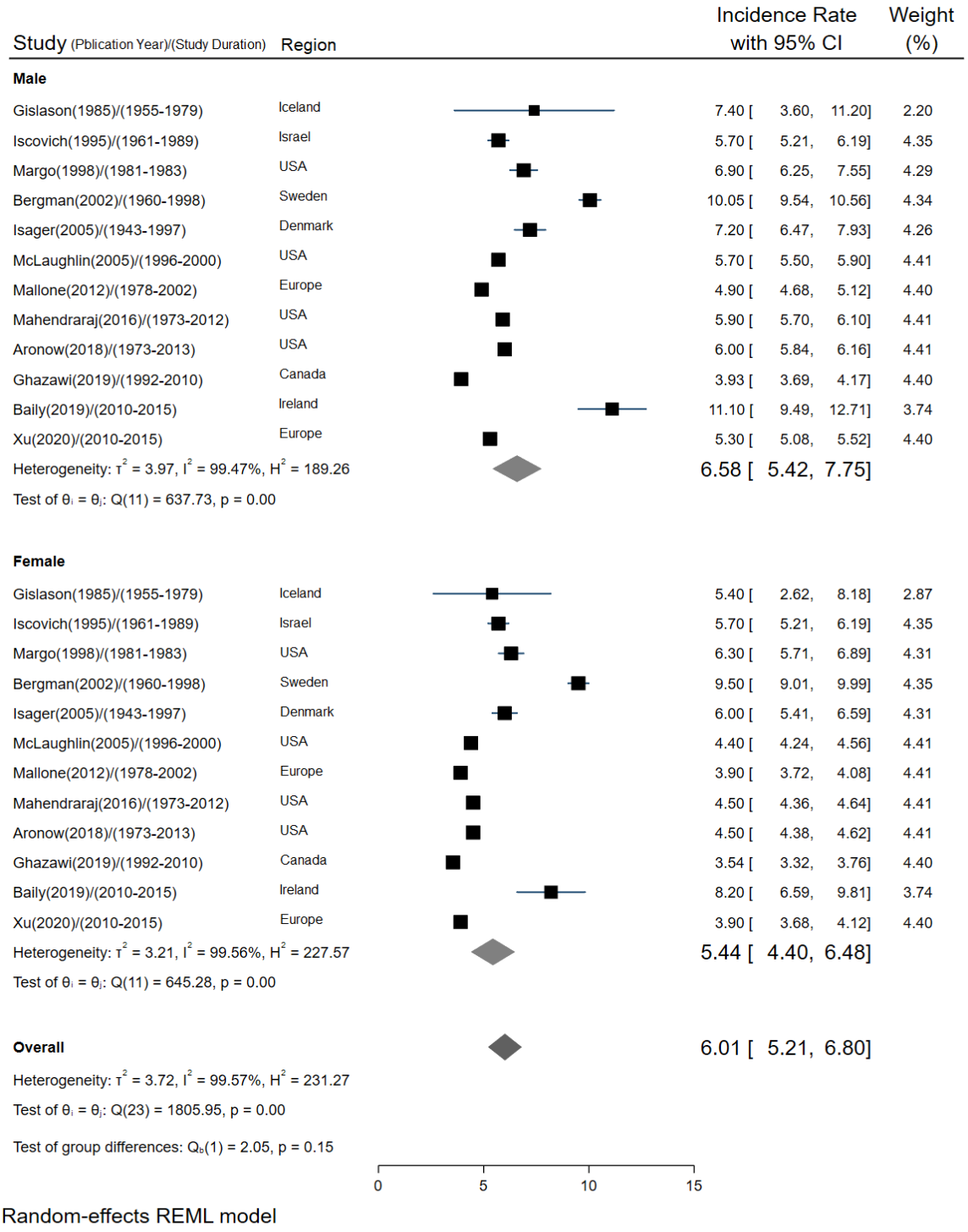

Figure 4. Forest Plots from Meta-Analysis of Published Incidence Trends for Male and Female UM.

Discussion

Summary of Main Outcomes

This systematic literature review, meta-analysis, and meta-regression is the first research to study pooled estimates of UM incidence of worldwide population based studies. Our findings revealed that in North America, the incidence rate of UM during more than last 4 decades (following deleting outliers) has been decreasing in terms of temporal trends. However this trend remained unchanged in European countries in the same period of time. In Asia, where the diversity of ethnic groups are present, until we're armed with enough data, we could not make a conclusion for this trend.

Geographical Burden of UM

In the current study, we have investigated the geographic pattern of UM incidence rates, which varied markedly among the North American, European and Asian countries. In our review, the overall incidence of UM in North America over the 44-year period from 1969 to 2015was 5.89 per million, and a statistical significant decreasing trend was found. It was expected that the risk of UM decreased about 0.09 per million persons per year.

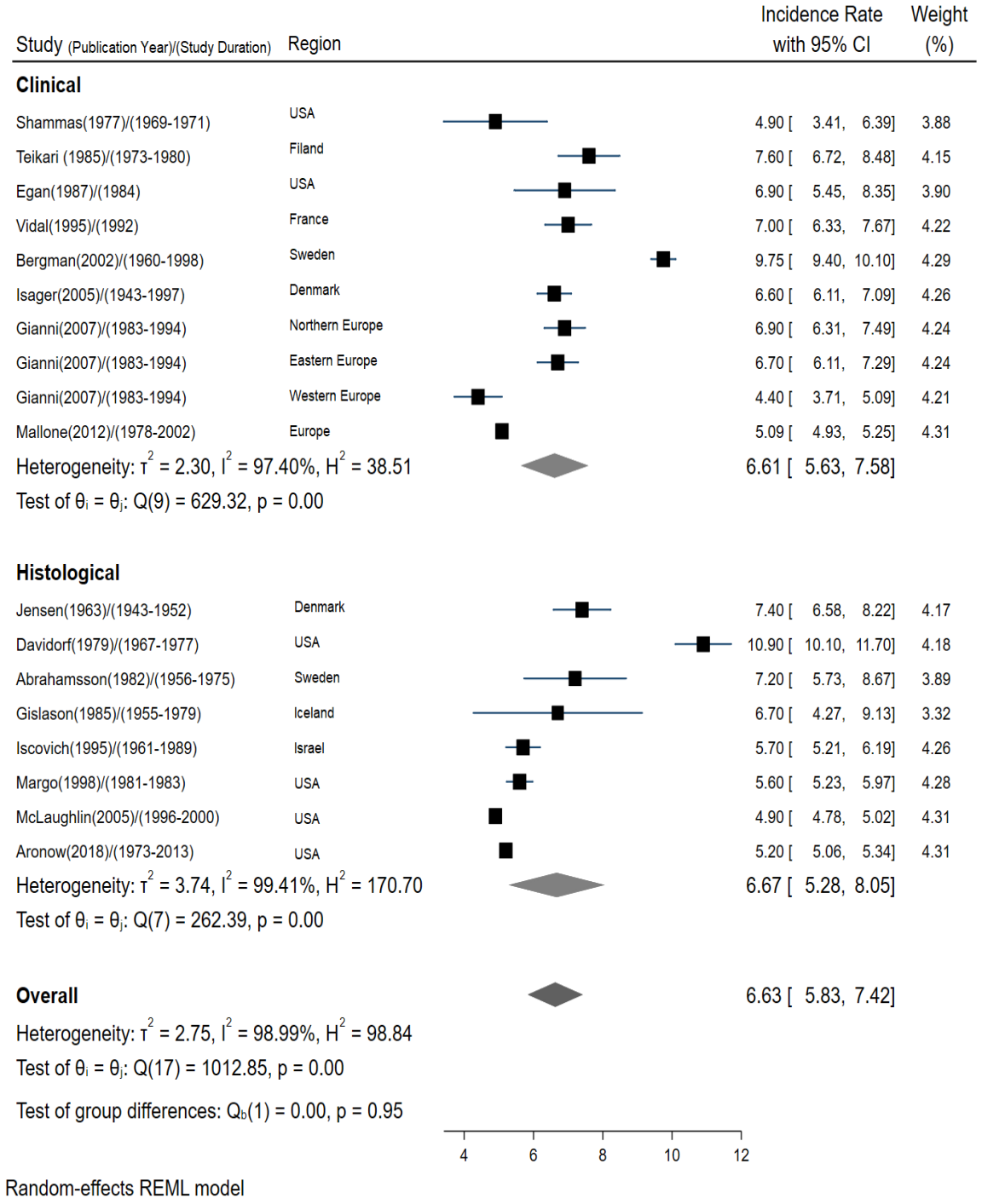

Figure 5. Forest Plots from Meta-Analysis of Published Incidence Trends for Clinical and Histological Diagnosis of UM.

Therefore, per 12 years, estimation showed a decrease of 1 case per million. For improving the estimates, studies were divided into two sections after omitting two outliers (Ghazawi et al., (????), for Canada and Davidorf et al., (????)). Despite a decreasing trend in both models, none of them were significant. This discrepancy along with the outliers can be the results of small sample size. There were only 9studies for northern America and one of the outliers (especially Ghazawi et al. (49) from Canada) affected the estimate significantly (weight= 12.9%).

Aronow et al., (2018) Using SEER database (1973-2013) reported the inci¬dence of UM has remained stable with a minor increase in Whites. Moreover, Singh et al., (2011) showed that between 1973 and 2008 the incidence of UM in the United States has not changed significantly.

Although these studies were almost inconsistence to our results, there was no any statistical analysis in this paper based on P-value calculation. Despite lack of trend analysis in those studies, the illustrated plot showed a decreasing trend from 1973 to 1988 and a flat trend till 2013.

The reported trend plot by Aronow et al., (2018) was in concordance by the attained result reported by

Table 1. The Characteristics of Included Studies

continent	Sub continent	country	reference	period	n	Age at diagnosis	Diagnosis method	metastasis	mortality	location	race
		US(Lowa)	Shammas (63) -1977	1969-1971	41		clinical				white
	North America	US(Ohio)	Davidorf (37)(1979)	1967-1977	698		histologic				white
America		US (New-England)	Eagan (56) (1987)	1984	85		clinical				
		US (Florida)	Margo (17) (1998)	1981-1983	873		histologic				White Black
		US	Mahandara Ji (4)(2016)	1973-2012	7516	61.4 (SD 15)	Clinical +histopatholgy	109		Cbd+choroid	White Black Other
		US	Aronow (3)(2017)	1973-2013		62(5-100)	Clinical + Histopathology			Cbd+choroid	White Black Other/unknown
		US	McLaughlin (64)(2005)	1996-2000	4030					Uveal	
		Canada	Ghazawi (49)(2019)	1992-2010	2215	61.49 (SD 14.21)				Uveal	
		US	Xu (65)(2020)	2010-2015	2631						White Black Other/unknown
		Denmark	Jensen (33)(1963)	1943–1952	305		Histologic				
	North Europe										
		Iceland	Gislason(35)(1985)	1955–1979	29		Histologic			Uveal	
Europe		Sweden	Bergman (30)(2002)	1960–1998	2997		Clinical			Uveal	
		Sweden	Abrahamsson (40)(1983)	1956–1975	91		Histologic				
	Center Europe										
		Denmark	Isager(53)(2005)	1943–1997	388		Clinical			Uveal	
		Finland	Teikari (27)(1985)	1973–1980	382		Clinical			Cbd+ choroid	
		Ireland	Baily (61)(2019)	2010 - 2015	235	61.7				Uveal	

Table 1. Continued

continent	Sub continent	country	reference	period	n	Age at diagnosis	Diagnosis method	metastasis	mortality	location	race
	Center Europe		(40)(1983)								
		England	Keenan (46)(2012)	1999-2010	2171					Uveal	
		Europe	Gianni (44)(2007)	1983-1994		60.4	Clinical			Uveal	
		Europe	Mallone (47)(2012)	1978–2002	4097		Clinical			Uveal	
		France	Vidal (29) (1992)	1995	412	61.5 (7 to 93 years		10		Uveal	
		Israel	Frenkel (62) (2008)	1988-2007	558	60.8 (SD 16.5 years) (range 5-95)		74	7	Uveal	
Asia	West Asia										
	East Asia										
		South Korea	Park (48) (2015)	1999 - 2011	326		Microscopic+ clinical				

Andreas Stang and Jockel, (2004). They showed that out of 14 studied populations, one population showed a slightly decreasing incidence trend (United States SEER Caucasian population), from 1974 to 1988 which is compatible with our result, 2 European registries from France and Italy showed an increasing incidence trend, and the remaining 11 registries did not revealed any significant change over time.

Andreas Stang et al., (2005) suggested that the decreasing incidence in the United States SEER Caucasian population is mainly due to the declining incidence early in the registration period (from 1974 to 76). Importantly, the immigration of African or Asian people with dark skin has changed the pigment profile of North American and European populations in recent decades (Jablonski and Chaplin, 2012). Decreasing incidence in North America may be justified with reduced UV exposure due to shifting of outdoor occupations to indoor ones or a change in lifestyle such as wearing sunglasses during leisure activities (Virgili et al., 2008). However it should be noted that in contrast to cutaneous melanoma, the role of sun exposure in development of UM is controversial. Although epidemiological and meta-analysis studies have failed to demonstrate an association between sun exposure and UM, the protective role of sunlight-induced vitamin D production should not be overlooked (Brożyna et al., 2020).

Considering the fact that the most of included studies were from northern Europe, the incidence rate of UM in this continent was between 4.6- 10 per million. The overall incidence of UM in Europe over the 72-year period from 1943 to 2015 was 7.10 per million. In these countries, there was no statistically significant trend during this interval. Bergman et al., (2002) analyzed incidence trend of the Swedish UM data from 1960 to 1998, In spite of initial incidence reduction by end of the 1980s; thereafter, the incidence rate was slightly increased or remained stable. In another study by Isageret al., (2005) in Denmark, substantially increase in incidence of iris melanomas was observed, whereas the incidence rate for choroid/ ciliary body was unchanged. In addition, Virgili et al., (2008) found stable incidence during the period time of 1983 – 1994.

It is also important to note that based on cancer registries in countries including England and Wales, Australia, United States, Finland, German Democratic Republic and Sweden a decrease in UM rates have been reported based on morphological confirmation (Vajdic et al., 2003, Inskip et al., 2003, Margo et al., 1998, Bergman et al., 2002, Foss and Dolin, 1996, Stang and Jockel, 2004, Lommatzsch et al., 1985, Singh and Topham, 2003).

We also analyzed the incidence rate of UM in terms of diagnosis methods, either histological or clinical based. The incidence rate based on clinical diagnosis during 1943-2013 years was 6.61, which was compatible with 6.67 per million for histological diagnosis method during 1943-2000 years.

One of them was by Iscovich et al., (1995) for Israel (IR=5.7, SE=0.37) and another ones were published by Park et al.,(2015) for South Korea (IR=0.42, SE=0.02) and Tomizuka et al., (2013) (IR=0.64, SE=0.05) for Japan

The incidence of UM in the Asian population is low (Hu et al., 2005, Park et al., 2015, Iscovich et al., 1995, Kivelä, 2014). It has been reported 5.7 by Iscovich et al., (1995) for Israel, 0.42 (SE=0.02) for Korea by Park et al., (2015) and 0.64 per million by Tomizuka et al., (2017) for Japan. Because of heterogeneous results, these two studies cannot be merged and make a conclusion (Egan et al., 1988; Paul et al., 1962; Shields and Shields, 2008; Phillpotts et al., 1995; Hu et al., 2005).

In the present study, the incidence of UM based on sex was 5.44 in females and 6.58 in males. This might be due to the intrinsic profile of population worldwide. Although the incidence rate in males is higher than females, the overlapping confidence intervals showed that the incidence rate is not significantly different between males and females. No sex predilection has been reported in some other studies (Hammer et al., 1996; Iscovich et al., 1995; Margo et al., 1998; Ghazawi et al., 2019).

Based on our results, the mean age at diagnosis was 61.32 which is consistent to previous studies (Baily et al., 2019; Jensen, 1963; Frenkel et al., 2009). Different incidence rates of UM in North America, Europe and Asia may reflect regional differences in ethnicity with lower risks among Asians and populations with higher levels of pigmentation in the iris.

Limitations

There are several limitations to this study. The first one is limited geographic distribution of published data regarding UM epidemiology. More than 90% of published studies have been conducted in North America and Europe in populations of Caucasian origin, and enough data from Asia and Africa are not available.

The second limitation of our study was related to wide range of heterogeneity in study design and considered time period in search result which urged us to eliminate low-quality studies.

In conclusion, this review summarizes published estimates of global incidence in UM. In general, a continuing decrease in incidence rates was evident across North America in recent decades. However, while the trends were stable in European countries; they still have the highest incidence rates, worldwide.

Ocular oncologists should consider a broad international consortium organization or global registration system to conduct a standardized method to analyze the relationship between environmental factors, UM incidence, phenotype and recent advances regarding the molecular characteristics of UM. Such an initiative may lead to significant advances in the knowledge of UM mechanisms. Epidemiological surveillance is essential to detect early changes in incidence trends.

Author Contribution Statement

M.N. supervised the study.F.A. performed the bibliography research and prepared the initial draft, R.M commented on and revised the manuscript, G.K prepared the part of the initial draft, A.P and S.C. performed the statistical analysis, and S.C contributed to the study design.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval

Our study was approved by the Ethical Committee of Iran University of Medical Sciences

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