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Beyond Positive vs. Negative: Cumulative fecal Hb level for risk prediction

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No conflict of interest to declare

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Background

Established programs are routinely using the quantitative information of FIT result to classify screenees based on a pre-defined positivity cut-off.

The threshold for defining a positive test varies between countries (ranging between 15 and 120 µg f-Hb/gr. faeces), to match local endoscopy capacity

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Background

There is increasing evidence that f-Hb concentration among people with a FIT result below the positivity threshold is a good predictor of future diagnosis of advanced neoplasia (AN).

Several studies analyzed the predictive value of a single test result

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DR at subsequent round

by f-Hb level at previous round

Strong association of f-Hb levels at previous round with the DR of CRC and advanced adenoma at subsequent round

Low-risk of AN at subsequent round for screenees with f-Hb level below the detectability threshold of the method

(Eiken OC Sensor; FOB-Gold; HM JackArc)

Digby J et al. JMS 2017
Gibson DJ, et al Gastroint Endoscopy 2019
Ribe SG et al. IJC 2022

maintained even among subjects with screening interval extended up to 3.5 years

Ribe SG et al. IJC 2022

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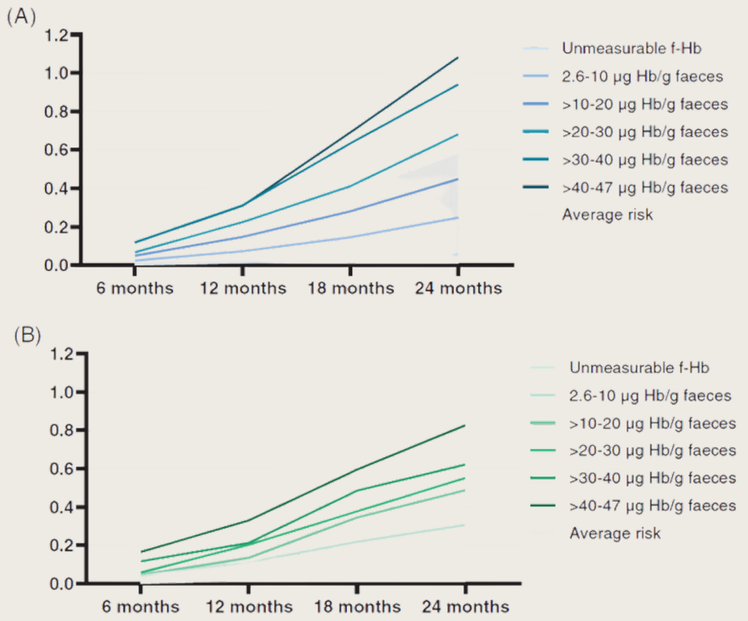
IC risk
by f-Hb level at previous round



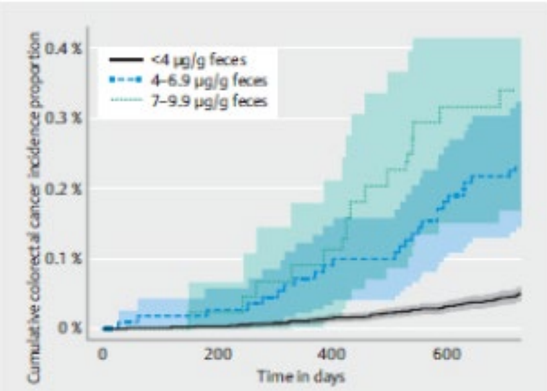
(A) Probability of detecting interval CRCs after the first round by subgroups of f-Hb concentrations.

(B) Probability of detecting interval CRCs after the second round by subgroups of f-Hb concentrations.

Breekveldt ECH, et al. IJC 2023

Plantener E, et al. Endoscopy Int Open 2022

		2-year follow-up		3-year follow-up	
FIT value (µg/g feces)	Individuals (%) (n = 121,855)	CRC (%) (n = 83)	HR (95 % CI)	CRC (%) (n = 173)	HR (95 % CI)
<4	113,328 (93.0)	56 (0.05)	Ref	135 (0.12)	Ref
4–6.9	5,918 (4.9)	16 (0.27)	4.617[1] (2.64;8.07)	25 (0.42)	3.017[1] (1.97;4.63)
7–9.9	2,609 (2.1)	11 (0.42)	6.970[1] (3.64;13.33)	13 (0.5)	3.451[1] (1.95;6.10)
Total	121,855	83 (0.07)		173 (0.14)	



▶ **Fig. 2** Cumulative incidence proportion with 95% confidence intervals of interval cancers in individuals having a FIT value < 10 µg/g feces within the next screening round.

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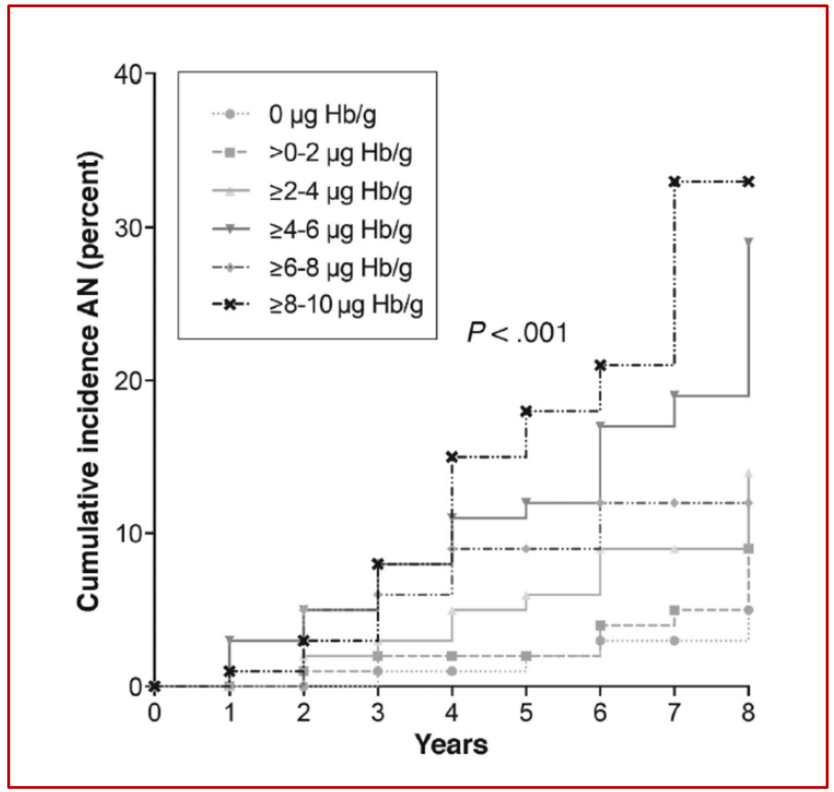
Association Between Concentrations of Hemoglobin Determined by Fecal Immunochemical Tests and Long-term Development of Advanced Colorectal Neoplasia

Esmée J. Grobbee,[1] Eline H. Schreuders,[1] Bettina E. Hansen,[1] Marco J. Bruno,[1] Iris Lansdorp-Vogelaar,[2] Manon C. W. Spaander,[1] and Ernst J. Kuipers[1]

Gastroenterology 2017; 153:1251-1259

Screenees with a f-Hb level between **8 and 10 µg** Hb/g **8-fold higher cumulative incidence of AN** after 5-year follow-up than screenees with a f-Hb concentration of **0 mg Hb/g.**



Life table and curve for AN by f-Hb level per 2µg Hb/g.

	Advanced Neoplasia		
	Multivariate		
	OR	95% CI	*P* value
Gender (*female*)	2.1	1.3–3.2	.001
Age (*y*)	1.0	1.0–1.1	.04
Combination of first and second $_f$Hb concentration			
0 µg Hb/g and 0 µg Hb/g	Ref.		<.001
1 µg Hb/g and 1 µg Hb/g	1.7	1.5–1.9	
1 µg Hb/g and 5 µg Hb/g	4.4	3.1–6.3	
5 µg Hb/g and 1 µg Hb/g	4.5	3.1–6.6	
5 µg Hb/g and 5 µg Hb/g	7.8	4.6–13.3	
1 µg Hb/g and 8 µg Hb/g	9.0	5.2–15.6	
8 µg Hb/g and 8 µg Hb/g	14.3	4.8–42.3	

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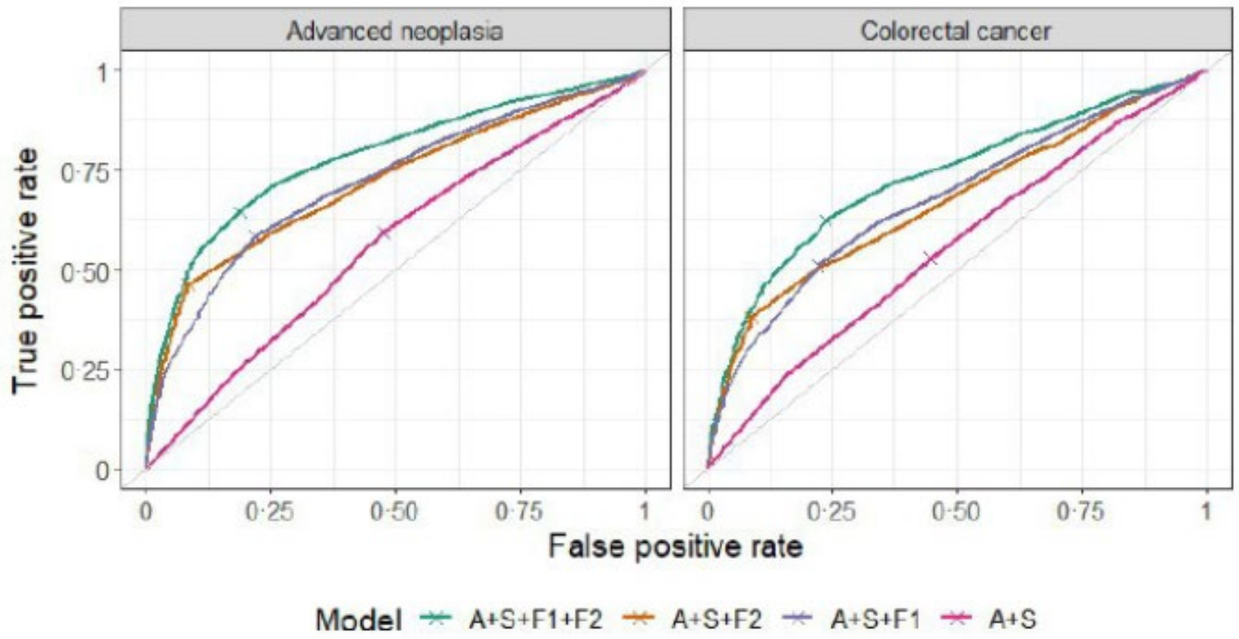
Combining results of two consecutive FIT exams

Faecal occult blood loss accurately predicts future detection of colorectal cancer. A prognostic model

Reinier G S Meester ,[1] Hilliene J van de Schootbrugge-Vandermeer,[1] Emilie C H Breekveldt ,[1] Lucie de Jonge ,[1] Esther Toes-Zoutendijk ,[1] Arthur Kooyker ,[1] Daan Nieboer,[1] Christian R Ramakers,[2] Manon C W Spaander ,[3] Anneke J van Vuuren,[3] Ernst J Kuipers ,[3] Folkert J van Kemenade,[4] Iris D Nagtegaal,[5] Evelien Dekker ,[6] Monique E van Leerdam ,[7,8] Iris Lansdorp-Vogelaar ,[1] the Dutch colorectal cancer screening working group



Receiver operating characteristic curves for predicted faecal immunochemical test (FIT) screening outcomes.

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.. how do we measure (classify) negative FIT results from previous rounds in order to best assess the risk of CRC and AN?

GI cancer

ORIGINAL ARTICLE

Faecal haemoglobin concentration among subjects with negative FIT results is associated with the detection rate of neoplasia at subsequent rounds: a prospective study in the context of population based screening programmes in Italy

Carlo Senore,[*1] Marco Zappa,[2] Cinzia Campari,[3] Sergio Crotta,[4] Paola Armaroli,[1] Arrigo Arrigoni,[5] Paola Cassoni,[6] Rossana Colla,[7] Mario Fracchia,[8] Fabrizio Gili,[9] Grazia Grazzini,[10] Roberto Lolli,[11] Patrizia Menozzi,[7] Lorenzo Orione,[12] Salvatore Polizzi,[13] Stefano Rapi,[14] Emilia Riggi,[1] Tiziana Rubeca,[12] Romano Sassatelli,[15] Carmen Visioli,[4] Nereo Segnan[1]

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For numbered affiliations see end of article.

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ABSTRACT

Objective To estimate the predictive role of faecal haemoglobin (f-Hb) concentration among subjects with faecal immunochemical test (FIT) results below the positivity cut-off for the subsequent risk of advanced neoplasia (AN: colorectal cancer—CRC—or advanced adenoma).

Design Prospective cohort of subjects aged 50–69 years, undergoing their first FIT between 1 January 2004 and 31 December 2010 in four population-based programmes in Italy.

Methods All programmes adopted the same analytical procedure (OC Sensor, Eiken Japan), performed every 2 years, on a single sample, with the same positivity cut-off (20 µg Hb/g faeces). We assessed the AN risk at subsequent exams, the cumulative AN detection rate (DR) over the 4-year period following the second FIT and the interval CRC (IC) risk following two negative FITs by cumulative amount of f-Hb concentration over two consecutive negative FITs, using multivariable logistic regression models and the Kaplan-Meier method.

Results The cumulative probability of a positive FIT result over the subsequent two rounds ranged between 7.8% (95% CI 7.5 to 8.2) for subjects with undetectable f-Hb at the initial two tests (50% of the screenees) and 48.4% (95% CI 44.0 to 53.0) among those (0.7% of the screenees) with a cumulative f-Hb concentration ≥20 µg/g faeces. The corresponding figures for cumulative DR were: 1.4% (95% CI 1.3 to 1.6) and 25.5% (95% CI 21.4 to 30.2) for AN; 0.17% (95% CI 0.12 to 0.23) and 4.5% (95% CI 2.8 to 7.1) for CRC. IC risk was also associated with cumulative f-Hb levels.

Conclusion The association of cumulative f-Hb concentration with subsequent AN and IC risk may allow to design tailored strategies to optimise the utilisation of endoscopy resources: subjects with cumulative f-Hb concentration ≥20 µg/g faeces over two negative tests could be referred immediately for total colonoscopy (TC), while screening interval might be extended for those with undetectable f-Hb.

Significance of this study

What is already known about this subject?
► A correlation of faecal haemoglobin (f-Hb) concentration at first screening tests with the subsequent risk of colorectal cancer (CRC) and advanced adenomas (AAs), has been documented. Two studies also shown an association of cumulative f-Hb concentrations in predicting the subsequent risk of CRC among screenees with two negative faecal immunochemical test (FIT) examinations.

What are the new findings?
► The positivity rate and advanced neoplasia (AN—CRC + AA) detection rate at subsequent screening tests, as well as the interval CRC rate, are associated with the f-Hb level at previous tests. Considering the first two FIT exams, subjects with cumulative f-Hb concentration ≥20 µg Hb/g faeces are showing a very high risk of being detected with AN at subsequent rounds, while the subsequent AN risk is very low among subjects with undetectable f-Hb levels. A similar trend could be observed for the IC risk.

INTRODUCTION

Faecal immunochemical tests (FITs) have been recommended as the faecal test of choice for population-based screening programmes.[1]

One of the main advantages of FITs is that they allow for faecal haemoglobin (f-Hb) quantification. Several reports[2–5] have documented a positive correlation between f-Hb concentration and those morphological and histological characteristics associated with the severity of colorectal neoplasms detected at colonoscopy (TC), among subjects with a FIT result exceeding the positivity

BMJ

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ScienceDirect
journal homepage: www.ejcancer.com

ELSEVIER

EJC

Original Research

Changes in FIT values below the threshold of positivity and short-term risk of advanced colorectal neoplasia: Results from a population-based cancer screening program

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KEYWORDS
Cancer;
Cancer screening;
Colon neoplasms;
Fecal occult blood test

Abstract ***Introduction:*** Increased values in the fecal immunochemical test (FIT) are correlated with increasingly severe colorectal neoplasia, but little attention has been given to FIT values below the cut-off point (negative FIT, nFIT). We analysed the relationship between the concentrations of two consecutive nFIT and the risk of following screen-detected advanced neoplasia and interval cancer (IC) in a population-based colorectal cancer screening program.

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Cumulative value

Italy

Sum of FIT values over 2 rounds:
0, 0.1-3.9, 4-9.9, 10-14.9, 15-19.9, ≥20 µg Hb/faeces

Change in FIT category

Barcelona

Change in the risk category over 2 rounds:

- Non-detectable (Nd 0-3.8),
- Low (3.9-9.9);
- High (10.0-19.9 µg Hb/g feces)

Nd-Nd, Nd-Low, Nd-High, Low- Nd, Low-Low, Low-High, High-Nd, High-Low, High-High.

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Combining results of two consecutive FIT exams

Logistic regression models adjusted by age and sex
(in Italy also by interval since last FIT)

		Advanced Neoplasia			
		Italy		Barcelona	
		OR	95% CI	OR	95% CI
Cumulative f-Hb level at previous 2 FITs (FIT1+FIT2)	0	1		1	
	0.1-3.9	1.81	1.55-2.12	3.09	2.35-4.07
	4-9.9	4.58	3.91-5.36	8.60	6.40-11.54
	10-14.9	9.32	7.73-11.23	17.15	12.39-23.72
	15-19.9	12.42	10.43-15.76	20.19	14.28-28.53
	≥ 20	32.52	26.19-40.39	44.94	30.25-66.77
Combinations of categories of previous 2 FITs	ND - ND	1		1	
	ND - Low	4.90	4.15 – 5.80	4.13	3.19-5.35
	ND - High	8.51	7.00 – 10.35	7.26	5.48-9.63
	Low - ND	2.70	2.26 – 3.24	4.15	3.09-5.57
	Low - Low	10.70	8.16 -14.03	10.93	6.99-17.06
	Low - High	17.18	12.71 - 23.22	19.29	11.94-31.18
	High - ND	5.66	4.55 – 7.03	7.04	5.06-9.78
	High - Low	18.63	13.64 – 25.44	18.42	10.99-30.88
	High - High	30.59	22.50 – 41.58	23.22	13.29-40.60

Courtesy Andrea Buron

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Cumulative AN DR and 3-year IC risk

by cumulative f-Hb level at previous rounds

81% of the screenees

0.7% of the screenees

µg Hb /g faeces Months	0 % (95% CI)	0.1–3.9 % (95% CI)	≥20 % (95% CI)
24	0.06 (0.05 to 0.08)	0.11 (0.08 to 0.14)	1.30 (0.77 to 2.18)
36	0.44 (0.39 to 0.49)	0.78 (0.70 to 0.87)	14.33 (12.14 to 16.88)
48	0.53 (0.48 to 0.59)	0.90 (0.81 to 0.99)	16.08 (13.70 to 18.82)
54	1.41 (1.27 to 1.57)	1.90 (1.71 to 2.11)	25.46 (21.38 to 30.15)

Sum f-Hb µg/g	Interval CRC		
FIT1 + FIT2	N	%	IR§ (95% CI)
0	9	0.02	9.84 (5.12 to 18.99)
0.1–3.9	9	0.05	10.88 (4.53 to 26.15)
4–9.9	16	0.13	50.48 (29.90 to 85.23)
10–14.9	6	0.18	39.37 (12.70 to 122.08)
15–19.9	4	0.23	75.54 (24.36 to 234.21)
≥20	5	0.67	238.07 (89.35 to 634.31)
Total	49	0.07	21.30 (15.50 to 29.27)

Senore C, et al. Gut 2020

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Risk tailored screening
previous FIT result

Prospective trial within ongoing Piedmont Region program.

Screenees with negative FIT result are randomized to different intervals based on the cumulative f-Hb level (present + previous FIT)

Cumulative f-Hb ≥20 µg/gr faeces	Cumulative f-Hb 4-19.8 µg/gr faeces	Cumulative f-Hb <4 µg/gr faeces
Immediate TC FIT 1-year interval	FIT 2-year interval	FIT 3-year interval
FIT 2-year interval	FIT 2-year interval	FIT 2-year interval

Randomization ratio 1:1:1

Randomization ratio 2:1

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Population

Subjects aged 50 to 69, performing FIT screening

- within the Piedmont population based CRC screening program
- who had performed a previous FIT in the program, with a negative result, within the previous 3 years

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Outcomes

- DR and PPV
  - CRC
  - Advanced adenoma (including ASPs)
- IC rates
- Participation rate (consent to be enrolled in the study)

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ERB**sinitially** approved an **opt-out approach** , but they subsequently requested to revise the procedure

During the recruitment period individuals invited for FIT screening and potentially eligible for recruitment will receive an information leaflet, together with the invitation letter.

The leaflet will provide information about the rationale and procedures of the trial and a consent form

Subjects willing to participate are asked to sign and return the consent form together with the stool sample in the pharmacies

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Preliminary results

Subjects enrolled (3/11/2022-31/3-2023)

Low risk groups: 2571 → 42% of screenees with a previous negative test

High risk groups: 84 → 1% of screenees with a previous negative test

Older age groups as compared to the previous study

Changes introduced in the laboratory procedures ???

New buffer

A comparative study of the new sampling buffer on test performance documented an increase in the mean f-Hb (from 5.0 to 6.3 µg Hb/g faeces) when using the new kit. Most of the gain in Hb occurred in samples with a small quantity of f-Hb

Grazzini G et al. European Journal of Cancer Prevention 2017,

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Nested case-control study

4000 samples
FIT+ and immediate TC

FIT leftover; additional faecal sample; blood sample for **miRNA and microbime analysis**
Life style questionnaire

4000 Samples:
FIT- (cumulative f-hb < detectability threshold)

FIT leftover; additional faecal sample; blood sample for **miRNA and microbime analysis**
Life style questionnaire

2000 Samples:
FIT- (cumulative f-hb 4-19.9 threshold)

FIT leftover; additional faecal sample; blood sample for **miRNA and microbime analysis**
Life style questionnaire

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Thank you for your attention

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ICSN
International Cancer Screening Network

ICSN2023

Cancer screening: in the present, the future

The future depends on what you do today
M. Gandhi

June 21-23, 2023 | **Turin (Italy)**

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