The Effects of Twins, Parity and Age at First Birth on Cancer Risk in Swedish Women

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The effect of reproductive history on the risk of cervical, colorectal and thyroid cancers and melanoma has been explored but the results to date are inconsistent. We aimed to examine in a record-linkage cohort study the risk of developing these cancers, as well as breast, ovarian and endometrial cancers, among mothers who had given birth to twins compared with those who had only singleton pregnancies. Women who delivered a baby in Sweden between 1961 and 1996 and who were 15 years or younger in 1961 were selected from the Swedish civil birth register and linked with the Swedish cancer registry. We used Poisson regression to assess associations between reproductive factors and cancer. Twinning was associated with reduced risks of breast, colorectal, ovarian and uterine cancers, although no relative risks were statistically significant. The delivery of twins did not increase the risk of any cancers studied. Increasing numbers of maternities were associated with significantly reduced risks of all tumors except thyroid cancer. We found positive associations between a later age at first birth and breast cancer and melanoma, while there were inverse associations with cervix, ovarian, uterine and colorectal cancers. These findings lend weight to the hypothesis that hormonal factors influence the etiology of colorectal cancer in women, but argue against any strong effect of hormones on the development of melanoma or tumors of the thyroid.

Reproductive influences on endogenous hormone levels are implicated in several adult female cancers. The evidence that the risk of breast, endometrial and ovarian cancers is lower among parous women is strong and compelling (Grady & Ernster, 1996; Kelsey & Bernstein, 1996; Whittemore, 1994), and cancer-dependent associations with ages at first and last pregnancies are significant. The effect of reproductive history on cervix, colorectal, melanoma and thyroid cancers has been explored, but the evidence is thus far inconsistent. Studying the relationship of cancer occurrence to unusual features of reproductive history, such as twinning, may help to shed light on the nature of these hormonal influences, as women who bear twins differ from those who do not in clearly definable ways with regard to the pregnancy itself and, in approximately two thirds of twin mothers, with regard to their cyclical hormonal milieu (Thomas et al., 1998).

Accordingly a historical cohort study has been conducted using a large linked database from Sweden to examine the relation of twinning, along with other reproductive variables, to risk of cervix, colorectal, melanoma and thyroid tumors. The cohort design facilitated the inclusion of multiple outcomes, so for completeness, breast, ovarian and uterine cancers have been included, although they have been analyzed in nested case-control datasets extracted from earlier similar versions of Swedish data (Lambe, Hsieh et al., 1996; Lambe et al., 1999; Mogren et al., 2001).

Materials and Methods

Women eligible for inclusion in the cohort were those women who had delivered a baby in Sweden between 1961 and 1996 and who were 15 years or younger in 1961 (i.e., born in 1946 or later) when the computerized birth register began. The birth and cancer registrations for women born prior to this may not have been complete, and these women were therefore not included in this study. Births were registered on the Civil Birth register between 1961 and 1972, which includes information about the sex of the baby, whether or not it was a twin or higher-order birth and the parity of the mother. From 1973 to the present, these data are also recorded on the Medical Birth Register, which records

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similar details, along with additional clinical information about mother and children (Cnattingius et al., 1990; http://www.sos.se/fulltext/112/2003-112-3/2003-112-3.pdf). Personal identity numbers of women in this cohort were linked to the Swedish Cancer Register which contained information on cancers diagnosed in Sweden from 1958 to 1996 at the time of linkage. Cancer sites were coded using ICD-7, and morphology according to WHO/HS/CANC/24.1. Only tumors that are malignant in nature were included in the analysis. Women whose cancer was not coded as malignant were excluded from all analyses of that particular cancer. For all cancers other than cervical, this was an insignificant number. However this resulted in exclusion from the analysis of cervix cancer for approximately 70,000 women diagnosed with carcinoma in situ. Further linkage with Statistics Sweden added information about migrations into or out of Sweden between 1961 and 1996, and the date of death of the mother.

SAS version 8.12 (SAS Institute Inc., 1996) and Stata version 7.0 (StataCorp., 2000) were used for all analyses. The cancers included in this analysis were breast (ICD 170), endometrial (ICD 172), ovarian (ICD 175), cervical (ICD 171), colorectal (ICD 153, 154), thyroid (ICD 194), and malignant melanoma (ICD 190). Poisson regression was used to analyze associations between these and twinning and other reproductive variables, namely parity and age at first birth. Results are presented as estimated relative rates (RR), with 95% confidence intervals (CIs) for the estimates.

The date of entry used was either 1961, the date the mother turned 15 or the date of immigration, whichever occurred later. The exit date was taken as the earliest of the following: date of diagnosis of the cancer being analyzed, the date of death, the emigration date or December 31, 1996.

Parity was calculated by adding the number of children recorded on the birth register to the birth order of the first child registered. Still births were included in this number when recorded. The number of maternities was calculated by subtracting the number of twins from the parity estimate.

Results

From the birth registers, 1,234,967 women were identified who were born in 1946 or later. The mean and median parity of the mothers was 2, including births not specifically recorded in the birth register, and the median age of first birth was 24 years. Two per cent of women (n = 25,549) experienced at least one twin pregnancy. Of these, 183 women (approximately 1%) had two or three twin pregnancies. Four hundred and ninety women had triplets, although not all were live born. These women were combined with those who had had twins for the purposes of multiple births analysis. The mean age at diagnosis of cancer was younger than expected due to the exclusion of women born prior to 1946 (Table 1).

Table 1

Descriptive Statistics for Cancer Occurrences

Cancer	Descriptive statistics
Breast	
N cases	6309
N (%) twin mothers	116 (1.8)
Mean parity of cases (*SD*)	2.11 (0.88)
Mean age at diagnosis	40.1
Cervix	
N cases	4498
N (%) twin mothers	88 (2.0)
Mean parity (*SD*)	2.15 (0.96)
Mean age at diagnosis	31.5
Ovary	
N cases	1062
N (%) twin mothers	20 (1.9)
Mean parity (*SD*)	2.00 (0.90)
Mean age at diagnosis	36.3
Uterus	
N cases	197
N (%) twin mothers	3 (1.5)
Mean parity (*SD*)	2.03 (0.87)
Mean age at diagnosis	43.6
Colorectal	
N cases	959
N (%) twin mothers	16 (1.7)
Mean parity (*SD*)	2.17 (0.90)
Mean age at diagnosis	35.7
Melanoma	
N cases	2285
N (%) twin mothers	47 (2.1)
Mean parity (*SD*)	2.13 (0.88)
Mean age at diagnosis	34.0
Thyroid	
N cases	986
N (%) twin mothers	23 (2.3)
Mean parity (*SD*)	2.24 (0.93)
Mean age at diagnosis	32.2

There was a small reduction in the risk of colorectal cancer among women who had given birth to at least one set of twins (RR 0.80, 95% CI 0.49–1.30; Table 2), although this finding may have been due to chance. There was a significant inverse association with number of maternities (p-trend = .02) and with increasing age at first birth (p-trend = .02).

Mothers of twins had the same risk of melanoma as mothers of singletons (RR = 0.97, 95% CI 0.72–1.29). There was a significant inverse association between melanoma risk and number of maternities (p-trend = .03) and a positive association between melanoma and age at first birth (p-trend < .0001; Table 3).

No significant associations were found between any reproductive factors examined and the risk of thyroid cancer (Table 4), although there was a small and nonsignificant increase in risk with increasing age at first birth. Women who had more than one birth were also at slightly increased risk, although there was no significant trend (p-trend = .24).

There was no association between twinning and the rate of occurrence of cervical cancer, but signifi-

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Table 2

Associations Between Reproductive Variables and Risk of Colorectal Cancer

	Number of cancers	Relative risk (95% CI)	
		Unadjusted	Adjusted
Twinning			
No twin pregnancy	943	1.00	1.00
Twin pregnancy	16	0.77 (0.47–1.26)	0.80 (0.49–1.30)
p-value		.30	.35
Number of maternities			
1	215	1.00	1.00
2	470	1.03 (0.88–1.21)	0.91 (0.77–1.07)
3	209	1.01 (0.84–1.22)	0.85 (0.69–1.03)
≥ 4	65	0.93 (0.70–1.22)	0.75 (0.56–0.99)
p-trend		.72	.02
Age at first birth			
< 20	176	1.00	1.00
20–24	393	0.86 (0.72–1.03)	0.94 (0.71–1.04)
25–29	267	0.77 (0.64–0.93)	0.86 (0.71–1.04)
30+	123	0.77 (0.61–0.97)	0.78 (0.62–1.00)
p-trend		.007	.02

Note: *Mutually adjusted for all listed variables and for date of birth of the mother as a continuous variable.

Table 4

Associations Between Reproductive Variables and Risk of Thyroid Cancer

	N cancers	Relative risk (95% CI)	
		Unadjusted	Adjusted
Twinning			
No twin pregnancy	963	1.00	1.00
Twin pregnancy	23	1.08 (0.72–1.64)	1.10 (0.73–1.66)
p-value		.71	.70
Number of maternities			
1	196	1.00	1.00
2	480	1.16 (0.98–1.36)	1.09 (0.92–1.29)
3	240	1.28 (1.06–1.54)	1.19 (0.98–1.45)
≥ 4	70	1.10 (0.83–1.44)	1.04 (0.78–1.37)
p-trend		.08	.24
Age at first birth			
< 20	144	1.00	1.00
20–24	402	1.08 (0.89–1.31)	1.15 (0.94–1.39)
25–29	307	1.08 (0.89–1.32)	1.18 (0.96–1.44)
30+	133	1.02 (0.80–1.29)	1.10 (0.86–1.41)
p-trend		.89	.37

Note: *Mutually adjusted for all listed variables and for date of birth of the mother as a continuous variable.

cant inverse associations were seen with both the number of maternities (*p*-trend < .0001) and the age at first birth (*p*-trend < .0001; Table 5). Mothers of twins had a slightly lower, albeit nonsignificant, risk of breast cancer 0.91 (0.75–1.09). The risk of ovarian and uterine cancer in mothers of twins did not differ from women who had not had twins. As expected there were significant inverse associations between maternities and breast, ovarian and uterine cancers (Tables 6, 7 and 8). Age at first birth was not associated with uterine cancer, but late age at first birth increased the risk of breast cancer and decreased the risk of ovarian cancer.

Discussion

The main aim of this study was to examine the effect of twinning and other reproductive influences on the risk of colorectal, cervical, melanoma and thyroid tumors. Breast, ovarian and endometrial cancers were included for completeness and to test the validity of the data and analysis, and indeed the associations found with these tumors are consistent with a large

Table 3

Associations Between Reproductive Variables and Risk of Melanoma

	N cancers	Relative risk (95% CI)	
		Unadjusted	Adjusted
Twinning			
No twin pregnancy	2238	1.00	1.00
Twin pregnancy	47	0.95 (0.71–1.27)	0.97 (0.72–1.29)
p-value		.73	.75
Number of maternities			
1	530	1.00	1.00
2	1132	1.01 (0.91–1.12)	0.97 (0.87–1.08)
3	501	0.98 (0.87–1.11)	0.97 (0.85–1.10)
≥ 4	122	0.70 (0.57–0.85)	0.71 (0.58–0.87)
p-trend		.01	.03
Age at first birth			
< 20	284	1.00	1.00
20–24	864	1.18 (1.03–1.35)	1.22 (1.07–1.40)
25–29	781	1.39 (1.22–1.60)	1.46 (1.27–1.67)
30+	356	1.38 (1.18–1.62)	1.37 (1.17–1.61)
p-trend		< .0001	< .0001

Note: *Mutually adjusted for all listed variables and for date of birth of the mother as a continuous variable.

Table 5

Associations Between Reproductive Variables and Risk of Cervical Cancer

	N cancers	Relative risk (95% CI)	
		Unadjusted	Adjusted
Twinning			
No twin pregnancy	4410	1.00	1.00
Twin pregnancy	88	0.90 (0.73–1.11)	0.95 (0.77–1.18)
p-value		.33	.76
Number of maternities			
1	1172	1.00	1.00
2	2047	0.82 (0.77–0.89)	0.68 (0.63–0.73)
3	941	0.84 (0.77–0.91)	0.60 (0.55–0.66)
≥ 4	338	0.89 (0.79–1.01)	0.56 (0.50–0.64)
p-trend		.003	< .0001
Age at first birth			
< 20	1249	1.00	1.00
20–24	1749	0.52 (0.48–0.56)	0.57 (0.53–0.61)
25–29	1030	0.40 (0.37–0.43)	0.43 (0.40–0.47)
30+	470	0.40 (0.36–0.44)	0.36 (0.32–0.40)
p-trend		< .0001	< .0001

Note: *Mutually adjusted for all listed variables and for date of birth of the mother as a continuous variable.

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Table 6

Associations Between Reproductive Variables and Risk of Breast Cancer

	N cancers	Relative risk (95% CI)	
		Unadjusted	Adjusted
Twinning			
No twin pregnancy	6193	1.00	1.00
Twin pregnancy	116	0.85 (0.71–1.02)	0.91 (0.75–1.09)
p-value		.07	.27
Number of maternities			
1	1502	1.00	1.00
2	3158	0.99 (0.93–1.06)	0.91 (0.85–0.97)
3	1301	0.90 (0.84–0.97)	0.83 (0.77–0.89)
≥ 4	348	0.71 (0.63–0.80)	0.66 (0.59–0.74)
p-trend		< .0001	< .0001
Age at first birth			
< 20	951	1.00	1.00
20–24	2296	0.93 (0.87–1.01)	1.09 (1.01–1.17)
25–29	1964	1.05 (0.97–1.13)	1.31 (1.21–1.42)
30+	1098	1.27 (1.17–1.39)	1.44 (1.31–1.57)
p-trend		< .0001	< .0001

Note: *Mutually adjusted for all listed variables and for date of birth of the mother as a continuous variable.

Table 8

Associations Between Reproductive Variables and Risk of Uterine Cancer

	N cancers	Relative risk (95% CI)	
		Unadjusted	Adjusted
Twinning			
No twin pregnancy	194	1.00	1.00
Twin pregnancy	3	0.70 (0.22–2.19)	0.81 (0.26–2.53)
p-value		.54	.72
Number of maternities			
1	57	1.00	1.00
2	91	0.75 (0.54–1.05)	0.61 (0.44–0.86)
3	41	0.75 (0.50–1.12)	0.57 (0.38–0.86)
≥ 4	8	0.43 (0.21–0.90)	0.31 (0.15–0.66)
p-trend		.02	.003
Age at first birth			
< 20	40	1.00	1.00
20–24	93	0.90 (0.62–1.30)	1.08 (0.75–1.57)
25–29	40	0.51 (0.33–0.79)	0.67 (0.43–1.05)
30+	24	0.66 (0.40–1.10)	0.74 (0.44–1.25)
p-trend		.004	.04

Note: *Mutually adjusted for all listed variables and for date of birth of the mother as a continuous variable.

body of evidence. That is, increasing maternities offers some protection from all three of these tumors (Grady & Ernster, 1996; Kelsey & Bernstein, 1996; Whittemore, 1994), and increasing age at first birth increases the risk of breast cancer (McPherson et al., 2000), and reduces the risk of ovarian (Whiteman et al., 2003) and endometrial cancers, albeit nonsignificantly for the latter (Hinkula et al., 2002).

No association between twinning and cervical cancer was found, in contrast to the previous analysis of data from Utah (Neale et al., 2004). However, an inverse association was found between number of maternities and age at first birth and risk of cervix cancer. These results appear to be somewhat discrepant as there is now moderately consistent literature suggesting that cervix cancer is the only one of the gynecological cancers for which risk increases with increasing parity (Brinton et al., 1989). Including the 70,000 women with carcinoma in situ as cases did not change these estimates (results not shown). Mogren and colleagues (2001), in their analysis of a smaller overlapping Swedish dataset, also reported this inverse association, which we are unable to adequately explain given that most of our results concur with what might be expected. Sweden was one of the first countries in the European Union to introduce screening for cervix cancer (Linos & Riza, 2000) and it is conceivable that differential selection into screening programs may contribute to these findings.

Table 7

Associations Between Reproductive Variables and Risk of Ovarian Cancer

	N cancers	Relative risk (95% CI)	
		Unadjusted	Adjusted
Twinning			
No twin pregnancy	1042	1.00	1.00
Twin pregnancy	20	0.87 (0.56–1.35)	0.93 (0.60–1.45)
p-value		.52	.81
Number of maternities			
1	332	1.00	1.00
2	487	0.69 (0.60–0.80)	0.55 (0.48–0.64)
3	185	0.58 (0.48–0.69)	0.54 (0.41–0.71)
≥ 4	58	0.42 (0.35–0.50)	0.36 (0.27–0.47)
p-trend		< .0001	< .0001
Age at first birth			
< 20	223	1.00	1.00
20–24	465	0.81 (0.69–0.95)	0.88 (0.75–1.03)
25–29	265	0.60 (0.50–0.72)	0.65 (0.54–0.78)
30+	109	0.54 (0.43–0.68)	0.45 (0.35–0.57)
p-trend		< .0001	< .0001

Note: *Mutually adjusted for all listed variables and for date of birth of the mother as a continuous variable.

The effect of reproductive variables on colorectal cancer has been extensively explored over the last 40 years, since Fraumeni first found that colorectal cancer was significantly increased in nuns (Fraumeni et al., 1969) and it was observed that the international incidence of colorectal cancer co-varies with breast cancer (Berg, 1975). The results regarding the effect of parity and age at first birth remain equivocal, but the majority of studies (Jacobs et al., 1994; Kampman et al., 1997; Marcus et al., 1995; Potter et al., 1993; Yoo et al., 1999), including one previously conducted in a similar Swedish dataset (Broeders et al., 1996), favor a small protective effect of increasing parity. A previous finding that reproductive factors appear to influence colorectal cancer risk in male partners of women (Talamini et al., 1998) argues in favour of a nonhormonal explanation for these findings. However, we

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found that women who had given birth to twins were at a lower risk of colorectal cancer, although this finding was not significant, supporting a case for at least some hormonal influence of reproductive factors. Similar investigations of the effect of twinning on colorectal cancer could not be found in the literature.

As in a previous study of a similar Swedish dataset (Lambe, Thorn et al., 1996), melanoma was found to occur less frequently among women with more children, and that giving birth later was associated with an increased risk. Lambe and colleagues argued that this was unlikely to be due to confounding by sun exposure. However other studies have reported similar associations that were mitigated by adjustment for sun exposure (Smith et al., 1998; Zanetti et al., 1990), suggesting that our association with reproductive factors may well have been similarly confounded. It was observed that the different hormonal milieu associated with conceiving and/or bearing twins did not significantly affect melanoma risk in this parous population, lending weight to the body of evidence indicating that endogenous hormones are unlikely to substantially influence the risk of melanoma (Green & Bain, 1985; Holly et al., 1983; Holman et al., 1983; Osterlind et al., 1988; Smith et al., 1998; Westerdahl et al., 1996; Zanetti et al., 1990).

The incidence of thyroid cancer among women at reproductive ages is approximately three times as high as that among men (Parkin et al., 1997). This peak during the reproductive period, compared to a steady age-related increase in incidence among men, suggests that this disease may be related to hormonal and reproductive factors. Despite this, most studies have found, at best, a small contribution of reproductive factors. The number of pregnancies appears to be relatively unimportant (Galanti et al., 1995; Iribarren et al., 2001; Negri et al., 1999; Sakoda & Horn-Ross, 2002), but several studies have found a late age at first birth and in particular, a recent birth, to confer an increase in risk (Galanti et al., 1995; Negri et al., 1999; Sakoda & Horn-Ross, 2002). It is possible that pregnancy confers a short-term increase in risk, perhaps by increasing levels of thyroid-stimulating hormone. Consistent with these conclusions, no effect of twinning or parity was found, but a small, nonsignificant increase in risk with increasing age at first birth was found.

This large linkage study has enabled us to examine associations between a relatively rare exposure, twinning, and seven different cancers. Several limitations must, however, be considered. We were unable to control for confounding by, or examine specifically, other potentially important variables such as miscarriage or abortion, use of the oral contraceptive pill or assisted reproductive technologies, use of exogenous steroids and other lifestyle factors such as sun exposure, diet or exercise. Perhaps the confounder most likely to have influenced the results is the use of the oral contraceptive pill. However, there is no consistent evidence of a positive or negative association between its use and the delivery of twins, and most estimates of risks of twin births according to contraceptive use are close to unity (Bortolus et al., 1999). As there were very few women who had finished childbearing, it was elected not to analyze age at last birth. The effects of nulliparity were not assessed, and only associations with cancers diagnosed before the age of 50 years were able to be examined. Despite these shortcomings, the exquisite sensitivity of breast tissue to hormonal variations during pregnancy has been demonstrated again. The nonsignificant finding that mothers of twins may be at a reduced risk of colorectal cancer lends some support to a possible hormonal contribution to the etiology of colorectal cancer and merits further investigation in other datasets.

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