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Does the time interval between first and last birth influence the risk of endometrial and ovarian cancer?

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ABSTRACT

Background: Age at first and last birth and the number of children are known to influence the risk of endometrial and ovarian cancers. However, it remains unknown whether the difference in years between first and last childbirth plays a role. The Swedish Family-Cancer Database allowed us to carry out the largest study ever on reproductive factors in these cancers.

Material and methods: We selected over 5.7 million women from the database. We estimated the effect of number of children, age at birth and difference between age at first and last birth by Poisson regression adjusted for age, period, region and socioeconomic status.

Results: The risk for endometrial cancer is negatively associated with increasing number of children and increasing age at first as well as age at last birth. Weaker associations are found for ovarian cancer. Age at last birth is the factor that shows highest influence. A large difference in first and last childbirth shows a protective effect on the risk of endometrial cancer.

Conclusion: Our findings suggest that the risk of endometrial cancer is significantly decreased for women having at least a difference of 10 years between their first and last birth. Ovarian cancer does not seem to be influenced by the time interval between first and last birth.

1. Introduction

Endometrial and ovarian cancers are known to be hormone dependent neoplasms. Parity and age at first or last birth influence their risks. Nulliparity is a risk factor and increasing numbers of births are protective, as is the age at first and last birth[1–7]; the effects are somewhat stronger for endometrial than for ovarian cancer.[8] Other protective effects for endometrial and ovarian cancer are use of oral contraceptives, early menarche and breast feeding.[8–12] In contrast, overweight and obesity are positively associated with the risk for these cancers.[13–16] Physical activity is shown to have a protective effect on the risk of endometrial cancer.[17,18] Smoking has a protective effect on endometrial cancer.[19–21]

The goal of this study was to analyse the effects of parity, age at first birth and age at last birth on the risk for endometrial and ovarian cancers. As we used the Swedish Family Cancer-Database with registered women having up to 18 children, we could even look at the risk for women having more than 10 children while the largest earlier study reached only

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up to 7 full-term pregnancies.[8] Our study was based on a total of over 5.7 million women with a follow-up time from 1961 till 2006, identifying 31,118 endometrial cancer cases and 28,414 ovarian cancer cases. This was more than 4 times as many endometrial cancer cases as in a previous study of this topic[22] and over 45 times as many ovarian cancer cases.[6] A completely novel analysis probed the effect of the difference between first and last birth on the risk. As we had a large dataset of women with endometrial and ovarian cancers we were able to analyse the effects stratified by the number of children.

2. Materials and methods

Data from the Second-Generation Register, the Swedish Cancer Registry, the National Census and the Death Notification Registry are included in the Swedish Family Cancer-Database. It covers all first and second cancers from 1961 to 2006 according to the seventh revision of the International Classification of Diseases (ICD-7).[23] A total of approximately 11 million individuals born after 1932 and their biological parents have been registered. The newest version assembled in 2009 contains also information on more than 1.2 million first and multiple primary cancers and *in situ* tumours.[24] For most of the individuals affected with cancer clinical information on tumours as well as residential and socioeconomic data are available.

The study includes all 5.7 million women from the database with known birth year. Primary or secondary cancer cases are counted as cases of endometrial cancer (ICD-7 code = '172') or ovarian cancer (ICD-7 code = '175'). Through the registration of individuals with their parents, the women could be assigned with the number of children (grouped 0, 1, 2, 3–4, 5–9 and 10+), with corresponding age at first birth (grouped –19, 20–29, 30–39 and 40+) and age at last birth (grouped –29, 30–39 and 40+). The difference in years between first and last birth of a women is at most 35 years (grouped 0–1, 2–4, 5–9 and 10+).

Patients were followed up for a specific time interval depending on the information available for each woman. Follow up started at year of birth, immigration, or 1961 when the cancer registration started, whatever came latest. Follow up ends at year of diagnosis, death, emigration or end of the study in 2006, whatever occurred first. Cancer cases and person-years were determined for every stratification class of the covariates included in the regression model. For the calculation of the relative risks and the corresponding 95% confidence intervals, age (grouped –29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69 and 70+), period (5 groups), region (4 groups), and socioeconomic status (6 groups) have been included as covariates in the model. The Genmod procedure in SAS (SAS version 9.2; SAS Institute, Cary, NC, USA) was used to fit the Poisson regression model. Parameter estimates (β) are obtained by maximum likelihood estimation (MLE) which are estimated numerically through an iterative fitting process. Cancer incidence as $\exp(\beta)$ for one group compared to the reference group was calculated to obtain relative risk estimates.

To control for a possible confounding effect of parity in our analyses we analysed the effects within strata of numbers of children.

P values for trend analysis were calculated using a Jonckheere–Terpstra test which is a non-parametric test for ordered differences among classes.

3. Results

Table 1 shows the distribution of women included in the study. Over 5.7 million women were registered, of whom 31,118 (0.54%) were diagnosed with endometrial and 28,414 (0.49%) with ovarian cancer.

Relative risks (RR) with corresponding 95% confidence intervals (CI) for endometrial and ovarian cancer with respect to the number of children, age at first birth and age at last birth are shown in Table 2. We used Poisson regression to analyse the data; significant results are shown in bold. Two sided *p*-values for trends were calculated using a Jonckheere–Terpstra test. Overall we found a negative association of both cancer sites with number of children (p for trend < .0001). For the analysis of age at first or last birth we included women with at least two children. Nearly all results were significant at the 5% confidence level. Later age at first birth showed a more decreased risk for endometrial (RR: 0.40) than ovarian cancer (RR: 0.61) in the category of first birth after age 40 (p for trend < .0001). The same can be seen for age at last birth (RR for endometrial cancer: 0.49 for age at last birth after age 40; RR for ovarian cancer: 0.67 for age at last birth after age 40). A stratified analysis for number of children showed the same negative association for risk of both cancer sites with respect to the age at first and age at last birth (data not shown).

The analysis of age at birth for women having only one child also showed a negative association with increasing age at birth for endometrial (p for trend < .0001) and ovarian cancer (Table 3).

Table 4 shows relative risks for endometrial cancer with respect to the age at first and last birth of the women. Analysing all women with at least two children at once the table shows that the lowest risks are found with an age at last birth of over 40 years of age. In this group the risks ranged with increasing age at first birth from 0.47 over 0.45 and 0.38 until 0.30. Stratifying the analysis for number of children the risks were still significantly decreased for women having their last child birth older than 40 years. The risk for two child women was especially low with a risk of 0.27 if the woman had both children born after age 40.

Also in the analysis for ovarian cancer (Table 5) the risks were significantly decreased in the group of women having their last childbirth over age 40 (RR: 0.55, 0.56, 0.64 and 0.49). For ovarian cancer the lowest risk for women was found at late age at first and last birth (RR: 0.49). The same results were found in the stratified analyses.

Table 6 shows similar negative associations for the risks of endometrial and ovarian cancer with respect to the difference between the first and the last birth of a woman. The risk for endometrial cancer decreased until 0.75 if the difference of the first and last birth was more than 10 years (p for trend < .0001). For ovarian cancer it showed a risk of 0.77 for a difference of at least 10 years (p for trend < .0001). The stratified analysis for number of children showed no significant re-

Table 1 – Number of all women (and cancer cases) included in the study with respect to their number of children.

Number of children	Individuals	Endometrial (%)	Ovarian (%)
0	2,129,625	2060 (0.10)	2576 (0.12)
1	978,128	9261 (0.95)	8648 (0.88)
2	1,559,186	11,643 (0.75)	10,283 (0.66)
3	731,900	5333 (0.73)	4528 (0.62)
4	234,634	1839 (0.78)	1592 (0.68)
5	76,211	610 (0.80)	484 (0.64)
6	28,390	216 (0.76)	178 (0.63)
7	11,662	93 (0.80)	71 (0.61)
8	5028	32 (0.64)	27 (0.54)
9	2320	15 (0.65)	17 (0.73)
10+	2036	16 (0.79)	10 (0.49)
Total	5,759,120	31,118 (0.54)	28,414 (0.49)

Table 2 – Number of children, age at first birth, age at last birth with relative risk (RR) and 95% confidence intervals (CI) for endometrial and ovarian cancer.

	Endometrial cancer		Ovarian cancer	
	Cases	RR (95% CI)	Cases	RR (95% CI)
Number of children				
0 (reference)	2060	1.00	2,576	1.00
1	9261	**0.47** (0.42–0.52)	8,648	**0.55** (0.49–0.62)
2	11,643	**0.41** (0.37–0.46)	10,283	**0.46** (0.41–0.51)
3–4	7172	**0.36** (0.32–0.40)	6,120	**0.39** (0.34–0.43)
5–9	966	**0.29** (0.25–0.34)	777	**0.30** (0.25–0.35)
10+	16	**0.25** (0.10–0.58)	10	**0.20** (0.06–0.60)
Total	31,118 *p* for trend <.0001		28,414 *p* for trend <.0001	
Age at first birth				
–19 (reference)	2076	1.00	1744	1.00
20–29	14,995	**0.92** (0.87–0.97)	12,586	0.96 (0.90–1.01)
30–39	2688	**0.67** (0.62–0.72)	2815	**0.87** (0.81–0.94)
40+	38	**0.40** (0.27–0.58)	45	**0.61** (0.44–0.86)
Total	19,797 *p* for trend <.0001		17,190 *p* for trend 0.04	
Age at last birth				
–29 (reference)	7,339	1.00	6097	1.00
30–39	11,162	**0.78** (0.76–0.80)	9696	**0.84** (0.80–0.87)
40+	1296	**0.49** (0.46–0.52)	1397	**0.67** (0.62–0.72)
Total	19,797 *p* for trend 0.03		17,190 *p* for trend <.0001	

Abbreviations: RR, relative risk; CI, confidence interval.
Bold type, 95% CI does not include 1.00. Poisson regression adjusted for age, period, region, socioeconomic status.

Table 3 – Relative risk for different age at birth for women having one child.

Age at birth	Endometrial cancer		Ovarian cancer	
	Cases	RR (95% CI)	Cases	RR (95% CI)
<20	378	1.00	410	1.00
20–29	4983	1.00 (0.91–1.10)	4287	**0.80** (0.72–0.89)
30–39	3499	**0.75** (0.68–0.83)	3475	**0.69** (0.62–0.78)
40+	401	**0.51** (0.44–0.58)	476	**0.56** (0.48–0.65)
Total	9261 *p* for trend <.0001		8648 *p* for trend 0.22	

Abbreviations: RR, relative risk; CI, confidence interval.
Bold type, 95% CI does not include 1.00. Poisson regression adjusted for age, period, region, socioeconomic status.

Table 4 – Relative risk for endometrial cancer with respect to age at first and age at last birth.

Number of children	Age at first birth	Age at last birth							
		<20		20–29		30–39		40+	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Any	<20	42	1.00	1316	0.86 (0.63–1.16)	668	0.74 (0.54–1.01)	50	**0.47** (0.31–0.70)
	20–29	–		5981	0.86 (0.64–1.16)	8353	**0.69** (0.51–0.93)	661	**0.45** (0.33–0.61)
	30–39	–		–		2141	**0.57** (0.42–0.77)	547	**0.38** (0.28–0.52)
	40+	–		–		–		38	**0.30** (0.19–0.46)
2	<20	42	1.00	689	0.87 (0.64–1.18)	66	**0.66** (0.45–0.98)	2	0.37 (0.09–1.54)
	20–29	–		4757	0.85 (0.63–1.16)	3909	0.74 (0.54–1.00)	107	**0.59** (0.41–0.84)
	30–39	–		–		1771	**0.57** (0.42–0.78)	268	**0.37** (0.27–0.51)
	40+	–		–		–		32	**0.27** (0.17–0.43)
				<29		30–39		40+	
3–4	<20			575	1.00	444	0.99 (0.89–1.11)	20	**0.55** (0.37–0.82)
	20–29			1183	0.93 (0.85–1.02)	3,965	**0.79** (0.75–0.85)	367	**0.56** (0.50–0.63)
	30+			–		364	**0.58** (0.51–0.65)	254	**0.47** (0.41–0.54)
5+	<20			52	1.00	158	0.80 (0.58–1.10)	28	0.66 (0.41–1.06)
	20–29			41	1.26 (0.83–1.92)	479	0.75 (0.56–1.01)	187	**0.54** (0.39–0.75)
	30+			–		6	0.49 (0.21–1.18)	31	**0.45** (0.28–0.72)

Abbreviations: RR, relative risk; CI, confidence interval. Bold type, 95% CI does not include 1.00. Poisson regression adjusted for age, period, region, socioeconomic status.

Table 5 – Relative risk for ovarian cancer with respect to age at first and age at last birth.

Number of children	Age at first birth	Age at last birth							
		<20		20–29		30–39		40+	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Any	<20	37	1.00	1133	0.91 (0.62–1.32)	526	0.72 (0.49–1.05)	48	**0.55** (0.34–0.90)
	20–29	–		4927	0.89 (0.61–1.28)	7035	0.75 (0.52–1.09)	624	**0.56** (0.38–0.82)
	30–39	–		–		2135	0.73 (0.50–1.06)	680	**0.64** (0.44–0.94)
	40+	–		–		–		45	**0.49** (0.29–0.80)
2	<20	37	1.00	632	0.96 (0.66–1.40)	71	0.87 (0.56–1.37)	2	0.45 (0.09–2.25)
	20–29	–		3947	0.87 (0.60–1.26)	3297	0.79 (0.55–1.14)	89	**0.63** (0.41–0.98)
	30–39	–		–		1794	0.74 (0.51–1.07)	371	0.69 (0.47–1.01)
	40+	–		–		–		43	**0.50** (0.30–0.83)
				<29		30–29		40+	
3–4	<20			472	1.00	327	0.90 (0.77–1.06)	29	0.99 (0.64–1.53)
	20–29			962	0.95 (0.84–1.08)	3,344	**0.86** (0.77–0.97)	370	**0.76** (0.65–0.89)
	30+			–		332	**0.69** (0.58–0.82)	284	**0.73** (0.61–0.87)
5+	<20			29	1.00	128	1.14 (0.80–1.61)	17	0.70 (0.42–1.17)
	20–29			18	1.01 (0.61–1.67)	394	1.08 (0.78–1.50)	165	0.83 (0.59–1.18)
	30+			–		9	1.22 (0.64–2.35)	27	0.64 (0.40–1.03)

Abbreviations: RR, relative risk; CI, confidence interval.
Bold type, 95% CI does not include 1.00. Poisson regression adjusted for age, period, region, socioeconomic status.

sults for ovarian cancer anymore even if the negative association could also be seen, whereas significantly decreased risks for a time difference of at least 10 years were still found in the stratified analysis for endometrial cancer.

4. Discussion

We analysed the effects of parity, age at birth and time difference between first and last birth. Using the worldwide largest database on familial cancer (Swedish Family Cancer-Database) with more than 5.7 million women and registered endometrial and ovarian cancer cases the study had power to distinguish a large range of family sizes and as a novel analysis to show the effect of age differences between the first and last childbirth. We classified the variable categorically rather than continuously to obtain direct estimates for the novel extreme categories. We confirmed the negative association of number of children, age at first birth and age at last birth with the risk for endometrial and ovarian cancer with a significant p value for trend and more precise risk estimates with smaller confidence intervals than in previous studies.[8] These negative associations and decreasing trend

Table 6 – Difference between first and last birth.

Number of children	Difference in years	Endometrial cancer		Ovarian cancer	
		Cases	RR (95% CI)	Cases	RR (95% CI)
Any	0–1	755	1.00	665	1.00
	2–4	6948	0.96 (0.88–1.04)	6109	0.96 (0.89–1.06)
	5–9	7462	**0.89** (0.82–0.96)	6345	**0.88** (0.80–0.97)
	10+	4632	**0.75** (0.69–0.82)	4071	**0.77** (0.70–0.85)
	Total	19,797		17,190	
		p for trend <.0001		*p* for trend <.0001	
2	0–1	750	1.00	654	1.00
	2–4	6,252	0.96 (0.89–1.03)	5533	0.98 (0.89–1.07)
	5–9	3,806	0.93 (0.86–1.00)	3320	0.96 (0.88–1.05)
	10+	835	**0.85** (0.77–0.94)	776	0.93 (0.83–1.05)
	Total	11,643		10,283	
		p for trend <.0001		*p* for trend <.0001	
3–4	0–4	699	1.00	586	1.00
	5–9	3,500	0.97 (0.90–1.05)	2912	0.97 (0.88–1.07)
	10+	2,973	**0.89** (0.83–0.96)	2622	0.95 (0.86–1.04)
	Total	7,172		6120	
		p for trend <.0001		*p* for trend <.0001	
5+	0–9	158	1.00	114	1.00
	10+	824	**0.75** (0.64–0.87)	673	0.84 (0.71–1.00)
	Total	982		787	
		p for trend <.0001		*p* for trend <.0001	

Abbreviations: RR, relative risk; CI, confidence interval.
Bold type, 95% CI does not include 1.00. Poisson regression adjusted for age, period, region, socioeconomic status.

held even for women with 10+ children. We focused on the influence of the time difference between first and last childbirth.

The strongly inverse association of parity and risk for endometrial as well as for ovarian cancer was already published before.[2,8,25,26] We confirmed these results for women with at least 10 children for whom the risk decreased even until 0.25 for endometrial and 0.20 for ovarian cancer. An explanation of this decreasing risk is that during anovulatory ovarian cycles the endometrium is exposed to oestrogen in the absence of progesterone which increases the risk of endometrial cancers.[5] Instead pregnancy is indicative of normal ovulatory function which explains our findings that women with at least one pregnancy had a decreased risk for endometrial cancer and it is even more decreasing with additional pregnancies. The risk of ovarian cancer is also related to a woman's ovulatory and anovulatory ovarian cycles.[27] Pregnancy or use of hormonal contraceptives suppress ovulation and therefore the risk of ovarian cancer decreases with increasing number of children or time of use of hormonal contraceptives. As women who are pregnant at later ages show a decreased risk it is also suggested that in every pregnancy a certain proportion of transformed ovarian surface epithelial cells are removed. Circulating hormones during pregnancy clear the ovary of precancerous cells.[28] In contrast, women who were not pregnant or had a childbirth at early age accumulated a higher number of these transformed cells that increase the risk for ovarian cancer. The protective effect of pregnancy showed up in a time interval directly after pregnancy as epithelial ovarian cells need time to transform again.[29]

The highest influence on the risk of endometrial and ovarian cancers was exerted by the age at last birth (the risk decreased until 0.30 for endometrial and 0.49 for ovarian cancer for age at last birth over 40 years). With increasing age at last pregnancy the risk of these cancers decreases.[22,29] The single analysis of the effect of age at first birth showed this inverse association for both cancers as it was already stated in previous publications[2] with more precise risk estimates as our study was the worldwide largest on reproductive factors.

Our findings in terms of the time interval between first and last birth show a protective effect for endometrial cancer if women had a time period of over 10 years between their first and last childbirth. This might be explained by the fact that with every pregnancy the oestrogen level decreases further which leads to a lower risk for endometrial cancer. That means if a woman decreased this oestrogen level with her first pregnancy and then further decreased it for more than 10 years she accumulated a lot of years in her life having a lower level of oestrogens in her body where endometrial cancer could not arise. Instead the analysis for ovarian cancer did not show a general protective effect of a long time interval between the first and last childbirth of a woman. It seems that the effect of giving birth to the last child at older age gives shows enough protection against ovarian cancer. The effect of removing the precancerous cells during the last pregnancy at an older age seems to decrease the risk more than enough.

5. Conclusion

As it is already known that the age at last birth has most influence on the risk of endometrial and ovarian cancer, our results suggest now that with having the first childbirth at an earlier age will additionally decrease the risk for endometrial cancers.

Conflict of interest statement

None declared.

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