Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Body mass index in childhood and adult risk of primary liver cancer

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Background & Aims: Childhood overweight increases the risk of early development of non-alcoholic fatty liver disease, which may predispose to carcinogenesis. We investigated if childhood body size during school ages was associated with the risk of primary liver cancer in adults.

Methods: A cohort of 285,884 boys and girls, born 1930 through 1980, who attended school in Copenhagen, were followed from 1977 to 31 December 2010. Their heights and weights were measured by school doctors or nurses at ages 7 through 13 years. Body mass index (BMI) z-scores were calculated from an internal age- and sex-specific reference. Information on liver cancer was obtained from the National Cancer Registry. Hazard ratios and 95% confidence intervals (95% CI) of liver cancer were estimated by Cox regression.

Results: During 6,963,105 person-years of follow-up, 438 cases of primary liver cancer were recorded. The hazard ratio (95% CI) of adult liver cancer was 1.20 (1.07–1.33) and 1.30 (1.16–1.46) per 1-unit BMI z-score at 7 years and 13 years of age, respectively. Similar associations were found in boys and girls, for hepatocellular carcinoma only, across years of birth, and after accounting for diagnoses of viral hepatitis, alcohol-related disorders, and biliary cirrhosis.

Conclusions: Higher BMI in childhood increases the risk of primary liver cancer in adults. In view of the high case fatality of primary liver cancer, this result adds to the future negative health outcomes of the epidemic of childhood overweight, reinforcing the need for its prevention.

Keywords: Body mass index; Childhood; Cohort study; Liver cancer; Overweight; Obesity.

Received 3 May 2013; received in revised form 14 August 2013; accepted 10 September 2013; available online 26 September 2013

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Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; CSHRR, Copenhagen School Health Records Register; ICD, International Classification of Diseases; HR, hazard ratios.

Introduction

During the last decades the prevalence of childhood overweight has reached epidemic proportions worldwide. In Europe, more than 20% of school-aged children are now overweight or obese [1]. Concurrent with the obesity epidemic, non-alcoholic fatty liver disease (NAFLD) has gained increased clinical recognition in children and adults [2–4].

NAFLD, in particular the advanced stages, may lead to primary liver cancer (hereafter denoted 'liver cancer') [5–7]. Liver cancer accounts for approximately 6% of all new cancer cases diagnosed worldwide, and each year more than half a million people are diagnosed with hepatocellular carcinoma (HCC) [7–9]. Most cases occur in developing countries, but the incidence has increased substantially in developed countries during the past two decades, and particularly in younger age groups [7–9]. The survival rate for HCC is very low, with only 5–9% of patients surviving beyond 5 years [8]. Although alcohol abuse remains an important etiological factor in HCC, one reason for the increasing incidence of HCC is suggested to be hepatitis C [9]. However, 30–40% of patients with liver cancer do not suffer from chronic infectious hepatitis. As such, the epidemic spread of obesity and the associated rise in NAFLD and diabetes may contribute significantly to the rising burden of liver cancer [8,9].

Adult obesity is a risk factor for several diseases, including liver cancer [8,10–13]. The long-term health consequences of childhood body size are less studied, but childhood overweight may, alarmingly, translate into a variety of diseases in adults [14–16]. None of these previous studies on childhood body size [14–16] have, however, addressed liver cancer. The mechanisms underlying the associations between childhood overweight and adult disease are incompletely understood [14,15]. A common explanation is that obese children become obese adults and that this tracking of obesity results in an elevated risk of adult disease. However, many obese children do not become obese adults [17,18]. Other mechanisms should therefore also be considered. The development of liver cancer may take decades and is rarely observed in children [19]. We hypothesize that childhood overweight increases the likelihood of adult liver cancer as a result of early hepatic fat accumulation, impaired glucose tolerance and slowly induced inflammatory damages [3,4,20–24]. Therefore, we investigated whether excess weight in childhood was associated with liver cancer in adults.

Materials and methods

Study population

A prospective cohort study was conducted using the source population of The Copenhagen School Health Records Register (CSHRR) [25], which contains information on 372,636 children, born during the years 1930–1989. The children underwent mandatory health examinations at public and private schools in Copenhagen annually through 1983 and thereafter only at school entrance and exit unless the children had special health needs. During the examinations, school doctors or nurses measured the children who were either naked or wearing light clothes. Each child was assigned a health card, on which the child's name, year of birth, height, and weight were recorded. This information has been computerized. Each child's body mass index (BMI) was calculated and transformed to a z-score based on an internal age- and sex-specific reference that was computed using the LMS method [26]. As previously described, the reference population was chosen from a period when the prevalence of obesity was low and stable. Z-scores were interpolated to the exact age if two measurements were available or extrapolated if only one was available [16,25].

The follow-up of the cohort was based on record linkages using the unique person identification number assigned to all Danish residents who were alive or born after 2 April 1968 when the Central Person Register was established [27]. Children in school at that time or later had their number recorded on their health card. Children who attended school prior to this time had their identification numbers retrieved from the Central Person Register on the basis of name and date of birth. Unique identification numbers were available for 329,968 children [25].

Outcomes

Information on vital status and liver cancer was obtained by linkage to the Central Person Register and the Danish Cancer Registry, respectively. The Cancer Registry has, since 1943, collected information on all cancer diagnoses in Denmark. The coverage and validity of both registers are very high [27,28]. Liver cancer was defined according to the modified Danish version of the International Classification of Diseases (ICD), 7th (155.0-155.1) and 10th (C22.0, C22.1, C22.7, C22.9) revisions. Three cases of angiosarcoma (C22.3) and five cases of sarcoma (C22.4) occurred in the study population, but due to their different pathology these were not defined as cases in the analyses. Since HCC may be most closely related to BMI, all analyses were also conducted examining associations with only HCC (ICD7: 155.0 and ICD10: C22.0).

Liver cancer may originate from hepatitis B or C infections, alcohol-related disorders or biliary cirrhosis [2,8,29]. To exclude the influence from these diseases on the association between childhood BMI and liver cancer, analyses were performed, in which individuals with any of these diseases were excluded or censored. Information on individuals diagnosed with these diseases was obtained by linkage to the Danish Patient Register [30] and The Danish Psychiatry Register [31], which include information on all somatic and psychiatric hospitalisations in Denmark since 1977 and 1970, respectively. Viral hepatitis was defined as ICD8 (070.00–070.09) and ICD10 (B15.0–B19.9), alcohol-related disorders as ICD8 (291.09–291.99, 303.09–303.99, 571.09, 571.10, 577.10) and ICD10 (F10.0–F10.9, G62.1, K70.0–K70.9, K86.0) and biliary cirrhosis as ICD8 (571.90, 571.91) and ICD10 (K74.3–K74.4).

We began the follow-up of the individuals at 30 years of age or on 1 January 1977 when information from all registers was available, whichever came later. Therefore, 290,056 individuals were eligible for inclusion in the study. Exclusions were made for subjects without a date of the liver cancer diagnosis (n = 2) or diagnosis prior to the beginning of follow-up (n = 1). Further exclusions were made for missing (n = 4165) or outlying (n = 4) BMI values at all available ages. Thus, 285,884 individuals were included in the study. Follow-up ended on the date of a liver cancer diagnosis, of death, of emigration, of loss to follow-up or 31 December 2010, whichever came first.

Statistical methods

Hazard ratios (HR) of liver cancer according to BMI z-scores at each age from 7 through 13 years were calculated from the Cox proportional hazard models with age as the underlying time axis. Analyses were conducted for each sex separately, and for the sexes combined with the baseline hazard estimated separately for boys and girls.

As changes in the determinants of liver cancer may have occurred throughout the long time period under study, hazard ratios (HR) of liver cancer according to year of birth (1930–34, 1935–39, 1940–44, 1945–49, 1950–54, 1955–59, 1960–80) were estimated. Moreover, all analyses of BMI z-scores and liver cancer were conducted with the baseline hazard estimated separately in 5-year strata of year of birth (1930–34, 1935–39, 1940–44, 1945–49, 1950–54, 1955–59, 1960–64, 1965–69, 1970–74, 1975–80) to adjust associations for such influences. Potential differences in the association between BMI z-score and liver cancer according to sex, year of birth and year of cancer diagnosis (1977–96, 1997–02, 2002–07, 2007–10) were investigated. These potential interactions (between BMI z-score and sex, BMI z-score and year of birth, BMI z-score and year of cancer diagnosis) were also tested on the multiplicative scale using likelihood ratio tests. Potential influences of viral hepatitis, alcohol-related disorders and biliary cirrhosis on the association between BMI z-score and liver cancer were investigated in analyses, in which individuals were censored on their date of diagnosis with any of these diseases.

The linearity of all associations was assessed by restricted cubic splines (3 knots), and no notable violations were detected. The proportional hazard assumption was assessed by a test based on Schoenfeld residuals and important violations were not detected.

Ethics

The analyses were conducted on anonymous data, and the study was approved by the Danish Data Protection Agency (*Datatilsynet*). According to the Danish Act of Processing of Personal Data (*Persondataloven*), informed consent is not required for register-based research of pre-existing personal data.

Results

Study population

At least one BMI z-score value was available for 141,467 girls and 144,417 boys, and, as expected, BMI increased with age (Table 1). The children were 30–81 years of age at follow-up. The analyses included 6,963,105 person-years of follow-up. During this period, 5383 individuals emigrated, 170 individuals were lost to follow-up and 49,090 individuals died. All were censored in the analyses of liver cancer at their last known date of residence in Denmark or date of death. The median age of the individuals at the end of follow-up was 60 years (range 30–81 years). During follow-up there were 438 cases of liver cancer (Table 2). The median age of a liver cancer diagnosis was 62 years (range 31–80 years). The incidence rate of liver cancer increased with advancing age from ~0.05 to ~0.3 per 1000 person years at 50 and 70 years of age, respectively (Supplementary Fig. 1). There were 2.8 times as many liver cancer cases in the men as in the women. For both sexes HCC was the most common type (Table 2).

Risk of liver cancer

The association between BMI z-scores at each age from 7 to 13 years and liver cancer in adults was positive in both boys and girls (Table 3). No notable differences in the association at each age were observed between the sexes (Table 3, $p > 0.05$), so analyses were conducted on boys and girls combined and stratified by sex. The association between BMI z-scores at each age from 7 to 13 years in boys and girls combined with liver cancer in adults was positive (Fig. 1). Thus, no notable violations of linearity were detected, and the risk of liver cancer in adults was highest for children with the highest BMI values and lowest for children with the lowest BMI values at each age from 7 through 13 years. The association between childhood BMI and the risk of liver cancer increased slightly with the child's age; for 7-year-old boys and girls, the HR was 1.20 (1.07–1.33) and for 13-year-old boys and girls the HR was 1.30 (1.16–1.46) per unit increase in BMI z-score (Fig. 1).

The association between BMI z-score at each age from 7 through 13 years and HCC was very similar to the association