Short Communication

Birth characteristics and risk of colorectal cancer: a study among Swedish twins

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Type-2 diabetes increases the risk of colorectal cancer, and is also associated with low birth weight. However, we found no evidence of associations between birth characteristics and risk of colorectal cancer (n = 248) among Swedish twins.

British Journal of Cancer (2009) 100, 803 – 806. doi:10.1038/sj.bjc.6604918 www.bjcancer.com

Keywords: birth length; birth weight; colorectal cancer; perinatal

Colorectal cancer is associated with type-2 diabetes (Hu et al, 1999) and with high concentrations of insulin-like growth factor I (IGF-I). Birth weight is commonly used as a proxy for foetal growth, and may be used as an indirect marker for foetal exposure to growth stimulating factors, such as IGFs (Osorio et al, 1996; Ong et al, 2000; Christou et al, 2001) and oestrogens (Petridou et al, 1990; Kajiser et al, 2000; Mucci et al, 2003). Low birth weight is associated with increased risk of type-2 diabetes (Harder et al, 2007), and high birth weight is associated with breast cancer (Silva Idos et al, 2008) and possibly also with prostate cancer (Tibblin et al, 1995; Platz et al, 1998; Ekbom et al, 1996, 2000; Boland et al, 2003; Nilsen et al, 2005b).

Little is known about early risk factors for colorectal cancer. Earlier studies of birth characteristics and colorectal cancer have been inconsistent (Sandhu et al, 2002; Nilsen et al, 2005a). We examined associations between birth characteristics and risk of colorectal cancer in like-sexed twins with known zygosity. The twin design also enabled us to take into account genetic and shared environmental factors in early life.

METHODS

In 1973, all like-sexed twins born in 1926 – 1958 included in the Swedish Twin Registry were sent a questionnaire, including questions of degree of likeness, anthropometric measures and lifestyle factors, with 81% response rate (Gederlof et al, 1961; Crumpacker et al, 1979; Lichtenstein et al, 2002). In this study, we restricted the cohort to twins with known zygosity, as determined by questions on childhood resemblance, which had earlier been validated with DNA markers (Lichtenstein et al, 2002). The person-unique national registration number, assigned to all Swedish citizens, permitted linkage among the Swedish Twin Registry, the Cancer and the Cause of Death Registers, and also enabled us to retrieve information from birth records. The study was approved by the research ethics committee of Karolinska Institutet.

Colorectal cancer cases were retrieved from the population-based Swedish Cancer Register, identified using the International Classification of Diseases (ICD) (ICD-7, ICD-8 and ICD-9 codes 153 and 154, and ICD-10 codes C18 – C21).

Information on birth characteristics was abstracted from the original birth records. Correct birth identification of each twin within a pair was ensured by restricting the data collection to twin pairs who were both baptised and named at birth, or who reported birth order with mutual within-pair agreement in a telephonic interview conducted in 1998 – 2002 (Bergvall et al, 2007). Information from birth records included anthropometric measures at birth, gestational age, maternal age, parity and occupational status of both parents. Gestational age was based on the date of the first day of the last menstrual period. Socio-economic status (SES) at birth was based on information of parental occupation, and was classified according to the recommendations by Statistics Sweden (Swedish Socioeconomic Classification, 1983). Information on education and SES in adulthood was based on Swedish Census data of 1970 and 1980, respectively. Information on adult weight, height, smoking and alcohol consumption was collected through the 1973 questionnaire. Body mass index (BMI) was calculated as the ratio between the weight and squared height (kg/m2). Alcohol consumption (estimated mean grams of alcohol per day) was classified according to the recommendations by World Health Organisation as low, medium or high (Ezzati, 2004). Other variables were categorised according to Table 1.

For this study, all like-sexed male and female twins with known zygosity born in 1926 – 1958 were considered. For the 32 011 twins who were alive and without earlier diagnosis of colorectal cancer at the time of entry (1 January, 1973) until a first diagnosis of colorectal cancer, the Cancer and the Cause of Death Registers were searched. Colorectal cancer cases were identified using the International Classification of Diseases (ICD) (ICD-7, ICD-8 and ICD-9 codes 153 and 154, and ICD-10 codes C18 – C21).

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For this study, all like-sexed male and female twins with known zygosity born in 1926 – 1958 were considered. For the 32 011 twins who were alive and without earlier diagnosis of colorectal cancer at start of follow-up in 1973, the birth record coverage was 73%. Restrictions were because of missing birth weight data in birth records (n = 6293) and uncertain correct identification of each twin within a twin pair at birth (n = 2381), resulting in a final study population of 23 337 twins (including 11 419 male and 11 918 female twins).

Statistical analyses

In the cohort analysis, risk time (person- years) was accrued from the time of entry (1 January, 1973) until a first diagnosis of colorectal cancer.
colorectal cancer or censored at the date of first emigration from Sweden, death or end of follow-up (31 December 2006). Cox proportional hazard models were used to estimate hazard ratios (HRs) for colorectal cancer with age (measured in months) as the underlying time scale, and robust standard error estimates to account for the dependence within twin pairs.

We estimated the independent risk of colorectal cancer for all exposure variables (Table 1). Different adjusted models were used in the cohort analyses to estimate risk (Table 2, models 1–4). All twins share early environmental factors, dizygotic and monozygotic twins share 50 and 100% of their segregating genes, respectively. To account for familial (genetic and shared early environmental factors), we calculated mean (± s.d.) birth weight and birth length among dizygotic and monzygotic twin pairs, discordant for colorectal cancer. Analyses were carried out in PROC PHREG in SAS 9.2.

RESULTS

In our cohort of 23,337 twins, 248 developed colorectal cancer during the follow-up period. Table 1 shows the distribution of birth and adult characteristics and crude HRs for colorectal cancer. Compared with males, females had a reduced risk. Risk increased with birth weight, but no risk estimates were significant. Other birth characteristics and parental factors at delivery did not influence the risk. Overweight in adulthood (BMI \( \geq 25 \)) was associated with an increased risk of colorectal cancer.

Table 2 shows birth weight and birth length categories and HRs. Generally, there were no significant associations between birth weight or birth length and risk in the (crude or adjusted) models. When we also adjusted in a subsample for adult characteristics, a long birth length (\( \geq 50 \) cm) appeared to be protective (HR 0.56; 95% CI 0.47–0.69, respectively) nor the fully adjusted models accounted for the dependence within twin pairs.

To account for familial (genetic and shared early environmental factors), we calculated mean (± s.d.) birth weight and birth length among dizygotic and monzygotic twin pairs, discordant for colorectal cancer. Analyses were carried out in PROC PHREG in SAS 9.2.
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Table 2 Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CI) of colorectal cancer in relation to birth weight and birth length in the cohort analyses of Swedish like-sexed twins born in 1926–1958

| Birth weight, g | Study population | Colorectal cancer | HR (95% CI), adjusted for | Birth and maternal characteristics<sup>a</sup> (n = 16 649) |
|----------------|------------------|------------------|---------------------------|------------------------------------------------------------|
|                | N                | n                | %                         | Birth characteristics<sup>b</sup> (n = 22 097)             |
| <2500          | 8904             | 86               | 1.0                       | 1.01 (0.72 –1.40)                                         |
| 2500–2999      | 8444             | 86               | 1.0                       | 1.00 (0.99 –1.02)                                         |
| ≥3000          | 5989             | 76               | 1.3                       | 1.15 (0.82 –1.61)                                         |
|                |                  |                  |                           | 1.00 (0.99 –1.02)                                         |
| Birth length, cm |                  |                  |                           | 1.00 (0.99 –1.02)                                         |
| <47            | 7220             | 68               | 0.9                       | 0.94 (0.65 –1.34)                                         |
| 47–49          | 6761             | 79               | 1.0                       | 1.00 (0.99 –1.02)                                         |
| ≥50            | 9183             | 101              | 1.1                       | 0.88 (0.64 –1.20)                                         |

All analyses are stratified by birth year and have accounted for the clustered data structure and between-cluster effect. <sup>a</sup>Adjusted for zygosity, sex and gestational age. <sup>b</sup>Adjusted for birth characteristics, mother's age, parity and socioeconomic status at birth.

To account for familial (genetic or shared environmental) factors, we also carried out analyses within disease-discordant twin pairs. In dizygotic disease-discordant twin pairs (n = 144), the mean birth weight (s.d.) was 2761 g (495) and 2756 g (487) among cases and co-twin controls, respectively (P = 0.94). In monozygotic disease-discordant twin pairs (n = 86), the corresponding mean birth weights (s.d.) were 2610 g (495) and 2624 g (550), respectively (P = 0.69). Similarly, there were no differences in mean birth length within dizygotic or monozygotic disease-discordant twin pairs (data not shown).

DISCUSSION

In a cohort study of Swedish twins, we found no evidence that birth characteristics influenced the risk of colorectal cancer. There were also no differences in mean birth weight and birth length among disease-discordant dizygotic and monozygotic twin pairs. As analyses within disease-discordant twin pairs account for familial (genetic and early environmental) factors and perfectly match for gestational age, these negative findings further strengthen the hypothesis that foetal growth is not related to offspring risk of colorectal cancer.

A J-shaped relation between self-reported birth weight and colorectal cancer was initially reported by a British study, including 96 cases (Sandhu et al, 2002). A Norwegian study, including 247 cases, found that the risk was increased among males with a short birth length (Nilsen et al, 2005a). However, the sex-specific analyses included only 150 male and 97 female cancer cases, and interaction analyses between birth characteristics and sex with respect to risk of colorectal cancer were not reported. In our negative study, we found no significant interactions between sex and birth characteristics with respect to risk of colorectal cancer.

The generalisability of results from twin studies may be questionable as twins are in general more growth restricted than singletons, have shorter gestational age, and because they may differ in prenatal environment and upbringing. However, the incidence of colorectal cancer does not appear to be different in twins compared with singletons (Verkasalo et al, 1999). As studies within twin pairs adjust for gestational age, differences in birth weight within twin pairs reflect the differences in foetal growth, and genetic factors are fully taken into account when analyses are restricted to monozygotic twin pairs. Thus, for the research question of the effect of foetal growth on offspring risk of disease, twin studies have a high internal validity.

This study lends no support for an association between birth characteristics and risk of colorectal cancer. The conflicting results from the few earlier studies may be because of limited statistical power, but it is relevant that the underlying biological reasons for an association with birth characteristics remain speculative.

ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish Cancer Society (grants No. 4594-B01-01XAC and 4594-B04-04XAB), the Swedish Council For Working Life and Social Research (grants No. 2004-0174 and 2007-0231), the Swedish Research Council (grants No. K2006-71X-14671-01-3 and K2008-54X-20638-01-3) and the European Union-funded Network of Excellence Lifespan (FP6 036894).

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