

*Short Communication*Self-Reported Birth Weight and Subsequent Risk of Colorectal Cancer¹

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Abstract

Case series data suggest that high birth weight and neonatal macrosomia in offspring are associated with an increased risk of colorectal cancer in parents. We therefore conducted a prospective analysis investigating the association among self-reported birth weight, neonatal macrosomia, and incident colorectal cancer in a population-based study of men and women. Participants were drawn from a cohort of men and women ages between 45 and 79 years: the European Prospective Investigation of Cancer in Norfolk study. A total of 4532 men and 7325 women who reported their birth weight were followed up between 1993 and 1999. The relation between birth weight and incident colorectal cancer was assessed using Cox's proportional hazards model. All Ps are two-sided. The association between self-reported birth weight and risk of incident colorectal cancer was nonlinear. Relative to individuals born weighing 2500–3249 g, the adjusted hazard ratio for people born with neonatal macrosomia was 2.57 (95% confidence interval = 1.15–5.74). There was also some evidence that low birth weight babies were at increased risk of colorectal cancer relative to the referent category. These risks were essentially unaltered after adjustment for potential confounders. There is a J-shape relation between self-reported birth weight and subsequent risk of colorectal cancer. Babies born with macrosomia appear to have the greatest risk.

Introduction

Several prospective observational studies have shown positive associations between birth weight and subsequent risk of breast and prostate cancer, suggesting that determinants of fetal

growth and development may influence the risk of these cancers in later life (1, 2). In contrast, epidemiological studies of colorectal cancer have largely focused on the role of adult determinants (3). Case series data, however, have indicated that neonatal macrosomia may be associated with an increased risk of colorectal cancer (4). Furthermore, probably as a result of the correlation between birth weights of parents and offspring, high birth weight in offspring has been shown to predict cancer development in both offspring and parents, including colorectal cancer (4, 5).

Birth weight also shows positive associations with adult height and BMI³ (6–8), both of which have been associated with an increased risk of colorectal cancer (9). Hence, together with case series data for neonatal macrosomia, these modest, positive correlations among birth weight, adult height, and body size suggest that birth weight could also be associated with risk of this cancer. To our knowledge, no prospective study has assessed the relation among birth weight, neonatal macrosomia, and incident colorectal cancer. We therefore conducted a preliminary analysis investigating these associations in a population-based study of men and women.

Materials and Methods

Participants were drawn from a population-based cohort of 30,466 men and women ages between 45 and 79 years, who were recruited from registers of general practices in Norfolk, United Kingdom, between 1993 and 1997: the European Prospective Investigation of Cancer in Norfolk study. The design and study methods have been described previously (10). All participants completed a detailed health and lifestyle questionnaire, which included questions on birth weight, smoking habits (current, former, and never), education, and occupation. We also used the Townsend social and material deprivation score as an area-based measure of socioeconomic position (11). Trained nurses examined the 25,639 participants who also attended a clinic visit. Height, weight, waist, and hip measurements were taken. BMI was estimated as weight (kg) divided by height (m) squared. We categorized birth weight into broad groups with intervals of 750 g. Neonatal macrosomia was defined as babies weighing >4000 g at delivery (12). We also used a more stringent definition, *i.e.*, those babies exceeding 2 SDs of the mean for the population (12), which for this cohort approximately equated to a birth weight of >4750 g.

Incident colorectal cancer (ICD 9th revision, 153.0–153.9, 154.0, and 154.1) was ascertained by matching all participants to the East Anglian Cancer Registry and the United Kingdom Office of National Statistics Register, which provided notification of all cancer registrations, deaths, and emigrations for the cohort. Thus, loss to follow-up was <0.1%. After excluding 1998 participants with prevalent cancer at the baseline survey, 41% (4532 men and 7325 women) of the remaining 28,448

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³ The abbreviations used are: BMI, body mass index; HR, hazard ratio; CI, confidence interval; IGF-I, insulin-like growth factor I.

Table 1 Distribution of selected characteristics by categories of birth weight in men and women^a

	Birth weight categories (g)				P for trend ^b
	<2500	2500–3249	3250–4000	>4000	
Men	<i>n</i> = 365	<i>n</i> = 1224	<i>n</i> = 1882	<i>n</i> = 1061	
Birth weight (kg)	1.91 (0.46)	3.03 (0.18)	3.58 (0.18)	4.52 (0.48)	
Age (yrs)	57.3 (8.8)	57.8 (9.1)	57.0 (9.1)	58.9 (9.1)	0.007
Height (cm) ^c	173.0 (7.7)	173.7 (6.4)	175.5 (6.5)	176.1 (6.7)	<0.001
BMI (kg/m ²) ^c	26.6 (3.4)	26.3 (3.2)	26.8 (3.5)	27.4 (3.5)	<0.001
Waist-hip ratio ^c	0.926 (0.056)	0.927 (0.058)	0.931 (0.061)	0.938 (0.062)	<0.001
Current smokers (%)	9.4	13.0	14.4	13.4	0.124
Socioeconomic position ^c (%) ^d	29.9	23.6	25.9	28.6	0.002
Women	<i>n</i> = 1103	<i>n</i> = 2508	<i>n</i> = 2609	<i>n</i> = 1105	
Birth weight (kg)	2.01 (0.41)	2.98 (0.19)	3.55 (0.19)	4.40 (0.38)	
Age (yrs)	58.2 (9.1)	57.1 (9.0)	56.4 (9.1)	58.6 (9.3)	0.641
Height (cm) ^c	158.9 (6.2)	161.0 (6.0)	162.3 (6.1)	163.3 (6.0)	<0.001
BMI (kg/m ²) ^c	26.5 (4.3)	25.9 (4.4)	26.0 (4.4)	26.9 (4.6)	0.036
Waist-hip ratio ^c	0.794 (0.062)	0.785 (0.062)	0.785 (0.063)	0.791 (0.063)	0.582
Current smokers (%)	11.0	11.3	12.0	13.2	0.016
Socioeconomic position ^c (%) ^d	23.8	25.9	26.8	24.1	0.376

^a Values are mean (SD) unless otherwise stated.

^b All *P*s are two-sided.

^c Based on data from cohort subgroup (*n* = 3889 for men and *n* = 6204 for women).

^d Proportion in least deprived quartile based on Townsend social and material deprivation score.

Table 2 HRs and 95% CIs for colorectal cancer according to birth weight category

Birth weight (g) ^a	Cases/number	Rate (per 1000)	HR (95% CIs) ^b	HR (95% CIs) ^c
<2500	9/1628	1.33	1.98 (0.82 to 4.79)	2.16 (0.89 to 5.22)
2500–3249	11/4266	0.62	1.00 (referent)	1.00 (referent)
3250–4000	19/4141	1.11	1.82 (0.87 to 3.83)	1.83 (0.87 to 3.86)
>4000	13/1770	1.76	2.54 (1.14 to 5.67)	2.57 (1.15 to 5.74)

^a Sex-standardized birth weight.

^b Age adjusted.

^c Age and sex adjusted.

participants had data for self-reported birth weight. With respect to incidence of colorectal cancer, there was no difference between individuals who self-reported birth weight and those who did not.

We analyzed the relation between self-reported birth weight and incident colorectal cancer using Cox's proportional hazards model (13). In all models, age was used as the time scale of interest. We assessed model assumptions by comparing plots of cumulative colorectal cancer rates over different birth weight strata. Because information on potential confounders was missing for some cases, we separately examined their possible influence on the effect of birth weight in subgroup analyses. As well as sex-specific and grouped analyses using absolute and sex-standardized birth weights (14), the potential confounding effects of adult height, BMI, waist-hip ratio, smoking status, and socioeconomic position were determined by comparing relative differences between adjusted and unadjusted risk estimates. Linear trends comparing continuous variables with their corresponding categorical and polynomial terms and, possible interactions, were assessed using likelihood ratio tests. All *P*s are two-sided.

Results

During a mean follow-up of >4 years, colorectal cancer was diagnosed in 52 participants (31 men and 21 women). Distributions of selected sex-specific characteristics by categories of birth weight are shown in Table 1. The only consistent association for both men and women was that for height, which

showed a positive linear association with self-reported birth weight.

Although we found a significant linear association between self-reported birth weight as a continuous variable and risk of incident colorectal cancer, with an age- and sex-adjusted HR of 1.41 (95% CI = 1.01–1.98)/1000 g increase in birth weight [χ^2 (1 *df*) = 3.98; *P* = 0.046], a nonlinear association was confirmed by adding a quadratic term for birth weight. This additional term significantly improved model fit [χ^2 (2 *df*) = 8.22; *P* = 0.016]. Additional analyses suggested that the relation between self-reported birth weight and risk of incident colorectal cancer was J-shaped (Table 2). Using the birth weight category that included the nadir of the risk curve as the referent category, we found that, relative to individuals born weighing 2500–3249 g, the age- and sex-adjusted HR for people born with neonatal macrosomia was 2.57 (95% CI = 1.15–5.74). Using the more stringent definition for neonatal macrosomia, the equivalent HR was 4.37 (95% CI = 1.39–13.78). There was also some evidence that low birth weight babies were at increased risk of colorectal cancer relative to the referent category. Additional stratification of the lowest birth weight category, reflecting a birth weight of <2 SDs from the mean, increased the associated relative risk (data not shown). However, this excess risk remained nonsignificant.

Sex-specific Cox models showed similar relations to the sex-stratified models reported in Table 2. In subgroup analyses, the association between birth weight and colorectal cancer was essentially unaltered after adjustment for potential confounders

Table 3 Multivariate HRs and 95% CIs for colorectal cancer according to birth weight category

Birth weight (g) ^a	Cases/number	HR (95% CIs) ^b	HR (95% CIs) ^c
<2500	6/1345	1.50 (0.54 to 4.12)	1.44 (0.52 to 4.01)
2500–3249	10/3571	1.00 (referent)	1.00 (referent)
3250–4000	16/3569	1.64 (0.74 to 3.61)	1.76 (0.78 to 3.91)
>4000	11/1489	2.35 (1.00 to 5.55)	2.63 (1.10 to 6.29)

^a Sex-standardized birth weight.

^b Age adjusted.

^c Adjusted for age, sex, BMI, waist-to-hip, smoking status (current, former and never), height, and Townsend social and material deprivation score.

(Table 3). There were no detectable interactions between birth weight and correlated adult risk factors, although the power for these analyses was limited.

Discussion

Our data indicate that birth weight may influence risk of colorectal cancer in later life. We found a J-shaped relation between self-reported birth weight and incident colorectal cancer, suggesting that both low and high birth weight babies may be at increased risk. Macrosomic babies appeared to have the greatest risk.

A number of methodological explanations could have accounted for our findings. One limitation of this study was reliance on self-reported birth weight. However, self-reports correlate well with birth records and mothers' reports of birth weight, showing correlations of between 0.6 and 0.8 (2, 15–19). Moreover, birth weight in this cohort showed the expected correlations with adult anthropometry (6–8). The prospective nature of the study also suggests that any misclassification of birth weight is likely to be nondifferential. Measurement of actual birth weight may help clarify the reported associations; however, in the United Kingdom, inter-war maternity records, the main source of birth weight data for this time period, are difficult to trace. One assessment of this approach indicated that <10% of records are likely to be recovered (20).

In this cohort, our self-reported birth weight data also showed the well-established inverse associations between repeated measures of blood pressure, glucose intolerance (19, 21), as defined by serum glycosylated hemoglobin concentrations, and coronary heart disease mortality.⁴ Nevertheless, we did not have data relating to other birth characteristics such as length of gestation and ponderal index, which could confound or modify the birth weight-colorectal cancer relation. In addition, confounding or effect modification by other correlates of birth weight and risk factors for colorectal cancer not accounted for in the subgroup analysis, or residual confounding, could explain the associations reported here.

Although only 41% of the cohort reported their birth weight, selection bias is an unlikely explanation for our findings because the rate of colorectal cancer incidence was similar in those who reported birth weight and those who did not. The proportion reporting birth weight is also consistent with other cohort studies in the United Kingdom and United States (15, 17). In addition, loss to follow-up for the complete cohort was <0.1%. More importantly, these analyses compared risk estimates for colorectal cancer based on strata of birth weight; hence, internal validity of the study is unlikely to be affected.

Alternatively, because of the small number of cases, our findings could have been the result of sampling variation. However, our results concord with case series data comparing birth weight of offspring and maternal risk of colorectal cancer (4). In addition, the J-shaped birth weight-cancer relation has been described previously (22).

The precise biological processes underlying our observations are uncertain. However, the interrelation among birth weight, glucose homeostasis, hyperinsulinaemia, and colorectal cancer in adulthood, although speculative, may provide one possible mechanism (23–25).

Neonatal macrosomia can largely be explained by the presence of impaired glucose tolerance or diabetes during pregnancy, although genomic factors, epigenetic processes, and congenital hyperinsulinemic syndromes may also contribute (12, 26). This intrauterine exposure to diabetes, in combination with other factors, may have long-term metabolic and somatic consequences for offspring. Observational investigations in humans, including Native American Pima Indians, and animal experimental studies suggest that macrosomic babies may be at increased risk of obesity, hyperinsulinaemia, and disturbances in glucose homeostasis in later life (6, 7, 21, 27–30), although findings are inconsistent (31).

Inverse and U-shape associations between birth weight and subsequent insulin resistance, impaired glucose tolerance, and noninsulin-dependent diabetes have also been documented (21, 27–29, 32–34). Indeed, a number of birth dimensions have been variously related to components of the metabolic syndrome (21, 34). The low birth weight-noninsulin-dependent diabetes relation has been attributed to programming by impaired fetal growth as a result of undernutrition or placental dysfunction, the so-called thrifty phenotype hypothesis (34), and, alternatively, to genetic determinants (27, 35, 36).

Observational studies have shown that colorectal adenomas and cancer show positive, if moderate, associations with diabetes (37, 38), which are consistent with other prospective reports indicating that hyperglycemia and hyperinsulinaemia are also associated with an increased risk of colorectal cancer (24, 25). These findings have prompted suggestions that hyperinsulinaemia may be the underlying link between diabetes and colorectal cancer (23). More recently, IGF-I and its binding proteins have been implicated in colorectal carcinogenesis (25, 39, 40). In addition, because insulin is an important regulator of IGF-I bioavailability, insulin may indirectly promote colorectal carcinogenesis through pathophysiological changes in the levels of circulating IGF-I (25). IGF-I and its binding proteins are also associated with fetal growth (41). Thus, factors influencing hyperinsulinaemia, IGF-I and its binding proteins, and glucose homeostasis in adulthood, modified by determinants of intrauterine growth, might alter the risk of colorectal cancer.

In conclusion, our data support a possible association between birth weight and subsequent risk of colorectal cancer. Conceivably, these associations may be the result of methodological limitations, limited study size, or residual confounding. Furthermore, although we have outlined a potential mechanism, the precise biological processes underlying these associations are unclear. Additional large-scale analyses of the birth weight-colorectal cancer relation may clarify this finding and its relative importance to other established adult risk factors.

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⁴ M. S. Sandhu, R. Luben, and K. T. Khaw, unpublished data.

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