Humes, David and Ludvigsson, Jonas F. and Jarvholm, Bengt (2016) Smoking and the risk of hospitalization for symptomatic diverticular disease: a population-based cohort study from Sweden. Diseases of the Colon and Rectum, 59 (2). pp. 110-114. ISSN 1530-0358

Title: Smoking and the risk of hospitalization for symptomatic diverticular disease: a population based cohort study from Sweden

Short Title: Smoking and diverticular disease

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Word Count text: 1887

Word Count abstract:258

Contributions:

DJH/JFL/BJ – all contributed to the design and interpretation of the results of the study.

BJ – undertook the analysis of the data and had full access to all data in the cohort. DJH/JFL helped direct the analysis.

DJH- drafted the first version manuscript with JFL and BJ revising the manuscript.

DJH/JFL/BJ- revised and approved the final version of the manuscript

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Acknowledgements: None of the authors have any disclosures of conflicts of interest to declare. David Humes is funded by an NIHR Post-Doctoral Fellowship award. Jonas F Ludvigsson is funded by the Swedish Research Council. Bengt Järvholm is funded by the Swedish Research Council for Health, Working Life and Welfare (contract 2011-426). None of the funders had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript

Abstract

Background: Current studies reporting on the risk of smoking and development of symptomatic diverticular disease have reported conflicting results.

Objective: The aim of this study was to investigate the association between smoking and symptomatic diverticular disease.

Design: Cohort study

Settings: Swedish Construction Workers Cohort 1971-1993

Patients: Construction workers in Sweden

Main Outcome Measures: Development of symptomatic diverticular disease and complicated diverticular disease (abscess and perforation) as identified in the Swedish Hospital Discharge Register. Adjusted Relative Risks of symptomatic diverticular disease according to smoking status were estimated using Poisson regression.

Results: In total the study included 232,685 men and 14,592 women. During follow-up 3891 men and 318 women had a diagnosis of later symptomatic diverticular disease. In males, heavy smokers (≥15 cigarettes a day) had a 1.6 fold increased risk of developing symptomatic diverticular disease compared to non-smokers (Adjusted Relative Risk 1.56, 95% CI 1.42-1.72). There was evidence of a dose-response relationship as moderate and ex-smokers had a 1.4 and 1.2 fold increased risk compared to non-smokers (Adjusted Relative Risk 1.39, 95% CI 1.27-1.52 and Adjusted Relative Risk 1.14, 95% CI 1.04-1.27). These relationships were similar in females but the risk estimates were less precise due to smaller numbers. Male ever-smokers had a 2.6 fold increased risk of developing complicated diverticular disease

(perforation/abscess) compared to non-smokers (Adjusted Relative Risks 2.73, 95% CI 1.69-4.41).

Limitations: We were unable to account for other confounding variables such as comorbidity, prescription medication or lifestyle factors.

Conclusions: Smoking is associated with symptomatic diverticular disease in both males and females and associated with an increased risk of developing complicated diverticular disease.

Introduction

Diverticular disease and its associated complications such as acute diverticulitis place a significant burden on health care services[1]. This burden is expected to increase as the population ages[2] with an already reported increase in the occurrence of the most serious complication perforation[3, 4] and hospitalisation for acute diverticulitis[5]. Given these increases there has been interest in possible aetiological factors that could be modified to prevent these complications such as smoking[6]. There are biologically plausible reasons why tobacco use may be important in the pathogenesis of symptomatic disease as tobacco use impairs immune function, alters gut transit times, reduces blood flow and is associated with other intestinal inflammatory conditions[7-9]. A small retrospective study of 80 patients reported an association between smoking and an increased risk of diverticular complications[10]. A further small retrospective study reported an increased risk of stricture and perforation in patients undergoing elective colectomy for diverticular disease among smokers[11]. A larger population-based study of females reported a 1.23 fold increased risk (Relative risks (RR) 1.23, 95% CI 0.99-1.52) in current smokers of symptomatic diverticular disease when accounting for other confounding factors compared to non-smokers. The study also reported a greater risk of developing a perforation or abscess in current smokers compared to non-smokers (RR 1.89, 95% CI 1.15 to 3.10)[12]. However a study of the American Health Care Professionals (AHCP) cohort found no increased association between smoking and symptomatic diverticular disease when accounting for other confounding factors in males[13]. Current studies therefore do not provide population-based evidence of an association between smoking and symptomatic diverticular disease and have failed to demonstrate a dose-response relationship. The aim of this study was to assess

the relationship between smoking and development of symptomatic and complicated diverticular disease in a cohort of Swedish construction workers.

Materials and Methods

Patients and data sources

The Swedish construction workers cohort is a population-based prospective cohort of 389,132 individuals of whom 369,174 were men and 19,418 were women[14, 15]. They had participated in health examinations from 1971-1993. On entry to the cohort, data were collected on smoking, occupation description and Body Mass Index (BMI) by administration of a questionnaire. Through the personal identity number[16] we linked these data with data on hospitalisation for acute diverticulitis and complicated diverticular disease (diverticular abscess formation and perforation) from the Swedish Hospital Discharge Register. The baseline examination data were taken as the baseline data for the current study. Persons with unknown BMI or unknown smoking habits were excluded (n=80,451) as were those born before 1908 (n=1,038), i.e. older than 79 years in 1987 as were those who died or emigrated before 1987 (n=20,824).

Follow up

Study follow up started from first recorded health examination and continued until death or December 2013. National coverage of the Swedish Hospital Discharge Register became complete from 1987 we therefore undertook a sensitivity analysis which included only those having health examinations between 1987-1993 as a start date to the end of follow up to ensure the relationships observed remained.

Outcome Definition

Hospitalisation for symptomatic diverticular disease was defined as any patient with a World Health Organization International Classification of Diseases (ICD) code for diverticulitis K57, 562 (ICD 10) and 562 (ICD 9). Perforated diverticular disease and

diverticular abscess were defined as complicated diverticular disease using ICD-10 code K57.0, K57.2, K57.4, K57.6 or K57.8 and restricted to cases occurring 1997 to 2013. The first outcome noted in the register for symptomatic or complicated disease was used in the analyses.

Exposures

We categorized smoking into four groups of non-smokers, ex-smokers, moderate (≤14 cigarettes per day or equivalent), and heavy smokers (≥15 cigarettes per day). A previous review of smoking data at the first and second health examination (2–3 years apart) among 18,593 subjects in the "Bygghälsan" cohort found a 89% perfect match with data[17]. Inconsistencies regarding never-smoking status (study participants first indicated that they were current/former smokers in one questionnaire and then reported never-smoking in the second questionnaire) were reported for 2.7% [17].

We categorized BMI into 18.5-19.9 kg/m^2, 20.0-24.9 kg/m^2, 25-29.9 kg/m^2, 30-34.9 kg/m^2, and ≥35 kg/m^2. This information was recorded from the first visit of the patient at baseline. As a marker for socioeconomic status we used job description dividing the cohort into office workers, foremen, skilled workers and unskilled/semi-skilled workers. Men with unspecified job title were excluded from analysis (N=39,532), while the majority of women with manual jobs had unspecified job title and were included in "unskilled/semi-skilled" category. All workers were employed in the construction industry.

Statistical Analysis

Person-years of follow up were calculated for each person from year of health examination within the construction worker service through 31 December 2013,

symptomatic diverticular disease, death or emigration, whichever occurred first. The person-years were stratified for age (10-year age strata), gender, BMI, socioeconomic status, tobacco smoking and lag-time. We studied age intervals from 20 to 79 years for men, but due to few cases in young women we restricted that analysis to 40-79 years in women. Lag-time, i.e. the time between health examination and time of follow- up were categorized in 10 year classes (0-9, 10-19, 20-29, 30+).

Relative risks were estimated by Negative binomial regression analysis and 95% confidence intervals were calculated by standard errors. We planned a sensitivity analysis for those examined between 1987 and 1993 when coverage of the inpatient register became universal. We used statistics software SAS® 9.3 (SAS Institute, Cary, North Carolina, USA) to perform the statistical tests. P values <0.05 were considered statistically significant and all P values shown are two sided.

Ethics

The study was approved by the Regional Ethical Review Board in Umea (2014-195-32M) and the board of the Swedish construction workers cohort.

Results

Demographics of cohort

In total the study included 232,685men and 14,592 women. We identified 4,209 individuals with a diagnosis of symptomatic diverticular disease with 3,891 males and 318 females. The median total follow up time was 30 years for men and 29 years for women. Men were less likely to develop symptomatic diverticular disease than females when accounting for age, BMI, smoking, lag-time and socioeconomy (adjusted RR 0.68 95% CI 0.59-0.78). The baseline demographics of the male and female smoking groups are shown in Tables 1.

Smoking and symptomatic diverticular disease

Heavy smoking in men was associated with an increased risk of developing symptomatic diverticular disease (RR 1.63, 95% CI1.43-1.85) (Table 2) compared to non-smokers. In the adjusted analysis this figure was attenuated but still represented a 1.6 fold increased risk (aRR 1.56, 95% CI 1.42-1.72). There was a dose-response relationship with those smoking less than 15 cigarettes a day and ex-smokers having a lower risk of developing symptomatic diverticular disease compared with non-smokers (<15 cigarettes a day adjusted aRR 1.39, 95% CI 1.27-1.52 and ex-smokers adjusted aRR 1.14, 95% CI 1.04-1.27).

In females the number of cases were fewer and the precision of risk estimates lower. Only moderate smokers had a statistically increased risk of developing symptomatic diverticular disease with a 1.6 fold increase compared to non-smokers (aRR 1.64, 95% CI 1.25-2.14)(Table 2).

Smoking and complicated diverticular disease (perforation/abscess)

Examination of the association between smoking and complicated diverticular disease was not possible in females as there were too few cases. In male ever-smokers we found an increased risk of diverticular abscess or perforation of 2.7 fold compared to non-smokers (aRR 2.73, 95% CI 1.69-4.41))(Table 3). There was again evidence of a dose-response relationship with heavy smokers having a 3.8 fold increase compared to non-smokers (adjusted HR 3.80, 95% CI 2.21-6.51) although the precision of this estimate was lower due to fewer outcomes.

Sensitivity analysis of men examined from 1987-1993

Restricting the analysis to those men with health examinations between 1987 and 1993 demonstrated a similar relationship between smoking and symptomatic diverticular disease with heavy smokers having a 1.8 fold increased risk of symptomatic diverticular disease compared to non-smokers(aRR 1.79, 95%CI 1.43-2.23).

Discussion

We found that smoking is associated with an increased risk of developing symptomatic diverticular disease in both men and women. Those men smoking more than or equal to 15 cigarettes a day had a 1.6 fold increased risk of developing symptomatic diverticular disease requiring hospitalization compared to non-smokers. In men there was also a 2.6 fold increase risk in the development of complicated diverticular disease in ever-smokers compared to non-smokers.

Two small retrospective studies have reported an increased risk of diverticular complications in smokers[10, 11]. These studies however did not report on the development of symptomatic disease. Two population-based studies have reported conflicting results as to the role of smoking in the development of symptomatic disease. Aldoori et al reported current smoking was not significantly associated with symptomatic diverticular disease (RR 1.25; 95% CI 0.75-2.09) however the cohort studied was formed of male health care workers only with only 10% of the cohort being current smokers[13]. The study also lacked power as the analysis of smoking was based on only 45 events as opposed to the 4209 events in our study. A study reporting on the risk of symptomatic diverticular disease from the Swedish Mammography cohort reported a 1.26 fold increase in risk of symptomatic diverticular disease in current smokers compared to non-smokers and they were unable to report a dose-response relationship[12]. Our current estimates are greater than these with a 1.6 fold increase in risk of symptomatic disease in those smoking more than 15 cigarettes a day compared to non-smokers. We report for the first time a dose-response relationship with increasing risk of symptomatic diverticular disease with increasing frequency of tobacco use.

We found an increased risk of diverticular abscess or perforation in men who smoked. This risk was greatest in those who were heavy smokers. Women who smoke have been reported to have a 1.9 fold increased risk of diverticular abscess and perforation[12]. Those smoking greater than 10 cigarettes a day had the greatest increase in risk (RR 2.30 95% CI 1.26-4.20)[12]. Other studies have also shown an increased risk of perforation associated with smoking[18, 19].

This is a large cohort study with use of standardised questionnaires to prospectively collect data on smoking limiting the potential for recall bias. As we have used only the first questionnaire collected there is a possibility of non-differential misclassification of current and ex-smokers however previous work has reported that the data on smoking remained similar between the first and second health questionnaires which were administered 2-3 years apart in 89% of cases reviewed[20]. The diagnosis of symptomatic diverticular disease was made using ICD 10 and ICD 9 coding. This has limited our ability to identify cases of acute diverticulitis as this is not included in the ICD 10 classification but we have been able to stratify into those with abscess/perforation and shown an increased risk of complicated disease in men who smoke. A review of NPR validation studies conducted by Ludvigsson et al,[21] concluded that the positive predictive value (PPV) varies based on the diagnosis but generally ranges between 85-95%. Furthermore a review of coding of symptomatic diverticular disease using the K572-9 code in 528 consecutive admissions to a single centre in Sweden found 95.8% of all cases to be correctly classified[22]. We have not been able to account for comorbidity, dietary and life style factors. However prior small studies adjusting for these factors have shown they are only weak risk factors[12, 13]. Coverage of the inpatient register became universal in 1987 and our sensitivity analysis demonstrated broadly similar associations with our analysis of

those with a first examination performed from 1971-1993. We exclude older person (>79 years) and the association may different for persons of high age. All cases identified in this study required hospitalization for their diverticular disease. It is likely that some patients with symptomatic disease will have been treated as out patients or in the community and therefore the current study does not allow us to report on the association between smoking and symptomatic disease in this group.

Our findings strengthen the hypothesis that smoking is associated with the development of symptomatic diverticular disease. Given these findings it may be advisable for patients diagnosed with colonic diverticulosis to abstain from smoking in order to reduce their risk of developing symptomatic disease.

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Table 1. Demographics of males and females by smoking classification

	Non-Smokers	Ex-Smokers	Moderate Smokers	Heavy Smokers
Males				
N	102486	36133	55807	38259
Year of birth(SD)	1951.6 (16.4)	1938.1 (14.7)	1940.3 (15.7)	1946.3 (13.4)
Mean BMI (kg/m2) (SD)	24.0 (3.1)	24.9 (3.1)	23.9 (3.0)	24.0 (3.2)
Worker Level				
Office worker (%)	3780 (3.7)	1597 (4.4)	1315 (2.4)	1403 (3.7)
Forman (%)	9663 (9.4)	3947 (10.9)	4169 (7.5)	3717 (9.7)
Skilled Worker (%)	76285 (74.4)	24576 (68.0)	40844 (73.2)	25531 (66.7)
Unskilled/Semi-skilled (%)	12758 (12.4)	6013 16.6)	9479 (17.0)	7608 19.9)
Females				
N	7317	1349	3274	2652
Year of birth(SD)	1945.3 (15.9)	1944.2 (11.9)	1945.4 (13.9)	1948.0 (12.1)
Mean BMI (kg/m2)(SD)	23.6 (4.0)	23.7 (3.7)	22.7 (3.5)	23.0 (3.6)
Worker Level				
Office worker (%)	3254 (44.5)	672 (49.8)	1413 (43.2)	1046 (39.4)
Forman (%)	331 (4.5)	22 (1.6)	59 (1.8)	68 (2.6)
Skilled Worker (%)	359 (4.9)	33 (2.5)	154 (4.7)	183 (6.9)
Unskilled/Semi-skilled (%)	3373 (46.1)	622 (46.1)	1648 (50.3)	1355 (51.1)

Table 2. All cases of symptomatic diverticular disease (SDD) in men and women examined 1971-93.

	Person-years	Cases of SDD	Unadjusted RR (95% CI)	Adjusted RR (95% CI)*
Males				
Tobacco-Smoking				
Non-Smokers	2753953	1219	1 (ref)	1 (ref)
Ex-smokers	849666	682	1.42 (1.24-1.63)	1.14 (1.04-1.27)
Moderate smokers <15 cig/day	1308270	1146	1.62 (1.43-1.84)	1.39 (1.27-1.52)
Heavy smokers >/=15 cig day	1004439	844	1.63 (1.43-1.85)	1.56 (1.42-1.72)
Females				
Tobacco-Smoking				
Non-Smokers	163065	133	1 (ref)	1 (ref)
Ex-smokers	31605	37	1.35 (0.86-2.11)	1.33 (0.92-1.92)
Moderate smokers <15 cig/day	74170	97	1.64 (1.15-2.35)	1.64 (1.25-2.14)
Heavy smokers >/=15 cig day	61689	51	0.97 (0.65-1.47)	1.12 (0.81-1.55)

* Adjusted for age, BMI, lag-time and socioeconomic status

Table 3. Association of smoking with complicated diverticular disease (CDD) (abscess/perforation)

	Person-years	Cases of CDD	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Tobacco-Smoking				
Non-Smokers	1713459	25	1 (ref)	1 (ref)
Ex-smokers	482036	17	1.43 (0.77-2.70)	1.55 (0.80-2.99)
Moderate smokers <15 cig/day	742908	45	2.79 (1.70-4.59)	2.80 (1.64-4.77)
Heavy smokers >/=15 cig day	599172	42	3.75 (2.28-6.16)	3.80 (2.21-6.51)

* Adjusted for age, BMI, lag-time and socioeconomic status