

Livelli di emoglobina fecale nei test precedenti e rischio di neoplasia: implicazioni per la pratica

Carlo Senore

**SSD Epidemiologia e screening – CPO
AOU Città della Salute e della Scienza**



Centro di Riferimento per l'Epidemiologia
e la Prevenzione Oncologica in Piemonte

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,¹⁰ Romano Sassatelli,¹⁵ Carmen Visioli,² Nereo Segnan¹

Gut 2019;**0**:1–8. doi:10.1136/gutjnl-2018-318198

Background

E' ben documentata l'associazione tra i livelli di emoglobina fecale nei soggetti con esito positivo al FIT e le caratteristiche istologiche delle lesioni identificate allo screening

Ciatto S et al BJC 2007
Guittet L et al BJC 2009
vanRossum L et al BJC 2009

I dati disponibili relativi al valore predittivo per adenoma avanzato, o cancro, ai round successivi dei livelli di emoglobina fecale misurati nei soggetti con test FIT negativo sono limitati

Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort

Lancet Oncol 2011; 12: 551-58

Li-Sheng Chen, Amy Ming-Fang Yen, Sherry Yueh-Hsia Chiu, Chao-Sheng Liao, Hsiu-Hsi Chen

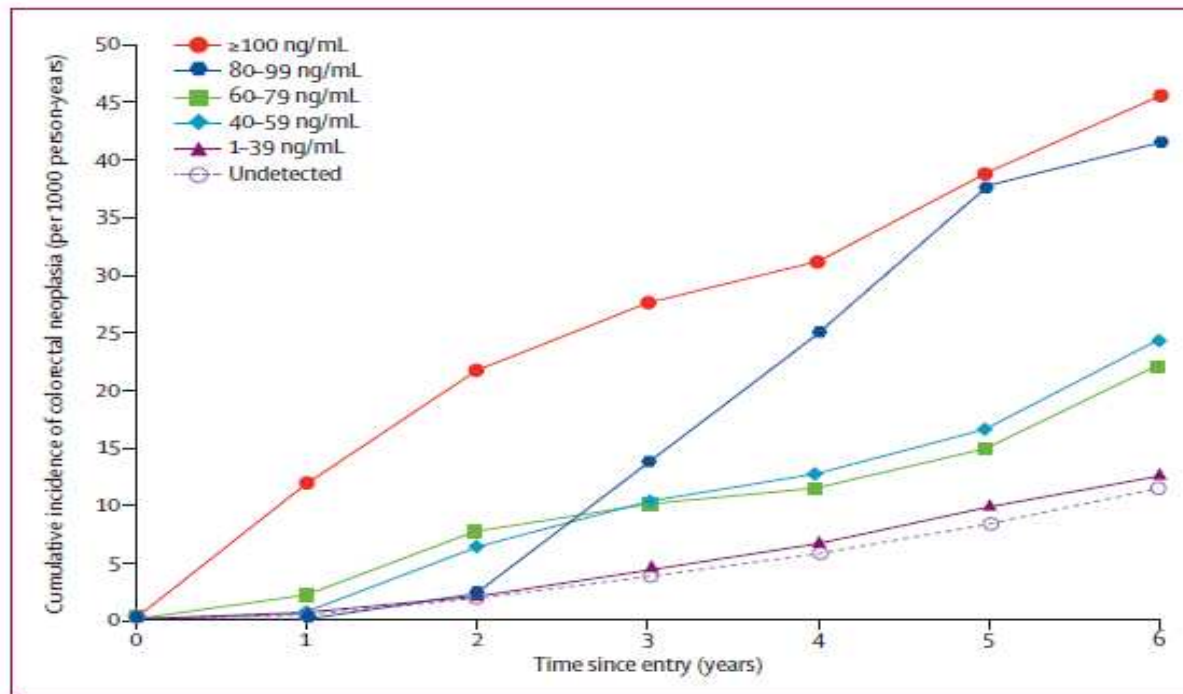


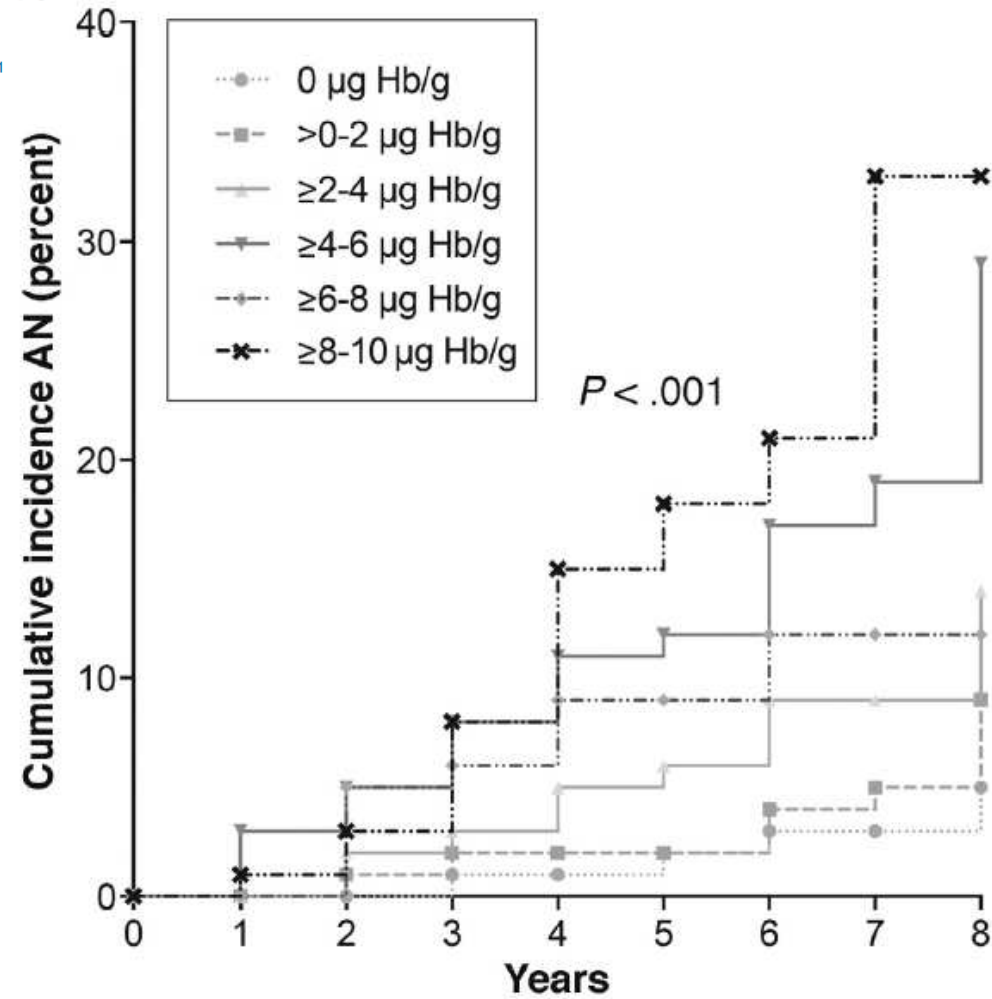
Figure 2: Cumulative incidence of adenoma and colorectal cancer, by faecal Hb concentration Hb-haemoglobin.

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. Kuipers¹

Gastroenterology 2017;153:1251–1259

Figure 2. Life table and curve for AN by r Hb level per $2\mu\text{g}$ Hb/g. This figure shows that the effect on cumulative incidence of AN at baseline FIT is most prominent for r Hb between 4 and $10\mu\text{g}$ Hb/g.



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. Kuipers¹

Gastroenterology 2017;153:1251–1259

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

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

European Journal of Cancer 107 (2019) 53–59

Distribution of outcomes at the third screen and interval cancers based on the FIT category at the first and second screen (N = 42,524).

Variables	Total population at risk	Outcomes - 3rd screen (N, ‰)									
		Low risk adenoma		Intermediate risk adenoma		High risk adenoma		Cancer		Interval cancer (N, ‰)	
FIT, change from 1st to 2nd screen											
Non-detectable to non-detectable	36605	293	8.0	186	5.1	105	2.9	19	0.5	16	0.4
Non-detectable to low nFIT	2101	38	18.1	54	25.7	12	5.7	8	3.8	2	1.0
Non-detectable to high nFIT	995	25	25.1	37	37.2	21	21.1	4	4.0	5	5.0
Low nFIT to non-detectable	1515	23	15.2	32	21.1	19	12.5	3	2.0	1	0.7
Low nFIT to low nFIT	248	8	32.3	11	44.4	8	32.3	4	16.1	1	4.0
Low nFIT to high nFIT	140	5	35.7	12	85.7	8	57.1	1	7.1	2	14.3
High nFIT to Non-detectable	711	25	35.2	24	33.8	15	21.1	4	5.6	2	2.8
High nFIT to low nFIT	121	4	33.1	12	99.2	4	33.1	2	16.5	2	16.5
High nFIT to high nFIT	88	5	56.8	8	90.9	5	56.8	3	34.1	0	0.0

FIT, fecal immunochemical test; nFIT, negative fecal immunochemical test. Non-detectable comprises FIT values ranging between 0 and 3.8 µg/ml; low negative FIT, values between 3.9 and 9.9 µg/ml; high negative FIT, values between 10 and 19.9 µg/ml.

Obiettivi

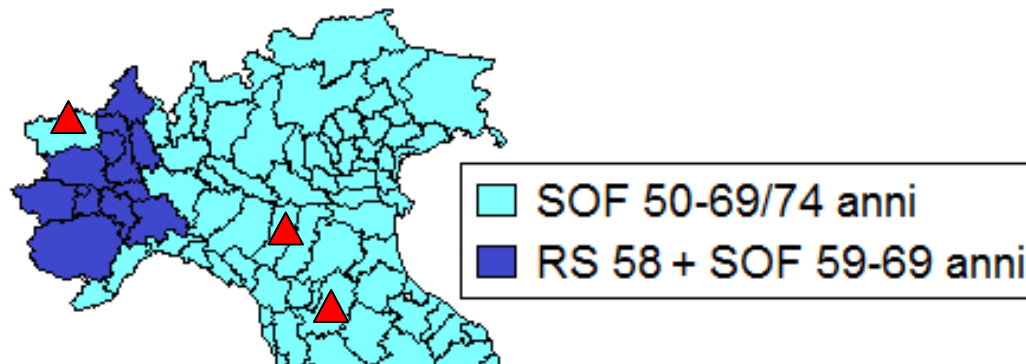
Stimare il rischio di neoplasia avanzata (CCR + adenoma avanzato) ai test successivi tra i soggetti con precedenti FIT negativi, per livello di emoglobina fecale misurato nei precedenti test negativi

Popolazione

Reggio Emilia, Firenze

Valle d'Aosta

Residenti di età 50-69 anni



Piemonte

Residenti 59—69 anni non invitati a FS

o aderenti all'offerta del FIT in alternativa alla FS

Coorte prospettica di soggetti che hanno effettuato il primo test

di screening tra Dicembre 2004 e Dicembre 2010

Protocollo di screening

Singolo campione (Oc Sensor, Eiken Co. Japan)

KIT distribuito in : Farmacia

Cut-off: 20 μg f-Hb /gr feci (100 ng/ml)

Intervallo di screening: 2 anni

Metodi

Abbiamo calcolato

- ❑ la proporzione di positivi (PR)
- ❑ il tasso di identificazione diagnostica (DR) di adenomi avanzati e cancro (AN)
- ❑ il valore predittivo positivo (PPV) per AN
al terzo FIT, dopo 2 precedenti test consecutivi negativi
al quarto FIT, dopo 3 precedenti FIT negativi.

Abbiamo calcolato il livello cumulativo di emoglobina fecale come la somma dei valori misurati sui primi 2 (3) esami in soggetti con FIT negativo e abbiamo classificato le persone esaminate in 6 gruppi:

0 / 0.1-3.9 / 4-9.8 / 10-14.9 / 15-19.9 / ≥ 20 $\mu\text{g Hb /gr feci}$

Metodi

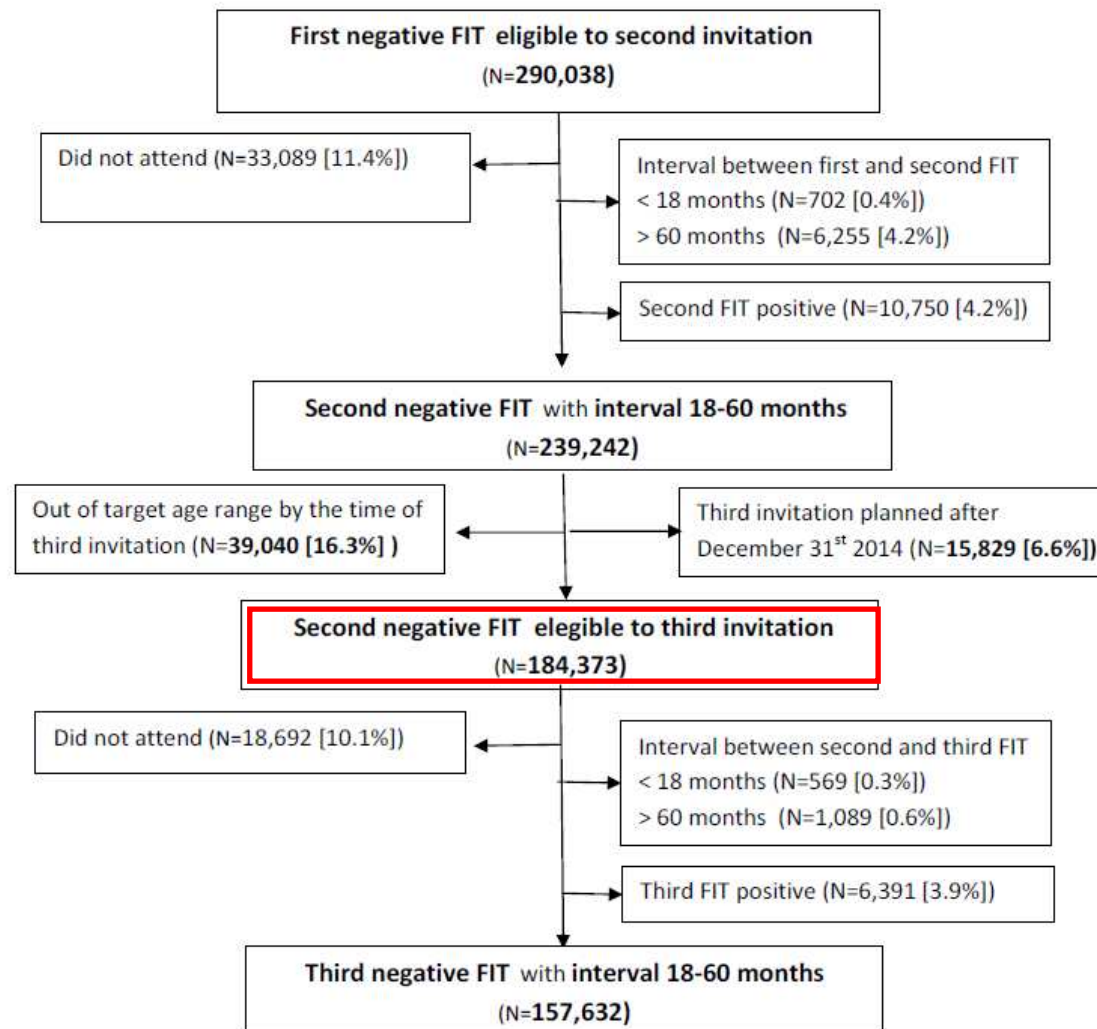
Modelli di regressione logistica per stimare l'associazione tra il livello cumulativo di emoglobina fecale e il tasso di identificazione di AN al terzo esame, aggiustata per :

- ❑ sesso
- ❑ età (50-59 e 60-69)
- ❑ intervallo dall'ultimo test negativo
(mesi: 18-22, 23-27, 28-32; 33-37, 37-60)

Rischio cumulativo di AN stimato su un intervallo di 4 anni dopo il secondo FIT negative, usando il metodo di Kaplan-Meier

164,023 soggetti
Aderenti al terzo round

6,391 (3.9%)
FIT positivo



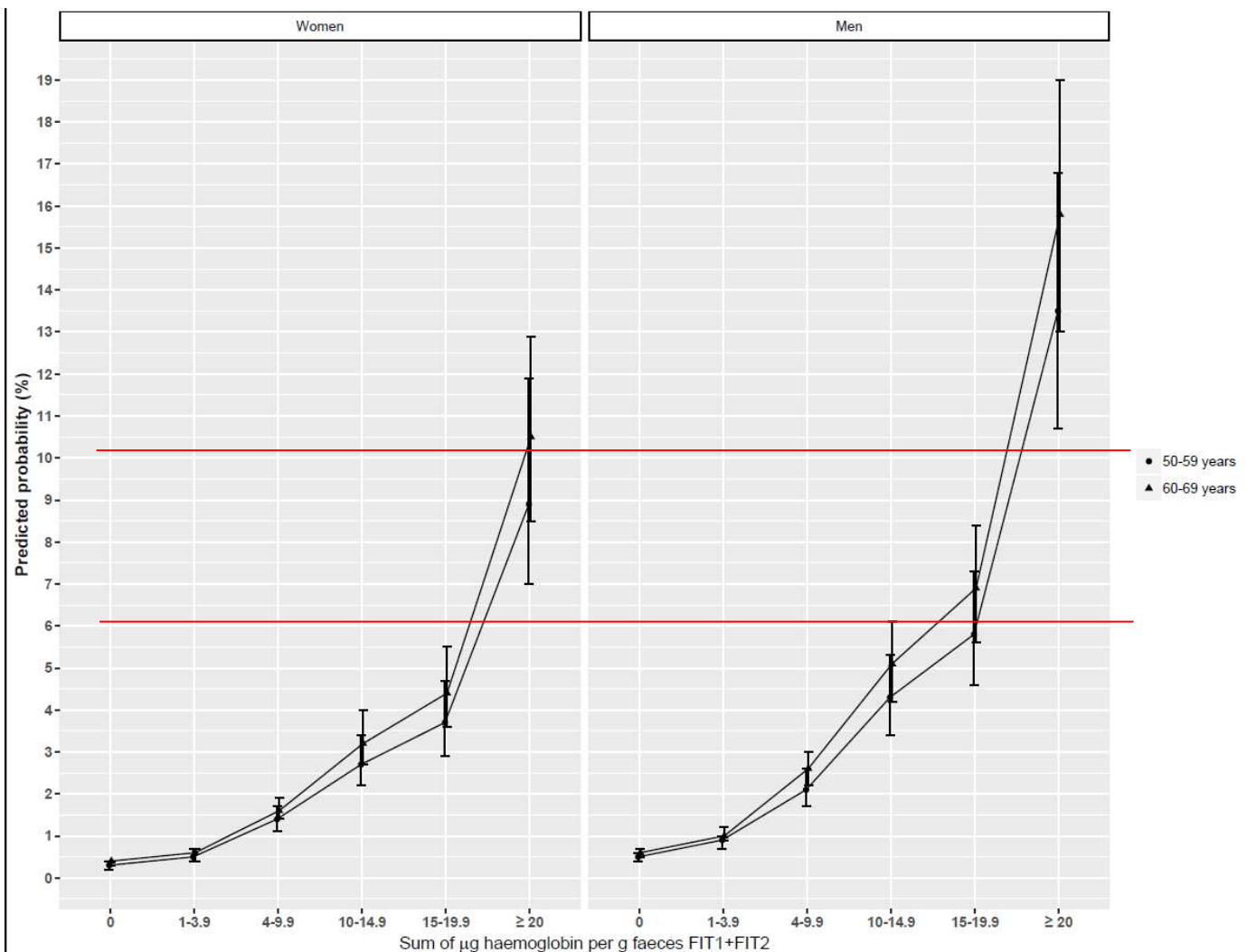
Risultati III round

Somma f-Hb µg/gr FIT1+FIT2	Esaminati N (%)	FIT +		Colonscopia		Adenoma avanzato	CRC	PPV AN % (95%CI)	DR adenoma Avanzato % (95%CI)	DR CRC % (95%CI)	NNScope (95%CI)
		N	% (95%CI)	N	% (95%CI)						
0	80,579 (49.1)	2,074	2.6 (2.5-2.7)	1,793	86.5 (84.8-88.0)	257	35	16.3 (16.0-16.5)	0.3 (0.3-0.4)	0.04 (0.03-0.06)	6.1 (6.0-6.2)
1-3.9	54,352 (33.1)	1,895	3.5 (3.3-3.6)	1,621	85.5 (83.7-87.2)	294	56	21.6 (21.2-21.9)	0.5 (0.5-0.6)	0.10 (0.08-0.13)	4.6 (4.6-4.7)
4-9.9	19,715 (12.0)	1,247	6.3 (6.0-6.7)	1,098	88.1 (86.0-89.9)	301	36	30.7 (30.0-31.3)	1.5 (1.4-1.7)	0.18 (0.13-0.25)	3.3 (3.2-3.3)
10-14.9	5,336 (3.3)	516	9.7 (8.9-10.5)	464	89.9 (86.7-92.5)	161	25	40.1 (38.8-41.4)	3.0 (2.6-3.5)	0.47 (0.31-0.70)	2.5 (2.4-2.6)
15-19.9	2,912 (1.8)	367	12.6 (11.4-13.9)	315	85.8 (81.4-89.4)	123	16	44.1 (42.3-46.0)	4.2 (3.5-5.0)	0.55 (0.33-0.90)	2.3 (2.2-2.4)
≥ 20	1,129 (0.7)	292	25.9 (23.4-28.5)	261	89.4 (84.8-92.8)	111	21	50.6 (47.6-53.5)	9.8 (8.2-11.7)	1.86 (1.18-2.86)	2.0 (1.9-2.1)
Totale	164,023	6,391	3.9 (3.8-4.0)	5,552	86.9 (85.9-87.7)	1,247	189	25.9 (25.7-26.1)	0.8 (0.7-0.8)	0.12 (0.10-0.13)	3.9 (3.8-3.9)

Fattori predittivi di cancro e adenoma avanzato al III round

		CRC		Adenoma avanzato		AN	
		OR	95%CI	OR	95%CI	OR	95%CI
SESSO	Women	1		1		1	
	Men	1.34	1.00-1.79	1.63	1.46-1.83	1.60	1.43-1.78
ETA' (anni)	50-54	0.54	0.32-0.91	0.67	0.55-0.82	0.65	0.55-0.79
	55-59	0.75	0.47-1.17	1.02	0.86-1.22	0.98	0.83-1.15
	60-64	0.95	0.67-1.36	1.00	0.86-1.16	0.99	0.87-1.14
	65-69	1		1		1	
INTERVALLO DALL'ULTIMO FIT (mesi)	18-22	0.67	0.30-1.49	0.80	0.59-1.08	0.78	0.58-1.03
	23-27	1		1		1	
	28-32	0.92	0.61-1.37	0.98	0.83-1.16	0.97	0.83-1.13
	33-36	0.96	0.39-2.40	1.23	0.86-1.77	1.19	0.85-1.67
	37-60	1.10	0.51-2.36	1.49	1.14-2.00	1.44	1.11-1.87
Valore cumulativo di f-Hb ai primi 2 test FIT (FIT1+FIT2) µg Hb /gr feci	0	1		1		1	
	0.1-3.9	2.26	1.47-3.46	1.75	1.47-2.07	1.81	1.55-2.12
	4-9.9	4.01	2.51-6.39	4.64	3.93-5.49	4.58	3.91-5.36
	10-14.9	10.11	6.04-16.93	9.13	7.48-11.15	9.32	7.73-11.23
	15-19.9	11.63	6.42-21.07	12.84	10.32-16.00	12.42	10.43-15.76
	≥ 20	38.92	22.50-67.31	30.40	24.09-38.38	32.52	26.19-40.39

Tasso di identificazione di neoplasia avanzata stimato per concentrazione cumulativa di emoglobina fecale al secondo FIT - per sesso ed età



Tasso di identificazione cumulativo di neoplasia avanzata

Per concentrazione cumulativa di emoglobina fecale su 2 FIT consecutivi e intervallo dal secondo FIT

µg Hb /gr feci	0	1-3.9	4-9.9	10-14.9	15-19.9	≥ 20
Mesi	% 95% CI	% 95% CI	% 95% CI	% 95% CI	% 95% CI	% 95% CI
24	0.06 0.05-0.08	0.11 0.08-0.14	0.38 0.30-0.48	0.59 0.41-0.84	0.50 0.30-0.84	1.30 0.77-2.18
36	0.44 0.39-0.49	0.78 0.70-0.87	1.98 1.78-2.21	4.24 3.67-4.90	0.57 0.48-0.67	14.33 12.14-16.88
48	0.53 0.48-0.59	0.90 0.81-0.99	2.27 2.04-2.52	4.71 4.10-5.41	6.84 5.84-8.00	16.08 13.70-18.82
54	1.41 1.27-1.57	1.90 1.71-2.11	4.79 4.30-5.34	8.65 7.44-10.06	11.97 10.13-14.13	25.46 21.38-30.15

Rischio di cancro intervallo

Per concentrazione cumulativa di emoglobina fecale sui primi due FIT

Table 4 CRC DR at the third FIT* and IC risk during the 36 months following second negative FIT by cumulative f-Hb concentration over two consecutive FITs—screenees from three centres

Sum f-Hb µg/g	Not invited†	Non-attenders	Screened	Uptake‡	SD CRCs		Interval CRC		
	N	N	N	%	N	%	N	%	IR§ (95% CI)
0	4382	2990	29553	90.8	15	0.05	9	0.02	9.84 (5.12 to 18.99)
0.1–3.9	2972	1584	14925	90.4	11	0.07	9	0.05	10.88 (4.53 to 26.15)
4–9.9	1825	932	9637	91.2	17	0.18	16	0.13	50.48 (29.90 to 85.23)
10–14.9	559	284	2522	89.9	9	0.36	6	0.18	39.37 (12.70 to 122.08)
15–19.9	290	142	1285	90.0	7	0.54	4	0.23	75.54 (24.36 to 234.21)
≥20	122	65	556	89.5	12	2.16	5	0.67	238.07 (89.35 to 634.31)
Total	10150	5997	58478	90.7	71	0.12	49	0.07	21.30 (15.50 to 29.27)

Classifications of previous negative f-Hb

Cumulative value: FITcum

Italy

Sum of FIT values of previous 2-3 rounds:

0, 0.1-3.9, 4-9.9, 10-14.9, 15-19.9, ≥ 20 μg Hb/faeces

Change in FIT category: FITcat

Barcelona

Change in the risk category of 2 previous nFIT:

- 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.

Methods and population

Screening programs in Northern and central-Italy and Barcelona:

- Target population : all residents, 50/59 to 69/74
- Screening interval : 2 years
- Single sample FIT (*OC Sensor, Eiken Japan*) cut-off 20 μ g Hb/g faeces
- Delivery at Pharmacies
- Colonoscopy after FIT+

Barcelona, Spain

Population for the analyses (n= 42,524)
participants with 2 consecutive screening
episodes with a negative FIT result who
afterwards either had a third screen or were
diagnosed with an IC after their second screen

1st screen between 2010 and 2011

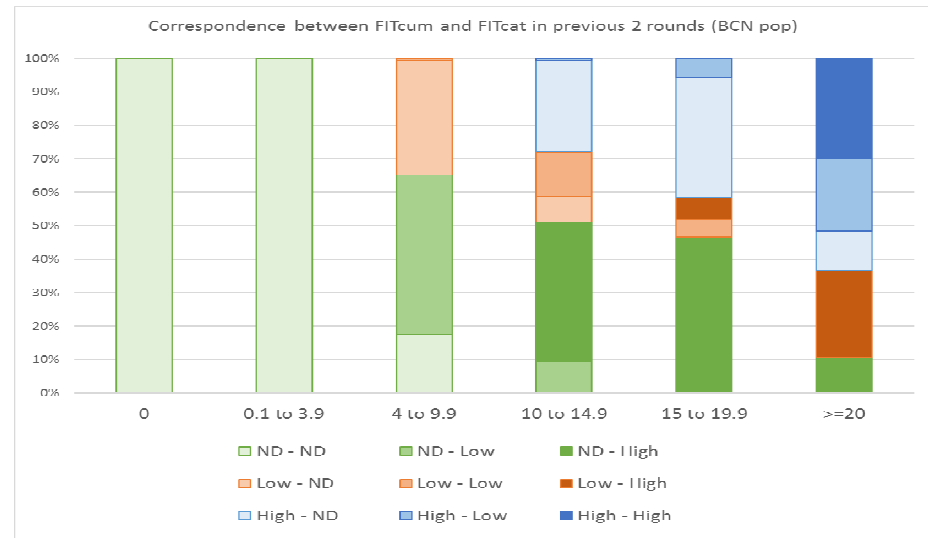
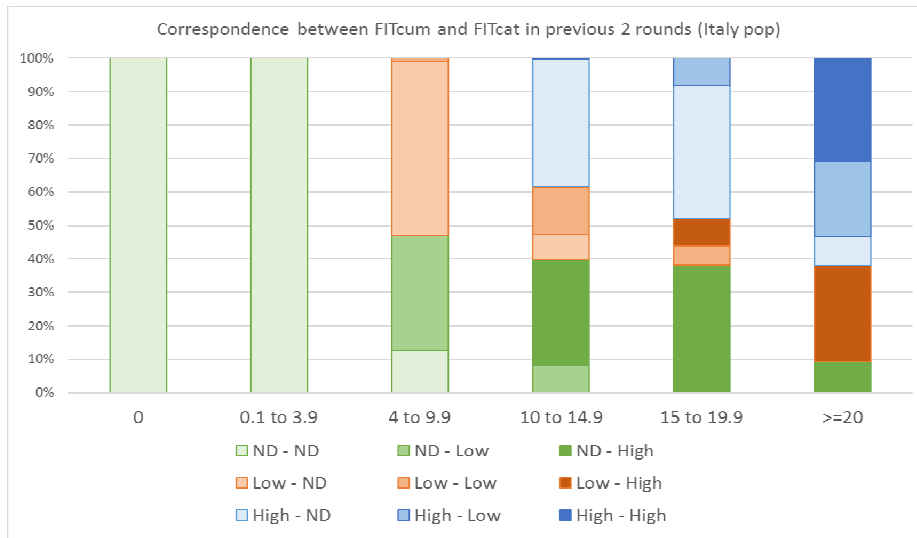
2nd screen between 2012 and 2013

3rd screen between 2014 and 2015

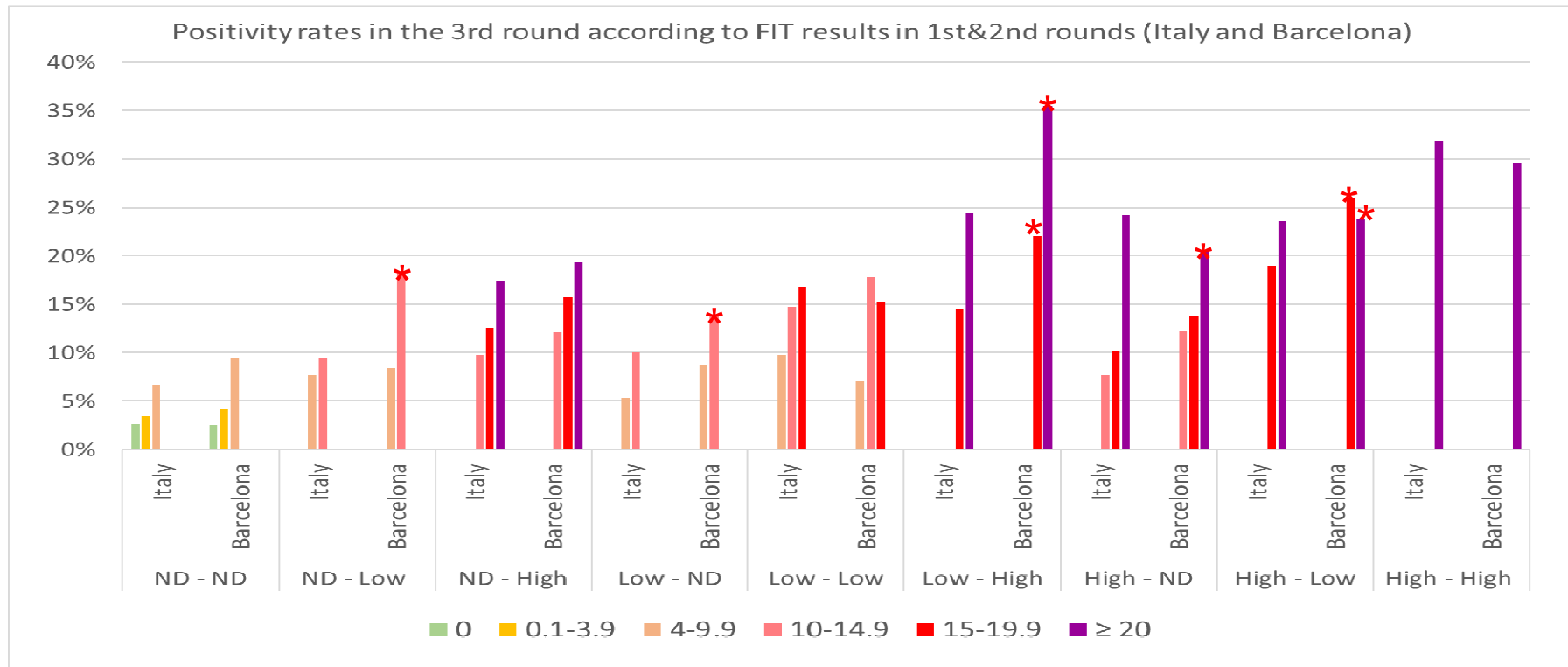
Results

- I. Correlation between the 2 classifications
- II. Positivity rates in the 3rd round (3R)
- III. Advanced neoplasia detection rates 3R
- IV. OR Advanced neoplasia 3R for single and combined classifications

I. Correlation between the 2 classifications

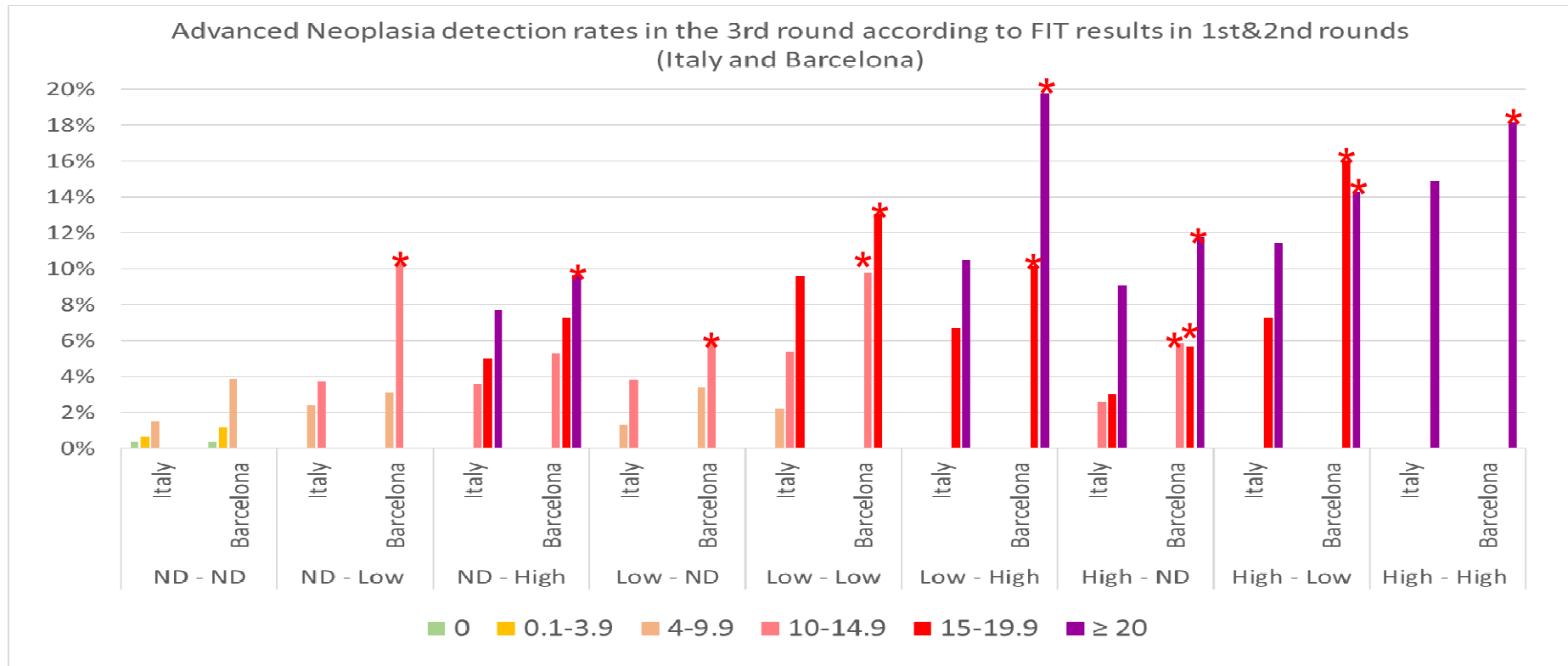


II. Positivity rates in the 3rd round



* Less than 25 cases in the numerator

III. Advanced neoplasia detection rates



* Less than 25 cases in the numerator

IV. OR for Advanced Neoplasia

		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

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

Conclusioni

La prevalenza di neoplasia avanzata ai round di screening successivi è associata al livello cumulativo di emoglobina fecale misurata sui test precedenti

Ipotizzabili strategie personalizzate in base al livello di rischio per utilizzare le risorse endoscopiche disponibili in modo più efficiente

Conclusioni

Gli assistiti con concentrazione cumulativa di emoglobina fecale $\geq 20 \mu\text{g /gr}$ sugli ultimi due FIT potrebbero essere indirizzati immediatamente alla colonscopia di approfondimento

Un intervallo di screening più lungo potrebbe essere considerato per il 40% della popolazione aderente allo screening che presenta livelli non misurabili di emoglobina fecale e mostra un rischio molto basso di neoplasia avanzata ai round successivi .

Il rischio tende a decrescere con il numero di test con emoglobina fecale non misurabile

Studi di valutazione di impatto di diversi intervalli di screening definiti in base al rischio sono in programma

Grazie per l'attenzione

Distribuzione per sede – Cancro e adenoma avanzato

Terzo round– per cincentrazione cumulativa di emoglobina fecale

sum f-Hb µg/gr FIT1+FIT2	CRC			Advanced adenoma			
	Distale N % (95%CI)	Prossimale N % (95%CI)	Totale	Distale N % (95%CI)	Prossimale N % (95%CI)	Distale + Prossimale N % (95%CI)	Totale
0	20	15	35	148	88	21	257
	57.1% (39.5-73.2)	42.9% (26.8-60.5)		57.6% (51.3-63.7)	34.2% (28.5-40.4)	8.2% (5.3-12.4)	
1-9.9	39	52	91	371	179	45	595
	42.9% (32.7-53.7)	57.1% (46.4-67.3)		62.4% (58.3-66.2)	30.1% (26.5-34.0)	7.6% (5.6-10.1)	
10-19.9	29	12	41	156	94	34	284
	70.7% (54.3-83.4)	29.3% (16.7-45.7)		54.9% (48.9-60.8)	33.1% (27.7-39.0)	12.0% (8.5-16.5)	
>20	15	6	21	53	40	18	111
	71.4% (47.7-87.8)	28.6% (12.1-52.3)		47.8% (38.3-57.4)	36.0% (27.3-45.8)	16.2% (10.2-24.7)	
Total	103	85	188	728	401	118	1,247
	54.8% (47.4-62.0)	45.2% (38.0-52.6)		58.4% (55.6-61.1)	32.2% (29.6-34.8)	9.5% (7.9-11.3)	
FIT + secondo test	214	130	344	1152	557	279	1,988
	62.2% (56.8-67.3)	37.8% (32.7-43.2)		58.0% (55.7-60.1)	28.0% (26.1-30.1)	14.0% (12.6-15.7)	

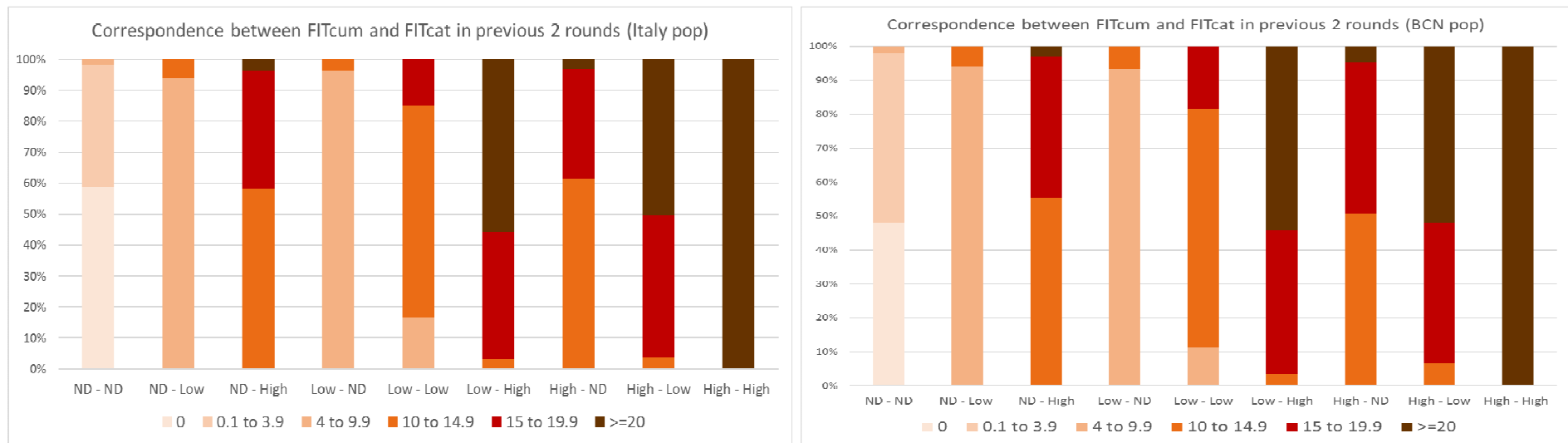
Conclusions

- ✓ Similar risk (DR and OR) obtained in both populations for each classification; trend very consistent → *external validation*
- ✓ Both classifications have similar patterns in risk
- ✓ Combined algorithm → increase in predictive value
- ✓ Using 2 previous nFIT relevant for screening personalisation; e.g. when high risk and
 - Invited and not participating
 - Not invited due to age
 - FIT+ and Not accepting colonoscopy
 - Advance colonoscopy one round, e.g. by lowering cut-off point

Food for thought (next steps)

- Change vs cumulative:
 - Change seems relevant when there is a “big jump”
- How many previous negative FIT values are relevant to study?
 - From a clinical/biological perspective
 - From an epidemiological perspective
- FIT results vary in time, but how relevant are previous FIT values and changes over time vs. the concomitant result? (assign weights?)

I. Correlation between the 2 classifications



Andrea Buron and Carlo Senore