



## Glaucoma and cigarette smoking: a review of narrative reviews

Francesca Di Murro<sup>1</sup>, Gianpaolo Smaldone<sup>2</sup>, Elena Pacella<sup>2</sup>, Giuseppe La Torre<sup>1</sup>

### Affiliations:

<sup>1</sup>Department of Public Health and Infectious Diseases, Sapienza University of Rome

<sup>2</sup>Department of Sense Organs, Sapienza University of Rome

\***Corresponding author:** Dr. Francesca Di Murro – Department of Public Health and Infectious Diseases, Sapienza University of Rome. Email: francesca.di.murro@hotmail.it

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### Abstract

**Background:** Glaucoma is an optic neuropathy associated with visual field changes for which high intra-ocular pressure is a major risk factor. Emerging research indicates that modifiable factors, among which the cigarette smoke, besides IOP may be associated with the presence of glaucoma.

**Objective:** The objective of the study was to perform a review of narrative reviews to examine on the relationship between cigarette smoking and glaucoma.

**Methods:** The results of all narrative reviews in the scientific literature about glaucoma and tobacco smoking were analyzed. A quality assessment was performed according to an easy and convenient tool for the quality assessment of narrative reviews for systematic reviews (International Narrative Systematic assessment) the INSA tool. Literature searches were performed using PubMed.

**Results:** 20 studies about relation between glaucoma and smoke were collected, no restriction language was applied. 15 of these studies have been excluded. We selected among them 5 reviews. With the INSA tool we measured the quality of the 5 selected narrative reviews. Studies that had a highest score with the INSA tool were two: A. Coleman et al. "Risk Factors for Glaucoma Needing More Attention" and R. Salowe et al. "Primary Open-Angle Glaucoma in Individuals of African Descent: A Review of Risk Factors".

**Conclusion:** The narrative reviews analyzed underline that there is no definitive association between cigarette smoking.

**Keywords:** glaucoma; smoking; narrative review

## Introduction

Glaucoma is an eye disease usually due to increased pressure within the eye. According to some sources it affects over 55 million people on Earth and is a major cause of visual impairment after cataract; in Italy it is estimated that about one million people will be affected, but it is estimated that half of the patients they are not aware (undiagnosed would then be about half a million). Blindness and low vision caused by glaucoma can be prevented as long as the disease is diagnosed and treated promptly. Chronic open-angle glaucoma is the most common form of glaucoma (about 80% of cases). It occurs due to an obstacle encountered by the aqueous humor in the flow. Iridocorneal angle is a complex located at the corner between the iris and the cornea. By this route the aqueous humor leaves the eye; its evaluation is crucial for a correct diagnosis of glaucoma.

The aqueous humor, directly responsible for ocular pressure (IOP), is produced behind the iris and precisely by the "ciliary processes", finger-like emanations of the ciliary body of the choroid. From this location, the aqueous humor flows out, always behind the iris (of the eye posterior chamber), to reach the pupil after which, along the anterior chamber (front of the iris) to arrive finally at a kind of filter (trabecular meshwork) located right on the corner formed between the root of the iris and the cornea, through which leaves the eye to be reabsorbed by the venous system. Thanks to the balance between the production and the elimination of aqueous humor the eye pressure is kept constant; in normal subject it varies between 10 mmHg (mmHg = millimeters of Mercury) and 21 mmHg. The aqueous humor, secreted directly into the posterior chamber by the ciliary processes, through the pupil reaches the anterior chamber from which it flows through three ways:

- trabecular outflow, which is the main street of the runoff (85%). At the level of the trabecular meshwork the passage of the liquid is less easy for the progressive narrowing of the pores and then other obstacles (Schlemm's canal, aqueous veins, episcleral veins) can influence the amount of water that leaves the eye.
- Outflow uveoscleral part of aqueous humor laterally deflects and comes out through the trabecular meshwork uveal until reaching the uveal tissue of the ciliary body and emerges from the eye with the veins of the choroid vessels. It represents about 14% of aqueous flow under normal conditions, but it could buy great importance in situations of altered trabecular outflow.
- Outflow iris. Finally there is a direct absorption by the iris is not well quantified, but surely it is of little importance in the dynamics of aqueous runoff. As well as the nerve fibers suffer a loss of their number in the

evolution of glaucoma, by the optic disc will recognize the progressive changes which change the appearance (degeneration of Schnabel and apoptosis). There are many individual variations papillary anatomy, but in general the papilla is pink and oval with a diameter of about 1.5 mm, a central part without retinal tissue said physiological excavation, a vermilion border (neural rhyme) and net margins separate it from the remaining retinal plane. In glaucoma it occurs a progressive increase of the excavation at the expense of the reduction of neural rhyme (ratio cup / disc = excavation / papilla; the normal is 0.3 in the advanced stages reaches 0.9) until the terminal stages with pale papilla and excavated in the pot.

But the excavation width is in itself be of limited significance if not associated with other risk factors and a large excavation is not necessarily pathological. Increased eye pressure (this is the most high, and longer, and the earlier the damage to the optic nerve), while not unique, is certainly one of the main and most obvious risk factors for the development of glaucomatous optic neuropathy premise on which they were based both theory, ischemic, according to which the increase in IOP interferes with the microcirculation of both the mechanical and optical nerve, according to which the high IOP directly damaging the nerve fibers in their passage through the head of the optic nerve. But today alongside other hypotheses to explain the death of retinal nerve cells in the optic nerve. First of all there is apoptosis, a "suicide" programmed cell, potentials that have all cells. Then they must understand what they are and how they interact factors that activate apoptosis in the nerve cells of the optic nerve and the relationship between them in the activation process. Apoptosis might be involved in addition to hereditary factors, vasospasm (as a hypothesis in normal tension glaucoma), the release of free radicals, impaired perfusion pressure, low blood pressure and vascular insufficiency, genetic mutations, toxic damage, and metabolic, immune or autoimmune mechanisms and the secondary nerve degeneration. These factors can contribute with different and more or less associated to the genesis and evolution of the damage to the optic nerve. So we tend to define chronic open-angle glaucoma: "as a multifactorial etiology progressive optic neuropathy characterized by morphological changes (excavation of the optic disc), resulting in a loss of retinal ganglion cells and their axons".

It develops slowly and usually has no symptoms, so we can realize that they are ill only when the damage to the optic nerve has already reached an advanced stage (thus should undergo periodic eye check-up). In the acute angle-closure glaucoma the iris can suddenly close the "discharge" (iridocorneal angle occlusion), causing a rapid increase in intraocular pressure in the case of the form called a "tight corner" (which affects about 10% of glaucoma, in 70% of cases of female).

This sudden increase in pressure, called acute attack of glaucoma, it is very serious if not treated in time can lead to blindness in a short time. The main symptoms are blurred vision, the appearance of anomalous halos around lights, violent eye pain, nausea and vomiting.

The factors that predispose to glaucoma are the reduction of the depth of the anterior chamber (reduced space between cornea and iris), that you can have in the case of high hyperopia, but also the total cataract. There are some risk factors that can increase the likelihood of developing the disease: Old age, ocular trauma, hereditary predisposition, diabetes, systemic hypertension, prolonged treatment with cortisone drugs, myopia. The only way to make an early diagnosis of glaucoma is to undergo a complete eye examination. During the visit, the parameters that must be controlled are essentially:

*Intraocular pressure:* With the tonometer can be assessed by the pressure within the eyeball so as to promptly detect a possible increase.

*The appearance of the optic nerve:* With the ophthalmoscope the optic nerve can be observed directly; in the case of glaucoma, there was an increase in the papillary excavation.

*Computerized perimetry:* It is a method of investigation with which we measure the sensitivity of the different areas of the retina. The examination allows early identification of the damage and to assess the effectiveness of the therapy much better than with the previous manual perimetry methods.

#### *New methods of assessment of the optic disc:*

Thanks to technological development have been introduced into clinical practice new methods of optic disc evaluation, as the CSLO (Confocal laser ophthalmoscopy), the SLP (scanning laser polarimetry) and OCT (optical coherence tomography).

It is simple instrumental examinations to be carried out which allow the detailed study of the optic disc and, above all, the measurement of the thickness of the nerve fibers around it, where the thinning is due to the loss of retinal cells (in particular those these ganglion and their axons).

The diagnosis of glaucoma can not be exclusively based on the use of these techniques. The glaucomatous require periodic inspections. The disease, in fact, may worsen without giving symptoms and, if so, may need to change the type of therapy. Once the damage occurred can not be reversed: we resort to drugs and possibly surgery to try to preserve at least the existing visual function [1].

The smoking habits is one of the biggest public health problems worldwide and is one of the biggest risk factors in the development of neoplastic diseases, cardiovascular and respiratory.

According to the World Health Organization (WHO) tobacco smoke is the second leading cause of death worldwide and the leading cause of preventable death [2]. Smoking is not only responsible for lung cancer, but also represents the main risk factor for non-malignant respiratory diseases, including chronic obstructive pulmonary disease (COPD) and is one of the most important cardiovascular risk factors: a smoker has a risk of mortality due to coronary artery disease, higher by 3 to 5 times compared to a non-smoker. An individual who smokes throughout life has a 50% chance of dying from a disease directly related to smoking, and his life may not exceed an age between 45 and 54 years of age.

In general, it is considered that the smoker is seriously impaired quality of life, because of the greater frequency of respiratory diseases (cough, phlegm, recurrent bronchitis, asthma etc.) And heart (blood pressure, stroke, heart attack, etc.) which may limit activities of daily life.

Poor understanding of the etiology of Primary Open-Angle Glaucoma (POAG) has hindered attempts at early identification and treatment of this disease. All studies agree that POAG is a complex and multivariate disease. As of now, elevated intraocular pressure (IOP) remains the only treatable component of this disease, but high IOP is neither necessary nor sufficient to develop glaucoma [3]. Several factors have been definitively linked to POAG, but the mechanisms of their association to POAG remain inconclusive.

Older age, male sex, lower central corneal thickness, decreased corneal hysteresis, elevated intraocular pressure, myopia, vascular abnormalities, and positive family history were definitively associated with increased risk of POAG whereas there is no definitive association between cigarette smoking and POAG. In order to improve prevention and treatment, it is important to understand the many other risk factors associated with POAG and their relationships to each other.

The objective of the present “paper/study” was to perform a review of narrative reviews to examine the literature about relationship between cigarette smoking and glaucoma.

## Materials and Methods

### *Identification of Relevant Studies:*

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4]. The electronic databases PubMed was selected and the following algorithm was applied: glaucoma AND smoking AND review. Eligible studies were selected through a multi-step approach: title reading, abstract and full-text assessment. No restriction of languages or date of publication was applied.

The articles identified by search strategy were selected initially analyzing the title and the abstract and then were evaluated the inclusion criteria by full-text. Narrative reviews were included. Primary study case-control, cohort studies, cross-sectional and clinical trial, were excluded.

#### *Data Extraction and Quality Assessment*

Data extraction was carried out with the same strategy of the selection of the studies. A quality assessment was performed according to the INSA (International Narrative Systematic Assessment) tool. Criteria for assessing scientific quality of research narrative reviews according to INSA tool are:

1. Background of the study clearly explained / state of the art
2. Objective is clear
3. Description/Motivation of selection of studies
4. Description of study the characteristics included is clear
5. Presentation of results (paragraphs, tables, summary of data)
6. Conclusion is clear
7. Conflict of interest is stated (if existing and if no statement bad)

## Results

### *Study selection*

The selection of articles is shown in the flowchart, which was performed according to the PRISMA statement (**Figure 1**). Overall 20 papers were found through PubMed. Successively 15 articles that did not respect the inclusion criteria were excluded. For the analysis, 5 papers were finally selected.

#### *Characteristics of the studies*

The characteristics of the studies included are shown in **Table 1**. In particular this five studies investigated the relationship between cigarette smoking and glaucoma. Coleman et al. [5] said that a case-control study found that current cigarette smoking was related to glaucoma presence in multiple logistic regression analysis [6]. Other studies failed to find an association between smoking and glaucoma. Specifically, smoking was not related to open-angle glaucoma in a population-based cross-sectional study of Hispanics aged older than 40 years residing in Arizona [7] Smoking status has a strong association with eye health, especially age-related macular degeneration [8], but population-based studies found no association in the area of glaucoma.

Cheng et al. [9] said that there is a weak correlation between smoking and intra-ocular pressure[10,11,12]. A recent population-based study of 3752 non-glaucoma

subjects aged 40 to 84 years in the West Indies has shown that smoking is associated with a slightly higher intra-ocular pressure ( $P < 0.05$ ); Selective vasoconstriction might lead to a rise in the episcleral venous pressure, thereby impeding the outflow tract. There is a positive correlation between intra-ocular pressure and progressive glaucomatous damage in primary open-angle glaucoma [13]. Smoking may be an avoidable risk factor for glaucoma, but the conflicting results obtained from different investigations of the effect of smoking on the intra-ocular pressure have not established a causal relationship between the two. More studies are required to confirm such a relationship, which are likely to be subject to interaction with other factors.

C. W. McMonnies et al. [14] claim that smoking studies of the association between glaucoma and smoking have been contradictory. It has been hypothesized that, in the presence of genetic risk factors, exposure to environmental stresses such as smoking, corticosteroid medication and diabetes, results in an earlier age of onset of glaucoma. The risk of glaucoma in smokers may be higher in men [15].

Salowe et al. [16] state that there is no definitive association between cigarette smoking and POAG. Several studies have shown a positive association between smoking and POAG [17,18], while others failed to confirm these findings[19]. However, these studies focused on very small cohorts with unmatched case-control groups [20,21] or examined only the short-term effects of smoking [18]. More large-scale studies examining the long-term effects of smoking on POAG risk are needed to confirm these findings.

Pasquale et al. [22] claim that cigarette smoking is linked to many systemic illnesses and ocular conditions such as cataract [23] and age-related macular degeneration[24].

On the other hand, nicotine (a major component of cigarette smoke) also increases blood flow in regions of the brain rich in nicotine receptors such as the thalamus[25]. Nonetheless, the effects of nicotine on directly measured optic nerve blood flow and tissue oxygenation are unknown at this time. Currently, there is no strong evidence that IOP increases appreciably in the time immediately after smoking a cigarette[26].

In the Blue Mountain Eye Study only a modestly elevated IOP was found among smokers (16.3 mm Hg) versus non smokers (16.04 mm Hg;  $p = 0.03$  after adjustment for age and gender) [27]. Case-control and cross-sectional studies that evaluated the relation between cigarette smoking and POAG produced mixed, although mostly null results[28-35]. The best evidence to date is from a large prospective study among 111,215 health professionals throughout the United States which assessed cigarette smoking exposure repeatedly over a decade and found that cigarette smoking did not increase the risk of developing POAG.

Using the INSA tool, was performed quality assessment of five selected narrative reviews. The INSA tool has 7 items. Each item was rated on a scale of 1 to 7, where 1 signified that the instrument was not meeting its goals and 7 signified that goals were fully met. We assigned to the narrative review of Coleman et al. a quality score of 5 (Background of the study clearly explained / state of the art= 0; Objective is clear =1; Description/Motivation of selection of studies= 1; Description of study the characteristics included is clear= 1; Presentation of results (paragraphs, tables, synthesizing of data)= 0; Conclusion is clear= 1; Conflict of interest =1).

To Cheng et al. we assigned a quality score of 4 (Background of the study clearly explained / state of the art= 0; Objective is clear =1; Description/Motivation of selection of studies= 1; Description of study the characteristics included is clear= 0; Presentation of results (paragraphs, tables, synthesizing of data)= 0; Conclusion is clear= 1; Conflict of interest =0).

To C. W. McMonnies was assigned a score of 3 (Background of the study clearly explained / state of the art= 1; Objective is clear =0; Description/Motivation of selection of studies= 0; Description of study the characteristics included is clear= 0; Presentation of results (paragraphs, tables, synthesizing of data)= 0; Conclusion is clear= 1; Conflict of interest =1).

Salowe et al. has a score of 5 (Background of the study clearly explained / state of the art= 1; Objective is clear

=1; Description/Motivation of selection of studies= 1; Description of study the characteristics included is clear= 1; Presentation of results (paragraphs, tables, synthesizing of data)= 0; Conclusion is clear= 1; Conflict of interest =0).

Finally to Pasquale et al. was assigned a score of 4 (Background of the study clearly explained / state of the art= 1; Objective is clear =1; Description/Motivation of selection of studies= 1; Description of study the characteristics included is clear= 0; Presentation of results (paragraphs, tables, synthesizing of data)= 0; Conclusion is clear= 1; Conflict of interest =0).

## Conclusion

With the INSA tool studies that had a highest score were two: A. Coleman et al. "Risk Factors for Glaucoma Needing More Attention" and R. Salowe et al. "Primary Open-Angle Glaucoma in Individuals of African Descent: A Review of Risk Factors".

Selected studies state that there is no definitive association between cigarette smoking and POAG.

Given the large number of noxious substances contained in cigarette smoke, more studies to help understand why smoking is not adversely related to glaucoma may yield insights into the pathophysiology of POAG. More studies are required to confirm such a relationship, which are likely to be subject to interaction with other factors.

Figure 1. PRISMA Diagram

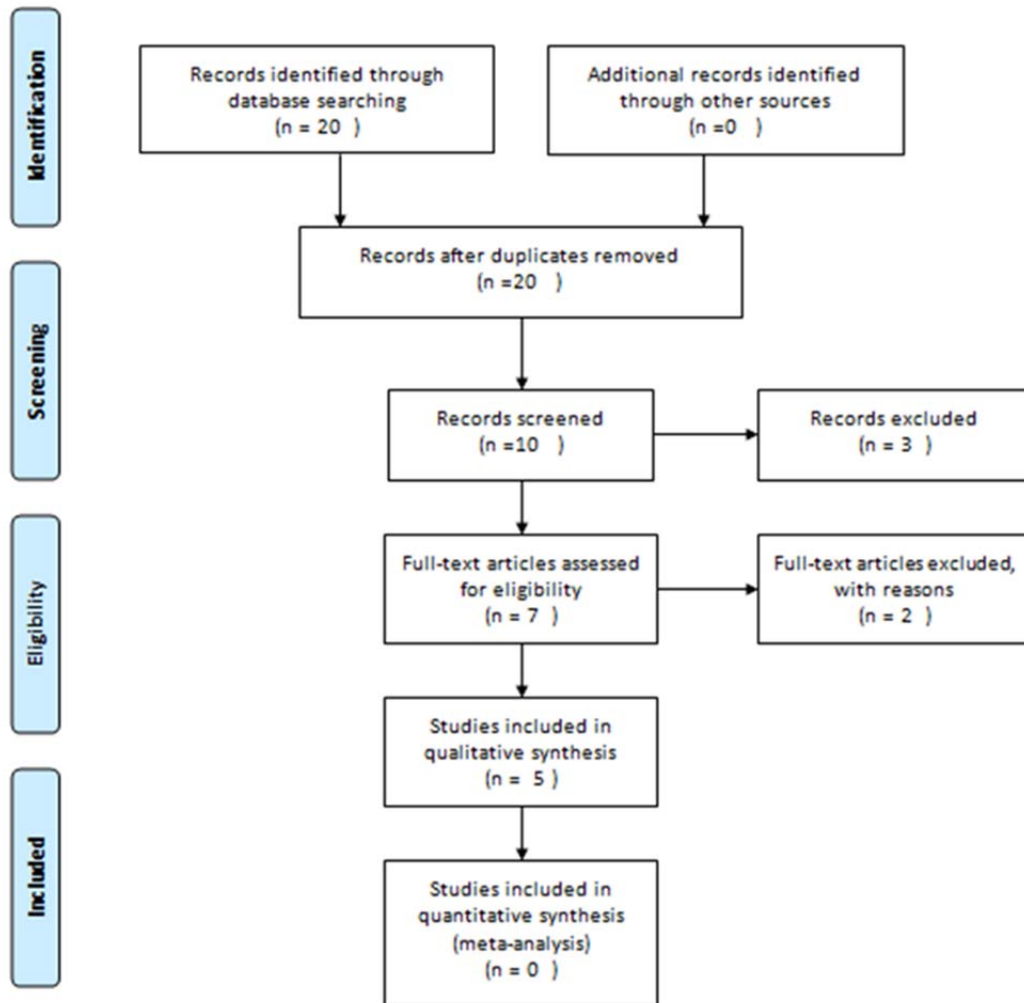




Table 1: characteristics of the studies included

First Author	Year	Country	Age	Study population	Smoke and glaucoma	Quality score
A. L. Coleman	2009	USA	Over 40	Narrative review	Population-based studies found no association between smoke and glaucoma	5
ACK Cheng	2000	China	Over 40	Narrative review	There is a positive correlation between intra-ocular pressure and progressive glaucomatous damage in primary open-angle glaucoma	4
C. W. McMonnies	2016	Spain	Over 59	Narrative review	In the presence of genetic risk factors, exposure to environmental stresses like smoke, results in an earlier age of onset of glaucoma	3
L. R. Pasquale	2009	USA	Over 40	Narrative review	There is no strong evidence that IOP increases appreciably in the time immediately after smoking a cigarette	4
R. Salowe	2015	USA	Over 50	Narrative review	There is no definitive association between cigarette smoking and POAG	5

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