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Endometrial cancer: Population attributable risks from reproductive, familial and socioeconomic factors

Kari Hemminki [a,b,*], Justo Lorenzo Bermejo [a], Charlotta Granström [b]

[a] *Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany*
[b] *Department of Biosciences at Novum, Karolinska Institute, 141 57 Huddinge, Sweden*

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Abstract

In this study, based on the Swedish Family-Cancer Database, risk factors and their population attributable fractions (PAFs) for endometrial cancer were studied. Over 700 000 women at ages 51–68 years, accumulating 23 million person-years at risk, were entered into Poisson analysis. Overall, reproductive factors (parity and age at last birth) showed a relative risk (RR) of 1.91 and a PAF of 45.51% when the reference group was women with a parity of 3+ and the last childbirth at ages over 34 years. The RR for family history was 2.33 but the PAF was only 2.09%. The RR for socioeconomic factors was a modest 1.12 but the PAF was 6.34%. The combined PAF of these three types of risk factors was 51.84%. Although the present analysis lacked data on some important risk factors for endometrial cancer, the results suggest that a large proportion of the etiology of endometrial cancer can be defined by known epidemiological risk factors.

Keywords: Uterine cancer; Parity; Age at first birth; Family history; Population attributable fraction

1. Introduction

Cancer of the endometrium (uterine corpus, code 172 in the 7th revision of the International Classification of Diseases) is the third most common cancer after breast and colon cancers in women in Sweden [1]. Adenocarcinoma is the overwhelming histological type, and the tumour usually presents with a well defined glandular structure, referred to as endometrioid carcinoma, which is sensitive to estrogen stimulation [2–4]. Some established risk factors of endometrial cancer are conditions where chronic unopposed estrogen stimulation takes place, including estrogen replacement therapy, early menarche, late menopause and nulliparity [4–11]. The age at first birth has had no effect, while a late last birth may be protective [12]. Tamoxifen has also been associated with a risk of endometrial cancer [13]. Illnesses and other conditions that are related to a risk of endometrial cancer are obesity, gallbladder disease, diabetes, hypertension, infertility, lack of physical activity and socioeconomic status [14–17]. Among dietary constituents, saturated fats have been suggested to increase the risk of endometrial cancer, whereas vegetables and fatty fish may decrease the risk [18–22]. Family history is another risk factor of endometrial cancer, which is the most common extracolonic manifestation in hereditary nonpolyposis colorectal carcinoma (HNPCC) [23–30]. Endometrial cancer is a common second cancer when breast, ovarian and colon cancer is the first cancer [5,31].

Population attributable fractions (PAFs) are often used as a measure of the population burden of a defined exposure or condition, usually in the context of preventability of the disease [32]. For endometrial cancer, the PAF for obesity was recently given as 45% in the

* Corresponding author. Tel.: +49 6221 421800; fax: +49 6221 421810.
E-mail address: K.Hemminki@dkfz.de (K. Hemminki).

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European population [33]. However, for etiological understanding of cancer it is meaningful to determine PAF for all causal factors, irrespective of the preventability of the causes. We use here the year 2002 update of the nation-wide Swedish Family-Cancer Database, covering 10.3 million individuals and over 1 million tumours retrieved from the Swedish Cancer Registry. We determine PAFs of endometrial cancer for reproductive, familial and socioeconomic factors; unfortunately no data are available on obesity. The Database offers unique possibilities for many types of family studies, because complete data are available on family members and their cancers, supplemented by socioeconomic and other background data from national censuses [34].

2. Patients and methods

The Swedish Family-Cancer Database was initially created in the middle of the 1990s by linking an administrative family register on all Swedish families to the Swedish Cancer Registry [34]. For each child there are data on both parents at the time of birth. Each person has been assigned a unique technical identification number (which is different from the national identification number, "personal number"), allowing construction of families for example through the mother. The Database includes all persons born in Sweden after 1931 with their biological parents, totalling over 10.3 million individuals. It has been updated at the end of year 2002 to include cancers from the nation-wide Swedish Cancer Registry from years 1958 to 2000. The Database is organised in 3.2 million families, with parents and offspring. The present study included women born between years 1932 and 1949, i.e., those whose maximal age at the end of the follow-up ranged from 51 to 68 years.

The completeness of cancer registration in the 1970s has been estimated to be over 95%, and is now considered to be close to 100%. The percentage of cytologically or histologically verified cases of breast cancers has been close to 100% [1]. The Swedish Cancer Registry is based on compulsory notification of cases [1]. A 4-digit diagnostic code according to the 7th revision of the ICD-7 has been used since 1958.

Follow-up was started at birth, immigration or January 1, 1961, whichever came latest. Follow-up was terminated on diagnosis of first cancer, death, emigration, or the closing date of the study, December 31, 2000. A Poisson regression analysis was performed to model endometrial cancer incidence using following variables: age at diagnosis (5-year bands), period of follow-up (5-year bands), family history, parity, age at first birth, age at last birth, socioeconomic status and residential area [35,36]. Relative risks (RRs) and confidence intervals (95% CI) were calculated using the result of the Poisson regression. For simplicity we do not show results of age at diagnosis and period of follow-up, although these two variables were always included as indicator variables in the models.

In order to assess the reduction in incidence that would be achieved if the population were entirely unexposed to the relevant risk factors we calculated PAFs. For each variable, the population was classified dichotomously (exposed/unexposed) and PAF was calculated according to the formula $(RR - 1)/RR \times$ the proportion of cases in the exposed population, where RR is the relative risk in the exposed population [37]. A total PAF was calculated by defining as an unexposed population those being unexposed to all risk factors at the same time. For total PAF we used the formula $(inc_{all} - inc_{ref})/inc_{all} \times 100$, where inc_{all} denotes the overall population incidence and inc_{ref} denotes the incidence in the unexposed population. CIs for PAF were estimated by bootstrapping with 1000 simulations [38].

3. Results

The number of women in various categories of the variables is shown in Table 1. A total of 735 212 women with 23 258 611 person-years at risk were included, and they were followed from 1961 to 2000. Endometrial cancer was identified in 3547 women, with data on family history, reproductive variables and socioeconomic status. In initial analyses, region and age at first birth were also included as variables but because they were not

Table 1
Number of women and their relatives with endometrial cancer

Variable	Cases	Person-years (thousands)
Family history		
Sister	25	78 075
Mother	105	304 391
No history	3417	22 876 122
Parity and age at last birth		
No children	693	2 729 006
1: 13–24	273	1 483 093
1: 25–29	222	1 188 031
1: 30–34	118	699 791
1: 35–53	57	402 345
2: 13–24	257	1 796 716
2: 25–29	650	4 365 280
2: 30–34	407	2 950 999
2: 35–53	115	1 016 116
3+: 13–24	37	332 591
3+: 25–29	218	1 799 067
3+: 30–34	341	2 601 281
3+: 35–53	159	1 894 273
Socioeconomic status		
Manual worker	1468	9 061 768
Professional	227	1 523 350
Blue collar	1447	10 345 180
Other	405	2 328 291
All combined	3547	23 258 588

associated with risk, they were deleted from testing of detailed models.

Poisson regression analysis included age at diagnosis and period (data not shown), and additionally, family history, parity, age at first birth, age at last birth and socioeconomic status (Table 2). Family history through a mother proband increased the risk to 2.37 and a sister proband to 2.03. Nulliparous women showed an RR of 3.13; low parity was a risk factor; in any parity category, age at last birth had an effect, particularly in the age group 35–53 years. Manual workers and the socioeconomic group 'other' (mainly self-employed) had a small excess risk of 1.18 and 1.26, respectively.

Variables that showed a significant effect in Table 2 were analysed dichotomously for calculation of PAF for individual variables and for all variables combined (Table 3). As only 3.7% of women with endometrial cancer had a family history, the resulting PAF for family history was also small at 2.09%. Socioeconomic status conveyed a small risk but it affected a larger proportion of population, giving a PAF of 6.34%. Parity and age at last birth showed the highest PAF of 45.51%, assuming that all women would have had a parity of at least 3 and the last childbirth after 34 years. The joint effect of the three variables was 51.84%, which was only marginally less than the sum of the individual PAFs in the model shown.

Table 2
Relative risks in endometrial cancer according to the Poisson model

Variable	RR	95% CI	$Pr > \chi^2$
Family history			
Sister	2.03	1.37 3.01	0.0004
Mother	2.37	1.95 2.87	<0.0001
No history	Ref		
Parity and age at last birth			
No children	3.13	2.63 3.72	<0.0001
1: 13–24	2.26	1.86 2.75	<0.0001
1: 25–29	2.28	1.86 2.79	<0.0001
1: 30–34	2.04	1.61 2.59	<0.0001
1: 35–53	1.77	1.31 2.40	00.0002
2: 13–24	1.80	1.47 2.19	<0.0001
2: 25–29	1.84	1.54 2.19	<0.0001
2: 30–34	1.67	1.39 2.01	<0.0001
2: 35–53	1.41	1.11 1.79	0.0052
3+: 13–24	1.32	0.92 1.89	0.1299
3+: 25–29	1.38	1.13 1.69	0.002
3+: 30–34	1.49	1.23 1.80	<0.0001
3+: 35–53	Ref		
Socioeconomic status			
Manual worker	1.18	1.10 1.27	<0.0001
Professional	1.10	0.96 1.26	0.1878
Other	1.26	1.13 1.41	<0.0001
Blue collar	Ref		

4. Discussion

The present study on the Swedish Family-Cancer Database has the advantages of being nation-wide and containing many types of registered and unbiased information, including for instance, the family history of endometrial cancer, for which recall bias in interview studies may be large [30]. The disadvantage of the data source is that it does not contain information on some relevant risk factors of endometrial cancer, such as obesity, menstrual history and use of hormone supplementation. The overall incidence of endometrial cancer has remained relatively stable in Sweden during the past 40 years; the annual incidence was approximately 20/100 000 until 1990 and since then it has climbed to about 26/100 000 [39]. However, the small overall change in incidence probably hides changes in the population prevalence of individual risk factors, such as lower parity (risk), delayed child bearing (protective), and increased use of hormonal replacement therapy (risk). Irrespective of this, the present study was limited to women born after 1931 who were aged 51–68 years. Thus the calendar years of follow-up were from 1983 to 2000, a short time for any macro-epidemiological changes to take place. The variables that were studied in the present article showed expected results: family history, nulliparity and low parity were risk factors, as well as socioeconomic status other than 'blue collar'. Moreover, age at last childbirth was protective, particularly

Table 3
Relative risks and PAF for women with endometrial cancer 1961–2000

Variable	RR	95% CI	$Pr > \chi^2$	Cases	Prop (%)	PAF (%)	95% CI
Family history							
Family history	2.33	1.95 2.77	<0.0001	130	3.67	2.09	1.88 2.27
No history	Ref			3417	96.33		
Parity and age at last birth							
Other	1.91	1.63 2.24	<0.0001	3388	95.52	45.51	43.05 47.70
3+: 35–53	Ref			159	4.48		
Socioeconomic status							
Other	1.12	1.05 1.20	0.0008	2100	59.20	6.34	5.37 7.43
Blue collar	Ref			1447	40.80		
All combined				3547	1.38	51.84	47.69 58.98

when it took place at ages over 34 years, in agreement with previous publications [12].

PAF is a commonly used epidemiological measure which summarises the etiological impact of a defined exposure or a protective variable [37,40]. It gives the proportion of cancer that would be prevented if the harmful exposures and conditions could be prevented or avoided. Large PAFs indicate that a large proportion of the etiology is understood at the level of the defined variable. A large PAF can only result from a high RR and relatively common exposure or from a moderate RR and common exposure. In the present study, reproductive factors accounted for an overwhelming PAF of 45.51%, which was the result of moderate risk but very large 'at risk' population. The overall PAF of 51.84% suggests that the three variables (reproduction with two separate subvariables) explained about half of endometrial cancer incidence. This is particularly remarkable because factors such as obesity could not be included [33]. An International Agency for Research on Cancer working group estimated that the PAF for obesity in endometrial cancer is 39% [21,41]; even though this figure may be lower among Swedish women, the contribution should be substantial [33,42]. Most likely, obesity correlates to some extent with some reproductive and socioeconomic factors that we were able to consider, thus reducing its effect on the total PAF. Nevertheless, it appears justified to conclude that the epidemiologically recognised risk factors of endometrial cancer cover most of its etiology.

The epidemiological data point to the importance of hormonal factors in endometrial cancer [4]. However, the understanding how these promote carcinogenesis at the cellular and molecular level remains an enigma and future challenge.

Conflict of interest statement

None declared.

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