Risks of breast, endometrial, and ovarian cancers after twin births

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Abstract

The concentrations of endogenous hormones differ between women with twin and singleton births, with a possible influence on the risk of cancer. We used the nationwide Swedish Family-Cancer Database, including 30 409 women with a twin birth, to examine the subsequent risks of breast, endometrial, and ovarian cancers. Relative risks (RRs) were calculated in a log-linear Poisson regression model of person-years as offset. Cancer data were retrieved from the Swedish Cancer Registry; a total of 1010, 210, and 174 women were diagnosed with breast, endometrial, and ovarian cancers respectively, after a twin birth. A significant decrease in the risk of breast cancer was noted among women with a twin birth compared with women with a singleton birth (RR 0.85, 95% confidence interval (CI) 0.74–0.98). The protective effects were observed throughout the intervals after last pregnancy and they were strongest shortly after the last pregnancy in women who delivered a twin birth before 30 years of age. Twin birth did not change the risk of endometrial cancer (1.08, 95% CI 0.79–1.47) but the RR was increased for women with the number of pregnancies ≥ 4 (1.39, 95% CI 1.11–1.76). The RR for ovarian cancer was 0.95 (95% CI 0.79–1.15). Our study showed that twin births significantly reduced the subsequent risk of breast cancer. However, the associations of twin births with endometrial and ovarian cancers were not substantial.

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Introduction

The physiology of twin and singleton pregnancies differ, as characterized by higher levels of estradiol and testosterone during twin pregnancy, and higher concentrations of follicle-stimulating hormone and sex hormone-binding globulin after twin pregnancy (Thomas *et al.* 1998, Hall 2003). These changes may influence the occurrence of hormone responsive cancers, such as breast, endometrial, and ovarian cancers (Neale *et al.* 2004, 2005a,b). A slightly reduced risk of breast cancer among women with multiple births has been reported earlier by Jacobson *et al.* (1989), but several subsequent studies have failed to confirm this observation (Nasca *et al.* 1992, Hsieh *et al.* 1993, Dietz *et al.* 1995). The possible association of twin births with endometrial and ovarian cancers has been difficult to assess because of the rareness of the affected women (Lambe *et al.* 1999, Mogren *et al.* 2001, Neale *et al.* 2005b). However, a reliable estimation of the consequences of twin pregnancies

will help us to better understand hormone-related cancers. To address this issue, a historical cohort study was implemented using the nationwide Swedish Family-Cancer Database, and the risks of breast, endometrial, and ovarian cancers were examined among a total of 30 409 women who ever delivered a twin birth.

Materials and methods

The Family-Cancer Database has been created by linking information from the Multigeneration Register, national censuses, Swedish Cancer Registry and death notifications (Hemminki *et al.* 2001). Data on family relationships were obtained from the Multigeneration Register, where children born in Sweden in 1932 and later, are registered with their biological parents as families. Twin births were called when two offspring were born at the same time. Women with triplets or high order of multiple births were not included in this

study; women with multiple twin births were also excluded. Register linkages were carried out using the individually unique national registration number (different from the national identification number). The Swedish Cancer Registry is based on compulsory reports of individual cases provided by physicians (clinical report) and by pathologists or cytologists (pathology report); the coverage of the cancer registration is currently considered to be close to 100%. The database (MigMed2) was updated in 2006 to include the cancer cases from years 1958 to 2004.

Parous women with the last pregnancy recorded in 1958–1989 were included in this study; a total of 30 409 women were noted with a twin birth and over 1.5 million women with only singleton births. The ages at pregnancy ranged from 13 to 58 years. The follow-up was started at last pregnancy, and terminated at the diagnosis of first cancer, death, emigration, or the closing date of the study, December 31, 2004. The mean follow-up time was 28 years, ranging from 0 to 46 years. Only cases classified as primary neoplasms of the breast (International Classification of Diseases 7th revision, code 170), endometrium (172), and ovary (175) were considered. The controls were women with singleton births in the defined parity and time interval class. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated in a log-linear Poisson regression model of person-years as offset (PROC GENMOD, SAS version 9.2; SAS Institute, Cary, NC, USA), and examined separately for breast, endometrial, and ovarian cancers. The RR was examined separately for mothers of twins with different numbers of pregnancies, using the risk for women with the same number of singleton births as a reference. The risks were adjusted for age (categorical variable in 14 five-year categories), period (categorical variable in four categories) and age at first childbirth (four categories, <20, 20–24, 25–30, and ≥30 years). In the analyses of all women with a twin birth, the number of pregnancies was also adjusted. However, the full term and premature births cannot be distinguished in our database: the information about the incomplete pregnancies, such as miscarriages and terminations, was also unavailable. All independent variables were from registered sources containing no missing values.

Results

Breast cancer was diagnosed in 1010 women with twin births and in 57 080 women with only singleton births respectively. Table 1 shows the RRs of breast cancer among women ever delivered a twin birth, using the risk for women with singleton births in the same

interval class (e.g. interval after last pregnancy) as reference (RR = 1.00). The risks were further analyzed according to the mothers' age at twin birth (<30 and ≥30 years) and the order of the twin pregnancy. Mothers with a twin birth had a significant decreased risk of breast cancer, with a RR of 0.85 (95% CI 0.74–0.98). The RRs ranged from 0.81 (number of pregnancies = 1) to 0.91 (number of pregnancies ≥4). The protective effects were observed throughout the intervals after last pregnancy, with few exceptions. Women who delivered a twin birth before 30 years of age had a decreased risk compared with those delivering twin later; the effect was consistent in all pregnancies and interval classes. We also calculated the RRs for all the women whose last pregnancy was a twin pregnancy (data not shown). The RR was 0.87 ($N=687$, 95% CI 0.79–0.95); the corresponding RRs for the women who delivered the last twin birth before or after 30 years of age were 0.78 ($N=267$, 95% CI 0.67–0.92) and 0.93 ($N=420$, 95% CI 0.82–1.05) respectively. The decreased RRs were observed throughout the intervals after the last pregnancy.

Table 2 shows the RRs of endometrial and ovarian cancers among mothers of twins. A total of 210 women were diagnosed with endometrial cancer after a twin birth. The RR was marginally increased compared with women with a singleton birth (1.08, 95% CI 0.79–1.47). A significant increase was noted for women with the number of pregnancies ≥4, with a RR of 2.18 (95% CI 1.19–4.01) and 1.61 (95% CI 1.11–2.19) when the twin pregnancy was the first and middle pregnancy respectively. For ovarian cancer, a total of 174 women were diagnosed after a twin birth with a RR of 0.95 (95% CI 0.79–1.15). There was a decrease in RRs for intervals 0–9 years after last pregnancy but the RR was significant only for pregnancy of one and when these intervals were combined ($N=10$, RR = 0.47, 95% CI 0.26–0.84). One RR (2.33) was increased for women with the number of pregnancies ≥4.

Discussion

The prevalence of twin births has increased greatly since 1980s because of frequent usage of the assisted reproduction techniques and fertility drugs (Herskind *et al.* 2005, Toledo 2005). The concentrations of endogenous hormones among women with twin births are known to differ from mothers of singletons. Thus, reliable cancer risk estimation in women following twin births can help to uncover hormonal effects on cancer development. A total of 30 409 mothers who ever delivered a twin birth were included in the present

Table 1 Relative risk of breast cancer among women with a twin birth

Parameter	Age at twin birth												Singleton reference
	All				<30				≥ 30				
	N	RR	95% CI		N	RR	95% CI		N	RR	95% CI		
Intervals after last pregnancy (years)													
Total	1010	0.85	0.74	0.98	501	0.79	0.65	0.97	509	0.91	0.74	1.12	57 080
Number of pregnancies=1													
0–9	15	0.74	0.44	1.24	5	0.65	0.25	1.72	10	0.79	0.43	1.45	1068
10–19	42	0.75	0.54	1.04	17	0.65	0.37	1.14	25	0.84	0.51	1.38	2884
20–	111	0.84	0.65	1.08	72	0.82	0.59	1.13	39	0.89	0.56	1.41	7497
All	168	0.81	0.67	0.98	94	0.76	0.57	1.00	74	0.88	0.66	1.19	11 449
Number of pregnancies=2, total													
0–9	41	0.87	0.62	1.22	20	0.99	0.63	1.56	21	0.78	0.48	1.28	2564
10–19	130	0.98	0.76	1.28	61	0.90	0.61	1.32	69	1.07	0.73	1.56	7488
20–	243	0.87	0.78	0.96	143	0.80	0.69	0.93	100	0.98	0.81	1.18	16 843
All	414	0.90	0.76	1.06	224	0.83	0.66	1.05	190	1.00	0.78	1.28	26 895
Twin first pregnancy													
0–9	12	0.81	0.45	1.46	9	0.81	0.41	1.60	3	0.81	0.26	2.52	2564
10–19	38	0.97	0.61	1.55	28	0.88	0.51	1.51	10	1.39	0.52	3.70	7488
20–	52	0.67	0.51	0.88	47	0.70	0.53	0.91	5	0.49	0.21	1.17	16 843
All	102	0.78	0.56	1.10	84	0.76	0.53	1.11	18	0.87	0.39	1.94	26 895
Twin last pregnancy													
0–9	29	0.90	0.61	1.32	11	1.21	0.63	2.32	18	0.78	0.47	1.30	2564
10–19	92	0.99	0.73	1.34	33	0.92	0.53	1.59	59	1.03	0.68	1.57	7488
20–	191	0.94	0.84	1.05	96	0.86	0.73	1.02	95	1.03	0.85	1.24	16 843
All	312	0.95	0.79	1.14	140	0.88	0.66	1.17	172	1.01	0.78	1.32	26 895
Number of pregnancies=3, total													
0–9	36	1.03	0.76	1.39	10	0.73	0.41	1.30	26	1.22	0.87	1.71	1556
10–19	69	0.81	0.62	1.05	30	0.79	0.52	1.20	39	0.82	0.58	1.16	3978
20–	145	0.85	0.71	1.02	74	0.82	0.63	1.05	71	0.89	0.64	1.24	7590
All	250	0.86	0.73	1.01	114	0.79	0.63	1.00	136	0.92	0.75	1.15	13 124
Twin first pregnancy													
0–9	5	0.91	0.45	1.85	3	0.63	0.26	1.54	2	2.77	0.88	8.74	1556
10–19	8	0.63	0.32	1.24	7	0.61	0.30	1.24	1	0.86	0.11	6.41	3978
20–	24	0.95	0.59	1.53	20	0.84	0.50	1.43	4	2.59	0.66	10.18	7590
All	37	0.85	0.57	1.27	30	0.75	0.49	1.16	7	2.06	0.83	5.13	13 124
Twin middle pregnancy													
0–9	12	1.26	0.74	2.15	5	0.80	0.36	1.78	7	2.18	1.09	4.36	1556
10–19	17	0.76	0.43	1.34	14	0.86	0.48	1.54	3	0.48	0.14	1.67	3978
20–	52	1.14	0.82	1.58	35	1.02	0.69	1.51	17	1.52	0.84	2.74	7590
All	81	1.05	0.78	1.41	54	0.95	0.67	1.35	27	1.33	0.81	2.17	13 124

(continued)

Table 1 continued

Parameter	Age at twin birth												Singleton reference
	All				<30				≥30				
	N	RR	95% CI		N	RR	95% CI		N	RR	95% CI		
Twin last pregnancy													
0–9	19	0.95	0.65	1.40	2	0.76	0.22	2.66	17	0.98	0.65	1.49	1556
10–19	44	0.87	0.66	1.16	9	0.87	0.44	1.72	35	0.87	0.61	1.24	3978
20–	69	0.69	0.54	0.89	19	0.58	0.34	1.00	50	0.75	0.51	1.09	7590
All	132	0.78	0.63	0.96	30	0.64	0.41	1.00	102	0.83	0.65	1.06	13 124
Number of pregnancies ≥4, total													
0–9	18	0.65	0.39	1.07	7	0.67	0.33	1.40	11	0.63	0.33	1.19	792
10–19	53	1.02	0.77	1.36	19	0.90	0.57	1.43	34	1.11	0.77	1.60	1531
20–	107	0.93	0.79	1.08	43	0.82	0.67	1.00	64	1.02	0.86	1.21	3289
All	178	0.91	0.77	1.09	69	0.82	0.62	1.07	109	0.99	0.80	1.22	5612
Twin first pregnancy													
0–9	2	0.72	0.23	2.26	2	0.81	0.25	2.61	0				792
10–19	8	1.62	0.84	3.11	7	1.55	0.75	3.17	1	2.46	0.33	18.19	1531
20–	10	0.99	0.70	1.40	10	1.04	0.73	1.47	0				3289
All	20	1.13	0.71	1.78	19	1.14	0.71	1.84	1	0.89	0.12	6.71	5612
Twin middle pregnancy													
0–9	7	0.49	0.25	0.96	5	0.68	0.31	1.48	2	0.29	0.08	1.05	792
10–19	22	0.86	0.56	1.33	11	0.74	0.41	1.35	11	1.02	0.53	1.96	1531
20–	54	0.93	0.79	1.10	31	0.86	0.68	1.08	23	1.04	0.85	1.27	3289
All	83	0.85	0.67	1.08	47	0.81	0.59	1.10	36	0.91	0.63	1.32	5612
Twin last pregnancy													
0–9	9	0.83	0.44	1.57	0				9	0.87	0.45	1.71	792
10–19	23	1.08	0.72	1.61	1	0.53	0.08	3.60	22	1.13	0.73	1.77	1531
20–	43	0.91	0.72	1.14	2	0.29	0.15	0.55	41	1.02	0.81	1.28	3289
All	75	0.94	0.73	1.22	3	0.31	0.10	0.94	72	1.03	0.78	1.35	5612

N, observed cases; RR, relative risk; Bold type, 95% CI does not include 1.00.

Table 2 Relative risk of endometrial and ovarian cancers among women with a twin birth

Parameter	Endometrial cancer					Ovarian cancer				
	N	RR	95% CI		Singleton reference	N	RR	95% CI		Singleton reference
Intervals after last pregnancy (years)										
Total	210	1.08	0.79	1.47	9001	174	0.95	0.79	1.15	8677
Number of pregnancies = 1										
0–9	1	1.26	0.23	6.89	49	1	0.22	0.06	0.77	248
10–19	5	1.12	0.48	2.61	252	6	0.69	0.35	1.34	467
20–	23	0.89	0.71	1.13	1476	24	1.20	0.94	1.54	1142
All	29	0.93	0.59	1.48	1777	31	0.93	0.67	1.29	1857
Number of pregnancies = 2, total										
0–9	2	1.58	0.70	3.60	67	5	0.71	0.35	1.42	404
10–19	9	0.89	0.48	1.65	548	13	0.72	0.43	1.21	1025
20–	64	1.10	0.77	1.59	3396	49	1.18	0.90	1.55	2476
All	75	1.08	0.77	1.50	4011	67	1.00	0.77	1.29	3905
Twin first pregnancy										
0–9	2	4.57	1.87	11.19	67	1	0.48	0.14	1.69	404
10–19	5	1.55	0.60	4.01	548	5	0.95	0.48	1.87	1025
20–	12	0.74	0.31	1.75	3396	13	1.13	0.70	1.83	2476
All	19	0.93	0.52	1.66	4011	19	0.99	0.65	1.51	3905
Twin last pregnancy										
0–9	0				67	4	0.80	0.37	1.76	404
10–19	4	0.58	0.21	1.63	548	8	0.63	0.32	1.23	1025
20–	52	1.25	0.83	1.87	3396	36	1.20	0.88	1.62	2476
All	56	1.13	0.81	1.59	4011	48	1.00	0.77	1.31	3905
Number of pregnancies = 3, total										
0–9	1	0.97	0.16	5.84	43	3	0.55	0.24	1.26	246
10–19	8	0.92	0.50	1.68	378	13	1.09	0.69	1.74	541
20–	41	1.08	0.78	1.49	1661	29	1.10	0.84	1.46	1157
All	50	1.04	0.72	1.52	2082	45	1.03	0.75	1.41	1944
Twin first pregnancy										
0–9	1	5.54	0.91	33.77	43	1	1.17	0.37	3.73	356
10–19	0				378	1	0.56	0.12	2.59	816
20–	6	1.06	0.45	2.47	1661	4	1.03	0.48	2.19	1743
All	7	0.95	0.35	2.55	2082	6	0.91	0.40	2.07	2915
Twin middle pregnancy										
0–9	0				43	0				356
10–19	3	1.21	0.47	3.16	378	3	0.94	0.35	2.50	816
20–	12	1.17	0.68	2.03	1661	10	1.42	0.89	2.27	1743
All	15	1.14	0.61	2.14	2082	13	1.10	0.61	1.98	2915

(continued)

Table 2 continued

Parameter	Endometrial cancer					Ovarian cancer				
	N	RR	95% CI		Singleton reference	N	RR	95% CI		Singleton reference
Twin last pregnancy										
0–9	0				43	2	0.64	0.23	1.75	356
10–19	5	1.03	0.46	2.29	378	9	1.30	0.77	2.19	816
20–	23	1.04	0.69	1.57	1661	15	0.98	0.66	1.46	1743
All	28	1.02	0.64	1.65	2082	26	1.02	0.69	1.53	2915
Number of pregnancies ≥ 4 , total										
0–9	1	1.00	0.44	2.29	25	1	0.26	0.06	1.16	356
10–19	11	1.39	1.06	1.82	221	15	1.55	1.06	2.26	816
20–	44	1.41	1.04	1.92	885	15	0.72	0.52	1.00	1743
All	56	1.39	1.11	1.76	1131	31	0.90	0.67	1.22	2915
Twin first pregnancy										
0–9	0				25	0				356
10–19	1	1.32	0.56	3.06	221	1	1.10	0.30	3.97	816
20–	7	2.57	1.22	5.43	885	2	1.10	0.50	2.43	1743
All	8	2.18	1.19	4.01	1131	3	0.95	0.41	2.23	2915
Twin middle pregnancy										
0–9	1	1.74	0.74	4.08	25	1	0.51	0.11	2.28	356
10–19	9	2.22	1.61	3.05	221	5	1.02	0.54	1.92	816
20–	23	1.46	0.97	2.20	885	6	0.57	0.38	0.87	1743
All	33	1.61	1.19	2.19	1131	12	0.69	0.43	1.10	2915
Twin last pregnancy										
0–9	0				25	0				356
10–19	1	0.32	0.14	0.75	221	9	2.33	1.42	3.82	816
20–	37	1.10	0.63	1.91	885	7	0.83	0.54	1.26	1743
All	38	0.94	0.58	1.51	1131	16	1.16	0.77	1.76	2915

N, observed cases; RR, relative risk; Bold type, 95% CI does not include 1.00.

study, which, to our knowledge, was the largest one on this issue, guaranteeing a reasonable statistical power. Another advantage is that all the cancer cases were retrieved from the Swedish Cancer Registry with a complete national coverage. The present study included the whole population covered by the nationwide registers, and it was thus not influenced by selection or recall bias. However, as a limitation, hormonally relevant factors, such as abortions, use of contraceptive pills or hormone replacement therapy, were unavailable in our database, which may confound our results. However, the associations between these factors and the delivery of twins have not been observed (Bortolus *et al.* 1999).

When interpreting the results, it is important to note that all comparisons were done between twin and singleton pregnancies. In singleton pregnancies, parity is known to be a protective factor for the three cancers studied (Tavassoli & Devilee 2003); young age at first childbirth is protective for breast cancer but may be a risk factor for endometrial and ovarian cancers.

The present study indicates that mothers of twins are at a decreased risk of breast cancer, in agreement with some (Wyshak *et al.* 1983, Jacobson *et al.* 1989, Albrektsen *et al.* 1995, Neale *et al.* 2005b) but not all (Dietz *et al.* 1995, Mogren *et al.* 2001, Neale *et al.* 2004) earlier reports; even an increased risk has been previously reported (Hsieh *et al.* 1993). The protective effects were consistent in all parity classes, further corroborating the findings. The decreased risk appeared to be more pronounced when women delivered the twins at an age below 30 years and it was particularly strong for these women with the number of pregnancies three or more, when the twin pregnancy was the last one for the women. Our study also showed that the order of twin pregnancies was not an important modifying factor for the decreased risk of breast cancer. Some hypotheses have been put forward to explain the protective effect of twin pregnancy on breast cancer, such as higher concentration of sex hormone-binding globulin (Murphy *et al.* 1990) and higher level of α -fetoproteins with anti-estrogenic effects in women bearing twins (Jacobson *et al.* 1989); the latter has been supported by an animal model (Jacobson *et al.* 1989). Similar to the twin pregnancy, pre-eclampsia has been associated with a decreased breast cancer risk. The decreased risk may be explained by increased progesterone levels compared with a normal pregnancy (Peck *et al.* 2002, Tamimi *et al.* 2003). In contrast to pre-eclampsia, where estrogen levels are decreased, a twin pregnancy increases the level. The simultaneous decrease of the level of sex hormone-binding globulin in

pre-eclampsia and the increase of its level during a twin pregnancy may partly compensate the effects of estrogens (Tamimi *et al.* 2003). It is noteworthy that the observed risk was decreased throughout the intervals after last pregnancy, in disagreement with the hypothesis that a higher level of estrogen during twin pregnancies will increase the breast cancer risk transiently.

It has been hypothesized that a high level of progesterone during a twin pregnancy will reduce the subsequent risk of endometrial cancer as progesterone inhibits endometrial cell division (Key 1995). A decrease in the risk of endometrial cancer has been observed in an earlier study on the Utah Population Database (Neale *et al.* 2004). However, the protective effect was present only for the women who had more than three children and the number of affected women was limited (19 cases), weakening the conclusion. Instead, our data showed that the risk of endometrial cancer did not differ between women with twins and singleton births, which was in agreement with an earlier Swedish study (Mogren *et al.* 2001). A significant increase was even noted for women with the number of pregnancies ≥ 4 when the twin pregnancy was not the last pregnancy. Obesity has been strongly associated with an increased risk of endometrial cancer (Friedenreich *et al.* 2007). The concentration of insulin-like growth factor-II (IGF-II) has been reported to be higher among obese individuals than among lean ones (Frystyk *et al.* 1999). Increased level of IGF-II has also been associated with endometrial cancer (Petridou *et al.* 2003, Oh *et al.* 2004), which could partly explain our observation.

A small decrease in the risk of ovarian cancer among women with a twin pregnancy has been reported in some earlier studies (Lambe *et al.* 1999, Whiteman *et al.* 2000, Neale *et al.* 2005b), and the elevated level of progesterone has been suggested to be related to the decrease by inducing apoptosis of transformed ovarian cells. In the present study, a marginally decreased risk was noted, but the overall effect was not significant. The risk of ovarian cancer was significantly decreased in the first interval (0–9 years) after the last pregnancy, which was in agreement with an earlier observation that the protective effect induced by pregnancy would reach its maximum at 2–3 years after the birth and then diminish (Liu *et al.* 2006). For women with the number of pregnancies ≥ 4 , a significant increase in the risk of ovarian cancer was observed, but it was present only when the twin pregnancy was the last one and only for interval of 10–19 years since the last pregnancy, thus a chance finding could be possible.

In conclusion, our study showed that women who ever delivered a twin birth had a significant decrease in the risk of breast cancer, and the decrease was consistent in each parity class and all intervals after last pregnancy. No consistent associations were noted for endometrial and ovarian cancers; women with high parity had an increased risk of endometrial cancer; the risk of ovarian cancer was transiently decreased after a twin pregnancy.

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