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Dietary behaviours and survival in people with head and neck cancer: results from Head and Neck 5000

Samantha Lang MBBS[1], Sarah Schimansky MC Chb[1], Rhona Beynon MSc[2], Christopher Penfold PhD[1], Amy Davies MSc[1], Andrea Waylen PhD[3], Steven Thomas MB BCh PhD[3], Miranda Pring BDS PhD[3], Michael Pawlita MD[4], Tim Waterboer PhD[5], Andrew R Ness BM BS, PhD[1]

[1]National Institute of Health (NIHR) Bristol Biomedical Research Centre, Nutrition Theme, University of Bristol, Upper Maudlin Street, Bristol BS2 8AE, United Kingdom

[2]Department of Population Health Sciences, University of Bristol Medical School, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, United Kingdom

[3]Department of Oral and Dental Sciences, Bristol Dental School, Lower Maudlin Street, Bristol, BS1 2YL, United Kingdom

[4]Molecular Diagnostics of Oncogenic Infections Division, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

[5]Infections and Cancer Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

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Corresponding Author: Samantha Lang

Email: samanthaclarelang@gmail.com

Postal address: NIHR Bristol Biomedical Research Centre, Upper Maudlin Street, Bristol BS2 8AE, United Kingdom

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Abstract

Background: The association between diet and head and neck cancer (HNC) survival is unclear.

Methods: Cox proportional hazard models measured the association between fruit, vegetable and deep-fried food intake and HNC overall survival adjusting for clinical, social and lifestyle variables including smoking, alcohol and HPV status.

Results: Fruit and vegetable intake and improved survival were associated in minimally adjusted analyses. Following adjustment for smoking and alcohol consumption (fully adjusted analyses), the association with survival disappeared for fruit (HR 0.91, 95% CI 0.67, 1.23 p for trend=0.55) and attenuated for vegetables (HR 0.79, 95% CI 0.61, 1.03 p for trend=0.04). We observed no association between survival and deep-fried food intake in minimally adjusted or fully adjusted analyses (HR 0.88 95% CI 0.72, 1.07 p for trend=0.13).

Conclusions: Vegetable intake and HNC survival are modestly associated. There is some confounding by tobacco and alcohol consumption.

Introduction

Head and neck cancer (HNC) is the sixth most common cancer in the world and seventh most common in Europe [1, 2]. Globally, 650,000 cases and 350,000 deaths are attributed to HNC each year [2]. The majority of HNC tumours are treated with curative intent and treatments include surgery, radiotherapy and chemotherapy [3]. Five-year survival rates in the UK are between 28-67% depending on the cancer sub-site [4]. Several behaviours are associated with HNC risk and prognosis. These include tobacco and alcohol intake [3, 5, 6]. Also, in oropharyngeal cancer, human papilloma virus (HPV) is an established risk factor and prognostic indicator [7-9].

People with HNC tend to eat less fruit and vegetables compared to their healthy counterparts [5]. Several large USA and European based cohort studies demonstrate an association between low fruit and vegetable intake and a higher risk of developing HNC, even after controlling for tobacco and alcohol consumption [10, 11]. High levels of fried food consumption may also increase the risk of developing HNC [12-14].

There is limited research into fruit and vegetable intake and subsequent survival in people with HNC [5, 6, 15-18]. Health risk behaviours, which may confound the association between dietary behaviours and survival, were not adjusted for in many of these studies. Of those that explore the protective effect of diet and have adjusted for smoking and alcohol, one study demonstrated that a whole-foods dietary pattern, which includes fruit and

vegetables, was inversely associated with HNC mortality independent of smoking [15]. In an ecological study, average energy intake from fruit and vegetables was associated with reduced mortality in common factor analysis alongside other factors including smoking and alcohol [16]. However, neither of these studies evaluated the specific association of fruit and vegetables with overall survival. One study has assessed the relationship between fruit and vegetable intake and survival controlling for smoking and alcohol, and reported a small protective association for vegetables [6]. We were unable to find studies assessing deep-fried food intake and HNC survival. No studies have evaluated fruit and vegetable intake and survival in the context of HPV status[19-21].

The aim of this study was to investigate the association between dietary behaviours at the time of diagnosis and overall survival in HNC in a large UK-based prospective clinical cohort with detailed data on potential confounders. We hypothesise that increased fruit and vegetable intake and lower deep-fried food intake will be associated with HNC survival.

Materials and Methods

Data were collected from participants in the Head and Neck 5000 prospective clinical cohort study (HN5000). Details on HN5000 have been published previously [22, 23], and a fully searchable data dictionary is available online (http://www.headandneck5000.org.uk/). In brief, HN5000 aimed to recruit 5,000 adults (aged 16 and over) newly diagnosed with HNC between April 2011 and December 2014 from 76 UK centres. People with lymphoma, skin tumours or a recurrence of a previous HNC were excluded. Written informed consent was sought from potential participants by trained research nurses, often at their first clinic appointment following their diagnosis. For each participating NHS trust, approval was sought from their research and development departments. Five thousand, five hundred and eleven people consented into the study, of whom 138 were subsequently found to be ineligible. The resultant study sample contained 5,373 people.

Ethical approval

The study was approved by the National Research Ethics Committee (South West Frenchay Ethics Committee, reference 10/H0107/57, 5th November 2010) and approved by the research and development departments for participating NHS Trusts.

Exposures

Baseline data were collected at/shortly after diagnosis, before starting treatment. Dietary data were collected at recruitment using three questions focused on frequency of fruit, vegetable and deep-fried food intake over the last year from a validated semi-quantitative food frequency questionnaire (FFQ) (Figure 1). Within the FFQ, one serving was defined as one piece of fruit or a “medium serving”, which is left for the respondent to decide. One portion of fruit or vegetables is defined by the British Dietetic Association as 80g[24]. For this study we collapsed the food frequency items into three categories for fruit and vegetables and two categories for deep-fried food intake: fruit intake was defined as high (more than 1 portion per day), medium (2 portions per week to 1 portion per day) and low (less than 2 portions per week); vegetable intake was defined as high (more than 1 portion per day), medium (5 portions per week to 1 portion per day), low (less than 5 portions per week); deep-fried food intake was either high (at least one portion per week) or low (less than one portion per week). The difference in categorisation of fruit and vegetables reflected eating habits as people eat more vegetables on average than fruit [25].

Outcomes

Follow-up of participants is on-going, regular death notifications are provided from the NHS cancer registry and NHS Digital with consent for data linkage obtained at recruitment. We receive updated data linkage records 6 monthly. Research nurses in local centres also reviewed hospital notes for deaths at 4 months and 1 year. Our primary outcome was all-cause-mortality. Survival

was defined as time between consent to the study and death or censored at the most recent follow-up.

Confounders

Participants completed baseline questionnaires that included questions on smoking status, alcohol consumption and social variables including relationship status and education. Relationship status was defined as single, currently in a relationship (cohabiting/married), and no longer in a relationship (widowed/separated). Education was defined as completing secondary school education, further education or vocational qualifications or having obtained a degree from university. Smoking status was categorised as never, former (previously smoked at least 100 cigarettes up until one year before diagnosis) or current smoker. Alcohol intake was categorised as none, moderate (1-14 units for men and women), hazardous (14-50 units weekly for men and 14-35 units weekly for women) or harmful (>50 units for men and >35 units for women) based on the UK government guidelines from 1995, inclusive of the new lower safe limit of 14 units per week for males. Clinical information regarding diagnosis including tumour site (classified using International Classification of Diseases (ICD 10), stage and intended treatment were taken from participants' medical records and pathology reports. Baseline comorbidity status was calculated using the Adult Comorbidity Evaluation (ACE) 27. Blood samples were taken at baseline for HPV-16 (E6, E7, E1, E2, E4, and L1) serology status and analysed at the German Cancer Research Center in Heidelberg, Germany. Using glutathione S-transferase multiplex

analysis, HPV16 E6 seropositivity was indicated if HPV-16 E6 median fluorescence intensity (MFI) was >1000 units [26, 27].

Statistical Analysis

Cases included in the analysis were restricted to complete data for a Caucasian population, with a diagnosis of oral cavity, oropharyngeal or laryngeal cancer, who were treated with curative intent.

Statistical analyses were performed using STATA version 14.0 (Stata 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP) using version 2.2 of the Head and Neck 5000 database. Descriptive statistics including frequencies and percentages were calculated by sub-site for all variables.

Associations between dietary behaviours and overall survival were estimated using Cox proportional hazard regression and Kaplan-Meier plots. We performed a series of regression models where additional variables were added to the preceding model(s) in the following order: minimally adjusted model (model 1): adjusted for age and gender only; clinical model (model 2): also adjusted for TNM staging, sub-site treatment modality and co-morbidity; social model (model 3): also adjusted for education, marital status, household income); health risk behaviour model (model 4): also adjusted for tobacco, alcohol and fried food consumption/fruit and vegetable consumption. Using comparators of low fruit, vegetable and fried food intake, hazard ratios (HR), 95% confidence intervals (CI) and p-values (for trend) were calculated for moderate and high fruit and vegetable intake, and for high deep-fried food

intake respectively. We tested for interactions between alcohol and tobacco with each of the different food types. Subgroup analyses of fruit, vegetable and deep-fried food intake and HNC survival stratified by HPV status were performed for oropharyngeal cancer cases only. HPV status and fruit, vegetable or deep-fried food intake were tested for interactions.

Confounders were included based on their relationship to dietary behaviours demonstrated either in previous studies or Chi squared analyses that we performed to evaluate the association of potential confounders with dietary behaviours (see online supplementary materials). All potential confounders were associated with fruit intake with the exception of comorbidity. All potential confounders were associated with vegetable consumption with the exception of age and HPV status. For deep-fried food intake, associations between consumption and potential confounding variables were less consistent but were present for gender, treatment intent, education, smoking and alcohol, fruit and vegetable consumption. Based on these results, all potential confounders were included in our survival analyses. Formal tests for collinearity were performed on all confounders using variance inflation factors (VIFs). It is generally accepted that VIFs larger than 10 are deemed problematic. Across all three fully adjusted models the largest VIF was 1.47, therefore, collinearity is not considered an issue within our analysis.

Data for Body Mass Index (BMI) was available for 1,769 cases. BMI is widely reported as a known predictor for survival in HNC[28, 29], we therefore conducted a sensitivity analysis restricting our health risk behaviour models to

the 1769 cases. Further investigation into whether BMI could be a potential confounder or effect modifier was conducted. BMI was added to the health risk behaviour models, followed by tests for interaction between BMI and fruit, vegetable and fried food intake.

Results

Participants with complete data for all confounding and exposure variables of interest within the sub-sites oral cavity (640), oropharyngeal (1045) and laryngeal cancers (517) (total n=2202) were included in the final analysis. Four hundred and forty five people died during 7057 person-years of follow-up. Mean follow-up time amongst this population was 3.2 years (SD: 1.2 years) from diagnosis.

Descriptive data from this cohort are detailed in Table 1. Within our cohort , for all HNC, 76% were men. Seventy-eight percent were current or previous smokers and 52% reported a hazardous or harmful alcohol intake. Regarding dietary behaviours, 30% and 40% of people in this cohort ate a diet high in fruit and vegetables (more than 1 portion per day) respectively and 50% ate a diet high in deep-fried food (at least once per week) (Table 1). Participants with laryngeal cancers were less likely to be never smokers, less likely to eat a diet high in fruit or vegetables and ate more fried food than those with other tumours. Those with oropharyngeal cancer were more likely to have higher stage tumours, higher annual income and positive HPV serology. The distribution of intake for each food group across the study population is detailed in Table 2. Never smokers and those with a university education had a high intake of fruit and vegetables and a low intake of deep-fried food.

Fruit Intake

In the minimally adjusted model for all HNC sites, high fruit intake was associated with a 44% reduction in mortality (hazard ratio (HR) 0.56, CI 0.44, 0.73, p for trend=<0.001) (Figure 2; Table 3). This association disappeared following adjustment for health risk behaviours (HR 0.91, CI 0.67, 1.23, p for trend=0.55). This pattern was also seen in sub-site specific analyses. The association with fruit and overall survival disappeared for laryngeal cancers and attenuated for oral squamous cell carcinoma OSCC and oropharyngeal cancer (OPC) after adjusting for health risk behaviours (Table 3). Moderate fruit intake was not associated with overall survival in minimally adjusted or fully adjusted analyses. There was no evidence of interaction between tobacco and fruit intake (p values ranged between: 0.05 – 0.41) or between alcohol and fruit intake (p values ranged between: 0.08 – 0.73).

For OPC, in HPV negative cancers, higher fruit intake was associated with survival but with a broad confidence interval (HR 0.58, CI 0.30, 1.11, p for trend=0.24), which disappeared following adjustment for health risk behaviours (high fruit intake HR 0.97, CI 0.44, 2.15, p for trend=0.52). In HPV positive OPC, HRs from all models suggest moderate fruit intake is associated with an increased risk of mortality but also displayed wide confidence intervals (Table 4). There was no evidence of interaction (p=0.37).

Sensitivity analysis on the health risk behaviour model including BMI showed similar results to that of the full sample (results not reported). There was no evidence to suggest high fruit intake was associated with mortality (HR 0.83,

CI 0.58, 1.18, p for trend = 0.29). No association was found between survival and fruit intake when adjusting for BMI in the health risk behaviour model (HR 0.88, CI 0.62, 1.26, p for trend = 0.42). There were no interactions found between fruit intake and BMI (moderate fruit intake p=0.56; high fruit intake p=0.77).

Vegetable intake

High vegetable intake across HNC cancer sites was associated with higher overall survival (Figure 2), which attenuated in the health risk behaviour model (HR 0.79, CI 0.61, 1.03, p for trend = 0.04) (Table 3). In sub-site analyses, the association between survival and vegetable intake also attenuated in the health risk behaviour model in oral cavity cancers. For laryngeal cancers, high vegetable intake was associated with a 54% improvement in overall survival that persisted in the health risk behaviour model (HR 0.46, CI 0.27, 0.81, p for trend=0.02). However, there was no dose response seen between vegetable intake and survival in laryngeal cancers. For OPC, the association between vegetable intake and survival seen in minimally adjusted analyses was lost after adjustment for social factors. There was no evidence of any interaction between tobacco and vegetable intake (p values ranged between: 0.33 – 0.94) or between alcohol and vegetable intake (p values ranged between: 0.13 – 0.96).

For OPC, in HPV negative cancers, higher vegetable intake appeared to be associated with a reduced risk in mortality for the basic and clinical models.

In HPV positive OPC there was no evidence to suggest an association (Table 4). There was no evidence of interaction (p=0.20).

Sensitivity analysis on the health risk behaviour model including BMI removed any association seen between high vegetable intake and survival within the health risk behaviour model (HR 0.87, CI 0.65, 1.18, p for trend = 0.34) (results not reported). No association was found between survival and vegetable intake when adjusting for BMI in the health risk behaviour model (HR 0.86, CI 0.64, 1.16, p for trend = 0.27). There were no interactions found between vegetable intake and BMI (moderate vegetable intake p=0.76; high vegetable intake p=0.76).

Deep fried food intake

A diet high in deep-fried food was not associated with poorer survival outcomes including in minimally adjusted analyses (Figure 2, Table 3). In OSCC only, eating deep-fried food was associated with higher overall survival. The association was not attenuated in the health risk behaviour model, although the effect size was modest and the confidence interval was broad (HR 0.72, CI 0.51, 1.00, p for trend=0.01). There was no evidence of any interaction between tobacco and deep-fried food intake (p values ranged between: 0.24 – 0.77) or between alcohol and deep-fried food intake (p values ranged between: 0.12 – 0.52). For deep-fried food intake, for HPV positive and HPV negative tumours deep-fried food intake was not associated with survival (Table 4). There was no evidence of interaction (p=0.73).

Sensitivity analysis showed similar results to that of the full sample for deep-fried food intake (results not reported). There was no evidence of an association between deep-fried food intake and survival (HR 0.95, CI 0.76, 1.18, p for trend = 0.46). Similarly, no association was found between deep-fried food intake and survival when adjusting for BMI in the health risk behaviour model (HR 0.97, CI 0.78, 1.22, p for trend = 0.64). There was no interaction found between fried food intake and BMI (high fried food intake p=0.89).

Discussion

In this large prospective clinical cohort of people with head and neck cancer we report that for all HNC sites, fruit and vegetable consumption before diagnosis were associated with higher survival in minimally adjusted analyses but this disappeared after adjustment for health risk behaviours for fruit and attenuated for vegetables. Sensitivity analysis performed adjusting for BMI removed the association between vegetable intake and survival. Deep-fried food intake before diagnosis (all HNC sites) was not associated with HNC survival. There were no associations between fruit, vegetable and deep-fried food intake and overall survival for HPV positive and negative oropharyngeal cancers in minimally or fully adjusted analyses. In site-specific analyses, vegetable intake may be associated with higher overall survival for laryngeal cancers and deep-fried food intake may be associated with higher overall survival for OSCC.

High fruit and vegetable intake is known to reduce the risk of developing head and neck cancer. In our study, when adjusting for health risk behaviours the association between survival and fruit intake disappeared and the association between survival and vegetable intake attenuated. This suggests potential confounding between fruit and vegetable intake, tobacco and alcohol consumption. We know from previous literature that people who smoke and drink alcohol eat less fruit and vegetables [30-32]. Results from one study on HNC risk showed no interaction between fruit and vegetable intake and smoking or alcohol consumption on the development of HNC [33]. However,

the interaction between diet and health-risk behaviours in healthy subjects and disease aetiology may be different from the interaction between health-risk behaviours and diet in people with established disease and their subsequent prognosis. Also, another study assessing HNC risk stratified analyses by fruit and vegetable intake and tobacco and alcohol consumption. This study demonstrated an interaction with a multiplicative risk of HNC in those with low fruit/vegetable intake and heavy alcohol/tobacco consumption, which aligns with our findings of potential confounding [34].

For vegetable intake, the attenuated effect that exists following full adjustment could represent a genuine, modest association between vegetables and HNC survival or alternatively could be secondary to residual confounding. A proposed mechanism of action to explain this link is the role of micronutrients present in vegetables. These include carotenoids and polyphenols that reduce reactive oxygen species and have been associated with reduced risk of developing HNC and in one study xanthophyll and carotenoids were associated with improved HNC survival and reduced HNC recurrence, lending further support to the link between vegetable intake and HNC survival [19, 35-37].

Our findings broadly agree with those of previous studies that demonstrate an association between HNC survival and vegetable intake. A small Spanish study (n=146) showed that vegetables were protective against both all-cause mortality and recurrence in newly diagnosed oral cavity and oropharyngeal cancers including in their adjusted analyses [17] . Another European study (n=215) demonstrated an independent protective effect for citrus fruits and

vegetables on all-cause-mortality in laryngeal cancers [18]. However, these studies did not adjust for health-risk behaviours, which may affect the relationship between vegetable intake and survival. Arthur et al (n=542) demonstrated that a whole foods diet high in fruit and vegetables was inversely associated with head and neck squamous cell carcinoma mortality after adjustment for smoking [15].

Site-specific associations between survival and dietary behaviours found in this study were post-hoc findings that should be interpreted with caution. We demonstrated that in laryngeal cancers high vegetable intake was associated with approximately 54% higher overall survival even after adjustment for health risk behaviours. Our results agree with those of Dikshit et al (n=932) who reported a modest independent association between vegetable intake and overall survival in laryngeal and hypopharyngeal cancers following adjustment for tobacco and alcohol consumption [6]. In another study (n=178), carotenoids were associated with higher progression free survival in people with head and neck squamous cell carcinomas treated with radiotherapy (likely including a large proportion of laryngeal cancer patients) even when adjusted for smoking [38]. Despite these consistencies with previous research, the possible link between laryngeal cancer survival and vegetable intake in this study may be due to chance and requires replication in other large studies also with detailed measures of confounders.

In oral cavity cancers, we saw a surprising modest association between high deep-fried food consumption and OSCC higher survival. This was

unexpected as the literature that suggests a higher risk of developing HNC with fried and deep-fried food intake and associations of fried food with cellular mutagenesis that lead to cancer [12, 39, 40]. No other studies directly assessed fried food intake and HNC survival. It is possible that those eating deep-fried foods had a higher overall energy intake, and/or higher BMI at the start of treatment, both of which are associated with higher HNC survival [15, 16, 28, 29].

We did not find an association between HPV status, fruit and vegetable intake and overall survival but our findings suggest that HPV negative cancers follow a similar pattern to all HNC sites; there is an association between higher survival and high intake of fruit and vegetables in minimally but not fully adjusted analyses. There was no clear association between HPV positive cancers and diet in this study. No other study has on HNC survival and diet has stratified by HPV status and these findings require replication.

Strengths and Limitations

Extensive research exists into dietary behaviours and HNC risk but there is limited evidence regarding survival in HNC related to diet. This was among the first studies assessing dietary behaviours and HNC survival that accounts for a wide range of potential confounders including smoking, alcohol intake and HPV status. Furthermore, this was a large, prospective, adequately powered cohort study of UK head and neck cancer patients with excellent mortality follow-up resulting in a minimal risk of attrition bias or chance findings (with the exception of sub-site analyses).

Despite the large sample size, fewer than 50% of those eligible consented to the study and there were missing data for many variables, reducing the number of cases included in data analysis. Data on certain potential confounder variables including physical activity and total energy intake before diagnosis were not collected. This may have led to residual confounding that could explain the association between survival and vegetable intake [5, 15]. Data on HNC specific mortality were not collected. BMI data were collected but were only available for a reduced sample. Sensitivity analyses which adjusted for BMI (and the accompanying reduction in sample size) produced similar results to those of the original analyses, showing no association between survival and fruit or deep-fried food intake. However, for vegetable intake previous associations did not remain. This may mean that associations between vegetable intake and mortality differed between those with and without BMI data, or simply that the smaller sample size reduced the precision of the effect size (i.e. reduced power). BMI was added to each of the health risk behaviour models but again showed no evidence of an association between food type and survival. Interactions were tested between food type and BMI to identify if BMI could be a potential effect modifier. No interactions were found and therefore we did not conduct stratified analysis.

Several limitations existed regarding our exposure variable. We analysed dietary behaviours before diagnosis, which is unlikely to be representative of life-long eating habits and doesn't account for possible recent changes to diet secondary to cancer symptoms. Equally, we did not analyse the association

between post-treatment dietary behaviours and HNC survival. In measuring dietary intake we used a self-reported measure that relied on a single question for each exposure. The resulting measurement error is likely to lead to an attenuation of associations[41]. Overall, this is a limited estimate of a complex behaviour such as diet. We did not analyse sub-types of fruit and vegetables with different nutritional value, and serving size was ambiguous. Also, overlap between the categories e.g. deep-fried vegetables were not accounted for resulting in a lack of precision. Salad vegetables and shallow-fried foods were excluded from the FFQ questions. Certain shallow-fried foods have been linked to HNC risk and could be associated with poorer survival outcomes [12, 39]. Vegetable intake may be underestimated without registering salad vegetables. Dietary self-reported questionnaires are vulnerable to social desirability bias with under-reporting of energy intake and over-reporting of fruit and vegetable intake [42-44].

Implications for Clinical Practice

In addition to evidence that suggests that fruit and vegetables may reduce the risk of HNC, our results suggest that pre-treatment vegetable but not fruit intake may be associated with HNC overall survival in the first two years after diagnosis. Encouraging patients to have a diet higher in vegetables therefore remains important but given the strong supporting evidence in the literature regarding tobacco and poor HNC survival outcomes, clinicians should prioritise behaviour change interventions to smoking cessation [5, 45, 46].

Implications for Research

In this large cohort of people with HNC, we have demonstrated a modest association between vegetable intake and short-term survival but the link between dietary behaviours and long-term HNC survival remains unclear. The unexpected observation of an association between OSCC survival and high deep-fried food intake requires replication. Future studies should consider exploration of lifelong dietary habits, the relationship between survival and post-treatment dietary change as well as the relationship between diet and long-term overall survival in HNC.

Conclusions

We have demonstrated an association between vegetable intake and survival in HNC that is consistent with previous studies but may also represent residual confounding. Fruit intake is not independently associated with HNC survival. Deep-fried food intake is not associated with HNC survival.

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