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Review Article

Relationship between Knee Osteoarthritis and Smoking: Literature Review of Recent Research

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Abstract

Background: The knee osteoarthritis is considered the most prevalent form of osteoarthritis worldwide. BMI, age and knee injury were implicated as a risk factor for knee osteoarthritis. The sole protective factor that was discussed extensively in literature was smoking. However, study design and multiple limitations were found in literature

Aim: In this study, we reviewed the recent literature to stand on the protective effect of smoking on knee osteoarthritis after handling study limitations in older period

Methods: We conducted an electronic database search for suitable studies during, published in the last ten years, in five databases including; Google Scholar, Scopus, Web of Science (ISI), PubMed, and Medline. A manual search of references was done to detect any possible related papers. Two independent reviewers reviewed the resulting papers and reviewed based on our inclusion criteria.

Results: Based on our results, all the studies except three studies proved that smoking decreased the risk for knee osteoarthritis. Moreover, it was found that the higher the dose and duration of smoking, the higher the risk. Furthermore, when adjusting for BMI, gender and age, the significant effect of smoking persisted which abolish the theory that the effect of smoking is mediated through other covariates not the nicotine itself.

Conclusion: In the last ten years, the study design and limitations previously reported in literature were handled well. The protective effect of smoking against the knee osteoarthritis were well pronounced. Furthermore, we deduced that the protective effect of the smoking was mainly due to its biological effect not due to BMI or higher incidence of smoking in male as implied earlier.

Keywords: *Osteoarthritis; Smoking; BMI; Risk; Knee; Cigarettes*

Introduction

Osteoarthritis is a worldwide painful condition that influence quality of life [1]. There is a still huge dispute among physician for the definition of osteoarthritis [1]. Based on a study by Pereira., *et al*. the incidence of the osteoarthritis differed based on the definition [2]. Once it is defined based on the radiological assessment, the incidence of the OA was high, meanwhile, symptomatic and self-reported OA had less incidence [2]. Furthermore, the incidence rate varied based on the age, gender and the joint affected. In a study by Prieto-Alhambra., *et al*. they found that knee osteoarthritis is the most common representing total incidence of 6.5 per 1000 person-years while in females it reached up to 8.3 per 1000 person-years and 4.6 per 1000 person-years for males [3]. It was followed by hip and hand osteoarthritis [3]. Based on other studies, the incidence increases more with age especially after 60. It was estimated that the 10% of elderly people have osteoarthritis after 60 [1,4].

In this study, our focus mainly on the knee osteoarthritis which is considered the most common form of osteoarthritis [1,4]. There are many studied risk factors for knee OA. It was estimated that women had higher risk for development of knee OA than males especially from 45 years old and onwards [5]. In addition, BMI and history of knee injury increased the risk for knee osteoarthritis. Another study implied that weight related risk factors were only implicated in females. Surprisingly, many studies found smoking as one of the protective factors against knee osteoarthritis [1,6-9]. It was estimated that those who smoke 10 cigarettes or more had less risk [10]. However, a study explained that this effect might be indirect as generally, the smoking is much higher than in males who are usually have less incidence compared to females [11]. Furthermore, it was found that smoking leads to weight loss which is associated with less risk for OA [10,12].

On the other hand, another study had found that the nicotine, the main constituent of cigarettes, had anti-inflammatory conditions [13]. It acts through enhancement of the neurotransmitter release. Moreover, it was found to increase the proliferation, nicotine increases glycosaminoglycan and collagen synthesis. It also affected the metabolism of chondrocytes enhancing the biological environment of smoking [13,14]Based on this controversy, our study was set on to investigate the latest research on this topic and to stand on the real risk of the knee OA in smokers.

Methods

We conducted an electronic database search for suitable studies during, published in the last ten years, in five databases including; Google Scholar, Scopus, Web of Science (ISI), PubMed, and Medline. We used the MeSH (Medical Subject Headings) terms for smoking and knee osteoarthritis. A manual search was conducted searching the references of the included studies and the related studies in PubMed. We also searched systematic reviews for any relevant papers. We only included human studies assessing the relationship between knee osteoarthritis and smoking from 2009. We excluded conference papers, reviews, abstract only papers and books.

Two reviewers independently reviewed the found papers for fulfilling the inclusion criteria. Then, qualitative and semiquantitative synthesis of the evidence was performed.

Results

Sixteen studies were included for the literature review. Among the included studies, seven studies were cohort studies conducted in community and was population based. Three studies were case-control studies and one of them was hospital based. Six studies were cross-sectional studies conducted as population-based study. The total sample size of the knee osteoarthritis patients was 136367 patients. The diagnosis of the patients was based either on radiographic characteristics (Kellgren-Lawrence (KL) scoring) or symptomatic or based on management as total knee replacement (TKA). Only one study diagnosed Knee osteoarthritis patient using clinical examination. Four studies used total knee osteoplasty as a criterion for the diagnosis of sever osteoarthritis. Other studies used Kellgren-Lawrence (KL) scoring table 1. In this review, there was two types of studies, some directly assessed the protective effects of smoking. While the other studies indirectly assessed smoking as one of the risk factors of the knee osteoarthritis.

ID	Country	Site of data collection	Sample size	Definition of Osteoarthritis	Definition of smoking
Johnsen/2017 [21]	Norway	Population-based	55 188	KL ≥ 2 and symptom	Never, former and current smokers
Johnsen/2017 [25]	Norway	Population-based		KL ≥ 2 and symptom	
Kang/2016 [16]	Korea	Population based	9047	KL ≥ 2 and symptom	Ever, current, former
Liu/2016 [15]	China	Population based	1661	KL ≥ 2 and symptom	No detail
Hussain/2015 [17]	Australia	Population based	3529	TKA	Ever, current, former
Luo/2015 [26]	China	Hospital	297	ACR standard criteria	Ever
Zhang/2015 [18]	China	Population based	3789	KL ≥ 2	No detail
Leung/2014 [9]	Singapore	Population based	63,129	TKA	Ever, current, former
Mnatzaganian/2013 [19]	Australia	Population based	44,614	TKA	Current
Nicholls/2012 [22]	United Kingdom	Population based	707	TKA	Ever
Jiang/2012 [8]	China	Population based	595	KL ≥ 2; KL ≥ 3	Ever
Nishimura/2011 [23]	Japan	Population based	261	KL ≥ 2	No detail
Toivanen/2010 [20]	Finland	Population based	823	Clinical examination	Ever, current, former
Klussmann/2010 [6]	Germany	Population based	737	KL ≥ 2, or findings from surgery	Ever
Vrezas/2010 [7]	Germany	Population based	620	KL ≥ 2	Ever
Callahan/2010 [24]	United States	Population based	2627	KL ≥ 2; KL ≥ 2 and symptom	Current

Table 1: *The characteristics of the included studies.*

Does smoking decrease the risk of knee osteoarthritis?

We reviewed the included studies to assess the prevalence of knee osteoarthritis if present and the risk of knee osteoarthritis compared to non-smokers.

Liu., *et al*. is one of the studies that assessed the risk of smoking indirectly. In this cross-sectional study, they only included patients aged more than 40 years. The prevalence of osteoarthritis in this study was 15.79 % in women, and 17.40 % in men with no significant differences. The overall risk of knee osteoarthritis was significantly decreased in smokers compared to non-smoker [15]. Another study assessed the difference between direct and indirect smoking on the risk of osteoarthritis. In this study, the smoking significantly decreased the risk for knee osteoarthritis. However, there was no difference between direct and indirect smoking as a risk for knee osteoarthritis [16]. The prevalence of osteoarthritis in this cohort was 5.7% in men, and 20.1% in women. In a study by Hussain., *et al.* they investigated the effect of smoking indirectly on the risk of osteoarthritis as they assessed the birth weight [17].

Leung., *et al.* is a population-based study of both males and females. They compared between smokers and nonsmokers in both males and females for the risk of total knee replacement. In this study, they also compared the duration, dosage and the years since smoking cessation in both males and females [9]. Based on their results, they found that the higher the number of cigarettes smoked, the less the risk. They also revealed that the current smoker and the longer the duration of the smoker, the lower the risk. Furthermore, unlike the theories that supported that smoking only decreases the risk as it is more prevalent in males who already had low risk for knee osteoarthritis, in this study, they did not find any difference in the results between both males and females [9]. In addition, they adjusted for the weight to

check if it affects the risk for osteoarthritis in smoker and did not have any effect on the risk. This supports the evidence that the decrease the risk is mainly due to biological factors. The study is considered of strong evidence and high quality since they had a large sample size and adjusted for the possible confounders.

Other studies in review confirmed the protective effects of smoking. For instance, Zhang., *et al.* found that only 28.4% of the cohort had radiographic osteoarthritis. They also confirmed the inverse relation between the smoking and knee osteoarthritis [18].

Mnatzaganian., *et al.* also proved that the smoking significantly decreased the risk of knee osteoarthritis [19]. They compared between the male and female risk difference. They found that female smoker had 30% decrease in the risk while male smoker decreased the risk by 40% [19]. Jiang., *et al.* assessed the risk of smoking and compared it in both rural and urban areas [8]. They found that smoking was associated with less risk of knee osteoarthritis. They found that rural areas had the highest protective effect of the smoking [8]. Vresas., *et al.* compared the heavy smoking (≥ 55.5 pack years) was associated with less risk for knee osteoarthritis compared to non-smokers [7]. In addition, a study in Germany used the same classification. They also proved that smoking reduced the odds ratio and the higher the number of packs per year, the less the risk [6]. Moreover, another study classified the smoking into three categories smoking (never-smoked, ex-smoker and smoker). In this study, they found that physical activity augmented the protective effect of smoking [20]. Johnsen., *et al.* found that smoking decreased the risk for the need of total knee replacement in men and women by about 7% [21].

There are other studies that assessed the smoking protective effect indirectly through including it in multivariate analysis. Nicholls., *et al.* revealed that there was no significant protective effect of smoking when it comes to high BMI [22].

On the other hand, other studies failed to prove any significant protective effect of smoking. Nishimora., *et al.* did not find significant difference between smoker and non-smoker regarding the risk of osteoarthritis in Japanese patients [23]. Callahan., *et al.* compared the protective effect of smoking in male and females. They found that protective effect of smoking was only present in males but not females [24]. Furthermore, a study by Johnsen., *et al.* they found that men who smokes frequently suffer from knee pain and cartilage loss [25].

How much the duration and dosage of smoking affects the risk?

We observed that each study had its own classification of smoking. Liu., *et al*. classified smoking into three categories one less than 10 cigarettes, 10 to 20 cigarettes and more than 20 cigarettes [15]. They found that the risk was the least in the last category. This study did not assess the effect of other confounders on this risk [15]. Kang., *et al.* classified the smoking patterns into multiple categories. First category was based on the state of smoking either non-smoker, past smoker, indirect smoker or current smoker. Unlike the results of the previous studies, there was no significant risk difference between the groups even when adjusted for BMI and age. Another classification was based on the duration that was classified into none, less than 26 years, less than 40 years and more than 40 years. However, it is still non-significant and there was no significant decrease in risk of osteoarthritis even after adjustment of the analysis [16]. They also classified the daily smoking amount into less than half pack or full pack but still there was no significant difference in the risk [16]. They also found that duration of indirect smoking did not affect the risk for osteoarthritis. The same was present in Mnatzaganian., *et al.* who did not find a significant relationship between different categories of smoking and risk of knee osteoarthritis [19]. Hussain., *et al.* classified the smoking into non-smoker, current smoker, and former smoker. However, they did not assess the difference of risk among these groups and how it is interacted by the birth weight [17]. Vresas., *et al.* classified the smoking groups into three groups based on packs per year. They classified it into > 0 to < 11.5 pack years, 11.5 to < 27.3 pack years, 27.3 to < 55.5 pack years and more than 55 packs per year. The highest protective effect was observed in the heavy smoker group [7]. The remaining studies had the same classification of smoker versus non-smoker.

The influence of smoking: is it biological or just a coincidence?

Some studies reported that effect of smoking as a protective effect against knee osteoarthritis was mediated through other covariates like BMI and gender [11,12]. Others had proved it is mainly through its effect through nicotine [13,14].

Kang., *et al.* did not find any significant difference of the risk in all their classified categories based on dose, duration, and type of smoking after adjustment of the analysis based on age, sex and BMI [16]. In multivariate analysis of Zhang., *et al*. BMI, age, and gender significantly affected the risk of osteoarthritis in smokers [18]. Vresas., *et al.* found that the protective effect of smoking persisted even after adjustment for other confounders [7]. The risk was more prevalent in males than females. Moreover, the risk of knee osteoarthritis increased with increased BMI in smokers. Mnatzaganian., *et al.* adjusted for the age, co-morbidities, body mass index (BMI), physical exercise, and socioeconomic disadvantage and they found that it did not affect the protective effect of smoking [19].

On the other hand, another study that controlled for smoking in high BMI patients, revealed that there was no protective effect of smoking [24]. Consistent with this study, Johnsen., *et al.* found that the effect of smoking was dependent on the weight of participants [25].

Another study assessed the genetic basis of osteoarthritis. Although the study did not assess directly the smoking protective effect on knee osteoarthritis. When they controlled for smoking in the multivariate analysis, the significance of the gene as a risk factor did not change [26].

Conclusion

Based on our recent review, we can deduce that smoking has a protective effect against knee osteoarthritis based on its biological effect of nicotine. Despite the low number of studies that proved that contrary, the power of the positive studies can override these studies. However, more careful consideration of the country and site of residence as a probable cause of this variation.

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Conflict of Interest

None.

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