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Cigarette smoking and risk of uterine myoma: systematic review and meta-analysis

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ABSTRACT

Objective: To review the literature on the relationship between smoking and the risk of uterine myoma, we conducted a systematic review and a meta-analysis of published studies. In this meta-analysis, we included all identified studies of association between smoking and uterine myoma where these were case–control or cohort studies, reporting original data, ultrasound or histological confirmed diagnosis of myomas and information on the association between tobacco smoking and myomas.

Study design: We carried out a literature search on MEDLINE/EMBASE of all studies published as original articles in English up to October 2015, using the Medical Subject Heading terms and free search terms about myoma and smoking.

We selected only studies published in English. Moreover, bibliographies of the retrieved papers were reviewed, to identify any other relevant publication.

A total of 14 different studies were eligible for a qualitative synthesis and data extract from 10 studies were combined in a meta-analysis.

Results: The summary OR of former compared to never smokers was 0.93 (0.88–0.99) with no heterogeneity. The summary OR of current smokers compared to never smokers, was 0.83 (0.65–1.04), even if the subtotal OR in cohort studies was 0.85 (0.73–0.98) with no heterogeneity. When sensitivity analysis was performed the summary OR was 0.83 (0.71–0.97).

Conclusion: The primary meta-analyses found no significant effect of smoking on risk of uterine myoma. Subgroup analysis for study design showed a small risk reduction for current and former smokers in cohort studies. A sensitivity analysis showed an inverse association between ever smoking and uterine myoma. However, given the limited number of studies in each sub-analysis, weak associations and the absence of a dose dependent effect, caution should be paid in the interpretation of these findings and further investigation are needed.

Introduction

Uterine myomas are the most common benign tumors derived from smooth muscle cells in the uterine myometrium. In an online survey the self-reported prevalence of myoma, in the age group of 40–49 years, ranged from 9.4% in United Kingdom to 17.4% in Italy [1], but many tumors are asymptomatic and may not be diagnosed. Although the etiology of uterine myoma is still not well known, advances have been made in the understanding of the hormonal factors, genetic factors and growth factors of these tumors [2]. They have considered a hormonal-dependent pathological condition, where growth is thought to depend on ovarian hormones. Both estrogen and progesterone appear to promote the development of myomas. Factors that increase exposure to estrogen, such as obesity and early menarche, increase the incidence [2]. On the other hand, exercise and increased parity, which decreased exposure to estrogen, appear to be protective [3].

Smoking is a modifiable risk factor that may affect endogenous levels of hormones and women who smoke have lower urinary estrogen levels during the luteal phase of the menstrual cycle than non-smokers [4]. Nicotine can reduce androgens conversion to

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estrone secondary to inhibition of aromatase [5]. Thus, smoking is associated with impaired production and reduced levels of endogenous circulating estrogens [6].

Epidemiological studies investigating the role of tobacco smoking have shown conflicting results: some have shown an inverse relationship between cigarette smoking and risk of uterine myoma [7–10], but in others smoking increased the risk [11,12], whereas in two cohort studies it was unrelated to myoma risk [13,14].

Thus, in order to provide a summary of the available literature on the relation between cigarette smoking and uterine myoma, we conducted a systematic review and to allow an overall quantitative estimate of any such relation, we combined in a meta-analysis all published data on the issue.

Materials and methods

The review and the meta-analysis were performed according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) [15] and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [16]. We executed a MEDLINE/EMBASE search of papers published until October 10, 2015, using the Medical Subject Heading terms in free research "myoma" or "leiomyoma" combined with "smoking" and "tobacco" and free search terms "tobacco" or "smoking" or "smok*" or "cigarette*" in combination with "fibroids" or "uterine fibroids" or "myoma" or "uterine myoma" or "leiomyoma" or "uterine leiomyoma".

We selected only studies on humans, published as full-length papers in English. Moreover, bibliographies of the retrieved papers were reviewed, to identify any other relevant publication.

In the review we included all identified studies of association of smoking and uterine myoma, whereas studies were included in the meta-analysis only if: they were case–control or cohort studies, reporting original data; diagnosis of myomas was ultrasound or histological confirmed and/or clinically based; studies reported information on the association between tobacco smoking and myomas, including estimates of the relative risk (RR) or the odds ratio (OR), with the corresponding 95% confidence interval (CI), or frequency distribution to calculate them.

When we found more than one publication based on the same study population and data, we included only the one with most detailed information, or published most recently.

Data extraction and selection of eligible studies was carried out in duplicate by two investigators (FC and ER). Disagreements were solved by discussing and reviewing the respective issue. Cross-referencing of selected articles revealed no further eligible records.

From each publication we extracted the following information: country of origin; study design; number and characteristics of subjects (cases, controls or cohort size); age, if available; categories of tobacco smoking (smoking status, smoking intensity and duration of smoking, if available); measures of association (RR or OR) of myomas and corresponding 95% CI for every category of tobacco smoking, or frequency distribution to calculate them; confounding variables allowed for in the statistical analysis. When more than one regression model was provided, estimates adjusted for the largest number of confounding variables were considered.

The quality of the studies included in the meta-analysis were assessed using the Newcastle–Ottawa scale. This instrument was developed to assess the quality of nonrandomized studies, specifically cohort and case–control studies [17]. Studies were judged based on three broad categories: selection of study groups, comparability of study groups, and assessment of outcome (cohort studies) or ascertainment of exposure (case–control studies). Maximum score was 9.

For some studies, we pooled estimates of different categories of cases or controls using the method by Hamling et al. [18], thus taking into account their correlation.

Pooled estimates of the odds ratios (OR) and the corresponding 95% confidence intervals (CI) were calculated using fixed or, when significant heterogeneity among estimates emerged, random effects models. Sensitivity analysis were also performed.

We assessed the heterogeneity among studies using the χ^2 test [19] and quantified it using the I^2 statistic, which represents the percentage of the total variation across studies that is attributable to heterogeneity rather than chance [20]. Results were defined as heterogeneous for p values less than 0.10 [19].

We computed summary estimates for ever tobacco smokers, former smokers, current smokers, moderate current smokers, and heavy current smokers, as compared to never smokers.

Among the selected studies, six reported more categories of current smokers, thus we could calculate separate estimates for moderate and heavy current smokers but we were able to combine data from four studies because two studies considered ever smokers and not only current ones. Moreover, different cut-points for moderate and heavy smoking were chosen, depending on those shown in the papers: thus the cut-point for moderate smoking was less than 10 cigarettes per day in two studies [8,14], less than 15 cigarettes per day in one study [13] and less than 1 pack/day in another [11]. For heavy current smokers the cut-point was more than 19 cigarettes per day in two studies [11,14], more than 24 in one study [13] and more than 10 in another one [8].

Publication bias was evaluated using funnel plot [21].

Results

From the literature search we identified 345 articles, after the exclusion of 170 as duplicates. 331 studies were excluded for the reason shown in Fig. 1 and 14 articles describing 14 different studies were eligible for a qualitative synthesis and data extract from 10 studies were combined in a meta-analysis.

The main characteristics of identified papers are presented in Table 1: eight case control studies, four cohort studies and two cross-sectional. Of the selected studies, 8 were from USA, 3 from Europe and 3 from Asia. The articles were published between 1986 and 2012.

The effect estimates according to smoking exposure published in the selected articles were summarized in Table 2.

In the meta-analysis we excluded two cross-sectional studies [12,22], since in this study design exposure and disease are recorded at the same time: we could not determine whether the exposure preceded the occurrence of uterine myoma.

Moreover, two studies were excluded because the categories of smoking exposure were not clear [23,24] and in the American cohort study the presence of myoma was self-reported without any other diagnosis confirmation [24]. Overall, data from ten studies, including 374,212 women, 7612 with uterine myoma, were used in the meta-analysis.

Ever smokers

In qualitative analysis seven studies reported information on ever smokers (Table 2). Among these, three of them, two case–control studies and one cohort study, showed no effect of ever smoking. Two case–control studies showed a protective effect of ever smoking [7,9] and in the American study was dose dependent [9] whereas the exposure to cigarette smoking increased the risk of myoma in Iranian premenopausal women and in Slovenian women [23,25].

In quantitative analysis the Iranian study was excluded because the categories of smoking exposure were not clear. In the random