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Active and passive cigarette smoking and the risk of endometrial cancer in Poland

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Abstract

Background—Epidemiological studies have consistently reported that active cigarette smoking is inversely associated with endometrial cancer risk. However, dose-response relationships with quantitative measures of active smoking or passive smoking remain less clear.

Methods—Data on lifetime active and passive smoking were collected for 551 endometrial cancer cases and 1925 controls in a population-based case-control study conducted during 2001–2003 in Poland (Warsaw and Łódz).

Results—Compared with never active smokers, active current (Odds Ratio (OR)=0.51, 95% Confidence Interval (CI): 0.39, 0.68) and former smokers (OR=0.60, 95% CI: 0.45, 0.80) were at a statistically significantly decreased risk. We did not observe statistically significant inverse dose-response relationships with increasing exposure with duration and cumulative measures. However, there was some indication that the highest category of number of years (OR=0.35, 95% CI: 0.23–0.55), intensity (OR=0.41, 95% CI: 0.24–0.69), and dose (OR=0.38, 95% CI: 0.24–0.60) of smoking among current smokers had the greatest inverse association compared to never smokers. Our data did not support the presence of an inverse association with passive smoking among never active smokers (OR=0.92; 95% CI: 0.65, 1.29).

Conclusion—Our results support that long-term and heavy smoking among current smokers strongly influence endometrial cancer risk.

Keywords

Endometrial cancer; Active smoking; Passive smoking

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1. Introduction

Epidemiological studies published as early as 1977 observed that active cigarette smoking is inversely associated with endometrial cancer risk (1,2). Associations with quantitative measures of smoking, such as intensity, duration, and latency, have been less clear (3). In a recent meta-analysis of six prospective and six case-control studies, Zhou and colleagues calculated study-specific slopes across categories of number of cigarettes smoked per day and reported a statistically significant inverse association with endometrial cancer risk (4). This meta-analysis, however, did not find inverse trends for smoking duration, smoking cessation, or age at first exposure of smoking, and did not report on pack-years. The meta-analysis examined smoking characteristics in former and current smokers combined, even though current smokers generally have a greater inverse risk for endometrial cancer than former smokers (3). Further examination of quantitative measures of smoking by smoking status is thus warranted.

The studies in the meta-analysis as well as other smoking-endometrial cancer studies have focused on active smoking. To date, only one study has reported on the association of passive smoking with endometrial cancer risk, finding a non-significant inverse association with adult residential and occupational exposures among postmenopausal women (Odds Ratio (OR)=0.9; 95% Confidence Interval (CI):0.7, 1.1) and a non-significant positive association among premenopausal women (OR=1.3; 95% CI: 0.7, 2.3) (5).

Given these data gaps, we evaluated lifetime active and passive smoking characteristics in a population-based case-control endometrial cancer study conducted in Poland.

2. Materials and methods

Data were derived from a population-based case-control study carried out during 2001–2003 in two Polish cities, Warsaw and Łódz. The design and conduct of this study have been previously described (6). Briefly, the cases were women 20–74 years of age who were newly diagnosed with pathologically-confirmed endometrial cancer. To ensure complete ascertainment of incident cancers, cases were identified through participating hospitals in Łódz and Warsaw and through the local cancer registries. Controls with no prior history of breast or endometrial cancer and with an intact uterus (self-reported) at time of enrollment were randomly selected from a database of all residents and frequency-matched to cases (1:2 case:control ratio) by study site and age in 5-year categories. For comparability, endometrial cancer cases did not have a history of breast cancer.

Personal interviews, including information on demographic characteristics and known or suspected endometrial cancer risk factors, were obtained from 551 cases (79% of the 695 eligible cases) and 1925 controls (68% of the 2843 eligible controls). The mean time between diagnosis and interview for cases was 97 ± 101 days and the mean time between identification and interview was 30 ± 39 days for controls. The study protocol was reviewed and approved by the local Polish and the US National Cancer Institute institutional review boards. All participants provided written informed consent.

2.1. Smoking information

As part of the personal interview, questions were asked about lifetime active and passive smoking. Active smoking questions included when smoking began, number of cigarettes smoked per day, and years of exposure for a particular smoking habit. A transition in smoking habit was defined as (a) stopped smoking or (b) changed amount smoked (decrease or increase in the number of cigarettes/day). Passive smoking at home questions asked about whether a woman lived with a smoker throughout life. Information was elicited on how many smokers

had lived in the household at different times, when smoking began, number of cigarettes smoked per day, years of exposure, and the number of hours and days that the relatives had smoked in the presence of the subject. In addition, women were asked similar questions about their exposures to other people's cigarette smoke at work in the occupational history section of the questionnaire. Passive exposure at work was assessed separately for each job held for 6 months or longer.

For active smoking, never active smokers were defined as women who smoked less than 100 cigarettes throughout life and who had never smoked cigarettes regularly (defined as smoking at least one per day for ≥6 months). Current active smokers were defined as active smokers on the reference date (date of diagnosis for cases and date of interview for controls) or those who stopped smoking during the past year. Former active smokers were defined as those who stopped smoking more than 1 year prior to the reference date. We categorised passive smoking according to the approach of Lissowska and colleagues (7). Passive smokers were defined as women who reported having been exposed to passive smoke at home and/or at work at least 1 hour per day for at least 1 year. We categorised passive smoking into exposure only at home, exposure only at work, and exposure both at home and work. We used 'hours per day-years' (sum of 'hours/day × duration' for all periods of passive exposure) as a measure of intensity and duration of exposure to passive smoking either at home or work.

2.2. Statistical analyses

We compared endometrial cancer risk factors for cases and controls using *t*-tests for continuous variables and χ^2 tests for categorical variables. We used unconditional logistic regression models to estimate the ORs and 95% CIs of endometrial cancer risk for smoking characteristics. We present the results adjusted for frequency matching variables (age, site) and known endometrial cancer risk factors such as education, age at menarche, number of full-term births, ever use of oral contraceptives, ever use of oral menopausal hormones, body mass index (BMI) at time of interview, and menopausal status. Tests for trend were calculated excluding the reference category of never smokers and using the median value of each smoking category.

We also evaluated whether the association between smoking and endometrial cancer risk was modified by endometrial cancer risk factors. Interactions are presented as smoking-associated risks across categories of endometrial cancer risk factors. Interaction was tested on the multiplicative scale by entering product terms in the multivariable logistic regression models to assess whether the smoking-associated ORs within categories of risk factors differed significantly from each other based on likelihood ratio tests.

3. Results

The distribution of endometrial cancer risk factors in the study population has been previously reported (6). In brief, compared with controls, cases were more likely to be older (mean age was 61 ± 8 years among the cases and 56 ± 10 years among the controls) and have earlier ages at menarche, fewer pregnancies, younger at first birth, higher BMI, and never used oral contraceptives. The majority of cases and controls (76% and 62%, respectively) were postmenopausal.

Ever active smoking was less frequent among cases (35%) compared with controls (53%) (Table 1). Compared to never active smokers, the adjusted OR for current and former smokers was 0.51 (95% CI: 0.39, 0.68) and 0.60 (95% CI: 0.45, 0.80), respectively. There was no statistically significant difference between the inverse association for current active and former active smoking (*P*=0.38). In general, ORs decreased with increasing duration, intensity (cigarettes/day), and pack-years of smoking, and with increasing ages at smoking initiation; and increased with decreasing time since cessation. Albeit the dose response was not

statistically significant, the trend was slightly stronger in the current smokers compared to the former smokers with increased intensity, pack-years, and age at first start smoking. The highest category of duration (OR=0.35, 95% CI: 0.23–0.55), intensity (OR=0.41, 95% CI: 0.24–0.69), and dose (OR=0.38, 95% CI: 0.24–0.60) among current smokers had the greatest inverse association compared to never smokers.

Among never active (current or former) smokers, the OR was 0.92 (95% CI=0.65, 1.29) for the association between ever passive smoking at home or work and endometrial cancer risk (Table 2). There was no evidence of a dose-response relation of endometrial cancer risk with increasing number of hours per day-years of passive exposure at home or work (*P* trend=0.69).

Table 3 summarises active smoking-associated risks across categories of endometrial cancer risk factors. Smoking associations were not significantly modified by menopausal status, oral contraceptive use, oral menopausal hormone use, age at menarche, number of full-term births, or age at first birth (*P* interaction>0.4). There was some indication of interaction with obesity, but this was also not statistically significant (*P* interaction=0.10). Overall, we observed an inverse association between cigarette smoking and endometrial cancer risk across all strata of these factors, except among oral contraceptive users in whom there was a positive association between smoking and risk (*P* interaction=0.02).

4. Discussion

In our population-based study of 551 cases and 1925 controls conducted in Poland, we observed that women who smoked had a lower risk of endometrial cancer, with long-term and heavy smoking among current smokers having the strongest influence on risk. Our data did not show a statistically significant inverse association with passive smoking among never active smokers.

In a recent meta-analysis of smoking-endometrial cancer studies, Zhou and colleagues (4) reported a decreased risk for an increment of 20 cigarettes per day (RR=0.84 [95% CI: 0.71,0.99] for prospective studies and RR=0.73 [95% CI: 0.60–0.89] for case-control studies). They also described null inverse trends for dichotomised categories of smoking duration (≤ 20 and > 20 years), smoking cessation (< 10 and ≥10 years), and ages at first exposure of smoking (≤ 20 and > 20 years). Dose-response might not have been evident in this meta-analysis based on current and former smokers combined, despite several studies included in the meta-analysis reporting quantitative measure of smoking separately for current and former smokers (5,8–10). Zhou and colleagues (4) also reported that compared to never smokers, the pooled RR for former smokers was 0.88 (95% CI, 0.78–0.99) based on 10 prospective studies and 0.80 (95% CI, 0.72–0.88) based on 15 case-control studies whereas the pooled RR for current smokers was 0.74 (95% CI, 0.64–0.84) based on seven prospective studies and 0.63 (95% CI, 0.55–0.72) based on 16 case-control studies.,

The meta-analysis did not report on the association for pack-years (4), but a qualitative comparison of previously reported point estimates for the lowest and highest category of pack-years reveals that some studies observed a dose-response for pack-years (9–11) whereas others did not (12,13). Only one of these studies examined pack-years stratified by current and formers smokers, and it reported a stronger trend among current smokers than in former smokers (9). These observations along with data from our Polish study suggest that long-term and heavy smoking among current smokers might strongly influence endometrial cancer risk.

Despite the compelling evidence that cigarette smoking is inversely associated with endometrial cancer, many questions regarding the potential mechanisms remain. Women who smoke are leaner (14) and have an earlier ages at menopause (15), which are factors associated with decreased oestrogen levels. However, inverse associations remain after adjustment for

such factors as obesity and age at menopause in our study, as well as in previous studies (5, 10). This suggests that additional mechanisms may contribute to the inverse association, although incomplete adjustment for the extent and distribution of adiposity could also be an explanation.

Smoking-induced alterations in steroid metabolism have been proposed as a mechanism by which smoking could lower risk (16–18). In contrast to the 4-oestrogen metabolite, the 2-oestrogen metabolite has been postulated to be anti-carcinogenic (19–21). However, only a few studies have assessed the effect of smoking on oestrogen metabolites, with inconclusive results (22–24). It is still unclear how oestrogen metabolites are involved in endometrial carcinogenesis, but the inverse association between smoking and endometrial cancer may be explained by shifting of the oestrogen metabolism towards the 2-hydroxylation pathway. Future studies with biological data on oestrogen and oestrogen metabolite level may be helpful in determining the most important quantitative smoking characteristic, and possibly in assisting with the interpretation of the associated biologic effects.

Among never active smokers, ever passive smoking was not statistically significantly associated with endometrial cancer risk. This is consistent with a recent cohort study based on residential and occupational exposures during adulthood (5). In our study, we captured detailed information on passive smoking both at home and at work based on childhood and adulthood exposures. We did not measure passive smoking exposure at social settings outside the home and work. Given the difficulties in accurately measuring passive smoking, relative risk estimates in this and previous studies are likely to be underestimated.

We did not observe a significant modification of the smoking association by known endometrial cancer risk factors such as BMI, although the power of our study to evaluate interactions was limited. The only exception was with usage of oral contraceptives, where an inverse association was seen only among non-users. Brinton and colleagues (8) also found a weaker inverse association among oral contraceptive users than nonusers, although the interaction was not statistically significant. These findings, however, need to be cautiously interpreted given that they are based on small numbers and most published studies have not seen an effect modification with oral contraceptives (9,13,25).

Our population-based case-control study was conducted in Poland, where the prevalence of cigarette smoking is high (26), presenting a wide-range of exposure of smoking. Other strengths of our study included the ability to assess detailed residential and occupational smoking exposure information by accounting for patterns of cigarette exposure over an individual's lifetime, including early adulthood and later ages. The present study also obtained information on known and suspected endometrial cancer risk factors, allowing for control of potential confounders.

A source of bias in this case-control study is the possibility that cases and controls recall their smoking history with different accuracy. However, it is not general knowledge that smoking has an inverse association with endometrial cancer, so we do not expect differential recall. Non-differential recall is possible and this source of bias would tend to attenuate associations. In addition, a comparison of urine cotinine and creatine concentrations to questionnaire-reported smoking status in case-control studies indicates that questionnaires provide an accurate assessment of active smoking (27,28). For passive smoking, several studies have shown high concordance rates when cases and controls were re-interviewed about exposure to parental and spousal smoking (29) and when spousal smoking histories provided by the cases and controls were compared with data from interviews with the spouse themselves (29,30).

In summary, findings from our study support a dose-response relationship between active smoking and endometrial cancer risk, with current heavy smokers perhaps having the strongest

inverse association with risk and some indication of a weak inverse association with passive smoking. Relating alterations in hormones and their metabolites to specific smoking characteristics appear to be promising for future pursuit to help clarify the potential mechanism of smoking on endometrial carcinogenesis.

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Table 1

Association of active cigarette smoking status, duration, average intensity, total dose, latency, and recency with endometrial cancer risk in a population-based endometrial cancer case-control study in Poland

	Case (n=551)		Control (n=1925)		OR (95% CI)[α]
	N	%	N	%	
Smoking Status					
Never Smoker[β]	358	65%	898	47%	1 (ref)
Ever Smoker	193	35%	1027	53%	0.55 (0.44 – 0.69)
Former Smoker	93	17%	361	19%	0.60 (0.45 – 0.80)
Current Smoker	100	18%	666	35%	0.51 (0.39 – 0.68)
Duration (years)					
Never Smoker[β]	358	66%	898	47%	1 (ref)
All subjects					
< 10	66	12%	333	17%	0.57 (0.41 – 0.80)
10–24	69	13%	358	19%	0.66 (0.48 – 0.91)
≥ 25	52	10%	324	17%	0.41 (0.28 – 0.58)
P-trend among smokers[†]					0.10
Former smokers					
< 10	40	9%	139	11%	0.66 (0.43 – 1.03)
10–24	33	7%	144	11%	0.60 (0.38 – 0.93)
≥ 25	18	4%	75	6%	0.52 (0.29 – 0.93)
P-trend among smokers[†]					0.27
Current smokers					
< 10	26	7%	194	18%	0.47 (0.30 – 0.76)
10–24	36	9%	214	19%	0.71 (0.47 – 1.08)
≥ 25	34	9%	249	22%	0.35 (0.23 – 0.55)
P-trend among smokers[†]					0.30
Intensity (cigarettes smoked per day)					
Never Smoker[β]	358	66%	898	47%	1 (ref)
All subjects					
<10	89	16%	426	22%	0.63 (0.47 – 0.84)

	Case (n=551)		Control (n=1925)		OR (95% CI)[α]
	N	%	N	%	
10–14	47	9%	330	17%	0.41 (0.29 – 0.60)
≥ 15	50	9%	261	14%	0.54 (0.37 – 0.79)
P-trend among smokers[†]					0.32
Former smokers					
<10	49	12%	188	17%	0.67 (0.46 – 0.98)
10–14	17	5%	87	9%	0.37 (0.20 – 0.69)
≥ 15	25	7%	82	8%	0.75 (0.44 – 1.26)
P-trend among smokers[†]					0.84
Current smokers					
<10	40	8%	238	17%	0.57 (0.38 – 0.84)
10–14	30	6%	243	16%	0.43 (0.27 – 0.66)
≥ 15	25	6%	179	11%	0.41 (0.24 – 0.69)
P-trend among smokers[†]					0.23
Total dose (pack-years)					
Never Smoker[β]	358	66%	898	47%	1 (ref)
All subjects					
< 5	78	14%	409	21%	0.57 (0.42 – 0.78)
5–15	53	10%	295	15%	0.58 (0.41 – 0.83)
≥ 16	54	10%	305	16%	0.46 (0.32 – 0.66)
P-trend among smokers[†]					0.23
Former smokers					
< 5	43	11%	168	16%	0.61 (0.41 – 0.92)
5–15	25	7%	103	10%	0.61 (0.37 – 1.01)
≥ 16	23	6%	86	9%	0.60 (0.35 – 1.01)
P-trend among smokers[†]					0.67
Current smokers					
< 5	35	9%	241	21%	0.52 (0.34 – 0.78)
5–15	28	7%	192	18%	0.55 (0.35 – 0.87)
≥ 16	31	8%	219	20%	0.38 (0.24 – 0.60)

	Case (n=551)		Control (n=1925)		OR (95% CI)[α]
	N	%	N	%	
P-trend among smokers[†]					0.23
Age at first started smoking (years)					
Never Smoker[β]	358	66%	898	47%	1 (ref)
All subjects					
≥ 22	80	15%	330	17%	0.64 (0.47 – 0.86)
19–21	59	11%	355	19%	0.52 (0.37 – 0.74)
< 19	49	9%	333	17%	0.44 (0.30 – 0.64)
P-trend among smokers[†]					0.06
Former smokers					
≥ 22	40	10%	114	11%	0.75 (0.49 – 1.14)
19–21	26	7%	121	12%	0.58 (0.35 – 0.96)
< 19	25	7%	123	12%	0.46 (0.28 – 0.78)
P-trend among smokers[†]					0.28
Current smokers					
≥ 22	40	10%	216	19%	0.55 (0.37 – 0.82)
19–21	33	8%	234	21%	0.48 (0.31 – 0.74)
< 19	24	6%	210	19%	0.41 (0.25 – 0.68)
P-trend among smokers[†]					0.13
Time since cessation (years)					
Former smokers					
Never Smoker[β]	358	80%	898	72%	1 (ref)
< 7	43	10%	115	9%	0.76 (0.50 – 1.16)
7–15	34	8%	116	9%	0.76 (0.48 – 1.19)
≥ 16	12	3%	115	9%	0.25 (0.13 – 0.50)
P-trend among smokers[†]					0.02

[*] Numbers of cases and controls for smoking characteristics vary due to missing values.

[α] Adjusted for age [± 5 years], study site [Łódz, Warsaw], education[<12, 12, >12th grade], age at menarche [≤12,13,14,≥15 years old], number of full-term births [0,1,2,≥3], ever use of oral contraceptives [never, ever], ever use of oral menopausal hormones [never, estrogen only, progesterone with/without estrogen], recent body mass index [<25, 25-<30, 30–40, >40 kg/m^2], menopausal status [pre, post, unclear].

[β] Never active smokers. Includes individuals with exposure to passive smoking.

[†] P-trend among smokers with increasing level of smoking characteristic (weighted by the median value of each category).

Table 2

Association of passive cigarette smoking status, source of passive exposure, and intensity with endometrial cancer risk among never active smokers[α] in a population-based endometrial cancer case-control study in Poland

	Case (n=358)		Ctl (n=898)		OR (95% CI)[β]
	N	%	N	%	
Smoking status					
No Passive Exposure	85	24%	184	20%	1 (ref)
Ever passive exposure at home or work	273	76%	714	80%	0.92 (0.65 – 1.29)
Source of passive exposure					
No passive exposure	85	24%	184	21%	1 (ref)
At home only	115	33%	348	40%	0.89 (0.60 – 1.32)
At work only	38	11%	70	8%	1.11 (0.64 – 1.93)
Both at home and work	111	32%	279	32%	0.89 (0.60 – 1.32)
(Hours/day-years at home or work)					
<100	77	22%	241	27%	0.85 (0.56 – 1.30)
100–200	96	27%	223	25%	1.06 (0.71 – 1.60)
>200	100	28%	250	28%	0.86 (0.58 – 1.28)
Trend[†]					0.69

[*] Numbers of cases and controls for smoking characteristics vary due to missing values.

[α] Among individuals who do not smoke (current and former active smokers excluded).

[β] Adjusted for age [± 5 years], study site [Łódz, Warsaw], education[<12, 12, >12th grade], age at menarche [<12,13,14,≥15 years old], number of full-term births [0,1,2,≥3], ever use of oral contraceptives [never, ever], ever use of oral menopausal hormones [never, estrogen only, progesterone with/without estrogen], recent body mass index [<25, 25-<30, 30–40, >40 kg/m^2], menopausal status [pre, post, unclear].

[†] P for linear trend with increasing level of intensity (weighted by the median value of each category).

Table 3

Association of active cigarette smoking status and endometrial cancer risk within strata of endometrial cancer risk factors[α] in a population-based endometrial cancer case-control study in Poland

	Smoking Status						
	Never (358 cases, 898 controls)		Ever (193 cases, 1027 controls)		OR (95% CI)[β] for ever smoking association within categories of risk factors		P int[†]
	case	control	case	control	OR	95% CI	
Body mass index (kg/m^2)							
<25	98	311	60	477	0.42	(0.28 – 0.63)	0.10
25–30	139	359	67	352	0.58	(0.40 – 0.83)	
30–40	104	200	56	167	0.67	(0.44 – 1.03)	
>40	17	28	10	31	0.80	(0.27 – 2.42)	
Oral contraceptive use							
Never	347	807	173	896	0.51	(0.41 – 0.65)	0.02
Ever	9	82	19	117	1.52	(0.62 – 3.77)	

[*] Numbers of cases and controls for smoking characteristics vary due to missing values.

[α] Adjusted for age [± 5 years], study site [Łódz, Warsaw], education[<12, 12, >12th grade], age at menarche [<12,13,14,≥15 years old], number of full-term births [0,1,2,≥3], ever use of oral contraceptives [never, ever], ever use of oral menopausal hormones [never, estrogen only, progesterone with/without estrogen], recent body mass index [<25, 25-<30, 30–40, >40 kg/m^2], menopausal status [pre, post, unclear].

[β] Reference is never smoker for each level of the category.

[†] Interaction was tested on the multiplicative scale by entering product terms in the multivariable logistic regression models to assess whether the smoking associated odds ratios within categories of risk factors differed