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Associations between birth weight and colon and rectal cancer risk in adulthood

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ABSTRACT

Background: Birth weight has inconsistent associations with colorectal cancer, possibly due to different anatomic features of the colon versus the rectum. The aim of this study was to investigate the association between birth weight and colon and rectal cancers separately.

Methods: 193,306 children, born from 1936 to 1972, from the Copenhagen School Health Record Register were followed prospectively in Danish health registers. Colon and rectal cancer cases were defined using the International Classification of Disease version 10 (colon: C18.0–18.9, rectal: 19.9 and 20.9). Only cancers classified as adenocarcinomas were included in the analyses. Cox regressions were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Analyses were stratified by birth cohort and sex.

Results: During 3.8 million person-years of follow-up, 1465 colon and 961 rectal adenocarcinomas were identified. No significant sex differences were observed; therefore combined results are presented. Birth weight was positively associated with colon cancers with a HR of 1.14 (95% CI, 1.04–1.26) per kilogram of birth weight. For rectal cancer a significant association was not observed for birth weights below 3.5 kg. Above 3.5 kg an inverse association was observed (at 4.5 kg, HR = 0.77 [95% CI, 0.61–0.96]). Further, the associations between birth weight and colon and rectal cancer differed significantly from each other ($p = 0.006$).

Conclusions: Birth weight is positively associated with the risk of adult colon cancer, whereas the results for rectal cancer were inverse only above values of 3.5 kg. The results underline the importance of investigating colon and rectal cancer as two different entities.

1. Introduction

Colorectal adenocarcinomas (hereafter denoted "colorectal cancer") are the third most common cancers worldwide, accounting for approximately 9% of global cancer incidence [1,2], with slightly higher rates in men than women [1–3]. The incidence rates show large geographical variation, but are generally higher in high-income countries such as Denmark and the United States than in low- and middle-income countries like China and India [2,3]. In the Nordic countries specifically, colorectal cancer incidence has risen in the past 50 years (1960–2011) by 12% in men and 9% in women [4].

Cancers of the colon and the rectum differ physiologically and histologically but are often considered as a single entity in studies. Additionally, risk factors for colon and rectal cancer differ. For example, body mass index (BMI; kg/m^2) has been shown to be a stronger risk factor for colon than for rectal cancer in adults [5]. BMI is positively associated with colon cancer in both sexes, whereas BMI is positively associated with rectal cancer in men, but not in women [6]. A high birth weight has been found to be associated with an increased risk of overweight or obesity in adulthood in several studies [7–9]. However, the possible early origins of colorectal cancer have been investigated in few studies

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with inconsistent results. This is possibly because these studies did not distinguish between colon and rectal cancers in their analyses [10–13], which may have masked different associations for the two cancer sites. Therefore, the aim of this study was to examine birth weight and its separate associations with colon and rectal cancer.

2. Methods

Data on birth weight were obtained from the Copenhagen School Health Records Register (CSHRR), which has been built in collaboration between the Institute of Preventive Medicine and the Copenhagen City Archives. The CSHRR contains health records for 372,636 children who attended school in Copenhagen, Denmark. Children born from 1930 to 1989 underwent annual health examinations at Copenhagen schools, and from 1936 onwards birth weight, as reported by parents, was recorded on each child's health card [14]. Correlations above 0.93 have been found between recalled birth weights from the cohort and birth records [15].

On April 2, 1968 the Danish Civil Registration System of vital statistics was established. Unique identification numbers were assigned to all Danish residents alive on or born after that date. The identification numbers were recorded on health cards for children who attended school in 1968 or after, and the identification numbers were retrieved for children who left school before this time.

A total of 329,968 (89%) computerized records from the CSHRR could be linked via the identification number with the vital statistics register and the Danish Cancer Registry which both have very high validity [16,17]. The Danish Cancer Registry classified disease according to the International Classification of Disease (ICD) version 7 until 1994 and according to ICD-10 thereafter. From 1978 to 2004 the ICD for Oncology (ICD-O) first edition was used, and the third edition (ICD-O-3) thereafter [16]. The Danish Cancer Registry was modernized in 2004, and all cancers diagnosed from 1978 to 2004 were converted into ICD-10 and ICD-O-3 codes. In this study, colon and rectal adenocarcinomas were identified from 1 January 1978 with ICD-10 codes; colon: C18.0–18.9 and rectal: C19.9 and C20.9. Adenocarcinomas were classified using the following morphology codes: 81403, 82103, 82203, 82303, 82603, 82613, 82633, 84803, 84813, and 84903.

To be eligible for this study, individuals had to be born from 1936 (when birth weight information was available in the register) and at least 40 years of age (to exclude colon or rectal cancers due to diseases with a heritable risk). Due to this age requirement, this analysis is based on the subgroup of children born from 1936 to 1972 (n = 269,539). After excluding individuals with missing birth weight information (n = 28,636) or with weights outside of the reliable range of 2–5.5 kg (n = 3796), there were 193,306 (51% men) individuals included in the study.

Follow-up began on 1 January 1978 (or at 40 years of age, whichever came later) and ended on 31 December 2012. Individuals were followed until the date of a colon or rectal cancer diagnosis, death, emigration, disappearance, or the end of the study; whichever came first.

2.1. Statistical analysis

The birth weight characteristics are presented as means and standard deviations. Analyses were performed using Cox proportional hazard models, with age as the underlying time scale and stratified by birth cohort and sex (when applicable). Potential interactions between sex and birth weight in their effect on colon and rectal cancers were examined in nested models with and without the product-term of the two variables using the likelihood ratio test. Also, we tested if the associations observed for colon and rectal cancer differed statistically by testing for an interaction in the association with the location of the cancer (colon versus rectum). The assumption of proportional hazards was assessed including time-varying effects and associations across birth cohorts were examined. The linearity of the associations was assessed by testing against a restricted cubic spline (3 knots).

Analyses for both colon and rectal cancer were repeated using categorical models with four categories (Supplementary Table 1 and 2).

3. Results

Among the 98,068 men and 95,238 women included in the study, the mean birth weight varied little over time (Table 1). During 3,813,621 person-years of follow-up, 1571 colon and 1000 rectal cancers were identified; of these 1465 colon and 961 rectal cancers were categorized as adenocarcinomas and were included in the analyses (Table 2 and Table 3). Of the disease-free individuals 27,576 died, 2402 emigrated, 49 were lost to follow-up, and 160,853 were alive at the end of follow-up. As expected, incidence rates of both colon and rectal cancer increased with age, and rates of colon cancer were higher than those for rectal cancer. Overall, there were no violations in the proportional hazard assumptions, which means that across the range of ages at diagnosis in this study, the associations between birth weight and colon and rectal cancer, respectively, were similar. Additionally, the association between birth weight and cancer (colorectal, colon, rectal) did not differ by birth cohort (all $p > 0.51$).

Most studies in this area show results for colon and rectal cancer combined. In this study, these associations were positive, albeit non-significant, with a HR of 1.05 (95% CI, 0.98–1.13) per kilogram birth weight in the sex-stratified model. Similar results were observed in sex-specific models (data not shown). In the present study, the associations between birth weight and colon and rectal cancer differed from each other ($p = 0.006$).

3.1. Colon cancer

In the examination of birth weight and colon cancer, deviations from linearity were not detected ($p = 0.89$). Also, no sex differences in the associations were detected ($p = 0.55$), thus, results from a sex-stratified linear model are presented. Birth weight was significantly and positively associated with colon cancer, with a HR of 1.14 (95% CI, 1.04–1.26) per kilogram birth weight (Table 2). For comparison purposes, results on men and women separately are also presented; the associations were positive in both sexes (Table 2). A similar pattern of results was observed in the categorical analyses as well (Supplementary Table 1)

Table 1
Birth weight characteristics of individuals in the Copenhagen School Health Records Register who were born from 1936 to 1972 by birth cohort.

Birth cohort	N	Men		N	Women	
		Birth weight (kg)			Birth weight (kg)	
		Mean	SD		Mean	SD
Overall	98,068	3.44	0.55	95,238	3.31	0.53
1936–1939	10,798	3.48	0.57	9854	3.37	0.56
1940–1944	19,406	3.46	0.56	18,850	3.33	0.53
1945–1949	20,009	3.46	0.56	19,635	3.32	0.53
1950–1954	14,269	3.41	0.55	14,112	3.29	0.53
1955–1959	11,679	3.39	0.55	11,339	3.27	0.52
1960–1964	9353	3.41	0.55	9156	3.29	0.51
1965–1969	8361	3.42	0.53	8301	3.29	0.51
1970–1972	4193	3.43	0.53	3991	3.30	0.50

Abbreviations: N: Number; SD: Standard Deviation; kg: kilogram.

Table 2
Hazard ratios of colon cancer in adulthood per kilogram of birth weight.

Sex	N	Cases	Hazard ratio	95% confidence interval	
All[a]	193,306	1465	1.14	1.04	1.26
Men[b]	98,068	781	1.17	1.04	1.33
Women[b]	95,238	684	1.11	0.97	1.27

[a] Stratified by sex and birth cohort.
[b] Stratified by birth cohort.

Table 3
Hazard ratios of rectal cancer in adulthood for birth weight at 2.5, 3.5 and 4.5 kilograms, from the restricted cubic spline model.[a]

			Birth weight						
			2.5 kg			3.5 kg		4.5 kg	
Sex	N	Cases	Hazard ratio	95% confidence interval		Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval	
All[b]	193,306	961	0.92	0.76	1.12			0.77	0.61	0.96
						1.00 (ref)				
Men[c]	98,068	582	0.97	0.75	1.24			0.80	0.61	1.05
						1.00 (ref)				
Women[c]	95,238	379	0.89	0.66	1.19			0.73	0.50	1.07
						1.00 (ref)				

[a] To facilitate the interpretation of the restricted cubic spline model, point estimates are presented for birth weight values of 2.5, 3.5, and 4.5 kg, with 3.5 kg as the reference.
[b] Stratified by sex and birth cohort.
[c] Stratified by birth cohort.

3.2. Rectal cancer

For rectal cancer, indications of deviations from linearity were observed ($p = 0.04$) and analyses were conducted using restricted cubic splines. To facilitate the interpretation of these models, point estimates are presented for birth weight values of 2.5, 3.5, and 4.5 kg, with 3.5 kg as the reference. No sex differences in the associations with birth weight were detected ($p = 0.93$). In the sex-stratified analyses, no association was observed for birth weights below 3.5 kg (Table 3). An inverse association, however, was found for birth weights above 3.5 kg. As an example, at 4.5 kg, the HR for rectal cancer was 0.77 (95% CI, 0.61–0.96). Similar patterns were observed in the sex-specific results, however with broader confidence intervals (Table 3).

4. Discussion

In this study, birth weight was found to be positively associated with the risk of colon cancer in analyses with sexes combined. Birth weight was not associated with rectal cancer below 3.5 kg. Above 3.5 kg, however, birth weight was inversely associated with rectal cancer. The opposite directions of the associations underscore the importance of investigating associations between early life factors such as birth weight with cancers of the colon and rectum separately.

In Denmark, the incidence rates of colon cancer are higher than those of rectal cancer [4]. Moreover, more men than women are diagnosed with colon and rectum cancers [4], which is in concordance with the results in our study. The positive and linear association between birth weight and colon cancer found in this study is consistent with a previous US women-only study on colon cancer [18] and a French women-only study that examined colon adenomas [19]. In further support of the increased risk at the high birth weight levels, a study from the UK found an increased risk of colorectal cancer with high birth weight above 4.0 kg [10]; however, they also found a higher, although non-significant, risk at birth weight levels below 2.5 kg, compared with a reference group of birth weights between 2.5–3.25 kg. This increased risk at low birth weight levels was supported by a Norwegian study, though only among the men, and not the women [11]. Methodological differences among the studies may explain the different results since the UK and Norwegian studies did not distinguish between cancers of the colon and rectum and were based on less than 100 cases. Other explanations for the diverging findings are the use of long-term recalled birth weight in three studies [10,18,19], whereas the birth weights recorded in the CSHRR were recalled by parents when their children were young.

Few studies have examined associations between birth weight and only rectal cancer or adenomas. In the French study on women, which included 220 cases of rectal adenomas, no associations with birth weight were detected [19]. Although the pattern of associations between birth weight and rectal cancer differed in our study, our findings of an inverse association between birth weight and rectal cancer at levels above 3.5 kg need to be interpreted cautiously. Given the number of cases included in the present study even minor deviations of non-linearity may be significant. There are not established biological mechanisms that explain these differences. We can only speculate that differences in the bowel content along the intestine relating to carcinogeneisis [20] or that differential effects of growth factors and insulin on the colon and rectum may underlie the result we observed [5]. Nonetheless, based on these findings, it is important for future studies to separately investigate the cancer sub-sites of the colon and rectum in the association with birth weight and possibly also other anthropometric measures, rather than combining the two forms in a common estimate.

Over the past decades accumulating evidence has supported the hypothesis that early life factors affect the risk of adult cancer [21]. Cancers of the colon and to a lesser extent rectum have been associated with adult body size [6,22,23] and type 2 diabetes [24–26]. This provides a link to the association for colon cancer in the

present study since a high birth weight is associated with increased risk of childhood and adult obesity [27,28] as well as type 2 diabetes at least in women [29]. High birth weight may also be linked to colon cancer via insulin-like growth factor 1 (IGF-1), that is thought to have a role in the development of colon cancer, possibly through intrauterine programming of the hormone axis [18,30,31] or to long-time exposure to elevated IGF-1 levels [32]. Finally, the number of stem cells that potentially can develop into cancer cells are related to birth weight [12,33].

The major strengths of this study were the prospective design and the inclusion of nearly all Copenhagen school children born from 1936 to 1972. Additionally, the Danish Cancer Registry has an extremely high coverage of clinically recorded neoplasms due to mandatory reporting [16]. Therefore, information and selection biases are unlikely with this study. Although a possible limitation was parental recall of birth weight, a study examining correlations between maternal recall of birth weight and birth records in part of this cohort found that all correlations were at least 0.93 [15]. As birth weight was obtained before and independently of the diagnosis of cancer, any errors are likely to bias the associations towards the null. Information about possible mediating variables (e.g. diet, smoking, physical activity and adult body size) were not available for this study. However, the observed associations were consistent across birth cohorts which suggest that the influence of such mediating factors is limited, since they have changed considerably over time.

5. Conclusion

In conclusion, a low birth weight was associated with a decreased risk of colon cancer whereas no association was observed for rectal cancer. However, a high birth weight was associated with an increased risk of colon cancer and a decreased risk of rectal cancer. This research suggests a possible effect of in utero or early life exposures on later life cancer risk, and underpins the importance of dividing colorectal cancers into sub-site specific effects.

Conflicts of interest

The authors have no conflicts of interest to declare.

Authorship contribution

Study concept and design: BWJ, MG, JLB.
Data acquisition: TIAS, JLB.
Data analysis: BWJ, MG.
Interpretation of data: BWJ, NRS, EZ, MG, TIAS, JLB.
Manuscript preparation: NRS, EZ, BWJ, JLB.
Manuscript review: NRS, EZ, BWJ, MG, TIAS, JLB.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2016.05.003.

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