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Alimentary Tract

No increased mortality in 109,000 first-degree relatives of celiac individuals

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ABSTRACT

Background: Several studies have shown an excess mortality in individuals with celiac disease (CD). However, it is unknown if also first-degree relatives (FDRs) to celiac patients are at increased risk of death.
Aim: We aimed to assess mortality in FDRs to celiac patients.
Methods: Individuals with CD were identified through biopsy reports (equal to Marsh grade III). Each celiac individual was matched on sex, age, county and calendar year with up to five control individuals. Through Swedish healthcare registries we identified all FDRs (father, mother, sibling, offspring) of CD individuals and controls. Through Cox regression we calculated hazard ratios (HRs) for mortality (all-cause death, circulatory, cancer and other).
Results: We identified 109,309 FDRs of celiac individuals and 549,098 FDRs of controls. Overall mortality was increased in FDRs to celiac individuals (HR = 1.02, 95%CI = 1.00–1.04, $p = 0.03$). This corresponded to an excess risk of 5.9 deaths per 100,000 person-years of follow-up. When limiting follow-up to time since celiac diagnosis in the index individual, we found no increased risk of death (HR = 1.01; 95%CI = 0.98–1.03).
Conclusion: FDRs to individuals with CD are at increased risk of death. This excess risk is however minimal and unlikely to be of any clinical importance to the individual.

1. Introduction

Celiac disease (CD) is an immune-mediated disorder that is triggered by gluten exposure in genetically predisposed individuals. It is characterized by chronic small intestinal inflammation, and the only available treatment is a gluten-free diet [1]. CD occurs in about 1% of individuals of which only a minority [2] are clinically diagnosed and this may partly explain its association with autoimmune disease [3,4]. The disease has also been linked to a large number of disorders such as cancer especially thyroid [5], lymphoproliferative [6], and gastrointestinal cancer [7] including small intestinal adenocarcinoma [8].

Earlier studies on CD and mortality typically reported mortality ratios around 1.5–2 or above [9,10] (sometimes with wide variation between different age strata [11]). In contrast more recent data have indicated only modest risk increases [12–14], or even no increased mortality at all [15]. Different estimates for mortality may be explained by different source populations (for instance Peters et al. identified individuals with CD from an Inpatient Registry (standardized mortality ratio = 2.0) while Ludvigsson et al. used data on CD from histopathology registers) [13]. Closely related to the patient source population is the introduction of new diagnostic methods in the 1990s and later, leading to physicians diagnosing milder cases of CD. This is reflected in the changing landscape of CD symptoms and signs over time [16]. Increased awareness of the importance of a strict adherence to a gluten-free diet, may also have influenced mortality in individuals with CD. Finally, there may be geographic differences in mortality among individuals with CD, as there seems to be differences in the socioeconomic background of CD [17]. In 2012, Tio et al. carried out a systematic review of

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studies on CD and mortality [18]. They concluded, on the basis of the studies published that far (did not include the Abdul Sultan et al. paper [15]) that the all-cause mortality in patients with CD was 1.24 (95%CI = 1.19–1.30).

Little is previously published about mortality in FDRs of celiac patients. One study from our group concerning offspring to celiac parents reported no increased death rate in the children [19] and another study investigated the risk of death in 3384 celiac FDRs without finding any increased risk [20]. A third small study from the 70s showed that the risk of specifically cancer deaths was increased in celiac relatives and particularly in women although it did not reach statistical significance [21].

We have previously demonstrated an increased risk of autoimmune disease in FDRs to individuals with CD [22]. In this paper we examine the risk of death in FDRs of CD patients using a nationwide population-based cohort consisting of more than 109,000 FDRs to individuals with CD compared to. FDRs of matched controls without CD. While we have previously presented data on mortality in offspring to mothers and fathers with CD [19], we chose to include also these data in the current paper for completeness.

2. Methods

2.1. Defining coeliac cases

Data on CD were collected in 2006–08 through computerized duodenal/jejunal biopsies performed between 1969 and 2008 from all Swedish pathology departments. Biopsies classified with villous atrophy equal to histopathology stage Marsh III [23] were considered as proof of CD with date of first pathological biopsy as the date of diagnosis. In total 29,096 celiac individuals were identified. Small-intestinal biopsy was clinical routine in Sweden during the study period [24] and more than 95% of individuals with Marsh III changes have CD in a Swedish setting [24]. However, it should be noted that our data did not allow us to rule out other causes of villous atrophy (Marsh III) such as drug-induced lesions, eosinophilic gastroenteritis [25], autoimmune enteropathy etc. [26]. Of note, Olmesartan is not approved for use in Sweden [27], and a recent paper from our group suggest that nonolmesartan angiotensin receptor blockers (ARBs) or any angiotensin-converting enzyme inhibitor (ACEI) are no major risk factors for villous atrophy [28].

2.2. Reference individuals (controls)

All celiac individuals were matched with up to five non-celiac controls by the government agency *Statistics Sweden* using the Swedish Total Population Register [29]. In total 144,522 controls matched for sex, county, age, and calendar year of birth was identified. Patients with CD and their matched controls have been described in detail earlier [13].

2.3. FDRs

Through the Swedish Multi-Generation Register [30] we obtained data on all FDRs (mother, father, sibling and offspring) to celiac individuals and controls (Fig. 1). Some FDRs were excluded due to data irregularities e.g. lifetime beyond 115 years ($n = 543$) and parents dying before reaching the age of 18 years ($n = 26$). Some of the FDRs of both celiac individuals and controls were themselves diagnosed with CD, exact number are available in Table 1. Each individual FDR was only counted once in the overall analysis (irrespective of type of relation). However, since you could be both sibling and mother of celiac relatives, you could be counted as both in the relative-specific analyses (for exact numbers in each analysis see Table 1).

2.4. Follow-up time

We used two different timeframes for our analyses. One timeframe was each individual's lifetime from birth until death, first emigration or the 31st of December 2010, whichever occurred first (Fig. 1). As an alternative timeframe we used the date of index individual's celiac diagnosis as the starting point for celiac FDRs (since only then would the individual know that he/she is a celiac FDR) with corresponding date as starting point for all FDRs of the matched controls. FDRs that were not born at the date of the corresponding index individuals study entry date entered the study at birth also in the second timeframe. End of follow up was similarly date of death, first emigration or the 31st of December 2010.

2.5. Exposure

Exposure was defined as being a FDR to a celiac individual.

2.6. Outcome measure

Our outcome was defined as all-cause mortality. We used the Swedish Cause of Death Registry to ascertain mortality [31,32]. We also performed separate analyses according to cause of death categorized into cardiovascular, cancer or other death defined according to relevant international of classification (ICD) codes. In our cause-specific analyses we used first underlying cause of death. Underlying cause of death is reported in some 99.5% of all deaths in Sweden.

2.7. Statistical analyses

We used Cox regression to estimate hazard ratios (HRs) adjusted for sex and age-group for both timeframes, for the second timeframe we additionally adjusted for calendar year. In our main analysis we examined the future risk of all-cause death in celiac FDRs (together: mother, father, sibling, offspring), but we also analyzed the risk stratified by relative (mother, father, sibling, brother, sister, offspring, son and daughter). In other analyses we examined the risk of death being due to cardiovascular disease, cancer or other causes. In two post hoc analyses we analyzed the risk of death in the lifetime frame additionally adjusted for own CD and stratified by calendar year of celiac diagnosis. Proportional hazard assumptions were checked using log minus log curves. Excess mortality was calculated as "$(1 - 1/\text{adjusted HR}) \times$ absolute mortality rate in exposed" thereby considering different distributions in age and sex between FDRs to celiac individuals and FDRs to controls.

Statistical significance was defined as 95% confidence intervals (CIs) for risk estimates not including 1.0. We used SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) for all analyses.

3. Results

3.1. Background data

All in all we identified 109,309 FDRs of celiac individuals and 549,098 FDRs of controls (99,372 and 500,618 respectively were included in the analysis using time since celiac diagnosis as the follow-up). Median follow-up time within the lifetime frame was 47.3 in celiac FDRs and 47.5 years in controls FDRs while the range in both groups were 0–115 years. Median follow-up since celiac diagnosis (and corresponding date in FDRs to matched controls)