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Inter-individual variation in susceptibility to colorectal neoplasia: the interaction between diet, DNA damage markers and genetic polymorphisms.

Submission date 23/01/2004	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 23/01/2004	**Overall study status** Completed	
Last Edited 02/10/2012	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N0499010351; Watson HSR/06/97

Study information

Scientific Title

Study objectives
CRC risk is affected by diet and by genetic polymorphisms leading to inter-individual variation in the metabolism of environmental carcinogens. Our first hypothesis is that these effects may combine to place certain individuals at greatly enhanced risk according to their diet. We shall examine how dietary factors known to affect CRC risk (including meats, fat, fruit and vegetables, cooking methods, dietary supplements and drugs) and genetic polymorphisms implicated in CRC (Glutathione S-transferase: GSTM1, GSTM3, GSTT1; N-acetyl transferase: NAT1, NAT2; and Cytochrome P450: CYP1A1, CYP2D6) combine to affect the prevalence of colorectal polyps, both adenomatous (the precursor lesion of CRC) and metaplastic.
Our second hypothesis is that diets associated with increased risk (high red meat, low vegetable and low fibre consumption) may affect DNA damage markers which may be elevated in people with colorectal adenomas.
We shall therefore examine the effect of diet on adduct rates (cross sectional) and adduct rates in people with and without colorectal adenomas. We shall examine malondialdehyde adduct rates in relation to anti-oxidant status and carboxymethyl adduct rates and k-ras mutation frequency in relation to meat consumption; and examine the effect of DNA repair enzyme (ATase) activity on any relationship found. In summary the aim of this population based study is to link dietary factors thought to be important in the genesis of colorectal polyps and cancer with genetic polymorphisms and DNA damage markers in rectal mucosa and in blood.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Not Specified

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Colorectal cancer

Interventions
The first arm involves volunteers common to both EPIC and Flexi-Scope studies. We shall study people with adenomatous polyps and matched controls only. The prospectively collected accurate dietary data collected within EPIC is favoured for analyses of diet and DNA damage markers. In those EPIC participants who have polyps (est. 100 adenomatous and 100 metaplastic) a peripheral blood sample will be taken for genotyping and malondialdehyde (MDA) adduct assay: and rectal biopsies for MDA and CBM adduct assay, ATase activity and k-ras mutation frequency. Polyp free age/sex/GP practice/race matched controls (est.100) will be identified for each subject with adenomatous polyps and the same samples collected.
The second arm involves non-EPIC participants (est. total 2000) and in these people dietary data will be collected by food frequency questionnaire compatible with that used within EPIC (and validated within EPIC).
We shall study people with adenomatous and metaplastic polyps and matched controls. This arm of the study will also be conducted in parallel in the Leeds and Portsmouth centres of the Flexi-Scope Trial permitting greater sample sizes and a diverse sample population. A peripheral blood sample will be taken from people with polyps (total 400 in Norwich, 200 adenomatous and 200 metaplastic) for genotyping. Matched polyp free controls will be identified for each person with adenomatous polyps (200).
Data from the Flexi-Scope trial is collected and processed on an EpiInfo (Version 6.0) database and data from this study will be incorporated within this. The food questionnaire will be scanned and processed within the Flexi-Scope Trial. DNA isolation will be performed by Mr Watson in Norwich. Genetic analysis and k-ras mutation frequency will be performed by Dr Alex Loktionov (MRC Dunn Clinical Nutrition Centre, Cambridge) using accepted techniques already running in that laboratory. DNA adduct assays will be performed by Dr Chiara Leuratti (MRC Toxicology Unit, Univ. of Leicester) by techniques established in that laboratory and adapted for colonic biopsies in a recent pilot study. DNA repair enzyme will be assayed by Dr Geoff Margison (Paterson Institute, Manchester) by accepted techniques currently running in that laboratory. Rarely do two large multi-centre studies such as the EPIC study and the Flexi-Scope Trial overlap in terms of the population studied. This overlap affords us an opportunity to conduct this research which would be difficult and costly to recreate.

As of 10/08/09 the start and end dates of this trial were updated from 01/07/97 and 01/07/99 to 01/08/97 and 01/02/2000 respectively. The initial dates were generated at the time of registration.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
We shall perform cross-sectional and case-control analyses of the effect of diet and genetic polymorphisms on the prevalence of adenomatous and metaplastic polyps. Genetic polymorphisms will be examined in isolation and paired combinations and in groups stratified

according to diet. We shall examine the effect of diet on MDA adduct rates (concentrating on foods relating to anti-oxidant status) and CBM adduct rates and k-ras mutations (concentrating on meat consumption and cooking methods) by categorical variables; and MDA and CBM adducts and k-ras mutation frequency in people with adenomatous polyps and polyp free controls (case-control). We shall examine the affect of ATase activity on any relationship found and ATase activity in people with adenomatous polyps and polyp free controls (case control). DNA will be stored for future analysis of as yet unrecognised polymorphisms which may be recognised as having a role in CRC. Samples taken from EPIC participants for adduct, ATase and k-ras measurement whose polyps are found to be metaplastic will be stored for possible future analysis: we shall investigate people with adenomatous polyps in the first instance as these are the precursors of colorectal cancer.

Secondary outcome measures
Not provided at time of registration

Overall study start date
01/08/1997

Completion date
01/02/2000

Eligibility

Key inclusion criteria
All people (male and female) randomised to the screening arm of the Flexi-scope Trial will be invited to participate in this study. General practioners are initially approached and if they agree to take part in the Flexi-Scope Trial all patients aged 55-64 are contacted by questionnaire to declare interest in that study.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Not provided at time of registration

Key exclusion criteria
1. People unable to provide informed consent.
2. People with a history of colorectal cancer, adenomatous polyps or inflammatory bowel disease.
3. People with severe or terminal disease, with life expectancy of less than 5 years.
4. People with a recent history of sigmoidoscopy or colonoscopy (within 2 years).
5. People unfit for flexible sigmoidoscopy.

Date of first enrolment

01/08/1997

Date of final enrolment
01/02/2000

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Norfolk and Norwich Health Care NHS Trust
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Sponsor information

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NHS R&D Regional Programme Register - Department of Health (UK)

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Sponsor type
Government

Website
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Funder(s)

Funder type
Government

Funder Name
NHS Executive Eastern (UK) (ref: RCC56354)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/03/2002		Yes	No