Risk of endometrial cancer in relationship to cigarette smoking: Results from the EPIC study

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Current epidemiologic evidence indicates that cigarette smoking reduces the risk of endometrial cancer. We examined data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to analyze further aspects of the smoking-endometrial cancer relationship, such as possible modifying effects of menopausal status, HRT use, BMI and parity. In a total of 249,986 women with smoking exposure and menopausal status information, 619 incident endometrial cancer cases were identified during 1.56 million person-years of follow-up. Among postmenopausal women, the hazard ratio (HR) for current smokers *versus* never smokers was 0.70 (95% CI = 0.53–0.93), while it was 1.75 (95% CI = 1.13–2.70) among premenopausal women at recruitment. After adjustment for risk factors, the HR for postmenopausal women was slightly attenuated to 0.78 (95% CI = 0.59–1.03). No heterogeneity of effect was observed with HRT use or BMI. Among premenopausal women, current smokers of more than 15 cigarettes per day or who smoked for 30 years or more at the time of recruitment had a more than 2-fold increased risk of endometrial cancer compared to never smokers (HR = 2.54; 95% CI = 1.47–4.38 and HR = 2.23; 95% CI = 1.04–4.77, respectively). Past smoking was not associated with endometrial cancer risk, either among pre- or post-

Grant sponsors: "Europe Against Cancer" Programme of the European Commission (SANCO); Ligue contre le Cancer (France); Société 3M (France); Mutuelle Générale de l'Education Nationale; Institut National de la Santé et de la Recherche Médicale (INSERM); German Cancer Aid; German Cancer Research Centre; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health; Participating Regional Governments and Institutions of Spain; Cancer Research, UK; Medical Research Council, UK; Stroke Association, UK; British Heart Foundation; Department of Health, UK; Food Standards Agency, UK; Wellcome Trust, UK; Greek Ministry of Health; Greek Ministry of Education; Italian Association for Research on Cancer; Italian National Research Council; Dutch Ministry of Public Health, Welfare and Sports; Dutch Ministry of Health; Dutch Prevention Funds; LK Research Funds; Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane, Sweden; Norwegian Cancer Society.

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menopausal women. In this prospective study, we observed an increased risk of endometrial cancer with cigarette smoking in premenopausal women. The reduction of endometrial cancer risk observed among postmenopausal women does not have direct public health relevance since cigarette smoking is the main known risk factor for cancer.

Key words: smoking; endometrial cancer; prospective cohort

Endometrial cancer is the most commonly diagnosed cancer of the female genital tract in the developed world.[1] Epidemiologic studies have shown that, in postmenopausal women, increased circulating levels of estrogens and androgens are strongly associated with increased risk of endometrial cancer.[2–4] In premenopausal women, data on the association between circulating levels of sex steroid hormones and endometrial cancer risk suggest a role for elevated levels of estrone and androgens (androstenedione, testosterone).[5] Some lifestyle factors, such as BMI, have been related to both bioavailable sex steroids[6,7] and endometrial cancer risk.[8]

Cigarette smoking has been associated with earlier age at menopause[9] and lower BMI,[10,11] which are factors known to be associated with endogenous estrogen concentrations. Therefore, it was proposed that smoking might be associated with a lower risk of endometrial cancer by exerting antiestrogenic effects, or by altering endogenous levels of estrogens. Many case-control studies have shown weak to moderate inverse association between cigarette smoking and endometrial cancer risk.[12]

To date, only 4 prospective cohort studies of smoking and endometrial cancer risk have been conducted.[13–16] Two of these studies[13,14] were based on small numbers of cases (36 and 12 cases among current smokers) and relative risks had wide confidence intervals (CIs). However, within the Canadian National Breast Screening Study, an analysis of 403 incident cases of endometrial cancer showed a significant 40% reduction in risk among heavy current smokers.[15] The largest and most recent cohort study,[16] based on 702 cases of endometrial cancer, also showed a significantly lower risk of endometrial cancer in current and former smoker compared to never smoker, and an inverse association of endometrial cancer risk with smoking intensity and duration, although the trend was not statistically significant.

The aim of the present study is to examine the association of different smoking exposure levels with the risk of endometrial cancer among the European Prospective Investigation into Cancer and Nutrition (EPIC).

Subjects and methods

Study cohort and data collection

The EPIC cohort is a large, multi-centre prospective study to investigate the relations of nutritional, lifestyle, metabolic and genetic risk factors and cancer incidence. It was initiated in 1992 in 10 European countries (Sweden, Denmark, Norway, the Netherlands, United Kingdom, France, Germany, Spain, Italy and Greece)[17] and involved about 370,000 women and 150,000 men. Blood samples were collected from about 80% of the individuals and subjects were followed-up until 2002 in most centres. Detailed and fully standardized questionnaires were used in all participating countries. The questionnaires included data about dietary, lifestyle and health factors, reproductive history, use of oral contraceptives (OCs) and HRT, history of any disorders or surgical operations, tobacco smoking and alcohol consumption, occupational history, physical activity, education level and socioeconomic status. The baseline questionnaire assessment of physical activity has been previously described in detail.[18] An index of total physical activity (inactive, moderately inactive, moderately active, and active) was derived from the levels of occupational activity (non-worker, sedentary, standing, manual, heavy manual and unknown) and levels of combined recreational and household activities, as described in Ref. 19.

Information about tobacco smoking was collected from individuals in all participating countries. Subjects were asked if they smoked cigarettes currently and whether they had smoked in the past. Information was available on the type of smoking (cigarettes, cigars, pipes), number of cigarettes per day, duration of smoking, age started smoking and age of smoking cessation (for former smokers). This information was not updated after baseline and thus, duration of smoking among current smokers refers to duration between initiation and time of recruitment into the study. Information on the number of cigarettes smoked per day over an individual's lifetime was not collected in France and Sweden and these countries were therefore excluded from analysis on this variable. Information on passive smoking was available in 16 centres, from 6 countries (France, Italy, The Netherlands, Germany, Denmark and Norway). Questions were asked on residential and occupational exposure (except in France, whose cohort population is mainly composed of teachers). Passive exposure during childhood was only documented in a few centres and was not taken into account.

Determination of menopausal status

Women were considered premenopausal at baseline when they reported having had regular menses over the past 12 months, or when they were less than 46 years of age. Women were considered postmenopausal when they reported not having had any menses over the past 12 months, or when they were older than 55 years. Women who were between 46 and 55 years of age and who had missing or incomplete questionnaire data for menopausal status were classified as having unknown menopausal status.

Follow-up and case ascertainment

Incident cancer cases were identified through several methods, including record linkage with regional cancer registries (Denmark, Sweden, Norway, Italy, the Netherlands, Spain and the United Kingdom), health insurance records, cancer and pathology registries and active follow-up of study subjects (France, Germany, and Greece). Data on mortality were obtained from cancer registries or mortality registries at the regional or national level. For each EPIC study centre, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status (dates varied between canters, from June 1999 to December 2003).

Case subjects included in the present study were women who developed endometrial cancer after they were recruited into the EPIC study and before the closure date of the study period. Among the 311,320 women included after exclusion of 35,444 women who had a hysterectomy, 19,953 prevalent cancer cases and 1,293 subjects with incomplete follow-up data, 779 cases of endometrial cancer were identified by the end of each centre's follow-up period. After further exclusion of women with unknown menopausal status (147 cases and 55,399 noncases) and with missing information on smoking status (13 cases and 5,775 non cases), 619 cases were included in the study, of whom 126 were premenopausal and 493 postmenopausal at recruitment. Detailed tumor morphology was specified for only 35% of the cases, of which 93% were classified as type I tumors.[20]

Statistical analysis

Cox proportional hazard models were used to estimate hazard ratio (HR) and 95% CI of endometrial cancer incidence for various exposure levels of smoking. Analyses were performed separately for pre- and postmenopausal women at recruitment. In all analyses, age was used as an underlying time variable, with entry and exit time defined as the subject's age at recruitment and age at endometrial cancer diagnosis or censoring (death, lost to follow-

TABLE I – BASELINE CHARACTERISTICS OF ENDOMETRIAL CANCER PATIENTS AND CONTROL SUBJECTS IN THE COHORT, ACCORDING TO MENOPAUSAL STATUS AT RECRUITMENT

	Premenopausal women		Postmenopausal women	
	Cases	Non cases	Cases	Non cases
N	126	115,789	493	133,578
Age at recruitment, mean (range)	46.7 (28.7–55.6)	41.0 (19.9–58.0)	60.1 (47.0–82.4)	58.4 (27.8–98.5)
Age at diagnosis/end of follow-up, mean (range)	50.5 (32.3–62.2)	47.0 (22.1–67.0)	63.6 (50.0–85.8)	64.9 (34.9–101.7)
Follow-up time (years),[1] mean (range)	3.8 (0.1–9.8)	6.0 (0.0–10.7)	3.6 (0.0–9.1)	6.5 (0.0–10.8)
Age at menarche, mean (SD)	12.5 (1.5)	12.9 (1.5)	13.0 (1.6)	13.3 (1.6)
Age at menopause, mean (SD)	–	–	51.2 (4.1)	49.3 (4.5)
Body mass index (kg/m^2), mean (SD)	25.3 (5.0)	25.2 (4.3)	26.8 (5.7)	25.6 (4.6)
Nulliparous (%)	17.7	22.9	17.2	12.2
Ever used oral contraceptive (%)	52.5	74.3	36.6	43.8
Ever used HRT (%)	–	–	47.1	42.0
Alcohol consumption (g/day),[2] mean (SD)	10.0 (13.6)	8.4 (11.4)	9.5 (11.4)	9.1 (12.4)
Non consumers of alcohol (%)	12.8	8.5	10.7	10.0
Total physical activity (%)				
Inactive	15.8	17.2	12.0	10.7
Moderately inactive	42.5	32.1	35.0	33.8
Moderately active	33.3	39.1	46.6	47.5
Active	8.3	11.6	6.4	8.0
Highest school level				
None	5.9	3.1	4.1	6.3
Primary school completed	21.9	14.4	30.9	30.5
Technical/Professional school	11.8	22.4	22.3	22.1
Secondary school	36.1	29.1	26.6	23.9
University degree	24.4	31.1	16.1	17.2
Diabetes (%)	0.8	1.1	4.4	3.4

[1]Closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status (dates varied between centres, from June 1999 to December 2003).–[2]Among consumers only.

up, end of follow-up), respectively. All multivariate models were stratified by study centre and by age at recruitment (in one-year categories) to minimize the sensitivity against violations of the proportional hazard assumption. Smoking status was categorized as never smoker, former smoker and current smoker. Smoking duration was divided into the following categories: never smoker; <10 years; 10–19 years; 20–29 years; ≥30 years for former smokers, never smoker; <30 years; 30–39 years; ≥40 years for postmenopausal current smokers, and never smoker; <25 years; 25–29 years; 30–39 years; ≥40 years for premenopausal current smokers). Number of cigarettes currently smoked per day was categorized into never smoker, <15 cigarettes/day and ≥15 cigarettes/day. Lifetime number of cigarettes smoked per day was categorized into never smoker, <10 cigarettes/day and ≥10 cigarettes/day among former smokers, and into never smoker, <15 cigarettes/day and ≥15 cigarettes/day among current smokers. Age at smoking initiation was categorized as never smokers, ≥26 years, 16–25 years, <16 years and time since quitting as current smokers, <10 years, 10–19 years and ≥20 years. The same exposure categories were used for the analyses among pre- and postmenopausal women. Trend tests across levels of exposure were performed on continuous variables, after exclusion of never smokers. Relative risk estimates were also estimated after mutual adjustment of smoking measures (duration, age at initiation and number of cigarettes).

For postmenopausal women, we also modeled separately the risk of endometrial cancer associated with years of smoking up to the reported age at menopause and after that age (on a continuous scale).

Two models are presented: one model only stratified by age and centre and a fully adjusted model stratified by age and centre and adjusted for BMI (as a continuous variable), parity (nulliparous; parous; missing), use of OC (never; ever; missing), total (including recreational, household and occupational), physical activity (inactive; moderately inactive; moderately active; active; missing), alcohol consumption (non consumers; 1–4 g/day, 5–9 g/day; 10–14 g/day; 15–19 g/day; ≥20 g/day, missing) and education level (highest school level: none; primary school completed; technical/professional school; secondary school; university degree; not specified). For the analyses on postmenopausal women, further adjustments for use of hormone replacement therapy (HRT: never; ever; missing) and age at menopause (≤50 years; 51–52 years; 53–55 years; >55 years; missing) were also performed.

Subgroup analyses by known endometrial risk factors were also performed. The following subgroups were examined: HRT use (never, ever) and BMI (<25, 25–29, 30+ kg/m^2). Tests of heterogeneity between HR in these subgroups, and in EPIC countries, were based on χ^2 statistics, calculated as the deviations of logistic β coefficients observed in each of the subgroups, relative to the overall β coefficient.

All statistical analyses were performed using the statistical analysis system (SAS) software package, version 9 (SAS Institute, Cary, NC).

Results

Up to the end of the study period defined by each study centre, 619 cases of endometrial cancers were diagnosed within the EPIC cohort during an average of 6.3 years of follow-up. Baseline characteristics of endometrial cases and non cases stratified by menopausal status are shown in Table I. The mean age of diagnosis of endometrial cancer was 50.5 years in premenopausal women and 63.6 years in postmenopausal women. The average time between recruitment and diagnosis was 3.8 years and 3.6 years for premenopausal and postmenopausal cases, respectively. In the premenopausal group, both cases and non cases had similar age at menarche, BMI and educational level. Compared to control subjects, premenopausal cases were more likely to be parous and to have never used OC. Postmenopausal cases had a higher BMI and a later age at menopause than noncases, were more likely to be

TABLE II – HAZARD RATIO (95% CONFIDENCE INTERVAL) OF ENDOMETRIAL CANCER BY SMOKING HISTORY STRATIFIED BY MENOPAUSAL STATUS AT RECRUITMENT

Variable	Premenopausal women				Postmenopausal women			
	Cases	P-years	HR (95 % CI)[1]	HR (95 % CI)[2]	Cases	P-years	HR (95 % CI)[1]	HR (95 % CI)[2]
Smoking status								
Never smoker	74	389,156	1.00	1.00	322	526,974	1.00	1.00
Former smoker	19	159,975	0.74 (0.44–1.23)	0.78 (0.46–2.78)	107	190,282	0.89 (0.71–1.12)	0.88 (0.70–1.11)
Current smoker	33	146,126	1.75 (1.13–2.70)	1.79 (1.15–2.78)	64	152,127	0.70 (0.53–0.93)	0.78 (0.59–1.03)
Current smokers								
Age at smoking initiation (years)								
Never smoker	74	389,156	1.00	1.00	322	526,974	1.00	1.00
26+	2	12,487	0.79 (0.19–3.26)	0.78 (0.19–3.24)	12	31,852	0.62 (0.34–1.10)	0.68 (0.38–1.21)
16–25	21	104,026	1.60 (0.96–2.67)	1.69 (1.00–2.84)	42	101,388	0.66 (0.47–0.92)	0.73 (0.52–1.03)
<16	10	26,654	4.99 (2.40–10.39)	5.12 (2.42–10.85)	5	14,898	0.53 (0.22–1.29)	0.59 (0.24–1.46)
p-trend[3]			*0.13*	*0.13*			*0.27*	*0.17*
Duration of smoking (years)[4]								
Never smoker	74	389,156	1.00	1.00	322	526,974	1.00	1.00
<25	13	89,798	1.58 (0.80–3.09)	1.61 (0.82–3.15)	11	32,812	0.73 (0.40–1.34)	0.78 (0.42–1.44)
25–29	11	40,823	1.79 (0.92–3.49)	1.92 (0.98–3.76)				
30–39	9	12,490	2.23 (1.04–4.77)	2.29 (1.05–4.99)	24	71,198	0.62 (0.40–0.96)	0.68 (0.44–1.06)
40+	0	57	–	–	24	44,127	0.61 (0.39–0.94)	0.70 (0.45–1.08)
p-trend[3]			*0.11*	*0.10*			*0.25*	*0.16*
Current number of cigarettes/day								
Never smoker	74	389,156	1.00	1.00	322	526,974	1.00	1.00
<15	15	82,533	1.40 (0.79–2.51)	1.45 (0.81–2.62)	39	80,147	0.75 (0.53–1.05)	0.84 (0.60–1.19)
15+	18	58,556	2.54 (1.47–4.38)	2.58 (1.48–4.50)	20	65,766	0.49 (0.31–0.78)	0.54 (0.34–0.87)
p-trend[3]			*0.10*	*0.07*			*0.41*	*0.43*
Lifetime number of cigarettes/day[5]								
Never smoker	41	263,590	1.00	1.00	205	302,160	1.00	1.00
<15	15	81,593	1.55 (0.83–2.90)	1.66 (0.88–3.13)	25	74,052	0.45 (0.29–0.69)	0.52 (0.34–0.80)
15+	7	30,425	2.38 (1.03–5.52)	2.38 (1.01–5.57)	13	28,020	0.68 (0.38–1.21)	0.73 (0.41–1.31)
p-trend[3]			*0.20*	*0.27*			*0.28*	*0.51*
Former smokers								
Age at smoking initiation (years)								
Never smoker	74	389,156	1.00	1.00	322	526,974	1.00	1.00
25+	2	7,121	1.12 (0.27–4.61)	1.26 (0.30–5.24)	15	30,861	0.74 (0.44–1.25)	0.69 (0.41–1.16)
18–24	13	117,367	0.64 (0.35–1.17)	0.68 (0.37–1.25)	68	130,372	0.82 (0.62–1.07)	0.82 (0.62–1.07)
<18	2	26,461	0.89 (0.21–3.68)	0.86 (0.20–3.62)	9	14,941	0.88 (0.45–1.73)	0.84 (0.43–1.65)
p-trend[3]			*0.28*	*0.09*			*0.85*	*0.97*
Duration of smoking (years)								
Never smoker	74	389,156	1.00	1.00	322	526,974	1.00	1.00
<10	4	58,673	0.51 (0.18–1.40)	0.56 (0.20–1.55)	12	34,254	0.62 (0.34–1.10)	0.62 (0.35–1.11)
10–19	6	60,901	0.64 (0.28–1.48)	0.67 (0.29–1.57)	29	47,742	1.03 (0.70–1.51)	1.00 (0.68–1.48)
20–29	7	25,544	1.21 (0.55–2.66)	1.21 (0.54–2.69)	25	45,702	0.87 (0.57–1.31)	0.83 (0.55–1.25)
30+	–	1,734	–	–	23	42,511	0.72 (0.46–1.10)	0.71 (0.46–1.10)
p-trend[3]			*0.30*	*0.11*			*1.00*	*0.85*
Lifetime number of cigarettes/day[5]								
Never smoker	41	263,590	1.00	1.00	205	302,160	1.00	1.00
<10	6	42,370	0.85 (0.35–2.03)	0.88 (0.36–2.14)	26	56,176	0.61 (0.40–0.92)	0.61 (0.40–0.93)
10+	4	55,368	0.61 (0.21–1.75)	0.62 (0.21–1.81)	23	50,573	0.63 (0.40–0.97)	0.58 (0.38–0.91)
p-trend[3]			*0.92*	*0.66*			*0.56*	*0.95*
Time since quitting (years)								
Current smoker	33	146,126	1.00	1.00	64	152,127	1.00	1.00
<10	10	70,104	0.67 (0.32–1.37)	0.69 (0.33–1.44)	31	56,548	1.22 (0.79–1.88)	1.07 (0.69–1.65)
10–19	5	56,628	0.34 (0.13–0.90)	0.38 (0.14–1.00)	26	51,537	1.05 (0.66–1.68)	0.91 (0.57–1.46)
20+	3	26,249	0.31 (0.09–1.04)	0.32 (0.09–1.12)	41	72,788	1.15 (0.77–1.73)	1.03 (0.68–1.56)
p-trend[3]			*0.14*	*0.03*			*0.73*	*0.98*

[1]Stratified for age and recruitment centre.–[2]Stratified for age and recruitment centre, adjusted for BMI, total physical activity, OC use, parity, educational level and alcohol consumption; in postmenopausal subgroup, further adjusted for HRT use and age at menopause.–[3]Test for trend performed on continuous variables, among smokers only.–[4]For current smokers, duration until recruitment.–[5]France and Sweden excluded (information not collected).

nulliparous, to have never use OC and to have ever use hormone replacement therapy (HRT).

Because endometrial cancer risk varies substantially between pre- and postmenopausal women, the HRs and the 95% CI of endometrial cancer risk with various smoking measures are presented separately for these 2 groups (Table II).

Among women who were premenopausal at recruitment, current smokers had a significant increased risk of endometrial cancer compared to never smokers (HR = 1.75, 95% CI = 1.13–2.70). Compared to never smokers, women who started smoking before the age of 16 and who were still smoking at the time of recruitment had a relative risk of endometrial cancer of 4.99 (95% CI = 2.40–10.39). The HR was 2.23 (95% CI = 1.04–4.77) for current smokers smoking for more than 30 years and 2.54 (95% CI = 1.47–4.38) for whom who were smoking more than 15 cigarettes per day at the time of recruitment. Former smokers who gave up smoking between 10 and 19 years before recruitment have a significant decreased risk of endometrial cancer compared to current smokers (HR = 0.34, 95% CI = 0.13–0.90). However, the number of cases among premenopausal former smokers was too small to examine properly the association with endometrial cancer in this subgroup. Adjustments for BMI,

TABLE III – HAZARD RATIO (95% CONFIDENCE INTERVAL) OF ENDOMETRIAL CANCER FOR CURRENT SMOKERS *VERSUS* NEVER SMOKERS—HETEROGENEITY BY RISK FACTORS

	Premenopausal women				Postmenopausal women			
	No. of cases		HR (95% CI) for current smokers *versus* never smokers[1]	$p_{heterogeneity}$	No. of cases		HR (95% CI) for current smokers *versus* never smokers[1]	$p_{heterogeneity}$
	Never smokers	Current smokers			Never smokers	Current smokers		
BMI (kg/m^2)								
<25	41	17	1.50 (0.83–2.71)	0.66	147	39	0.86 (0.59–1.25)	0.38
25–29	21	11	2.26 (1.01–5.09)		97	13	0.52 (0.29–0.95)	
30+	12	5	2.31 (0.68–7.83)		78	12	0.72 (0.38–1.36)	
HRT use								
Never					171	24	0.56 (0.36–0.88)	0.32
Ever					130	30	0.77 (0.50–1.17)	

[1]Stratified by age and recruitment center.

parity, use of OC, total physical activity, alcohol consumption, and education level did not alter the results. Analyses restricted to premenopausal women diagnosed before the age of 50 (59 cases) showed a HR of 2.35 (95% CI = 1.18–4.67) for current smokers compared to never smokers.

Among postmenopausal women, smoking was associated with a significant reduction in cancer risk among current smokers (HR = 0.70, 95% CI = 0.53–0.93). After adjustment for possible associated risk factors (BMI, parity, use of OC, total physical activity, alcohol consumption, education level, HRT use and age at menopause), this association was moderately attenuated, and no longer reached statistical significance (HR = 0.78, 95% CI = 0.59–1.03). The inverse association of smoking with cancer risk among the current smokers was stronger among women who smoked more than 40 years (HR = 0.61, 95% CI = 0.39–0.94) or more than 15 cigarettes per day (HR = 0.49, 95% CI = 0.31–0.78). No significant association was observed between endometrial cancer risk and smoking habits among the group of former smokers. Among current smokers, the HR was 1.03 (95% CI = 0.99–1.08) per year of premenopausal duration of smoking, and 0.91 (95% CI = 0.84–0.99) per year of postmenopausal duration. After adjustment for premenopausal duration of smoking, the HR for postmenopausal duration was 0.92 (95% CI = 0.84–1.02) (data not shown).

In centres where information on passive smoking was available, current smokers have a significant decreased risk of endometrial cancer compared to women never exposed to either active or passive smoking (HR = 0.66, 95% CI = 0.48–0.92), in the postmenopausal group. In this group, the relative risk for passive smokers compared to never smokers was 0.85 (95% CI = 0.65–1.11). In the premenopausal group, women currently exposed to tobacco smoke either by active or passive smoking has a non significant increased risk of endometrial cancer (HR = 1.56, 95% CI = 0.82–3.03 for active current smokers and HR = 1.31, 95% CI = 0.74–2.34 for passive smokers).

Test of heterogeneity of the effect between pre- and postmenopausal women was highly significant for current smokers ($p_{heterogeneity}$ = 0.0005). No significant heterogeneity of the HR for current smokers compared to never smokers was observed between various categories of HRT use (never, ever), and BMI (<25, 25–29, 30+ kg/m^2), either in pre- or in postmenopausal women (Table III). There was no evidence of heterogeneity of the association between smoking and endometrial cancer risk between the EPIC countries (data not shown).

Discussion

In this large prospective study, we observed a reduced risk of endometrial cancer with tobacco smoking among postmenopausal women and an increased risk among premenopausal women.

In postmenopausal women, our data showed a 22% reduction in risk, limited to current smokers and a 51% reduction for heavy smokers of more than 15 cigarettes per day. This inverse association between smoking and endometrial cancer risk had already been reported by several epidemiological studies.[12] In most of these studies, analyses restricted to postmenopausal women showed a 40–60% significant reduction of endometrial cancer risk. Our study also showed no interaction between smoking and HRT use, contrary to some previous reports,[21,22] but consistent with others.[11]

One proposed mechanism to explain the observed effect of smoking on endometrial cancer among postmenopausal women would be an earlier age at menopause. Smoking had been previously reported to decrease the age at menopause,[9] and an earlier age at menopause had generally been associated with a lower risk of endometrial cancer.[23] However, adjustment for age at menopause only slightly attenuated the relative risks that we observed for smoking.

Another possible mechanism is a lower degree of adiposity among smoking women. Excess body weight is a well established risk factor for endometrial cancer and smoking women tend to be leaner than non smoking women. Previous studies[10,11] also reported a weight-smoking interaction effect on endometrial cancer risk. In our study, however, adjustment for BMI did not materially alter the relative risk estimates for smoking and we also observed no interaction between BMI and smoking in relation to endometrial cancer risk.

Smoking may also have various effects on endogenous sex steroid metabolism. Among postmenopausal women, the risk of endometrial cancer is strongly related to levels of bioavailable estrogens,[8] and the major source of estrogens is the conversion of androgens within adipose tissue. However, although cigarette smoking has been associated with increased postmenopausal blood concentrations of androstenedione and DHEAS,[24–26] circulating estrogen levels have not been reported to differ clearly between smokers and non smokers.[27–29] Within the EPIC study, we did not observe any clear relationship of cigarette smoking with serum levels of androgens, but circulating levels of estrogens were higher among current smokers (unpublished results).

Our study is the first prospective study showing, in premenopausal women, a statistically significant increase in the risk of endometrial cancer among current smokers compared to never smokers. Current smokers with the highest duration (30–39 years) and intensity (more than 15 cigarettes per day) of smoking had a more than 2-fold increased risk. Few case-control studies[11,30–33] have previously reported an increased risk of endometrial cancer with smoking among premenopausal women. In Brinton *et al.*[11] study, former smokers had a 3-fold significant increased risk of endometrial cancer compared to never smokers, whereas in the other studies the increased risk was less strong and not statistically significant. Contrary to postmenopausal women, among whom relative

risks of endometrial cancer may be determined largely by differences in circulating estrogens, among premenopausal women, endometrial cancer could be mainly related to chronic anovulation and progesterone deficiency.[8] Smoking may have a direct toxic effect on the ovaries. It was shown that the polycyclic aromatic hydrocarbons found in tobacco smoke cause ovarian failure in the exposed mice.[34] Similarly, premenopausal smoking women may have an increased risk of ovarian dysfunction, ovarian failure and subsequent progesterone deficiency.[35,36]

Major strengths of the present study are the prospective design, the large sample size and the fact that it is representative of different regions in Europe. Collection of data on smoking habits was fully standardized across the cohorts, except for information on lifetime consumption of cigarette, which was not collected in France and Sweden, and on passive smoking which was not collected in a uniform format in all countries. A limitation of the study is the lack of information about changes in smoking habits after recruitment. This limitation may concern the appropriate categorization of current smoking, as some subjects who were current smokers at baseline may have stopped smoking after the recruitment. However, such overestimation of smoking duration would likely only attenuate relative risk estimates. A second limitation is the comparatively small number of premenopausal endometrial cancer cases accumulated during the follow-up period. Although this number was sufficient to examine association of smoking habits, duration and intensity and endometrial cancer risk, it did not allow a careful analysis of heterogeneity of effects across subgroups of risk factors.

Finally, another limitation is the lack of information about histopathological classification of endometrial cancer in a high percentage of the cases (65%). Although it is known that the majority of cases of endometrial carcinomas are type I tumors that are related to hormonal imbalance, type-II tumors, which are unrelated to these features can represent up to 15% of all endometrial carcinomas.[20,37] Since type II tumors appear mostly in women >60 years of age and are estrogen-independent, it is unclear how many of these cases were represented in our study and whether this lack of information can help explain the absence of modifying effects of estrogens on smoking-related cancer risk. However, even if we had had this information from all the cases, their total number still would have been insufficient (as in most other studies) for an examination of the relationship between smoking and type-II endometrial cancer separately. With further follow-up it would be possible to analyze this relationship by tumor type in the future.

In conclusion, in this prospective study, we showed an adverse effect of cigarette smoking on endometrial cancer in premenopausal women. The reduction of endometrial cancer risk observed among postmenopausal women does not have direct public health relevance since cigarette smoking is the main known risk factor for cancer and have negative consequences in several other diseases.

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