European Journal of Cancer (2013) 49, 2207–2213

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Risk of oesophageal adenocarcinoma among individuals born preterm or small for gestational age

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Available online 13 March 2013

KEYWORDS
Gastro-esophageal reflux
Barrett's Oesophagus
Precancerous conditions
Preterm birth
Epidemiology

Abstract ***Background:*** Gastroesophageal reflux is a main risk factor for oesophageal adenocarcinoma (EAC). Infants born preterm or small for gestational age (SGA) regurgitate more than infants born at term, and some data support the hypothesis of an association with oesophagitis, Barrett's oesophagus and EAC. This study aimed to assess the association between risk of EAC and preterm or SGA birth.

Methods: In this population-based case–control study, all incident cases of EAC in Sweden between 1st January 1998 and 31st December 2004 with retrievable birth records were eligible as cases. We sampled three matched controls per case from the birth ledger at the same delivery ward as the respective case. Data on gestational age, birth weight and other perinatal exposures were extracted from the original birth records. For comparison, we collected perinatal data for cases of cardia adenocarcinoma and oesophageal squamous cell carcinoma and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: The risk of EAC increased by 13% per week of shorter duration of gestation (OR 1.1, 95% CI 1.0–1.3), while SGA did not influence the risk. No effect of preterm birth or SGA was found on the risk of cardia adenocarcinoma or oesophageal squamous cell carcinoma.

Conclusion: Preterm birth, but not SGA, might lead to an increased risk of EAC as an adult.

1. Introduction

The incidence of oesophageal adenocarcinoma (EAC) has increased markedly in the industrialised world during the past 40 years,[1–4] EAC is overrepre-

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http://dx.doi.org/10.1016/j.ejca.2013.02.014

sented among Caucasian males,[5–8] and the major known risk factors for EAC are gastroesophageal reflux,[5] Barrett's oesophagus,[9] and abdominal obesity.[10,11] The prognosis is poor, with a 5-year survival of less than 15%.[12,13]

Preliminary evidence suggests that the tumour development may occur already in infancy. In a cohort of 3364 individuals born preterm or small for gestational age (SGA), we previously found an unexpected 7-fold increase in risk of EAC, a finding which was based on four exposed cases.[14] This finding led us to hypothesise that being born preterm or SGA may be causally linked with EAC development, either due to increased oesophageal regurgitation of gastric contents, or increased vulnerability to reflux in the undeveloped oesophageal mucosa. In a subsequent small case–control study, we could not confirm the initially reported strong association, although the data supported a weaker association between preterm birth and risk of oesophageal and cardia adenocarcinoma.[15] The results of two other case–control studies performed by our group suggested an association between preterm birth and the risk of oesophagitis as well as a risk of Barrett's oesophagus later in life.[16,17]

In the current study we aimed to investigate in a larger study whether individuals born preterm or SGA may have an increased risk of EAC as adults. For comparison we also studied patients diagnosed with cardia adenocarcinoma (CAC) and oesophageal squamous cell carcinoma (ESCC).

2. Population and methods

2.1. Study design

This was a case–control study within the source population of everyone born in Sweden 1912 through 1983. Within this population we identified cases diagnosed with EAC, CAC or ESCC, and collected data on exposures from their birth records. Controls were sampled from the source population.

Eligible individuals were those in the Swedish Cancer Register diagnosed with EAC (PAD 094, 096; ICD-9 150x), CAC (PAD 094, 096; ICD-9 1510) and ESCC (PAD 144, 146; ICD-9 150x) between 1st January 1998 and 31st December 2004 with retrievable birth records. To limit the number of patients with ESCC, we restricted the selection to only patients born on uneven dates. Information on the cases' birth places (births until 1947) or maternal residence at time of giving birth (1948 and onwards) was obtained from the Register of the Total Population. Only the individuals with a retrievable hospital birth record were included in the study. For each case we sampled controls by identifying three singleton live births of the same sex, following the birth of the case at the same hospital ward. In this way controls were incidence-density sampled in a randomised fashion from the source population, and they were matched for age, sex and hospital of birth. Potential controls were followed up in the Register of the Total Population to ascertain that they were alive on the date of the case's diagnosis.

Of the 4473 patients with oesophageal or cardia cancer from the Cancer Register, 3415 (76%) did not have retrievable birth records due to archive restrictions. Of the remaining 1058 records, we found 967 (91%). After exclusion of twin births ($n = 51$), persons with a severe congenital malformation ($n = 3$), persons with incomplete birth records ($n = 120$), or persons with uncertain identity ($n = 4$), 789 eligible cases patients remained. The birth records of 2310 control individuals were collected. Exclusions criteria for control individuals were diagnosis of severe congenital malformations ($n = 10$), or death before the diagnosis of the corresponding case individual ($n = 489$). In total, 1811 control individuals were analysed.

2.2. Data collection and study variables

We obtained information on location and histopathological tumour classification and date of diagnosis from the Cancer Register, while date of death was retrieved from the Register of the total Population. From the birth records, we collected data on birth weight and length, gestational age, mode of delivery, maternal age, parity, number of miscarriages, diseases during or after pregnancy and delivery and albuminuria before, during or after pregnancy, marital status and father's profession. The variables number of miscarriages, maternal diseases and albuminuria were excluded from the analysis due to a large number of missing values. Birth weight was categorised in <3000 g, 3000–3999 g, or ⩾4000 g. Gestational age was categorised as <259 days (<37 completed weeks), 259–293 days (37–41 weeks), or ⩾294 days (⩾42 weeks). Birth weight for gestational age was estimated using the Swedish reference curve for foetal growth,[18] and was categorised using data from the Swedish Medical Birth Record with predefined reference values: <10th, 10th to <25th, 25th to 75th, >75th to 90th, and >90th percentile. Anyone with a birth weight for gestational age greater or lesser than 5 standard deviations was excluded from further analysis. We calculated ponderal index (PI) as $PI = 100 * (\text{child's weight in grams}/(\text{child's length in centimetres}\hat{}3))$ for case and control individuals. PI is commonly used as a measure of asymmetrical weight for gestational age in infants, and a low values indicates foetal growth restriction.[19] The father's profession was used as a proxy for the family's socioeconomic status, and was categorised into three groups: high (academic work with college education or higher), medium (white-collar work or farmer) or low (blue-collar worker