Identification of predictors of CRC development in MMR mutation carriers under colonoscopy surveillance

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Background

Mutation carriers in Lynch syndrome families have a high risk for developing colorectal cancer during their lifetime. Colonoscopy screening and surveillance every <3 years decreases incidence and mortality of CRC. However, up to 40% of patients in during colonoscopy follow-up develop a CRC. Although the impact in mortality seems to be low, it is crucial to identify the factors that predict CRC development in this setting to further improve prevention in LS.

Aim

This study is designed to assess the clinic-pathological, genetic and endoscopic factors that predict the development of CRC during colonoscopy surveillance in LS mutation carriers.

Patients and Methods

Patients: Mismatch repair gene mutation carriers diagnosed of Lynch syndrome undergoing colonoscopy surveillance-screening. Study participants under screening-surveillance program and who underwent at least 1 surveillance colonoscopy will be included in the analysis. Patients will be stratified according to the previous development of CRC:

a) Patients without CRC at inclusion colonoscopy surveillance date or in the first year of screening.
b) Patients with a CRC prior to colonoscopy surveillance. Information about the type of surgery will be collected.

Methods: We propose the use of an online tool as Research Electronic Data Capture (REDCap). Cumulative risk for the development of colorectal adenoma or carcinoma in prospective colonoscopic surveillance will be calculated. Evaluation of the following variables in relation to adenoma and CRC formation: demographic, genetic (gene mutated), compliance with the interval between colonoscopies, colonoscopy characteristics (quality indicators) and endoscopy findings. The methods that will be used for the analysis comprise a variety of panel data or longitudinal data models, the structure of the data will be unbalanced because of the nature of the sources and different specifications will be carried on comprising, linear probability models with either random or fixed-effects, conditional logit/fixed effects logit, LASSO models and support vector machines SVM. All models will be calibrated and cross-validated with a 10-k fold approach. The aim of the enumerated methods can be described in two simple points, the first is to understand the underlying mechanisms that are associated

with the appearance of CRC and the second is to have solid and accurate predictions for individual risk-assessment.

Variables:

General information:

1. Ascertainment: CRC, other cancer, family history of mutation, family history of cancer with unknown mutation.
2. Sex
3. Date of birth
4. Gene
5. Mutation
6. Date/Age inclusion: first prospectively planned colonoscopy under LS diagnosis
7. Date/Age last observation
8. Date/Age death
9. Cause of death
10. Family tree
11. Cancer information:
    - Age cancer diagnosis
    - Type of cancer
    - Histopathology
    - Vascular, lymphatic invasion
    - TNM and stage of cancer
    - Treatment:
        - Type surgery
        - Chemotherapy
        - Radiotherapy
    - Organectomy: age, organ, reason (cancer/prophylactic)

Clinic-pathological data:

1. Race
2. Geographic distribution (postal code – country of birth)
3. BMI (at CRC diagnosis and at beginning of screening)
4. Smoking (at CRC and at beginning of screening)
5. Alcohol consumption habit (at CRC and at beginning of screening)
6. ASA consumption
7. Cardiovascular risk factors (diabetes, hypertension, cholesterol: drug intake)

Endoscopic quality indicators and findings: collect data per colonoscopy and per polyp
1. Date of colonoscopy
2. Type of colonoscopy: conventional or high definition
3. Bowel preparation: descriptive/Boston scale per segment/not indicated
4. Cecal intubation: yes/no
5. Enhancement techniques: yes/no
    a. Chromoendoscopy with stains / Digital chromoendoscopy.

b. Extension of the technique: complete or partial

6. Withdrawal time (min)

7. Polyp detection rate from the endoscopist who performed the colonoscopy

8. Results:

    a. Total number of polyps

    b. Total number of resected polyps

    c. Total number of polyps retrieved

    d. Results: collect the information per polyp

        i. <u>Adenoma:</u> location (rectum, sigma, transverse colon, ascending or cecum), dysplasia (high grade, low grade), villous component, size (mm), morphology (Paris classification).

        ii. <u>Serrated polyps:</u> type (hyperplastic, sessile serrated adenoma, traditional serrated adenoma), dysplasia (yes/no), size (mm), morphology (Paris classification).

        iii. <u>Cancer:</u> location, histopathologic features, endoscopic size and TNM stage.

References:

1. Järvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 2000;118:829–834

2. Hampel, Heather, MS; Frankel, Wendy L, MD; Martin, Edward, MD; Arnold,Mark, MD; Khanduja, Karamjit, MD; et al. Screening for the Lynch Syndrome: Hereditary nonpolyposis colorectal cancer. The New England Journal of Medicine; May 2005: 1851-60.

3. De Jong AE, Hendriks YMC, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology. 2006;130:665–671

4. Jukka–Pekka Mecklin, Markku Aarnio, Esa Läärä, Matti V. Kairaluoma, Kirsi Pylvänäinen,Päivi Peltomäki, Lauri A. Aaltonen, Heikki J Järvinen. Development of Colorectal Tumors in Colonoscopic Surveillance in Lynch Syndrome. Gastroenterology 2007, 133:1093–1098

5. Pal Moller, Toni Seppala, Inge Bernstein, Elke Hollinski-Feder et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 2015 Dec 9.