



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.

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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.

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