Identifying genetic determinants of Familial Barrett*s esophagus and adenocarcinoma of the gastro-esophageal junction

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Ethical review	Not approved
Status	Will not start
Health condition type	Benign neoplasms gastrointestinal
Study type	Observational invasive

Summary

ID

NL-OMON41007

Source
ToetsingOnline

Brief title
IFAMBAR study

Condition

- Benign neoplasms gastrointestinal
- Gastrointestinal neoplasms malignant and unspecified

Synonym
adenocarcinoma of the gastro-esophageal junction, Barrett's esophagus

Research involving
Human

Sponsors and support

Primary sponsor: Maag-, Darm- en Leverziekten
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Adenocarcinoma, Barrett, Esophagus, Genetics

Outcome measures

Primary outcome

Determine the prevalence of BE among first degree relatives of index patients

of families that fulfil criteria for familial BE/adenocarcinoma of the GEJ

Determine the number and type of (pre) malignant lesions in first degree

relatives of index patients of families that fulfil criteria for familial

BE/adenocarcinoma of the GEJ

Secondary outcome

Not applicable

Study description

Background summary

Worldwide esophageal cancer is a significant and an increasing health problem. In 2005, there were 497,700 new cases, and the prevalence is expected to increase by approximately 140% by 2025. Esophageal adenocarcinoma (EAC) account for most cases of esophageal cancer in the Western world. Most esophageal adenocarcinomas arise at the gastro-esophageal junction (GEJ) and are thought to arise from Barrett*s epithelium, which is characterized by columnar metaplasia with intestinal differentiation that has replaced the normal squamous cell lining of the esophagus. Environmental factors as gastro-esophageal reflux disease (GERD) and smoking contribute to chronic inflammation, which promotes the transition from normal squamous cell epithelium towards Barrett*s epithelium and ultimately leads to adenocarcinoma.

Circumstantial evidence on the role of genetics is provided by familial clustering of BE and adenocarcinoma of the GEJ in certain families. Identifying these families could be useful to study the exact phenotype of hereditary Barrett*s esophagus (BE)/ adenocarcinoma of the GEJ and could be the key to the identification of causal gene defects that underlie this condition. In the current study we will explore the phenotype in families with multiple cases of BE and EAC which enables genetic analysis in the near future aiming at identifying putative susceptibility genes. Furthermore, it should allow (more tailored) screening recommendations for relatives at increased risk.

Study objective

The main goals of this study
1) To determine the prevalence of BE among first degree relatives of index patients in families that fulfil criteria for familial BE/adenocarcinoma of the GEJ
2) Collect tissues of the index patients and all first degree relatives (blood or formalin fixed and paraffin embedded tissue) for genetic analyses in the near future
3) Explore the phenotype of familial BE and adenocarcinoma of the GEJ

Study design

In a collaborative effort (with the Departments of Surgery and Medical Genetics) we identified 20 families that met the criteria for familial BE or adenocarcinoma of the GEJ.

Recruitment of the index patients
To ensure that only patients that are alive at baseline will be contacted, data on vital status of these patients will obtained from the death register of the Municipal Personal Records Database, which registers all deceased in the Netherlands via the municipal civil registries. To ensure that only patients that are alive at baseline will be contacted, data on vital status of these patients will obtained from the death register of the Municipal Personal Records Database, which registers all deceased in the Netherlands via the municipal civil registries. The index patients from families meeting our inclusion criteria will be invited to participate in this study by their treating physician (surgeon, gastroenterologist, medical geneticist). If the index patient is interested, he/she will receive an information letter. Within one or two weeks, the patient will be contacted by telephone, by the researcher. If the index patient is interested, he or she will be invited to visit the outpatient clinic of the department of Gastroenterology. The patient will receive together with a written confirmation of their outpatient clinic visit, the *Barrett Esophagus* questionnaire, by mail. In one part of the questionnaire, the patient is asked to fill in the contact information about their first degree relatives (elder, siblings and children). At the outpatient

clinic, the study designs and implications will be discussed, and remaining questions will be answered. If the patient is willing to participate, he/she will be asked to sign the informed consent form, to sign the biobank form and to provide the filled in *Barrett Esophagus* questionnaire. Directly after the outpatient clinic visit, an experienced research nurse will take one blood sample by venipuncture. This blood sample will be stored at the Central Biobank at the UMC Utrecht and will be used in the next future for DNA research. After informed consent, the first degree relatives will be invited for the study.
If the index patient is deceased, a first degree relative (in order of partner, children or siblings) will be contacted, by the treating physician of the deceased index patient (surgeon, gastroenterologist, medical geneticist). If the individual is interested, he/she will receive an information letter and will be contacted by telephone. If the individual is still interested, he/she will be invited for an outpatient clinic visit to the department of Gastroenterology. The individual will receive together with a written confirmation of their outpatient clinic visit, the *Barrett Esophagus* questionnaire, by mail. He or she will be asked to fill in the part of the questionnaire that is about the contact information about the first degree relatives (elders, siblings and children). He or she will receive a written confirmation of their outpatient clinic visit. If the patient is willing to participate, he/she will be asked to sign the informed consent and to provide the filled in *Barrett Esophagus* questionnaire. After informed consent, the first degree relatives will be invited for the study.

Recruitment of first degree relatives
All first degree individuals (alive and between 25 and 75 years old) will receive an recruitment letter with a reply coupon on which they can indicate whether they are interested in participating in this study. In case the first degree relative is interested (thus reply their response form and indicate that they are interested) , the study information and biobank information letter will be sent. Within two weeks after receiving these letters, the individual will be contacted by telephone. During this telephone consult, question of individuals will be answered and (when applicable) the possibility of sedation during the endoscopy will be discussed. If the individual underwent a duodenoscopy in the past five years, he/she will be invited for an outpatient clinic visit. Together with the written invitation to the outpatient clinic of the department of Gastroenterology the individual will also receive the *Barrett Esophagus* questionnaire. At the outpatient clinic remaining questions will be answered. If the patient is willing to participate, he/she will be asked to sign the informed consent form, to sign the biobank form and to provide the filled in *Barrett Esophagus* questionnaire. Directly after the outpatient clinic visit, an experienced research nurse will take one blood sample by venipuncture.
When the individual had no prior duodenoscopy or more than five years ago, he/she will be invited for a duodenoscopy at the endoscopy unit of the department of Gastroenterology. Together with the written invitation for the duodenoscopy, the individual will also receive the *Barrett Esophagus*

questionnaire. At the endoscopy unit, prior to endoscopy or venipunture, the individuals will be asked to sign the study informed consent form, the biobank form and to provide the filled in *Barrett Esophagus* questionnaire. At the endoscopy unit the venipuncture will be carried out by an experienced research nurse. After the duodenoscopy he/she (if preferred) will be informed directly by the endoscopist about the findings. If biopsies are taken, the individual will be invited for an outpatient clinic visit within two weeks to discuss the pathological findings and further treatment.
If a first degree relative is deceased, the index patient will be asked permission to obtain the medical record of the involved institution and permission to check the PALGA database to search for (pre)malignant lesions and if available to obtain tissue for DNA studies in the near future.

All individuals, index patients en first degree relatives, are asked permission to check the PALGA database if patients are known with other (pre)malignant lesions. This PALGA search will be repeated over 10 years.

Study burden and risks

For the index patient the burden consists of filling in the Barrett questionnaire, one visit to the outpatient clinic and donation of one tube of blood. This all together will take approximately 60 minutes and one extra hospital visit.
For first degree family members the burden consists of filling in the Barrett questionnaire, one telephone call, a duodenoscopy and donation of two tubes of blood. This all together will take approximately 60 minutes, and one extra hospital visit.

Venipuncture is a safe routine procedure and will be performed conform the standard protocol. In approximately 10% of the venipunctures a hematoma may develop, which heal scar less within a couple of days. Other complication such as syncope and diaphoresis occur seldom. A duodenoscopy is considered as a safe procedure. Complications are rare during and after upper endoscopy under local anesthesia (1-2:1000 patients). The most common complain after the procedure is a sore throat. Major complications such as an upper gastrointestinal bleeding and perforation are rare (0.1% and 0.0001%, respectively).

The potential benefits for the participating individuals is early detection of a BE. This premalignant requires treatment with a protonpomp inhibitor and follow-up which will be done accordig the Dutch guidelines for BE.

Contacts

Public

Selecteer

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

As described earlier, we identified in a collaborative effort (with the Departments of Surgery and Medical Genetics) 20 index patients from families that fulfill the criteria for familial BE or adenocarcinoma of the GEJ. Apart from the retrospectively identified index patient, new index patients identified during this study by the department of Medical Genetics will also be eligible for this study,;The criteria for familial BE or adenocarcinoma of the GEJ:
A. Two or more first- or second degree relatives with BE or adenocarcinoma of the GEJ, with at least one diagnosed before the age of 50
B. Three or more first- or second degree relatives with BE or adenocarcinoma of the GEJ, irrespective of age
C. One patient with BE or adenocarcinoma of the GEJ < 40 yrs;For this study, individuals that meet the following inclusion criteria are eligible:
All first degree relatives (i.e. sons, daughters, sisters, brothers and father and mother of the index patient) of the index patient

Exclusion criteria

A potential individual who meets any of the following criteria will be excluded from participation in this study:
1) Individuals < 25 and > 75 years old
2) Unable to fill out questionnaire

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	60
Type:	Anticipated

Ethics review

Not approved

Date:	02-09-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL47860.041.14