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Dietary fat and meat intakes and risk of reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma

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Abstract

The aim of this study was to investigate whether dietary fat and meat intakes are associated with reflux esophagitis (RE), Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). In this all-Ireland case-control study, dietary intake data was collected using a food frequency questionnaire in 219 RE patients, 220 BE patients, 224 EAC patients, and 256 frequency-matched controls between 2002 and 2005. Unconditional multiple logistic regression analysis was used to examine the association between dietary variables and disease risk using quartiles of intake, to attain odds ratios (OR) and 95% confidence intervals (95%CI), while adjusting for potential confounders. Patients in the highest quartile of total fat intake had a higher risk of RE (OR=3.54; 95%CI=1.32–9.46) and EAC (OR=5.44; 95%CI=2.08–14.27). A higher risk of RE and EAC was also reported for patients in the highest quartile of saturated fat intake (OR=2.79; 95%CI=1.11–7.04; OR=2.41; 95%CI=1.14–5.08, respectively) and monounsaturated fat intake (OR=2.63; 95%CI=1.01–6.86; OR=5.35; 95%CI=2.14–13.34, respectively). Patients in the highest quartile of fresh red meat intake had a higher risk of EAC (OR=3.15; 95%CI=1.38–7.20). Patients in the highest category of processed meat intake had a higher risk of RE (OR=4.67; 95%CI=1.71–12.74). No consistent associations were seen for BE with either fat or meat intakes. Further studies, investigating the association between dietary fat and food sources of fat are needed to confirm these results.

Keywords

adenocarcinoma; Barrett's esophagus; dietary fat; epidemiology; meat

Introduction

Incidence of esophageal adenocarcinoma (EAC) has dramatically increased in recent decades, and is the most rapidly increasing cancer in the United States and Western Europe [1-4]. Despite improvements in surgery and chemotherapy, the outlook for patients diagnosed with EAC remains poor, with a 5-year survival rate of less than 20% [5, 6]. Barrett's esophagus (BE) is a metaplastic change of the distal esophagus in which the normal stratified squamous epithelium is replaced by specialized intestinal columnar epithelium; a potential complication of reflux esophagitis (RE). Although BE patients have

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an overall approximate 30–125 fold increased lifetime risk of developing EAC, their absolute risk is less than 1% per year [7], with both environmental and genetic susceptibility factors being thought to be important in determining individual risk. Nevertheless, successful cancer prevention depends on the identification of modifiable risk factors.

Diet is one such potential modifiable risk factor of EAC. Previous studies have reported adverse associations between EAC and dietary fat intakes [8-13], and a recent case-control study reported non-significant trends for inverse associations between BE and intakes of monounsaturated fat and polyunsaturated fat, and a positive association between long-segment BE and saturated fat [14]. These adverse associations may be explained by the fact that these intakes are characteristic of diets based primarily on meat, which may be potentially associated in part with EAC risk. Previous studies have reported positive associations between meat intakes and EAC [15-18]; but these have not all been consistent [19]. Other epidemiologic studies suggest that a plant-based diet with high-fiber, low-fat foods, is associated with a reduced risk of BE [14] and EAC [20].

Using data and samples collected as part of an all-Ireland case-control study, the Factors INfluencing the Barrett's Adenocarcinoma Relationship (FINBAR) study, we examined the association between dietary fat and meat intakes with RE, BE and EAC.

Subjects and Methods

Study population and design

Study methods have been described in detail elsewhere [21]. Briefly, the FINBAR study commenced in Ireland in March 2002 and continued until July 2005. The study included three groups: (a) patients with EAC, (b) patients with long-segment BE, and (c) normal population controls, recruited from Northern Ireland and the Republic of Ireland. In addition, from September 2004 to July 2005, a group of RE patients were recruited from Northern Ireland only.

EAC cases (aged <85 years) were patients with histologically confirmed adenocarcinoma; with verification that the tumor was located in the esophagus. *In situ* cancers were not included. BE cases (aged <85 years) were included if they had long length BE at endoscopy (> 3 cm) and specialized intestinal metaplasia without dysplasia on histological examination. RE patients were included if there was macroscopically visible erosive esophagitis at endoscopy (grades 2–4 in the Savary Miller/Hetzel-Dent classification or grades B, C, or D in the Los Angeles classification). Population controls (aged <85 years) were participants without a history of esophageal or other gastrointestinal cancer, or a known diagnosis of BE. They were selected at random from general practitioner lists in Northern Ireland and the Dublin and Cork areas. RE patients, BE patients and the population controls were frequency matched, using 5-year age and sex strata, to the distribution of EAC patients, with a maximum age of 85 years.

Overall, FINBAR included 230 RE patients, 224 BE patients, 227 EAC patients, and 260 population controls. The participation rate of eligible, alive patients was 74%, and the overall response rate was 64%. The participation rates of RE, BE and control subjects was 69%, 82% and 42%, respectively. Patients with RE (n = 11), BE (n = 4), EAC (n = 3), and population controls (n = 4) who did not provide complete dietary information were excluded, giving a maximum of 219 RE patients (95%), 220 BE patients (98%), 224 EAC patients (99%), and 256 population controls (98%) for inclusion in the analysis.

Dietary assessment

Dietary information was obtained using a modified version of the semiquantitative European Prospective Investigation into Cancer and Nutrition (EPIC) food frequency questionnaire (FFQ) [22]. Habitual intake of 101 food items relating to a period 5-years before interview (pre-morbid diet) was collected. Macronutrient intakes (total fat, saturated fat, monounsaturated fat and polyunsaturated fat) were calculated using McCance and Widdowson's food composition tables [23]. The FFQ contained 17 meat and fish food items. In light of the fact that over 70% of participants reported never eating or eating <1 medium serving/month of liver, we decided to omit this intake from the primary analysis, but did perform some exploratory analysis using this variable as liver is a main source of heme iron. To derive an individual medium serving size for each of the 17 items, standard portion sizes were used [24], and these were recoded into daily intakes in grams before being grouped into their respective groups for analysis; total meat - beef, beefburgers, pork, lamb, chicken, bacon, bacon rashers, ham, corned beef/luncheon meat, sausages and savory pies; red meat - beef, beefburgers, pork, lamb, bacon, bacon rashers, ham, corned beef/ luncheon meat, sausages and savory pies; fresh red meat - beef, beefburgers, pork and lamb; white meat – chicken; processed meat - bacon rashers, ham, corned beef/luncheon meat, sausages and savory pies; and total fish - fried fish, fish fingers, white fish, oily fish and shellfish.

The FINBAR study was approved by the Research Ethics Committee of Queens University Belfast, the Clinical Research Ethics Committee of Cork Teaching Hospitals, and the Research Ethics Committee Board of St. James's Hospital Dublin.

Statistical analysis

Firstly, analyses relating to RE patients were limited to controls recruited in Northern Ireland only, because RE patients were recruited only from this region. All dietary intakes were adjusted for energy intake using the residual method; dietary intakes were regressed on energy intake, residuals collected, and then added to the mean [25].

Comparison of descriptive statistics between cases and controls were investigated using student's *t*-tests for continuous variables and Chi-squared tests for categorical variables; the variable 'smoking status' was tested using the more appropriate Mantel-Haenszel Chi-squared test; preferred for ordinal variables. Unconditional multiple logistic regression analysis was used to examine the association between dietary variables and disease risk using quartiles of intake, to attain odds ratios (OR) and 95% confidence intervals (95%CI). Quartile cut-points were based on the distribution of intake among controls. To test for trend, each participant within a particular quartile was assigned the median intake value for that quartile prior to inclusion in the regression model.

We fitted age, sex and energy intake adjusted models (data not shown) for comparison to fully adjusted models that included sex, age (years), smoking status (never, former, current), gastro-esophageal reflux (GER) symptoms (ever/never), total energy intake (kcal/day), alcohol consumption (g/wk), body mass index (BMI) 5-years prior to the interview date (kg/m^2), education (years), type of occupation (manual/non-manual), nonsteroidal anti-inflammatory drug (NSAID) use more than 5-years prior to the interview (weekly use for six months or more), location (Northern Ireland/Republic of Ireland) and *Helicobacter pylori (H.pylori)* infection. Risk estimates for each type of meat were adjusted for the intake of other types of meat such that the meat variables in each model added up to total meat intake. For example, red meat was adjusted for white meat, and processed meat was adjusted for non-processed meat. Also, because the sources of monounsaturated and saturated fats are quite similar (meats), and due to collinearity, we did not mutually adjust the fat sub-types.

Effect modification by sex was assessed by evaluating interaction terms, although tests were not significant for RE, BE or EAC (all P for interaction >0.05). Further, we evaluated interaction with smoking, GER symptoms and alcohol intake by doing stratified analysis and by evaluating interaction terms. Smokers and GER symptoms were defined as never/ever; whilst alcohol intake was stratified according to alcohol content of one standard glass with 12 g ethanol as 0 to 6 g/day (up to half a glass per day) and >6 g/day. Pearson correlation coefficients were calculated to estimate collinearity between the dietary variables of interest.

Statistical analysis was conducted using STATA version 9.2 (StataCorp, TX, USA). All statistical tests were 2-sided and a P value <0.05 was considered significant.

Results

Population characteristics

Data from 219 RE patients, 220 BE patients, 224 EAC patients, and 256 population controls were available for this analysis (Table 1). RE patients were younger, were more likely to be male and were less likely to have *H.pylori* compared with the Northern Ireland controls. BE patients had a higher energy intake, were more likely to work in manual jobs, and had received less education than controls. Compared with the population controls, EAC cases had a higher BMI, higher energy intake, were more likely to smoke, were less educated, were more likely to hold manual occupations, consumed less alcohol, and were less likely to have *H.pylori*. All three case groups were more likely to have experienced GER symptoms than controls.

Correlation coefficients for fat intakes

RE patients – saturated fat and monounsaturated fat, r = 0.41; saturated fat and polyunsaturated fat, r = −0.56; monounsaturated fat and polyunsaturated fat, r = 0.31; all *P* <0.01.

BE patients - saturated fat and monounsaturated fat, r = 0.56; saturated fat and polyunsaturated fat, r = −0.27; monounsaturated fat and polyunsaturated fat, r = 0.41; all *P* <0.01.

EAC patients - saturated fat and monounsaturated fat, r = 0.58; saturated fat and polyunsaturated fat, r = −0.30; monounsaturated fat and polyunsaturated fat, r = 0.26; all *P* <0.01.

Fat and cholesterol intakes

Multivariate adjustment had minor influence on the observed risk estimates for RE and EAC, and associations were in the same direction as the minimal (age, sex and energy) adjusted models (data not shown). The 95% confidence intervals for the risk estimates in each model also overlapped. However, some of the risk estimates for BE were attenuated after full adjustment. No consistent associations were seen for fat intakes and BE risk in the fully adjusted models, although there was significant positive associations in the minimally adjusted models for those in the fourth quartile versus the referent for total fat, saturated fat, and monounsaturated fat intake (OR = 3.03; 95%CI = 1.71–5.36; OR = 1.83; 95%CI = 1.09–3.08; and OR = 1.95; 95%CI = 1.13–3.34, respectively).

In the fully adjusted models (Table 2), patients in the highest quartile of total fat intake had a higher risk of RE (OR = 3.54; 95%CI = 1.32–9.46; *P* for trend = 0.03) and EAC (OR = 5.44; 95%CI = 2.08–14.27; *P* for trend <0.01). A higher risk of RE and EAC was also reported for patients in the highest quartile of saturated fat intake (OR = 2.79; 95%CI = 1.11–7.04; *P* for

trend = 0.07; OR = 2.41; 95%CI = 1.14–5.08; *P* for trend = 0.01, respectively) and monounsaturated fat intake (OR = 2.63; 95%CI = 1.01–6.86; *P* for trend = 0.10; OR = 5.35; 95%CI = 2.14–13.34; *P* for trend <0.01, respectively). Patients in the third quartile of polyunsaturated fat intake had a higher risk of EAC (OR = 2.68; 95%CI = 1.23–5.85), but no further increase in risk, or main effect of intake on risk, was observed beyond this quartile (*P* for trend = 0.30). Patients in the highest quartile of cholesterol intake had a higher risk of EAC (OR = 3.59; 95%CI = 1.71–7.54; *P* for trend <0.01). No consistent associations were seen for BE risk with any of the intakes.

Meat and fish intakes

As with the fat intakes, multivariate adjustment had minor influence on the observed risk estimates for RE and EAC, and associations were in the same direction as the minimal (age, sex and energy) adjusted models (data not shown). The 95% confidence intervals for the risk estimates in each model also overlapped. However, some of the risk estimates for BE were attenuated after full adjustment. For example, no consistent association was seen for processed meat intake and BE risk in the fully adjusted models, although there was a significant positive association in the minimally adjusted model for the fourth quartile versus the referent (OR = 2.27; 95%CI = 1.28–4.01). Also, although not significant, the risk estimates for total meat, red meat, and fresh red meat intakes were attenuated in the fully adjusted models e.g. No association for red meat intake in the fourth quartile versus the referent in the fully adjusted model (OR = 1.09; 95%CI = 0.47–2.51), but a borderline significant positive association was observed in the minimally adjusted model (OR = 1.62; 95%CI = 0.96–2.72).

Interestingly, in the fully adjusted models (Table 3), no consistent association between total red meat intake and EAC risk was reported, but patients in the fourth quartile of fresh red meat intake had a higher risk of EAC compared to the referent (OR = 3.15; 95%CI = 1.38–7.20; *P* for trend = 0.01). Patients in the fourth quartile of processed meat intake had a higher risk of RE (OR = 4.67; 95%CI = 1.71–12.74; *P* for trend = 0.01). Again, no consistent associations were seen for BE risk with any of the intakes.

As outlined previously, we performed some exploratory analysis looking at liver intake individually. Patients in the fourth quartile had a higher risk of EAC compared to the referent (OR = 2.61; 95%CI = 1.05–6.50; *P* for trend <0.01), and patients in the third quartile also had a higher risk of RE compared to the referent (OR = 3.76; 95%CI = 1.11–12.76); but no further increase in risk, or main effect of intake on risk, was observed beyond this quartile (*P* for trend = 0.17). No consistent association was seen for BE risk and liver intake (data not shown).

Additional exploratory analysis of the individual meat and fish items with risk of RE, BE and EAC corroborated well with what we found in relation to fat, meat and fish intakes. For example, we found that patients in the fourth quartiles of corned beef/luncheon meat and sausages (processed meats and a high source of saturated and monounsaturated fats) had a higher risk of RE compared to the referent (OR=3.33; 95%CI=1.06–10.51; and OR=2.47; 95%CI=0.97–6.31, respectively). Similar increases in risk for EAC were seen in patients in the fourth quartile of corned beef/luncheon meat (OR=2.81; 95%CI=1.10–7.15), and also in the fourth quartiles of beef and lamb intakes (OR=2.53; 95%CI=1.03–6.19; and OR=4.61; 95%CI=1.94–10.96, respectively). Those in the second quartile for sausages were also at increased risk for EAC (OR=3.28; 95%CI=1.50–7.18) (data not shown).

Analyses of interaction

Stratified analyses were conducted based upon smoking, GER symptoms and alcohol intake, to determine if there was an interaction between dietary intakes of fats, meat and fish, and EAC risk (data not shown). We looked at intakes continuously to increase power. For instance, the heightened risk of EAC that was found for total fat intake, when examined continuously (OR = 1.50; 95%CI = 1.25–1.81), remained across stratification by smokers and never-smokers (OR = 1.47; 95%CI = 1.17–1.86; and OR = 1.83; 95%CI = 1.24–2.71, respectively), GER symptoms and no GER symptoms (OR = 1.40; 95%CI = 1.00–1.95; and OR = 1.61; 95%CI = 1.27–2.06, respectively), and in >6 g/day and 0 to 6 g/day (OR = 1.41; 95%CI = 1.14–1.75; and OR = 2.32; 95%CI = 1.36–3.95, respectively). Conversely, the heightened risk of EAC that was found for fresh red meat intake, when examined continuously (OR = 1.27; 95%CI = 1.00–1.61) did appear to change across stratification by smokers and never-smokers (OR = 1.06; 95%CI = 0.81–1.39; and OR = 5.24; 95%CI = 2.10–13.08, respectively), in >6 g/day and 0 to 6 g/day (OR = 1.15; 95%CI = 0.86–1.54; and OR = 1.96; 95%CI = 1.04–3.72, respectively), but not GER symptoms and no GER symptoms (OR = 1.39; 95%CI = 0.87–2.23; and OR = 1.25; 95%CI = 0.92–1.70, respectively). However, formal tests for interaction failed to reach statistical significance in any of the investigations (all P for interaction >0.05), and not all of the risks were statistically significant owing to limited power within some subgroups.

Discussion

This is one of the largest case-control studies to examine the association between dietary fat and meat intakes in humans and the risk of RE, BE, and EAC utilizing the same control group. Our data suggested that total fat, saturated fat, and monounsaturated fat intakes were adversely associated with the risk of RE and EAC. Plant-based fats (e.g. polyunsaturated fat) were not associated with RE or BE, but there was a suggestion of an adverse association with EAC risk. Cholesterol intake was also found to be a risk factor for EAC. Meat intakes were not associated with the majority of the case groups, although omitting processed meat from the total red meat intake variable (fresh red meat variable) resulted in a significantly positive association being reported for EAC. Processed meat intake was adversely associated with RE only.

The results presented in this current study with regards to BE are in agreement with those from a recent case-control study [14]; both studies did not find consistent associations between fat intakes or cholesterol with BE risk, although [14] did report non-significant inverse trends for polyunsaturated fat, which is not evident within this current study. However, two previous rat models have demonstrated adverse effects of total dietary fat or animal-fat on BE [26, 27]. Chen *et al*. hypothesized that a high dietary animal-fat intake plays a crucial role in the development of BE and EAC, by inducing a significant increase in taurine-conjugated bile acids in bile juice, and by increasing the pH in the esophagus [27]. Physiological studies of human volunteers have also shown increased frequency of transient lower esophageal sphincter relaxation and increased esophageal acid exposure with high fat consumption [28, 29]. Our results would seem to support these hypotheses because we found total fat, saturated fat, and monounsaturated fat to be strongly associated with increased RE and EAC risk, and the associations observed in this current study for EAC and fat have also been shown in other case-control studies [8-13]. Therefore, our results suggest that higher animal (meat) based fat intakes may lead to increased exposure of the distal esophagus to excess acid, which may result in a metaplastic change of the epithelium leading to BE formation. Dietary fat intakes were not associated with BE risk, but the fact we found a strong association with EAC risk does suggestthat animal (meat) based fat intakes may be a risk factor for progression to cancer (not necessarily via BE). In addition, this finding supports the hypothesis that high fat intake may be at least partially responsible

for the rising rates of EAC in the United States and Western Europe, as the fat content has increased in these diets. Our additional exploratory analysis of the individual meat and fish items with risk of RE, BE and EAC further supported this hypothesis e.g. patients in the fourth quartile of corned beef/luncheon meat (processed meat and a high source of saturated and monounsaturated fat) had a higher risk of RE and EAC.

Conversely, plant based foods are a key dietary source of polyunsaturated fats, and epidemiologic evidence suggests that a diet rich in plant based, high-fiber, low-fat foods, can provide protection against BE [14] and EAC [20]. However, polyunsaturated fat intake was not associated with RE or BE in this current study, but there was a suggestion of an adverse association with EAC risk; no consistent effect of intake on risk was observed. The finding that cholesterol intake was associated with EAC risk is also in agreement with other case-control studies [8, 30].

It was thought that the associations which we report for dietary fat intakes may not be attributable specifically to the various fats *per se*, but rather may reflect dietary patterns. This was because the adverse associations reported for the case groups tended to be from animal (meat) based fats (saturated fat and monounsaturated fat). However, it was not feasible to examine the association for animal fat and plant sources of fat separately within FINBAR because in order to do this we would have needed to know the contribution of foods to fat intake in the study and have detailed information on the type of fat used in cooking and at the table. Also it is impossible to know what fats were used in manufactured foods such as cakes/biscuits/pastries, and it is likely that it is a mixture of both animal and plant sources. Additionally, fat used in cooking or at the table was not defined well enough from the FFQ to categorize participants accurately in terms of animal versus plant sources. Fats used in take-away restaurants are also likely to vary hugely so we could not make an assumption that they used lard (animal) or sunflower oil (plant) to cook foods for example. Additionally, the total fish intake variable used in this study contained fried fish, and we do not have information on the type of fat used in frying, which could help explain the lack of associations reported. However, omitting fried fish from the total fish intake variable did not attenuate the results reported (data not shown).

Previous studies have reported an increased risk of EAC in relation to intakes of total meat [15, 16] and red meat [15-17], whereas others reported no association between EAC and processed meat [17] or red meat [19], with a recent study also reporting a reduced risk of long-segment BE with higher meat intakes [14]. A diet characterized by high intakes of red meat and processed meat was also shown to be associated with an increased risk of EAC [31]. Even though the exact mechanisms remain unclear, several hypotheses have been suggested to explain possible causal relationships between meat intakes and cancer risk, including mutagens formed in meats cooked at high temperatures (heterocyclic amines and polycyclic aromatic hydrocarbons) and the endogenous formation of N-nitroso compounds, which are carcinogens found in abundance in processed meats [32-35]. Unfortunately, we did not have information on cooking methods or doneness, and therefore could not investigate this hypothesis further within FINBAR. However, when we omitted processed meat from the total red meat variable (fresh red meat), it resulted in a significantly positive association being seen between fresh red meat intake and EAC risk. Therefore, it would appear that only fresh red meat has an adverse association with EAC risk, and not processed meat; processed meat intake was not associated with EAC either. However, processed meat intake was adversely associated with RE risk. Additionally, red meat and liver is a key dietary source of heme iron, which is more readily absorbed than iron from other sources, and is thought to contribute to carcinogenesis by generating free radicals and inducing oxidative stress [36]. This heme iron hypothesis has been demonstrated in animal models [37-39], but human data remains inconsistent [19, 40-43]. Additionally, heme iron from both

red and processed meat has been shown to significantly increase the formation of N-nitroso compounds in the upper gastrointestinal tract, which may result in increased risk from esophageal cancer [44]. The fact we also found significant adverse associations between EAC risk and liver intake in exploratory analyses further strengthens this heme iron hypothesis, and adds weight to the argument that increased risk of esophageal cancer may be promoted through the increased formation of N-nitroso compounds by heme iron. Cross et al. [35] used liver pate and blood pudding as a heme-iron supplement and found increased fecal N-nitroso compounds compared with a low meat diet.

GER symptoms, smoking and alcohol consumption have been implicated in the RE-BE-EAC spectrum previously [45-47]. Therefore, we evaluated interaction by doing stratified analysis and by evaluating interaction terms. However, the analysis of risk estimates and effect modification was limited by small case numbers within some of the stratum, and there was no evidence of interaction between dietary intakes with smoking, GER symptoms or alcohol intake for RE, BE or EAC patients.

There are several strengths to this study. The FINBAR study has a relatively large sample size, is population-based and used stringent inclusion criteria throughout. Information was collected on a wide range of potential confounders such as BMI, smoking status, *H.pylori*, and GER symptoms. There are also limitations to this study including the possibility of residual confounding from unmeasured variables and the potential for recall bias. This is because the FFQ used recorded dietary intakes during a 12 month period, 5-years ago, and there would be a tendency for RE, BE or EAC patients to recall past intakes differently than healthy controls(selective recall). Also, within FINBAR, EAC patients were incident cases and were interviewed shortly after diagnosis. However, we did not have reliable information to confirm incident/prevalent BE cases as the diagnosis date was retrieved from patient histology reports, and therefore many may have been prevalent cases. When asked, many of the BE patients could not remember or did not know that they had a diagnosis. Therefore, patients were likely to have had BE long before diagnosis and this cannot be accurately determined. This inability of separating incident from prevalent BE is the same limitation seen for other asymptomatic pre-cursor lesions, such as colon polyps, and incident lesions can only be identified in cohorts with multiple endoscopic screenings. As for RE patients, there was no restriction placed on recruitment of incident or prevalent cases. Therefore, the fact that both incident/prevalent cases were recruited may also have resulted in recall bias of dietary intakes and stratification by incident/prevalent cases was not possible within FINBAR. Also, the response rate of the controls was lower compared with cases, which may have introduced selection bias. Nevertheless, the mean daily intake of total fat among controls (99.6 g/day) was similar to intake reported in the North/South Ireland Food Consumption Survey (approximately 90 g/day) [48], suggesting that our controls are representative of the general population with regard to fat intake. Additionally, it is widely understood that the incidence of BE and EAC is higher among males than females, and this is reflected in the numbers recruited as part of FINBAR (Table 1). Population controls were frequency matched by sex and 5-year age band to the distribution of EAC patients to ensure that the age and sex profile of BE patients and population controls resembled that of the EAC cases.

Overall, the most recent review of the evidence by the World Cancer Research Fund & American Institute for Cancer Research, in 2007, concluded that no recommendation could be reliably made regarding intakes of total fat, saturated fat, monounsaturated fat or polyunsaturated fat and esophageal cancer risk, and there is currently limited suggestive evidence that higher intakes of red and processed meat can increase risk [49]. Our data suggested that total fat, saturated fat, and monounsaturated fat intakes were adversely associated with the risk of RE and EAC. Meat intakes were not associated with RE, BE or

EAC, although fresh red meat (excluding processed meat) was significantly associated with EAC risk, and processed meat was adversely associated with RE. Further studies, investigating the association between dietary fat intakes and food sources of fat are needed to confirm these results.

Novelty

Previous epidemiological studies have examined the association between dietary fat and meat intakes, and esophageal cancer risk. However, results have been mixed and many studies did not differentiate between the specific cancers e.g. esophageal adenocarcinoma and esophageal squamous cell carcinoma. Additionally, associations between dietary fat and meat have not been widely researched. This study allowed us to look at total dietary fat and meat intakes, along with their subtypes concurrently in reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma patients, and provided us with an opportunity to hypothesize at which stage in the carcinogenic pathway these intakes may have an effect.

Impact

The incidence of esophageal adenocarcinoma has dramatically increased in recent decades, and the outlook for patients diagnosed with esophageal adenocarcinoma remains poor. Therefore, successful prevention depends on the identification of modifiable risk factors, with diet being one such potential modifiable risk factor for both esophageal adenocarcinoma and its precursor state, Barrett's esophagus. This study provides findings that could have significance for the growing number of people diagnosed with Barrett's esophagus in order that they may minimize their risk of development of cancer.

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Abbreviations used

95%CI	95% confidence interval
BE	Barrett's esophagus
EAC	esophageal adenocarcinoma
FFQ	food frequency questionnaire
GER	gastro-esophageal reflux
OR	odds ratios
RE	reflux esophagitis

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Table 1

Characteristics of controls, reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma cases

Characteristics	NI controls	RE	*P* value	All controls	BE	*P* value	EAC	*P* value
Number	119	219		256	220		224	
Age, mean (SD)	68 (10)	62 (11)	<0.01	63 (13)	62 (12)	0.50	64 (11)	0.25
Sex, Men, %	69.8	83.6	<0.01[1]	84.4	82.3	0.54[1]	84.4	1.00[1]
BMI 5 yrs prior (kg/m^2), mean (SD)	27.2 (4.1)	27.7 (4.5)	0.25	27.1 (3.9)	26.9 (4.0)	0.74	28.6 (4.9)	<0.01
Education (years)	11 (3)	11 (2)	0.15	12 (3)	11 (3)	0.02	11 (3)	<0.01
Occupation type, %								
Manual	47.0	49.5		49.4	58.5		60.1	
Non-manual	53.0	50.5	0.66[1]	50.6	41.5	0.05[1]	39.9	0.02[1]
GER symptoms[a], %[g]								
Ever	23.5	39.7		19.2	72.3		48.2	
Never	76.5	60.3	<0.01[1]	80.8	27.7	<0.01[1]	51.8	<0.01[1]
NSAID use 5 yrs prior, ever, %	12.8	17.4	0.27[1]	12.2	13.2	0.75[1]	10.3	0.52[1]
Smoking status, %								
Current	18.8	21.5		17.7	22.8		34.7	
Previous	37.6	29.0		42.2	37.4		44.8	
Never	43.6	49.5	0.72[2]	40.2	39.7	0.42[2]	20.6	<0.01[2]
H. pylori, seropositive, %	65.0	42.4	<0.01[1]	58.5	50.5	0.09[1]	49.0	0.04[1]
Location, %								
Northern Ireland	100	100		46.5	68.2		50.9	
Republic of Ireland	0	0	-	53.5	31.8	<0.01[1]	49.1	0.34[1]
Calories (kcal), mean (SD)	2,588 (893)	2,692 (747)	0.26	2,576 (811)	2,721 (770)	0.05	2,756 (813)	0.02
Fruit (portion/day), mean (SD)	2.7 (2.9)	2.6 (2.7)	0.77	2.5 (2.9)	2.1 (2.2)	0.09	2.4 (2.6)	0.55
Vegetables (portion/day), mean (SD)	5.6 (3.2)	5.4 (2.1)	0.49	5.3 (2.8)	5.0 (2.6)	0.13	5.5 (2.9)	0.41
Alcohol (g/day), mean (SD)	20.2 (22.7)	22.0 (21.5)	0.55	26.3 (23.3)	22.3 (25.4)	0.13	19.8 (22.0)	0.01

BE, Barrett's esophagus; BMI, body mass index; EAC, esophageal adencarcinoma; GER, gastroesophageal reflux; NI, Northern Ireland; NSAID, nonsteroidal anti-inflammatory drug; RE, reflux esophagitis.

Some columns may not total 100% due to rounding.

RE cases compared to Northern Ireland controls only; EAC cases compared to all controls.

[1] Cases compared to controls by student's *t*-test, except chi-squared test and

[2] Mantel-Haenszel chi-squared test.

[a] GER: symptoms of heartburn/acid reflux occurring more than 50 times per year, more than 5 years prior to the interview date.

Table 2

Risk of reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma in relation to fat and cholesterol intake

Dietary intake NI controls/all controls (median)	NI controls	RE		All controls	BE		EAC	
		No.	Adjusted OR (95% CI)[a]		No.	Adjusted OR (95% CI)[a]	No.	Adjusted OR (95% CI)[a]
Total fat (g/day)								
94.2/78.3	30	39	Ref	64	27	Ref	16	Ref
105.4/95.2	30	60	1.20 (0.47-3.04)	64	57	2.08 (0.89-4.89)	46	3.62 (1.43-9.12)
114.3/107.4	30	38	0.71 (0.25-1.97)	64	57	1.62 (0.67-3.95)	70	5.02 (1.99-12.64)
122.8/121.2	29	82	3.54 (1.32-9.46)	64	79	1.81 (0.70-4.67)	92	5.44 (2.08-14.27)
P for trend			0.03			0.35		<0.01
Saturated fat (g/day)								
32.1/29.9	30	41	Ref	64	42	Ref	31	Ref
38.7/36.4	30	52	1.91 (0.75-4.89)	64	42	0.91 (0.40-2.06)	28	1.02 (0.44-2.38)
46.6/42.1	30	49	1.25 (0.47-3.31)	64	59	1.34 (0.60-2.99)	65	1.62 (0.74-3.52)
54.8/53.8	29	77	2.79 (1.11-7.04)	64	77	1.07 (0.48-2.36)	100	2.41 (1.14-5.08)
P for trend			0.07			0.75		0.01
Monounsaturated fat (g/day)								
32.0/26.5	30	45	Ref	64	36	Ref	19	Ref
35.1/32.5	30	38	0.56 (0.22-1.46)	64	44	1.03 (0.45-2.38)	40	1.76 (0.73-4.25)
37.6/36.4	30	51	0.61 (0.23-1.62)	64	72	1.28 (0.55-3.01)	70	3.21 (1.30-7.96)
41.4/41.2	29	85	2.63 (1.01-6.86)	64	68	1.59 (0.64-3.96)	95	5.35 (2.14-13.34)
P for trend			0.10			0.28		<0.01
Polyunsaturated fat (g/day)								
12.1/10.6	30	53	Ref	64	59	Ref	43	Ref
15.3/13.5	30	51	1.48 (0.56-3.89)	64	47	0.85 (0.38-1.94)	64	1.29 (0.59-2.82)
20.3/16.5	30	59	1.01 (0.40-2.52)	64	50	1.27 (0.53-3.06)	67	2.68 (1.23-5.85)
27.7/24.8	29	56	1.69 (0.67-4.27)	64	64	0.94 (0.40-2.17)	50	1.60 (0.73-3.49)
P for trend			0.38			0.94		0.30
Cholesterol (mg/day)								
260.6/248.2	30	67	Ref	64	57	Ref	29	Ref

Dietary intake NI controls/all controls (median)	NI controls	RE		All controls	BE		EAC	
		No.	Adjusted OR (95% CI)[a]		No.	Adjusted OR (95% CI)[a]	No.	Adjusted OR (95% CI)[a]
329.1/317.1	30	47	0.69 (0.28-1.71)	64	40	0.66 (0.30-1.46)	30	1.42 (0.62-3.23)
374.5/363.3	30	46	0.60 (0.24-1.48)	64	37	0.75 (0.32-1.76)	41	1.63 (0.69-3.83)
484.7/462.3	29	59	1.20 (0.51-2.84)	64	86	1.54 (0.73-3.23)	124	3.59 (1.71-7.54)
P for trend			0.68			0.14		<0.01

Unconditional multiple logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence intervals (95%CI).

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; NI, Northern Ireland; RE, reflux esophagitis.

Fat and cholesterol intakes represent quartiles based on Northern Ireland controls for RE cases only, and all controls for BE and EAC cases.

[a]Risk estimates adjusted for age at interview, sex, smoking status (never, former, current), body mass index 5 years prior to interview date (kg/m^2), job type (manual, non-manual), education (years), energy intake (kcal), fruit intake (portions per day), vegetable intake (portions per day), alcohol intake (grams per day), *Helicobacter pylori* infection (seronegative, seropositive), nonsteroidal anti-inflammatory drug use 5 years prior to interview date (weekly use for 6 months or more), gastroesophageal reflux symptoms (yes, no), and location (Northern Ireland, Republic of Ireland) (for BE and EAC analyses only).

P for trend across quartiles is based on the median category values being assigned to each subject within quartiles and modeled as a continuous variable.

Table 3

Risk of reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma in relation to meat and fish intakes

Dietary intake NI controls/all controls (median)	NI controls	RE		All controls	BE		EAC	
		No.	Adjusted OR (95% CI)		No.	Adjusted OR (95% CI)	No.	Adjusted OR (95% CI)
Total meat (g/day)								
79.9/82.6	30	40	Ref	64	42	Ref	43	Ref
114.8/118.7	30	39	0.55 (0.19-1.60)	64	43	0.75 (0.32-1.76)	52	1.08 (0.49-2.39)
145.1/145.4	30	50	0.73 (0.27-2.02)	64	61	0.83 (0.37-1.88)	54	0.82 (0.37-1.82)
199.3/195.3	29	79	1.19 (0.44-3.25)	64	68	0.95 (0.43-2.08)	72	1.32 (0.63-2.78)
P for trend			0.31			0.92		0.44
Total red meat (g/day)								
50.4/54.7	30	46	Ref	64	47	Ref	44	Ref
85.2/87.6	30	37	0.45 (0.16-1.29)	64	43	0.69 (0.29-1.67)	44	0.41 (0.17-1.00)
115.0/113.4	30	50	0.43 (0.16-1.17)	64	52	0.91 (0.40-2.09)	60	1.34 (0.62-2.88)
166.3/161.1	29	75	1.07 (0.40-2.88)	64	72	1.09 (0.47-2.51)	73	1.18 (0.55-2.54)
P for trend			0.50			0.59		0.21
Fresh red meat (g/day)								
22.3/20.6	30	59	Ref	64	50	Ref	44	Ref
54.4/53.5	30	45	0.40 (0.14-1.09)	64	55	0.63 (0.28-1.43)	45	1.78 (0.76-4.19)
59.7/59.8	30	30	0.29 (0.11-0.81)	64	36	0.39 (0.16-0.94)	49	1.90 (0.80-4.50)
69.8/72.8	29	74	0.64 (0.24-1.68)	64	73	1.11 (0.50-2.46)	83	3.15 (1.38-7.20)
P for trend			0.17			0.77		0.01
White meat (g/day)								
8.8/8.6	30	43	Ref	64	53	Ref	56	Ref
18.8/18.7	30	65	1.83 (0.70-4.77)	64	67	1.21 (0.56-2.61)	68	0.93 (0.46-1.89)
54.9/54.8	30	58	1.17 (0.46-2.94)	64	52	0.68 (0.31-1.52)	57	0.70 (0.34-1.46)
56.7/56.5	29	42	0.66 (0.24-1.81)	64	42	0.56 (0.23-1.34)	40	0.51 (0.23-1.13)
P for trend			0.32			0.14		0.10
Processed meat (g/day)								
14.7/11.1	30	23	Ref	64	28	Ref	43	Ref

Dietary intake NI controls/all controls (median)	NI controls	RE		All controls	BE		EAC	
		No.	Adjusted OR (95% CI)		No.	Adjusted OR (95% CI)	No.	Adjusted OR (95% CI)
30.7/31.3	30	54	3.11 (1.09-8.83)	64	64	2.33 (0.97-5.59)	61	1.39 (0.64-3.04)
52.3/53.3	30	51	1.84 (0.67-5.05)	64	60	1.64 (0.70-3.85)	45	1.07 (0.50-2.27)
98.6/96.1	29	80	4.67 (1.71-12.74)	64	62	1.91 (0.81-4.49)	72	1.41 (0.67-2.95)
P for trend			0.01			0.40		0.49
Total fish (g/day)								
11.4/9.3	30	43	Ref	64	44	Ref	50	Ref
23.5/21.7	29	33	0.54 (0.19-1.50)	64	47	1.00 (0.44-2.28)	45	0.95 (0.44-2.08)
33.2/31.2	30	56	1.04 (0.38-2.81)	64	56	1.35 (0.61-3.00)	55	1.49 (0.70-3.18)
60.0/57.0	29	76	1.76 (0.68-4.52)	63	67	1.39 (0.62-3.11)	71	1.49 (0.72-3.10)
P for trend			0.06			0.35		0.20

Unconditional multiple logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence intervals (95%CI).

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; NI, Northern Ireland; RE, reflux esophagitis.

Meat and fish intakes represent quartiles based on Northern Ireland controls for RE cases only, and all controls for BE and EAC cases.

[a]Risk estimates adjusted for age at interview, sex, smoking status (never, former, current), body mass index 5 years prior to interview date (kg/m^2), job type (manual, non-manual), education (years), energy intake (kcal), fruit intake (portions per day), vegetable intake (portions per day), alcohol intake (grams per day), *Helicobacter pylori* infection (seronegative, seropositive), nonsteroidal anti-inflammatory drug use 5 years prior to interview date (weekly use for 6 months or more), gastroesophageal reflux symptoms (yes, no), and location (Northern Ireland, Republic of Ireland) (for BE and EAC analyses only). Risk estimates for each type of meat were adjusted for the intake of other types of meat such that the meat variables in each model added up to total meat intake. For example, red meat was adjusted for white meat, and processed meat was adjusted for nonprocessed meat.

P for trend across quartiles is based on the median category values being assigned to each subject within quartiles and modeled as a continuous variable.