Association between smoking and uveal melanoma: a systematic review

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Abstract

Background: The aim of this study is systematically review the scientific literature on the relationship between tobacco smoking exposure and UM.
Methods: The search was performed on Medline and Scopus databases. For each database, we used the following query: "smok AND (eye OR uveal) melanoma".*
Results: 3 observational studies were considered suitable, two case-control studies and one cohort study. There is no significant evidence in the scientific literature about the association between smoking and UM.
Conclusions: More complete and multi-center studies are desirable, giving the importance of smoking as a risk factor in the development of cancers.

Keywords: *Tobacco smoking, tumors of the eye, uveal, melanoma*

1.Introduction

Uveal melanoma (UM) is the most common intraocular primary tumor in adults: it represents about 90% of ocular tumors. However, it is a relatively uncommon disease since the incidence cases are approximately 350-400 per year in Italy, equivalent to about 6-7 cases per million people [1-3]. The tumor can affect all three sections of the uvea, i.e. iris, ciliary body and choroid, and its localization is the most frequent after the cutaneous one. UM is extremely rare in non-Caucasian races; according to data reported in literature, white race has an eight times greater risk of developing this cancer than the black race [4,5]. The pathogenesis is multifactorial: the interaction between genetic and environmental factors causes the development of the neoplasia [6]. As far as the genetic factors are concerned, different studies, conducted on a wide range of patients, have allowed the identification of an increased incidence of UM in some family groups; it is still a rare condition and can be attributed either to genetic predisposition (monosomy 3) or family exposure to specific environmental factors [7]. Keeney et al. at the beginning of '80 of the last century pointed out the localization of nitroso-nor-nicotine in the choroid of experimental animals and provided preliminary data suggesting that smoking might be a significant risk factor in ocular melanoma. They concluded that "this work should be followed up by appropriate experimental and epidemiologic studies" [6]. Moreover, Ajani in 1993 confirmed this hypothesis [8].

The aim of this study is systematically review the scientific literature on the relationship between tobacco smoking exposure and UM.

2. Material and Methods

Identification of Relevant Studies

The scientific literature review was based on Electronic medical databases. The search was performed on Medline and Scopus databases. For each database, we used the following query: "smok* AND (eye OR uveal) melanoma".

Articles were retrieved from the medical area of PubMed and Scopus. Moreover, all potentially relevant studies found in the references of the selected articles were included. Only articles published until May 2014 were considered.

Data Extraction and Quality Assessment

The selection of articles, performed according to the PRISMA statement [9], is shown in the flowchart (Figure 1). The duplicate papers coming from PubMed and Scopus consultation were removed.

The inclusion criteria were as follows:

(i)observational studies;

(ii)English language;

(iii)availability of full text;

(iv)data concerning the association between smoking and UM.

The full texts of included publications were analyzed by two different researchers independently.

3. Results

Identification of Relevant Studies

A total of 58 studies were found through PubMed (15) and Scopus databases (43). Of these, 6articles were excluded because of duplicates of Medline and Scopus outcomes, whereas 44 were excluded because they did not fit with the inclusion criteria.

Finally, 3 observational studies were considered suitable, two case-control studies [10, 11] and one cohort study [12].

Case-control studies

Stang et al. investigate potential risk factors of UM in a case-control study implemented in Germany (Bremen Institute for prevention and Social Medine) from1995 to 1998. The authors select 118 patients (59 men and 59 women) with UM and 475 controls. Each case is matched with 4 potential controls according to sex, age and place of residency. The cases are selected whether from the patients with diagnosis of primary UM at the Division of Ophthalmology at the University of Essen or from the mandatory list of residence that covers the total population of the local district.

The eligibility criteria are: date at diagnosis (between July 1, 1995 and December 31, 1997), age at the time of diagnosis (between 35 years and 69 years), language prophecy (being capable to complete the interview) and place of residency at diagnosis (Hamburg, Bremen, Essen, Saarbrucken and Saarland without Saarbrucken).

The controls are recruited both from the population of the local district or from those with newly diagnosed begin diseases of the posterior aye segment who matched on sex, age, geographic region and size of city. In this way the authors define two study groups: the population based study and the hospital-based study.

Data are collected by giving a questionnaire to the patients in order to assess the exposure smoking factors. They assess smoking up to five years before interview. The smoking history is expressed as pack-years. For hand-rolled cigarettes, 1g of tobacco is counted as equivalent to one cigarette.

The patients are divided in 4 sub-groups: non-smoker, smoker 1-14 pack-years, smoker 15-29 pack-years, and smoker 30+ pack-years. Considering both populations, as before mentioned, the OR estimate for the first sub-group (181 controls/45 cases) is 1.0; for the second (96 controls/24 cases) is 1.1 (95%CI 0.6-2.1); for the third (77 controls/31 cases) is 1.3 (95%CI 0.7-2.7); for the fourth (96 controls/27 cases) is 1.2 (95%CI 0.9-1.7).

While the OR estimates for the sub-groups of the hospital-bases study are: 1.0 for the first sub-group (70 controls/31 cases, 1.1 (95%CI 0.5-2.3) for the second sub-group (33controls/17 cases), 2.1 (95%CI 0.8-5.3) for the third one (14 controls/15 cases), 1.3 (95%CI 0.8-1.9) for the fourth (24 controls/17 cases). Moreover, considering only the population-based study, the OR estimate for the first sub-group (111 controls/14 cases) is 1.0; for the second (63 controls/7 cases) is 1.2 (95%CI 0.4-3.3); for the third (63 controls/5 cases) is 0.8 (95%CI 0.3-2.5); for the fourth (72 controls/10 cases) is 1.2 (95%CI 0.7-2.0). According to the authors the evidence is that there is no association between smoking addiction and UM risk. Zinkhan et al. investigate the UM incidence and the association with past pregnancy, sociocultural level and smoking by conducting a case-control study.

The authors select eligible cases and control among the population located in the centre for eye tumors in North Rhine-Westphalia in Germany and contact them between September 2002 and March 2005. In particular they pick out 455 cases (241 male and 214 female) with UM and 827 controls (454 male and 373 female) with age between 20 and 74 years.

Both cases or controls are contacted by telephone in the case of non-response to the invitation letter; the authors asked people who refused to part95%CIipate to answer to a brief questionnaire, about 35 minutes on average, consisting of a few questions about the exposition to the risk factors considered in the study. The results refer to the kind of OR index: OR1 without additional adjustment and OR2 with additional adjustment for social class. The population of regular

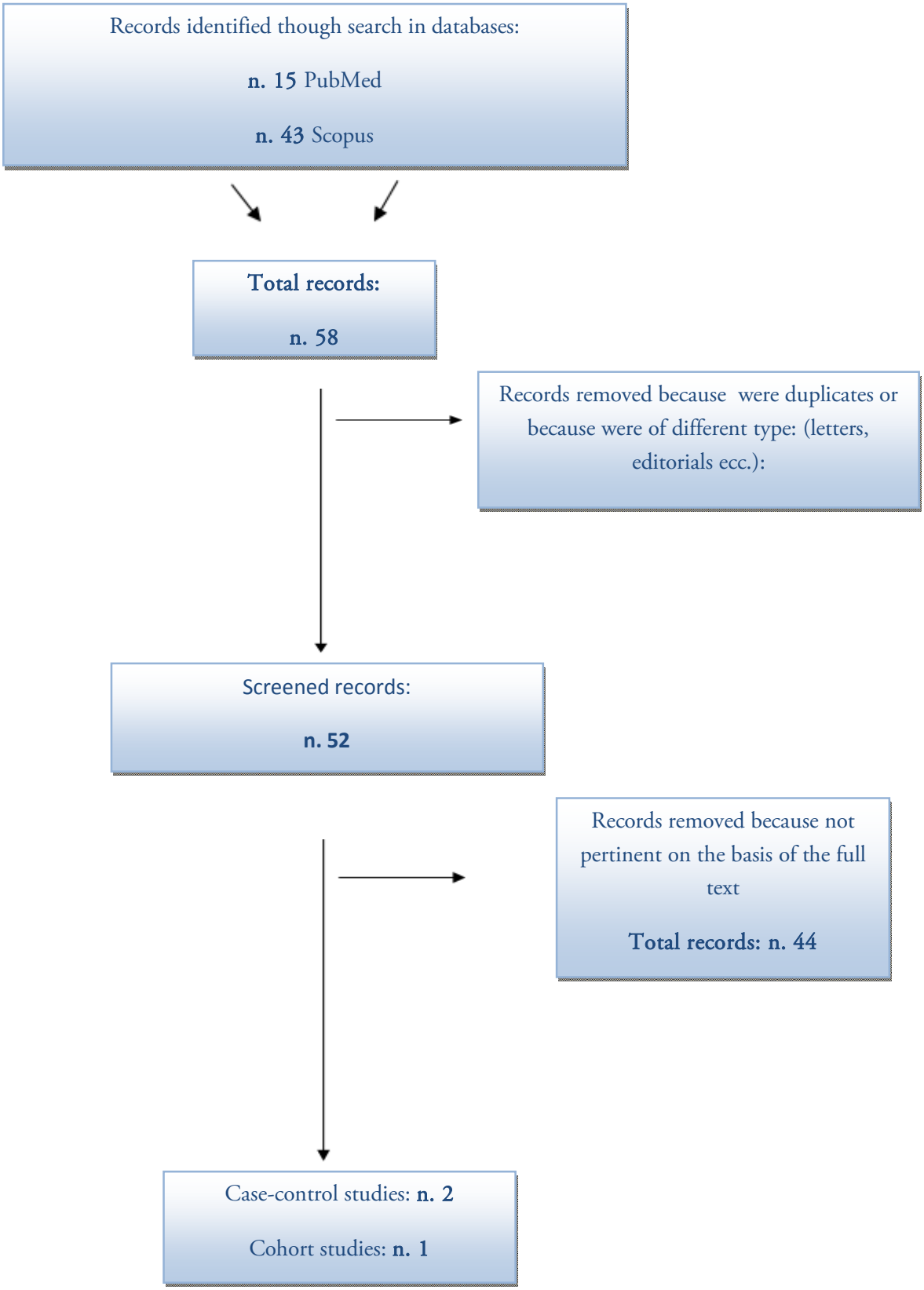

Figure 1. Flow chart of the selection of the studies of the systematic review.

smokers is divided into two big groups: non-smoker and smock users. Moreover the last group is divided into: current smoker and former smokers.

Specif95%CI ally for non-smokers (173cases\341 controls) the OR1 is 1.0 and the OR2 is 1.0; for smoker users (282cases\483controls) the OR1 is 1.19 (95%CI 0.99-1.55) and the OR2 is 1.20 (95%CI 0.92-1.56). For the current smokers group (92cases/178controls) the OR1 is 0.99 (95%CI 0.70-1.39) and the OR2 is 0.99 (95%CI 0.70-1.39) and for the former smokers (190cases\305controls) the OR1 is 1.31(95%CI 0.99-1.75) and the OR2 is 1.33 (95%CI 1.00-1.77).

The authors' conclusion is that there is no association between the current smokers and the UM, while the overall OR for the former smokers with respect to non-smokers is increased.

Cohort study

The cohort study conducted by of A. Odenbro et al. focus on the association between body mass index (BMI) and tobacco use on the risk of cutaneous malignant melanoma (CMM), and melanoma in situ (MIS) and intraocular malignant melanoma (IMM). Analyses were performed on a nationwide cohort of 339 802 Swedish construction workers from 1975 to 1977 and from 1978 and 1992 thanks to The Construction Industry's Organization for Working Environment, Safety and Health (Byggha¨lsan). Since the 95% of the cohort is male, the results cannot be extended to the female population.

Each cohort member was followed from date of entry into the cohort until cancer diagnosis, death, emigration, or end of follow up (31 December 2004), which ever occurred first.

Data are collected by giving a questionnaire to the patients in order to assess the exposure risk factors considered and every cohort member is exposed to three med95%CIal controls.

The authors identify in one cigarette 1 g of tobacco, 6 g for one cigar, in order to assess the daily amount of tobacco consumed by each worker.
Whereas for the snuff users and for the pipe users is recorded the weekly amount of tobacco consumed.

A total of 1639 on 339802 workers develop a cutaneous malignant melanoma (CMM) or melanoma in situ (MIS) and only 63 develop an intraocular malignant melanoma (IMM).

Moreover the 47% of the 690 smokers uses only one kind of tobacco while the 25% uses two or more types of tobacco.

The results are based on different characteristics of the tobacco addiction: for what concerns the smoking status, the formers have a RR index of 1.05 (95%CI 0.52-2.13), the current smokers have a RR of 0.57 (95%CI 0.28-1.13); the smoking duration is measured daily in gr. And the RR is 0.92 (95%CI 0.36-2.32), from 6 to 15 g the RR is 0.78 (95%CI 0.39-1.58), for more than 15 g the RR is 0.50 (95%CI 0.20-1.25). The smoking duration is measured in years and the RR is 1.07 (95%CI 0.42-2.76) from 1 to 10 years, 1.23 (95%CI 0.59-2.52) from 11 to 20, and 0.39 (95%CI 0.17-0.90) for more than 20 years. As regard to the amount of tobacco smoked, measured in gr. (duration * quantity), for 1-499 gr the RR is 1.19 (95%CI 0.64-2.18), for 500 to 999 gr RR is 0.17 (95%CI 0.04-0.72), for more than 999 gr the RR is 0.22 (95%CI 0.03-1.62). As far as concerns the UMcessation in years, the RR is 0.72 (95%CI 0.27-1.93) from 1 to 10 years, while for more than 10 years the RR is 1.76 (95%CI 0.74-4.17). For what concerns the type of tobacco consumed, the RR is 0.86 (95%CI 0.45-1.62) for cigarettes consumers; the RR is 0.64 (95%CI 0.24-1.72) for pipe consumers. For the tobacco snuff the RR is 1.14 (95%CI 0.43-3.07) while for who consumes more than one kind of tobacco the RR is 0.57 (95%CI 0.28-1.16).

4. Discussion

Melanoma arises ex novo in most cases, while, in a lower percentage of cases it develops starting from a pre-existing nevus. [13, 14] The risk of developing a melanoma from a choroidal nevus is low (the rate of transformation is 1:5000), however this risk is surely higher than the case in which there is no pre-existing nevi [15].

Since there is evidence of an increasing rate of melanoma growth and onset during the pregnancy, it is possible to consider also hormonal influences as cancer progression. The presumed onset mechanism would recognize the effect of the stimulus on the melanocytes played by estrogen; however it has not yet been identified the expression of estrogen receptors by neoplastic cells [16]. Other risk factors for choroidal melanoma are important; these include exposure to sunlight, especially in subjects with clear iris, since they are less protected from the harmful effect of radiation. Moreover viral infections, ocular trauma (in particular occupational exposure to chemicals radiation and environmental contaminants) seem to play an important role. However, the search for an association of those factors with the onset of choroidal melanoma shows controversial results.

In this systematic review we consider, in particular, another risk factor, i.e. tobacco smoking. This choice is due to the fact that there are no enough papers that study the correlation between the chroidal melanoma incidence and smoking habits. In fact, according to our search algorithm-smok * AND (OR eye uveal) melanoma- only three studies (two case-control and a cohort-study) were pertinent.

The first case-control, Stang et al. evaluate the

potential risk factors for UM in German population. The main risk factors taken into account were: medical history, the phenotypic characteristics, lifestyle and occupational risk factors. They assess tobacco consumption in the previous five years from the interview. Concerning cigarette smoke exposure, the interviewees were stratified into 4 groups: non-smokers, smokers with 1-14 pack-years, 15-29 pack-years smoking and smokers with 30 + pack-years. The authors conclude, based on the results obtained, that there is no association between smoking status and the risk of development of UM.

In the second case-control study, conducted by Zinkhan et al. the incidence of UM and its association with previous pregnancies, socio-cultural level and smoking habits in the population of the German federal state of Rhine-Westphalia are evaluated. The study population was divided into 2 main groups: non-smokers and current smokers. The second group was stratified into two groups: current smokers and former smokers. The authors observe the absence of association between current smokers and UM and an increasing OR for former smokers with respect to non-smokers. The increased risk of onset UM in former smokers may be attributable to multiple genetic and environmental factors that would add up over time, especially if we consider the multifactor pathogenesis of cancer.

The final study considered is by Odenbro A. et al. with a cohort design that examines the association between body mass index (BMI) and tobacco consumption with the risk of developing cutaneous malignant melanoma, cutaneous melanoma in situ and intraocular malignant melanoma. The exposure to these risk factors is evaluated in a cohort of 339 802 Swedish construction workers. The 95% of the cohort is male. In relation to the habit smoking status, the study population is stratified into different groups on the basis of actual exposure, duration of exposure and the amount of tobacco consumed. From this study there is no association between tobacco smoke and UM.

The present systematic review has some limitations, especially concerning the relatively low number of primary studies conducted on this issue.

In conclusion, there is no significant evidence in the scientific literature about the association between smoking and UM. Therefore, more complete and multi-center studies are desirable, giving the importance of smoking as a risk factor in the development of cancers.

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