Associations between symptoms and colorectal cancer outcome in GP/hospital e-referrals

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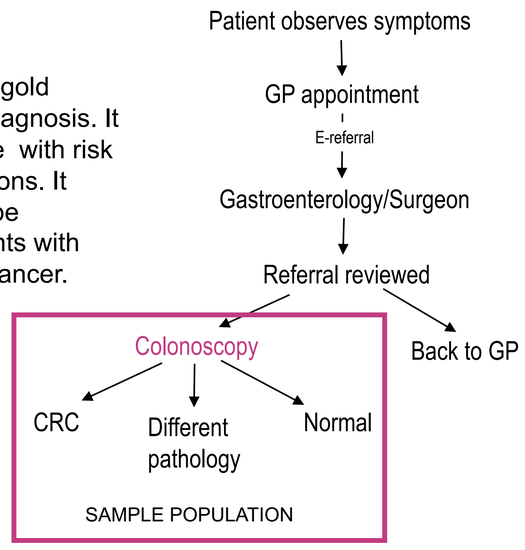
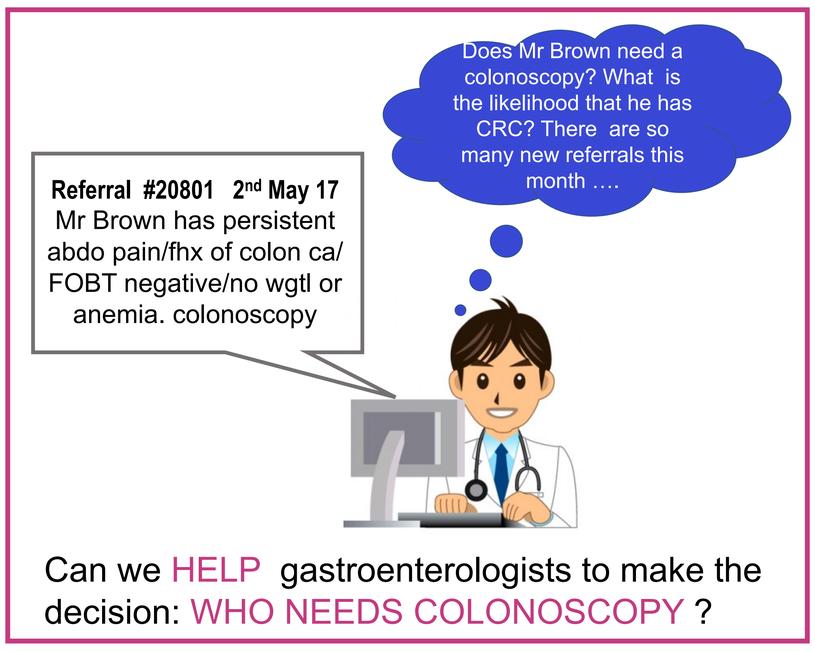
Background

Colorectal cancer (CRC) is second leading cause of cancer related deaths in the Western world. Survival depends largely on the stage of the disease at diagnosis. Early diagnosis can be challenging. The ideal pathway can be summarized as follows:



Colonoscopy is the gold standard in CRC diagnosis. It is a limited resource with risk of health complications. It should, therefore, be performed on patients with high probability of cancer.

Gastroenterologists, as suggested in many practice guidelines, make the decision based on bowel symptoms



Can we HELP gastroenterologists to make the decision: WHO NEEDS COLONOSCOPY ?

- the evidence for the accuracy of symptoms for CRC detection is conflicting[1]. It can be due to the change of perception of symptoms in recent years, differences in study designs, studied population or the lack of universally used reference standards for CRC diagnoses
- single symptoms have low predictive values but the accuracy improves when combination of symptoms, demographics, test results and comorbidities are included[2]
- statistical models and risk assessment tools were developed and presented previously. Their accuracy for prediction of CRC risk has been shown to be better than selection of patients for colonoscopy based on existing guidelines[3]

However, according to our knowledge the predictive accuracy of symptoms were not studied in New Zealand patients before. The demands for colonoscopies are increasing and the number of negative colonoscopies performed each year is high. The choice of patients with highest risk of CRC is beneficial for patients and for the health services providers.

Study aim: In this study therefore, we investigated the associations between symptoms and colorectal cancer in NZ patients

***Abbreviations**
AIC: Akaike's Information Criterion
ROC: Receiver Operating Characteristic
AUC: Area Under the ROC Curve
abd: abdomen

Acknowledgement
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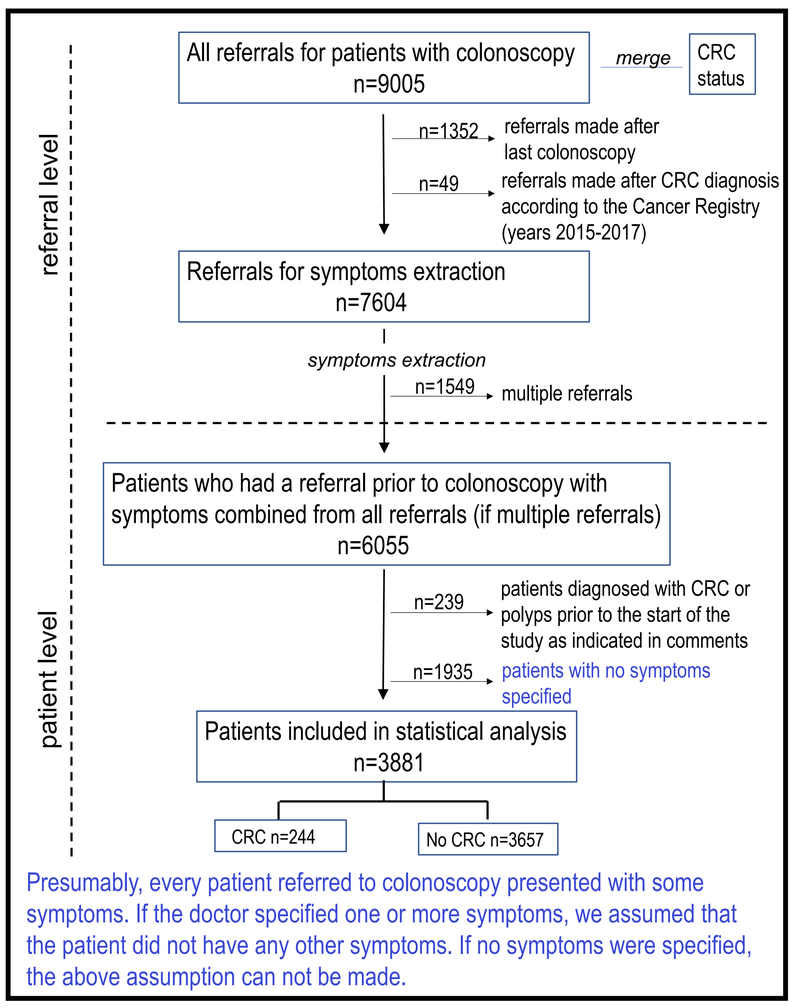
References
[1]Adelstein et al. (2010) Alimentary Pharmacology and Therapeutics
[2]Adelstein et al. (2011) BMC Gastroenterology
[3]Williams et al. (2016) BMC Gastroenterology
[4]Camp & Slattery (2002) Cancer Causes and Control

Methods

Data: referrals made to the gastroenterology and general surgery departments in Waikato Hospital and NZ Cancer Registry data from 1/01/2015-31/12/2017

Participants: patients 18+ years old, who had performed colonoscopy, had at least one referral made before colonoscopy and had at least one symptom relevant to CRC, specified in the referrals. Patients with CRC diagnosis or known polyps prior to their first referral were excluded from the study.

Figure 1. Preparation of the cohort for statistical analysis



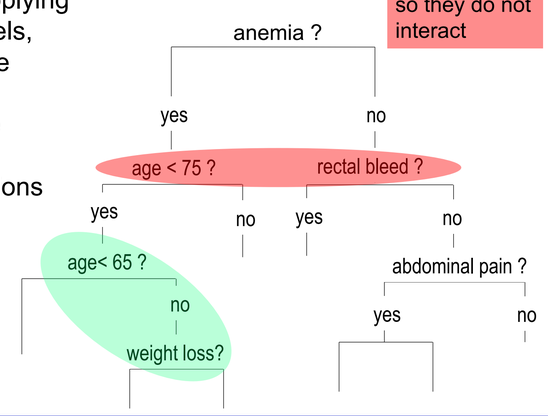
Presumably, every patient referred to colonoscopy presented with some symptoms. If the doctor specified one or more symptoms, we assumed that the patient did not have any other symptoms. If no symptoms were specified, the above assumption can not be made.

Statistical analysis

Symptoms were extracted from free-text notes included in referrals, using automated extraction based on words and phrases used by doctors to describe the symptoms presented by patients. Logistic regression models with CRC as response variable was fitted in the following steps:

- the initial model with all symptoms, demographics and test results was simplified using backward elimination (minimizing AIC*)
- interaction terms were added to the initial model which was subsequently simplified
- each model was cross validated using 224 folds (a fold = 1 CRC case and 16/17 random controls)
- ROC* curves was constructed and the AUC* calculated for the validated models
- the final model was selected based on AUC

Interaction terms were chosen based on a regression tree. It has been suggested that interactions may be very important when predicting cancer risk[4]. To identify interaction terms five regression trees, using the same set of variables as in the initial logistic model but applying different pruning levels, were fitted. Each tree was cross validated and the tree with the highest AUC was Selected for interactions identification.



Results

- 96% of patients had all symptoms specified in comments correctly classified
- most patients with errors had only one wrongly classified symptom
- 3881 patients were eligible for statistical analysis
- the prevalence of cancer in our cohort was 5.8%
- the cohort included in the analysis was representative of the population of patients who had colonoscopy except that the proportion of patients referred from Emergency Department is ~ 14 times higher in those without symptoms specified

Table 1. Demographics for patients with presented symptoms (included in the analysis) and without specified symptoms

	Patients with symptoms		Patients without symptoms n=1935
	all n=3881	CRC n=224	
Median age (IQR)	63 (51; 72)	71 (65; 80)	62 (51; 71)
% male	42.3	54	46.8
% Maori	10.6	10.2	11.0
% CRC	5.8	-	6.2
% Emergency	1.2	0.4	17.5

The final model contained only main effects. Adding interaction terms did not improve the predictive accuracy of the model.

Table 2. Model selection

Model	Variables or interaction left in the model	AUC (SE)	AIC
1: regression tree	all symptoms	0.675 (0.020)	-
2: model with interactions from tree + all symptoms (reduced)	interactions: rectal bleed: mass in abd*, anemia: mass in abd, age: mass in abd, anemia: age main terms: sex, pain in abd, lack of appetite, weight loss	0.776 (0.015)	1499.3
3: reduced model, without interactions	abdominal pain, weight loss, rectal bleed, lac of appetite, mass in abdomen, sex, age, anemia	0.776 (0.015)	1504.5
4: model with plausible interactions	mod 3 + anemia: sex: age, rectal bleed: hemorrhoids	0.771 (0.015)	1507.8

Other things being equal, patients with:

- anemia had about three times higher odds of having CRC than patients without anemia (OR 3.1, 95% CI 2.3; 4,2)
- rectal bleeding had nearly twice higher odds of CRC than those without (OR 1.9, 95% CI 1.4; 2,5)
- weight loss had higher odds of detecting CRC (OR 1.7, 95% CI 1.1; 2.5)
- mass in abdomen or rectum had 3.6 times higher odds of CRC (95% CI 1.8; 7.0)

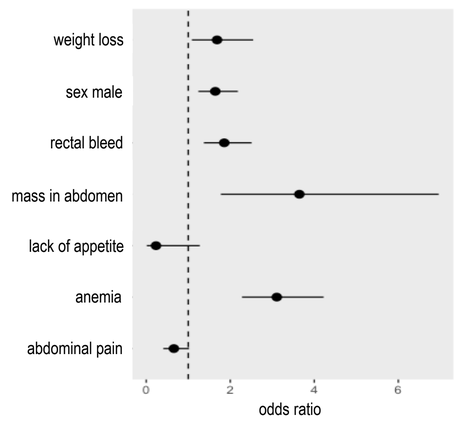


Figure 2. Associations between symptoms and CRC risk in patients with a symptom, compared to those without the symptom from the final multivariable logistic regression model adjusted for age, sex, comorbidities and ethnicity presented as OR with 95% CIs

According to our final model (model 3 in Table 2), if colonoscopy was performed only on the 60% of patients with the highest risk of CRC, 93% of CRCs would still be detected. To detect over 98% of cancers would be enough to perform 80% of the colonoscopies. In this case, in our study, four cases out of 224 would not have been diagnosed.

Discussion

All symptoms were binary and we did not distinguish between degrees, frequency and the duration of any symptom. This information was not specified in the comments for many patients. The study was affected by minimal selection bias. The results are difficult to compare with earlier studies in which the symptoms were recorded systematically using a questionnaires but predictive power of our model is only slightly worse than the power of the model fitted in an Australian study which predicted 95% of the cancers when giving colonoscopy to only 60% of patients included in their study[1].