FETAL GROWTH AND SUBSEQUENT MATERNAL RISK OF COLORECTAL CANCER

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Abstract

Background—High birth weight has been associated with subsequent increased risk of breast cancer in the infant's mother, possibly related to maternal estrogen and growth factor pathways. However, its association with maternal risk of colorectal cancer, the third most common cancer among women, is unknown.

Methods—We conducted a national cohort study of 1,838,509 mothers who delivered 3,590,523 babies in Sweden in 1973-2008, followed up for colorectal cancer incidence through 2009.

Results—There were 7,318 mothers diagnosed with colorectal cancer in 36.8 million person-years of follow-up. After adjusting for maternal age, body mass index, diabetes, and other potential confounders, high fetal growth was associated with a subsequent increased risk of colorectal cancer in the mother (incidence rate ratio [IRR] per additional 1 standard deviation relative to mean birth weight for gestational age and sex, 1.05; 95% CI, 1.03-1.07; *P*<0.0001). Each 1,000 g increase in the infant's birth weight was associated with a 12% increase in the mother's subsequent risk of colorectal cancer (IRR, 1.12; 95% CI, 1.07-1.17;*P*<0.0001). Multiple gestation also was independently associated with increased maternal risk of colorectal cancer (IRR for twin or higher order vs. singleton, 1.22; 95% CI, 1.04-1.44;*P*=0.02).

Conclusion—In this large cohort study, high fetal growth and multiple gestation were independently associated with subsequent higher maternal risk of colorectal cancer. These findings warrant further investigation of maternal growth factor and estrogen pathways in the etiology of colorectal cancer.

Impact—If confirmed, our findings may help identify subgroups of women at high risk of colorectal cancer.

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INTRODUCTION

High birth weight has been associated with long-term health consequences in both the child and mother. As early as the 1930s, for example, associations have been described between high birth weight and subsequent risk of diabetes mellitus in both the child and mother [1]. More recently, a growing body of research has suggested that this is also true for cancer [2], although it has been much more widely studied in the offspring than in the mother. Numerous studies have reported associations between high birth weight and increased risk of cancer in the offspring later in life [3-6], especially breast cancer [7, 8]. Among the smaller number of studies examining a link between high birth weight and cancer risk in the mother, some [9-11] but not all [12, 13] have reported associations with breast cancer, possibly related to maternal estrogen and growth factor pathways [14-17]. More limited evidence for endometrial cancer also has been inconsistent [13, 18]. However, gestational factors have rarely been examined in relation to other outcomes in the mother such as colorectal cancer, which is the third most common cancer in women [19] and may share common risk factors with breast and endometrial cancer [20, 21]. A small study of 92 Russian women with colorectal cancer observed that a significantly higher percentage (42.6%) had delivered large babies (>4000 g) compared with 421 healthy controls (18.1%) [22], but to our knowledge this association has not been further or more rigorously examined. Because the average birth weight has grown progressively larger over the last few decades in Western countries [23-25], it is important to understand the potential long-term health consequences and their underlying mechanisms. Large cohort studies have the potential to shed further light on the role of fetal growth in the mother's subsequent risk of cancer, which is still largely unknown.

We conducted a national cohort study to examine associations between gestational factors including fetal growth in the offspring and subsequent risk of colorectal cancer among all ~1.8 million women who gave birth during 1973-2008 in Sweden. Detailed information on gestational factors and colorectal cancer incidence were obtained from birth and cancer registries that are nearly 100% complete nationwide. Our aims were to examine whether fetal growth and other gestational factors in the offspring are associated with increased risk of colorectal cancer in this large national cohort of mothers.

MATERIALS AND METHODS

Study Population

We identified 3,595,055 live births among 1,840,473 mothers in the Swedish Birth Registry from 1973 through 2008. We excluded all 913 (0.03%) births that occurred after a prior diagnosis of colorectal cancer in the mother. To remove possible coding errors, we also excluded 3,619 (0.1%) births that had a reported birth weight more than four standard deviations (SD) above or below the mean birth weight for gestational age and sex based on a

Swedish reference growth curve (26). A total of 3,590,523 births among 1,838,509 mothers (99.9% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

Ascertainment of Colorectal Cancer

The study cohort was followed up for colorectal cancer incidence from the time of first delivery through December 31, 2009. All incident colorectal cancer cases were identified using *International Classification of Diseases* (*ICD*) codes in the Swedish Cancer Registry (codes 153-154 in *ICD*-7, -8, and -9; and C18-C20 in *ICD*-10). This registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide.

Ascertainment of Gestational Factors

Gestational and maternal characteristics that are potentially associated with colorectal cancer were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number (27). The following variables were examined as adjustment variables or predictors of interest: maternal age at delivery (modeled simultaneously as a continuous variable and categorical variable [<25, 25-29, 30-34,   35 years] to allow for a non-linear effect); date of delivery (included to adjust for follow-up time, and modeled simultaneously as a continuous variable and categorical variable by decade to allow for a non-linear effect); fetal growth of the offspring (a standardized fetal growth variable defined as the number of SD from the mean birth weight for gestational age and sex based on a Swedish reference growth curve (26), modeled alternatively as a categorical [<−1; −1 to <1;   1 SD] and continuous variable); gestational age at birth of the offspring (based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; modeled alternatively as a categorical [<34, 34-36, 37-41,   42 weeks] and continuous variable); multiple gestation (singleton vs. twin or higher order); maternal parity (1, 2, 3,   4); maternal pre-pregnancy body mass index (BMI, modeled alternatively as a categorical [<18.5, 18.5-24.9, 25.0-29.9,   30.0] and continuous variable; included because high BMI has been associated with delivering a high birth weight infant (28, 29) and increased risk of colorectal cancer (30)); maternal diabetes (yes or no, identified by any inpatient or outpatient diagnosis of diabetes mellitus prior to delivery, using the Swedish Hospital Registry which includes all inpatient diagnoses from the six most populous counties of southern Sweden since 1964 and nationwide since 1987, and the Swedish Outpatient Registry which includes all outpatient diagnoses nationwide since 2001; included because diabetes has been associated with delivering a high birth weight infant (29) and increased risk of colorectal cancer (31)); maternal education level (compulsory high school or less [9 years], practical high school or some theoretical high school [10-11 years], theoretical high school and/or some college [12-14 years], college and/or post-graduate study [15 years]); maternal marital status (married/cohabiting, never married, widowed/divorced); and maternal country of birth (Sweden, other Western countries [Europe, U.S., Canada, Australia, New Zealand], other non-Western countries).

As alternatives to the standardized fetal growth variable, we also examined birth weight (modeled alternatively as a categorical [<2500, 2500-3999,   4000 g] and continuous

variable) and birth length (crown-heel length in cm, modeled alternatively as a categorical [<48, 48-52,   53 cm] and continuous variable) in separate models.

Missing data for each variable were imputed using a standard multiple imputation procedure based on the variable's relationship with all other covariates (32, 33). Missing data were infrequent for the standardized fetal growth variable (0.5%), birth weight (0.3%), birth length (1.1%), gestational age at birth (0.2%), maternal age (0.1%), parity (5.9%), and maternal education (4.1%). Maternal BMI was missing for 44.9% of all births because it was available only starting in 1982. A sensitivity analysis was performed after excluding births for which maternal BMI was unavailable (as an alternative to multiple imputation). Data were complete for all other variables.

Statistical Analysis

Poisson regression with robust standard errors was used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for associations between gestational or maternal variables and subsequent maternal risk of colorectal cancer (34). Clustering of births by mother was used to account for correlation among siblings while allowing information from each birth to contribute to the risk estimates. Sensitivity analyses were also performed after restricting alternatively to each mother's first or last birth. All models were adjusted for maternal age, date of delivery (to account for follow-up time), parity, BMI, diabetes, and education level; and fetal growth, gestational age at birth, and multiple gestation of the offspring. All adjustment variables were modeled as categorical variables (as defined above), except for maternal age and date of delivery (modeled simultaneously as continuous and categorical variables) and fetal growth (modeled as a continuous variable). Poisson model goodness-of-fit was assessed using deviance and Pearson chi-squared tests, which showed a good fit in all models, and a better fit than Cox proportional hazards models. Logistic regression was alternatively examined and produced virtually identical results as Poisson regression.

Multinomial logistic regression was used to test for heterogeneity in the association between fetal growth and the mother's risk of colorectal cancer by age at diagnosis (comparing <50 to   50 years) or by time since delivery (comparing <5 to   5 years); and for heterogeneity in the association between fetal growth and the mother's risk of colon cancer or rectal cancer examined as separate outcomes. A likelihood ratio test was used to assess for interaction between fetal growth and maternal BMI in relation to the mother's risk of colorectal cancer. All statistical tests were 2-sided and used an α-level of 0.05. All analyses were conducted using Stata version 13.0 (33).

RESULTS

Among the 1,838,509 mothers in this cohort, 7,318 (0.4%) were subsequently diagnosed with colorectal cancer in 36.8 million person-years of follow-up. The median age of all women at the end of follow-up was 47.7 years (mean 48.0, SD 11.6, maximum 78.5), and the median age at diagnosis of colorectal cancer was 54.1 years (mean 53.0, SD 9.9, maximum 77.3).

High fetal growth in the offspring was associated with a subsequent increased risk of colorectal cancer in the mother (adjusted IRR for fetal growth 1 vs. −1 to <1 SD, 1.17; 95% CI, 1.09-1.27; $P<0.0001$), including a highly significant linear trend across the full range of fetal growth (adjusted IRR per additional 1 SD, 1.05; 95% CI, 1.03-1.07, $P<0.0001$) (Table 1). A similar positive linear trend was found in the mother's colorectal cancer risk by her offspring's birth weight and birth length when examined as alternatives to the standardized fetal growth variable (Table 1). Each 1,000 g increase in the offspring's birth weight was associated with a 12% increase in the mother's subsequent risk of colorectal cancer (adjusted IRR, 1.12; 95% CI, 1.07-1.17, $P<0.0001$). In contrast, no linear trend was found in the mother's risk of colorectal cancer by her child's gestational age at birth (Table 1). With the exception of age and follow-up time, adjustment for any combination of other covariates had a negligible effect on any of the risk estimates.

Multiple gestation pregnancies also were associated with a modestly increased risk of colorectal cancer in the mother, relative to singleton pregnancies (adjusted IRR, 1.22; 95% CI, 1.04-1.44, $P=0.02$). Older maternal age was the strongest risk factor for colorectal cancer ($P_{trend}<0.0001$), whereas high BMI was associated with a slightly increased risk ($P_{trend}=0.04$) and high parity was associated with a slightly reduced risk ($P_{trend}=0.001$) (see Table 1). Divorced or widowed mothers also had a very slightly increased risk of colorectal cancer relative to married or cohabiting mothers (Table 1). Sex of the child, maternal diabetes, and maternal country of birth were not associated with maternal risk of colorectal cancer.

The association between high fetal growth and risk of colorectal cancer in the mother appeared slightly stronger among women diagnosed at age 50 years (adjusted odds ratio [OR] per additional 1 SD, 1.06; 95% CI, 1.03-1.09; $P<0.001$; based on 4,758 colorectal cancer cases) than those diagnosed at age <50 years (adjusted OR, 1.03; 95% CI, 0.99-1.06; $P=0.13$; based on 2,560 cases), although the difference between these risk estimates was non-significant ($P_{heterogeneity}=0.14$; data not shown in the table). In addition, this association appeared very similar among those diagnosed 5 years after delivery (adjusted OR per additional 1 SD, 1.05; 95% CI, 1.03-1.07; $P<0.001$; based on 6,983 colorectal cancer cases) compared with those diagnosed <5 years after delivery (adjusted OR per additional 1 SD, 1.05; 95% CI, 0.97-1.13; $P=0.23$; based on 335 cases) ($P_{heterogeneity}=0.90$; not shown in the table). Examining colon cancer and rectal cancer as separate outcomes, we found no significant heterogeneity in the association between fetal growth and maternal risk of colon cancer (adjusted OR per additional 1 SD, 1.06; 95% CI, 1.03-1.09; $P<0.001$; based on 4,286 women with cancer of the colon but not rectum) compared with the risk of rectal cancer (adjusted OR per additional 1 SD, 1.03; 95% CI, 1.00-1.07; $P=0.06$; based on 2,911 women with cancer of the rectum but not other sites of the colon) ($P_{heterogeneity}=0.17$; not shown in the table).

Sensitivity analyses that were restricted alternatively to each mother's first or last birth produced very similar results as the main analysis, including virtually identical risk estimates for fetal growth (adjusted IRRs per additional 1 SD, first births: 1.05; 95% CI, 1.02-1.07; $P<0.001$; last births: 1.06; 95% CI, 1.03-1.08; $P<0.001$) ($P_{heterogeneity}=0.35$; data not shown in the tables). A sensitivity analysis that excluded births with missing data for

maternal BMI also produced a similar risk estimate for fetal growth (adjusted IRR per additional 1 SD, 1.04; 95% CI, 1.01-1.08; P=0.02). There was no evidence of interaction between fetal growth and maternal BMI in relation to maternal risk of colorectal cancer ($P_{\text{interaction}}$=0.37).

DISCUSSION

In this large national cohort study, we found that high fetal growth and multiple gestation were associated with a subsequent higher maternal risk of colorectal cancer, independently of other factors such as maternal age, BMI, and diabetes. There was no trend in the mother's risk of colorectal cancer by her child's gestational age at birth. These findings from a large population-based cohort contribute to previous evidence for a role of gestational factors including fetal growth in the mother's later risk of cancer.

To our knowledge, the only previous study of birth weight and the mother's risk of colorectal cancer was a small case-control study of women who had delivered singleton full-term births in Russia, which reported that a significantly higher percentage of those subsequently diagnosed with colorectal cancer (40/94=42.6%) had delivered large babies (>4000 g) compared with healthy controls (76/421=18.1%) (crude OR, 3.36; 95% CI, 2.02-5.56) (22). Our risk estimates from a large national cohort are much lower in magnitude but in the same direction as those findings (22). Our findings also add to other evidence linking high birth weight in the offspring with increased cancer risk in the mother, including an association with breast cancer reported in several (9-11) though not all (12, 13) studies, and more limited evidence for endometrial cancer (13). The largest of those previous studies was a U.S. case-control study of 22,646 breast cancer cases and 224,721 controls, which reported a 6% increased risk of breast cancer in the mother per 1,000 g increase in the child's birth weight (OR, 1.06; 1.03-1.09) (9). In our cohort study, the corresponding risk estimate for colorectal cancer was slightly higher (IRR, 1.12; 95% CI, 1.07-1.17).

The underlying mechanisms are not yet established but may involve an interplay of maternal estrogen and growth factor pathways (14-17). Fetal growth is correlated with maternal estriol levels (15, 35, 36), umbilical cord levels of insulin-like growth factor-1 (IGF-1) (36), and the rate of increase in maternal IGF-1 levels in mid-pregnancy (37). Cross talk between estrogen and IGF-1 receptors has also been shown to regulate cell proliferation and resistance to apoptosis (38). IGF-1 is known to have pro-carcinogenic properties including inhibition of apoptosis (39), and high IGF-1 levels in adulthood have been associated with increased risk of breast (40) and colorectal (41) cancer. Additional experimental and epidemiologic studies are needed to delineate the underlying mechanisms, which could potentially facilitate the identification of high-risk subgroups and new targets for preventive or therapeutic interventions.

We also found that multiple gestation was associated with a modestly increased risk of colorectal cancer in the mother. To our knowledge, this relationship has not been previously examined. However, a link between multiple gestation and subsequent increased risk of breast cancer in the mother has been reported (11), which may be related to increased

maternal estrogen stimulation during multiple gestation pregnancies. In addition, our finding of decreased colorectal cancer risk with increasing parity is consistent with some previous findings (42), possibly related to lower IGF-1 levels or reduction of secondary bile acid production (43, 44), although results across other studies have been inconsistent (45).

Important strengths of this study include its large population-based cohort design, which can yield more robust and generalizable results. Linkage of birth and cancer registries provided detailed information on gestational factors and colorectal cancer incidence that was nearly 100% complete nationwide (46, 47). A cohort design prevented selection bias that may potentially occur in case-control studies, and the use of prospectively ascertained registry data prevented bias that may result from self-reporting. We were able to examine the specific components of birth weight—fetal growth and gestational age—while adjusting for potential confounders including maternal BMI and diabetes. Obese women deliver heavier babies on average (28, 29), and obesity is associated with a modestly increased risk of colorectal cancer (30), although this association has been more evident among men and is not consistently found among women (48, 49). Similarly, diabetic mothers also deliver heavier babies on average (29), and diabetes has been associated with a modestly increased risk of colorectal cancer (31). We were able to adjust for both maternal obesity and diabetes, which had a negligible effect on risk estimates.

Limitations included a lack of information for certain other exposures that may be associated with colorectal cancer, including alcohol use, smoking, and diet, hence we were unable to examine their potential influences on our findings. This cohort was also relatively young, with a median age of 48 years (maximum 78 years) at the end of follow-up. Additional follow-up will be needed to examine our observed associations at older ages when colorectal cancer is more common. Studies with more specific information on colon cancer site would be useful to examine for heterogeneity by this factor, as well as additional diabetes information to examine for potential effect modification by maternal diabetes type.

In summary, this is the first large cohort study to examine associations between gestational factors and subsequent maternal risk of colorectal cancer. We found that high fetal growth and multiple gestation were independently associated with a subsequent increased risk of colorectal cancer in the mother. Additional studies are warranted to examine these associations in other populations and at older ages. Further elucidation of the possible growth factor and estrogen pathways will improve our understanding of disease etiology and may help identify subgroups of women at high risk of colorectal cancer.

Acknowledgments

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Table 1

Adjusted incidence rate ratios for associations between gestational factors and subsequent risk of colorectal cancer in the mother (1973-2009)[a]

	Subsequent Colorectal Cancer				
	No (N=3,577,984 births among 1,831,191 mothers)	Yes (N=12,539 births among 7,318 mothers)	IRR	95% CI	P
Offspring variables					
Sex					
Female	1,739,064 (48.6)	6,018 (48.0)	1.00		
Male	1,838,920 (51.4)	6,521 (52.0)	1.02	0.99, 1.06	0.26
Fetal growth (SD)					
<-1	527,227 (14.7)	1,998 (15.9)	1.04	0.99, 1.10	0.14
−1 to <1	2,519,511 (70.4)	8,530 (68.0)	1.00		
1	531,246 (14.9)	2,011 (16.0)	1.17	1.09, 1.27	<0.001
Per SD (trend test)			1.05	1.03, 1.07	<0.001
Birth weight (g)					
<2500	151,673 (4.2)	553 (4.4)	0.92	0.82, 1.04	0.19
2500-3999	2,783,705 (77.8)	9,618 (76.7)	1.00		
4000	642,606 (18.0)	2,368 (18.9)	1.08	1.03, 1.14	0.004
Per 1000 g (trend test)			1.12	1.07, 1.17	<0.001
Birth length (cm)					
<48	381,873 (10.7)	1,266 (10.1)	0.93	0.87, 1.01	0.07
48-52	2,617,718 (73.2)	8,981 (71.6)	1.00		
53	578,393 (16.2)	2,292 (18.3)	1.11	1.06, 1.17	<0.001
Per cm (trend test)			1.02	1.01, 1.03	<0.001
Gestational age at birth (weeks)					
<34	54,691 (1.5)	199 (1.6)	1.10	0.94, 1.29	0.23
34-36	154,202 (4.3)	578 (4.6)	1.07	0.97, 1.18	0.15
37-41	3,070,834 (85.8)	10,487 (83.6)	1.00		
42	298,257 (8.3)	1,275 (10.2)	1.08	1.01, 1.15	0.02
Per week (trend test)			1.00	0.99, 1.02	0.48
Multiple gestation					
Singleton	3,492,817 (97.6)	12,229 (97.5)	1.00		
Twin or higher order	85,167 (2.4)	310 (2.5)	1.22	1.04, 1.44	0.02
Maternal variables					
Age (years)					
<25	765,425 (21.4)	1,762 (14.0)	0.60	0.56, 0.64	<0.001
25-29	1,257,777 (35.2)	3,871 (30.9)	1.00		
30-34	1,035,956 (28.9)	3,939 (31.4)	1.61	1.54, 1.68	<0.001
35	518,826 (14.5)	2,967 (23.7)	2.95	2.78, 3.13	<0.001
Per higher category (trend test)			1.69	1.65, 1.74	<0.001
Parity					

	Subsequent Colorectal Cancer				
	No (N=3,577,984 births among 1,831,191 mothers)	Yes (N=12,539 births among 7,318 mothers)	IRR	95% CI	P
1	1,503,979 (42.0)	4,246 (33.9)	1.00		
2	1,302,161 (36.4)	4,710 (37.6)	0.97	0.94, 0.99	0.03
3	541,966 (15.1)	2,383 (19.0)	0.92	0.87, 0.97	0.001
4	229,878 (6.4)	1,200 (9.6)	0.88	0.81, 0.97	0.007
Per higher category (trend test)			0.96	0.93, 0.98	0.001
Body mass index					
<18.5	83,168 (2.3)	184 (1.5)	1.00	0.85, 1.19	0.96
18.5-25	2,887,403 (80.7)	11,150 (88.9)	1.00		
25-30	459,649 (12.9)	1,031 (8.2)	1.01	0.94, 1.09	0.81
>30	147,764 (4.1)	174 (1.4)	1.14	0.95, 1.37	0.17
Per 1 unit higher (trend test)			1.01	1.00, 1.02	0.04
Diabetes					
Yes	15,965 (0.4)	55 (0.4)	1.00		
No	3,562,019 (99.6)	12,484 (99.6)	1.04	0.74, 1.47	0.81
Education (years)					
9	705,400 (19.7)	3,239 (25.8)	1.00		
10-11	1,201,348 (33.6)	4,561 (36.4)	1.05	0.99, 1.13	0.13
12-14	1,092,093 (30.5)	2,880 (23.0)	0.97	0.90, 1.04	0.40
15	579,143 (16.2)	1,859 (14.8)	0.97	0.89, 1.06	0.48
Per higher category (trend test)			0.98	0.95, 1.01	0.15
Marital status					
Married/cohabiting	2,874,398 (80.3)	9,187 (73.3)	1.00		
Never married	350,693 (9.8)	1,912 (15.2)	1.05	0.99, 1.11	0.14
Divorced/widowed	352,893 (9.9)	1,440 (11.5)	1.07	1.01, 1.14	0.03
Country of birth					
Sweden	2,858,477 (79.9)	10,280 (82.0)	1.00		
Other Western countries	418,264 (11.7)	1,756 (14.0)	1.05	0.97, 1.13	0.19
Other non-Western countries	301,243 (8.4)	503 (4.0)	1.05	0.91, 1.21	0.52

IRR = incidence rate ratio.

[a]The model included maternal age, date of delivery, parity, diabetes, body mass index, and education level; and fetal growth, gestational age at birth, and multiple gestation of the offspring. Birth weight and length of the offspring were examined in separate models as alternatives to the standardized fetal growth variable. The reference category for all variables is indicated by an IRR of 1.00.