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South Hall

Systematic review and bivariate/HSROC meta-analysis of immunochemical and guaiac fecal occult blood tests for colorectal cancer screening

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Introduction

- Proposed biennially to approximately 17 million individuals aged 50 to 74 years old in France, non-rehydrated Hemoccult has been the established screening test of choice to detect colorectal cancer in an average risk population.

- Immunological screening alternatives are believed to overcome the main limitations of the guaiac-based tests, namely: low sensitivity, qualitative reading and low specificity for human hemoglobin.

- Our objective is to assess the performances of two immunochemically-based fecal occult blood tests (iFOBTs) (i.e. OC-Sensor and Magstream) compared to an established guaiac-based test (gFOBT) (i.e. Hemoccult), using colonoscopy as the gold standard.

Methods I

Database search

We searched PubMed and EMBASE from 1980 to 2012 and the Cochrane Central Register of Controlled Trials from inception to the last quarter of 2012. Only English and French language articles were searched.

Criteria for inclusion and exclusion

Articles were included in the meta-analysis if they satisfied all of the following criteria:

1. the study patients were 40 years of age or older, with an average risk of colorectal cancer
2. the screening intervention included either non-rehydrated Hemoccult, Magstream, or OC Sensor
3. the reference tests used were either colonoscopy for all cases, colonoscopy for positive tests and follow-up registry for negative tests, or colonoscopy for positive tests and sigmoidoscopy for negative tests
4. the findings presented permitted the calculation of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN)
5. the study followed either a single-gate or a two-gate design

Methods II

Validity assessment

All qualifying studies were assessed on the basis of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) protocol, using the Cochrane's Review Manager Software (version 5.2.6).

Data abstraction

For every study, the number of true positives, true negatives, false positives and false negatives was retrieved and documented. Sensitivity and specificity were then calculated for colorectal cancer and advanced adenoma screening, when available.

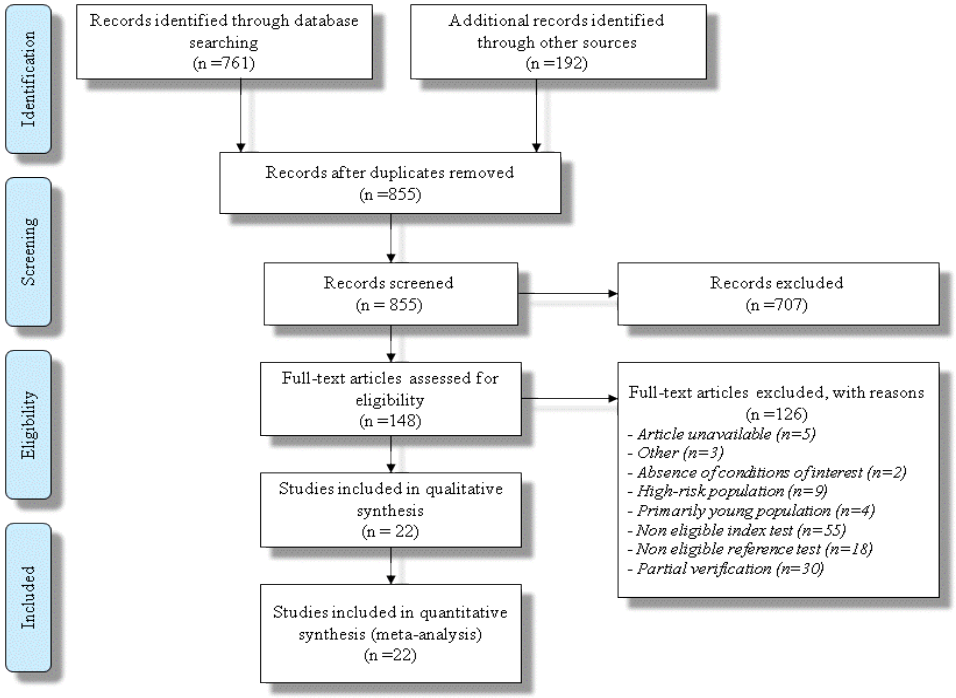
Quantitative data synthesis

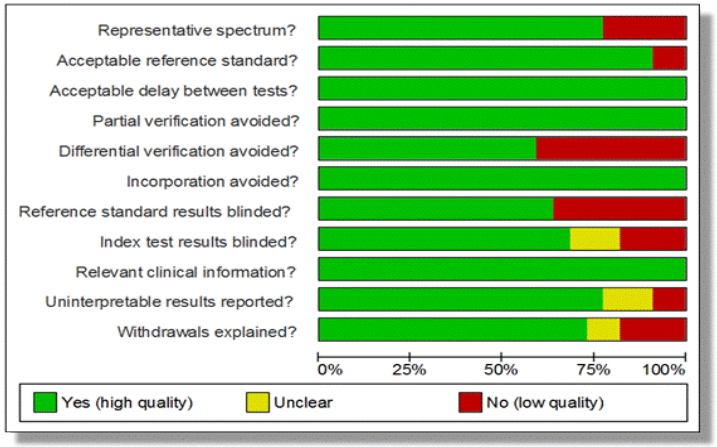
We used two hierarchical logistic regression models: a bivariate model and a hierarchical summary receiver operating characteristic (HSROC) model, which respect the binomial structure of the data and account for between-study heterogeneity. In practice, we used the bivariate model in order to synthesize the data into summary points for sensitivity and specificity, and the HSROC model to arrive at a summary line illustrating how the average sensitivity could vary with the average specificity.

Literature Review

Articles selection process

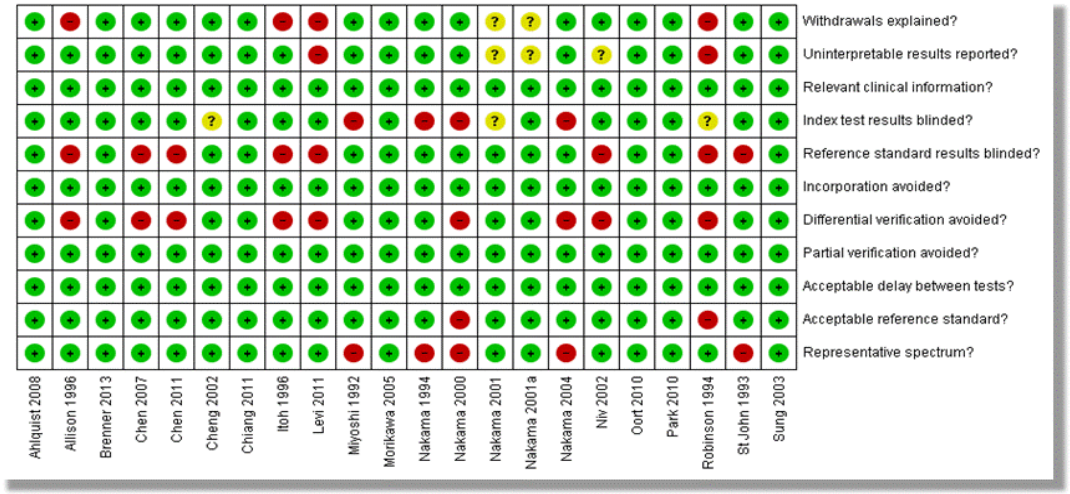
Our search identified 953 records: 761 of them were identified through database searches and an additional 192 through reports published by HTA bodies. Having removed all duplicates, our search identified 855 studies, of which 148 were relevant based on their title and abstract and 22 met predetermined selection criteria . Hence, we included 22 studies in the qualitative synthesis and meta-analysis.





Quality assessment using QUADAS

The total number of patients screened for advanced adenoma was 114,764 and the total number of patients screened for colorectal cancer was 174,469.



Data Extraction

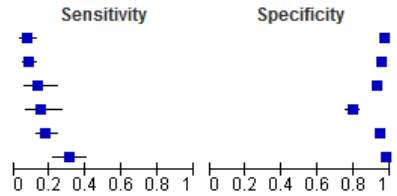
Forest plots

The analysis reveals that 25-85% of patients screened with Hemoccult, 61-100% of patients screened with Magstream, and 26-100% of patients screened with OC-Sensor obtained a TP CRC diagnosis.

Advanced Adenoma

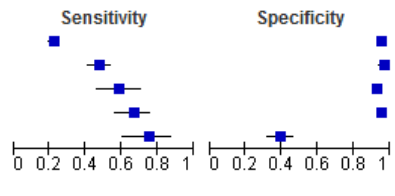
Hemoccult

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ahlquist 2008	11	70	134	2282	0.08 [0.04, 0.13]	0.97 [0.96, 0.98]
Brenner 2013	19	92	203	1921	0.09 [0.05, 0.13]	0.95 [0.94, 0.96]
Park 2010	8	53	51	648	0.14 [0.06, 0.25]	0.92 [0.90, 0.94]
Sung 2003	9	92	50	354	0.15 [0.07, 0.27]	0.79 [0.75, 0.83]
Oort 2010	35	87	159	1540	0.18 [0.13, 0.24]	0.95 [0.93, 0.96]
Allison 1996	33	165	74	7793	0.31 [0.22, 0.41]	0.98 [0.98, 0.98]



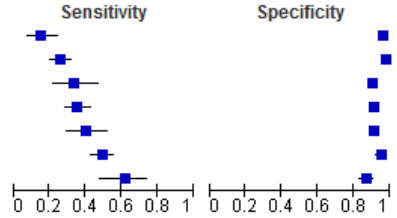
Magstream

Study	TP	FP	FN	TN	Sensitivity	Specificity
Morikawa 2005	145	1086	503	20071	0.22 [0.19, 0.26]	0.95 [0.95, 0.95]
Nakama 2000	119	8	131	242	0.48 [0.41, 0.54]	0.97 [0.94, 0.99]
Nakama 2001	41	745	29	9137	0.59 [0.46, 0.70]	0.92 [0.92, 0.93]
Allison 1996	68	372	34	7019	0.67 [0.57, 0.76]	0.95 [0.94, 0.95]
St John 1993	34	117	11	76	0.76 [0.60, 0.87]	0.39 [0.32, 0.47]



OC Sensor

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chen 2011	12	1656	68	44256	0.15 [0.08, 0.25]	0.96 [0.96, 0.97]
Brenner 2013	57	53	165	1960	0.26 [0.20, 0.32]	0.97 [0.97, 0.98]
Park 2010	20	67	39	644	0.34 [0.22, 0.47]	0.91 [0.88, 0.93]
Oort 2010	69	145	125	1482	0.36 [0.29, 0.43]	0.91 [0.90, 0.92]
Cheng 2002	31	652	46	6682	0.40 [0.29, 0.52]	0.91 [0.90, 0.92]
Nakama 2000	123	11	127	239	0.49 [0.43, 0.56]	0.96 [0.92, 0.98]
Nakama 2004	37	45	23	297	0.62 [0.48, 0.74]	0.87 [0.83, 0.90]

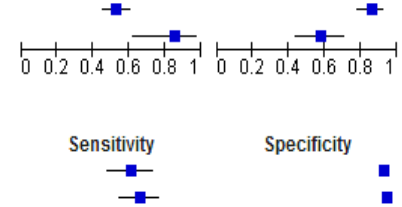


Abbreviations: TP=True Positives; FP= False Positives; FN= False Negatives; TN= True Negatives

Colorectal Cancer

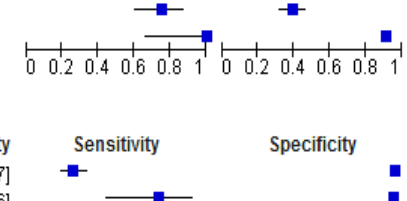
Hemoccult

Study	TP	FP	FN	TN	Sensitivity	Specificity
Sung 2003	1	100	3	401	0.25 [0.01, 0.81]	0.80 [0.76, 0.83]
Park 2010	4	57	9	690	0.31 [0.09, 0.61]	0.92 [0.90, 0.94]
Brenner 2013	5	106	10	2114	0.33 [0.12, 0.62]	0.95 [0.94, 0.96]
Allison 1996	13	185	22	7845	0.37 [0.21, 0.55]	0.98 [0.97, 0.98]
Niv 2002	13	89	21	2145	0.38 [0.22, 0.56]	0.96 [0.95, 0.97]
Ahlquist 2008	6	75	6	2410	0.50 [0.21, 0.79]	0.97 [0.96, 0.98]
Nakama 1994	106	14	94	86	0.53 [0.46, 0.60]	0.86 [0.78, 0.92]
Miyoshi 1992	17	25	3	34	0.85 [0.62, 0.97]	0.58 [0.44, 0.70]



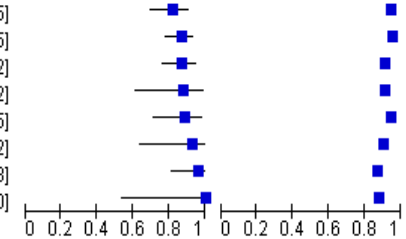
Magstream

Study	TP	FP	FN	TN	Sensitivity	Specificity
Nakama 2001	39	747	25	9141	0.61 [0.48, 0.73]	0.92 [0.92, 0.93]
Morikawa 2005	52	1179	27	20547	0.66 [0.54, 0.76]	0.95 [0.94, 0.95]
Allison 1996	22	418	10	7043	0.69 [0.50, 0.84]	0.94 [0.94, 0.95]
St John 1993	34	117	11	76	0.76 [0.60, 0.87]	0.39 [0.32, 0.47]
Robinson 1994	9	136	0	1344	1.00 [0.66, 1.00]	0.91 [0.89, 0.92]



OC Sensor

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chen 2011	39	1629	111	44213	0.26 [0.19, 0.34]	0.96 [0.96, 0.97]
Brenner 2013	11	99	4	2121	0.73 [0.45, 0.92]	0.96 [0.95, 0.96]
Chen 2007	53	1289	12	21318	0.82 [0.70, 0.90]	0.94 [0.94, 0.95]
Itoh 1996	77	1413	12	26358	0.87 [0.78, 0.93]	0.95 [0.95, 0.95]
Oort 2010	54	160	8	1599	0.87 [0.76, 0.94]	0.91 [0.89, 0.92]
Cheng 2002	14	669	2	6726	0.88 [0.62, 0.98]	0.91 [0.90, 0.92]
Nakama 2001	24	254	3	3979	0.89 [0.71, 0.98]	0.94 [0.93, 0.95]
Park 2010	12	75	1	682	0.92 [0.64, 1.00]	0.90 [0.88, 0.92]
Chiang 2011	27	370	1	2398	0.96 [0.82, 1.00]	0.87 [0.85, 0.88]
Levi 2011	6	147	0	1051	1.00 [0.54, 1.00]	0.88 [0.86, 0.90]



Abbreviations: TP=True Positives; FP= False Positives; FN= False Negatives; TN= True Negatives

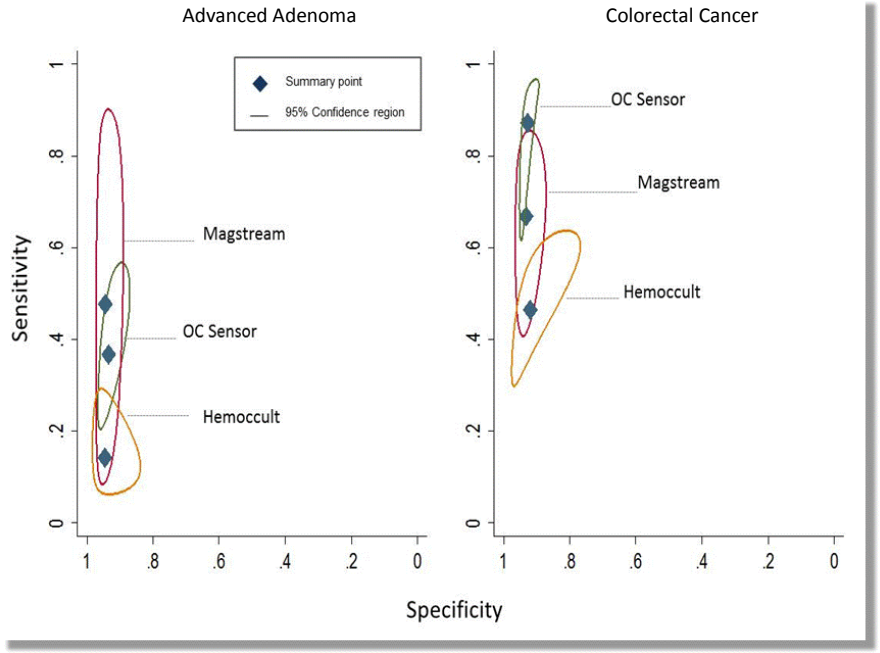
Bivariate/HSROC Meta-analysis

Likelihood and Diagnostic Odds Ratios

	Se	Sp	LR+	LR-	DOR
Screening modalities for advanced adenoma					
Hemoccult	0,142	0,946	2,612	0,908	2,878
Magstream	0,477	0,945	8,667	0,553	15,665
OC-Sensor	0,367	0,934	5,561	0,678	8,205
Screening modalities for colorectal cancer					
Hemoccult	0,474	0,92	5,944	0,571	10,400
Magstream	0,668	0,933	9,929	0,357	27,917
OC-Sensor	0,872	0,928	12,101	0,137	88,051

- OC Sensor has the best sensitivity among the three screening modalities analyzed for CRC screening.
- OC Sensor is the best performing test for CRC screening, as it has the highest LR+ (12.101) and lowest LR- (0.137).
- Patients presenting with colorectal cancer are 88 times more likely to have a positive test with OC Sensor than disease-free individuals (DOR: 88.051).

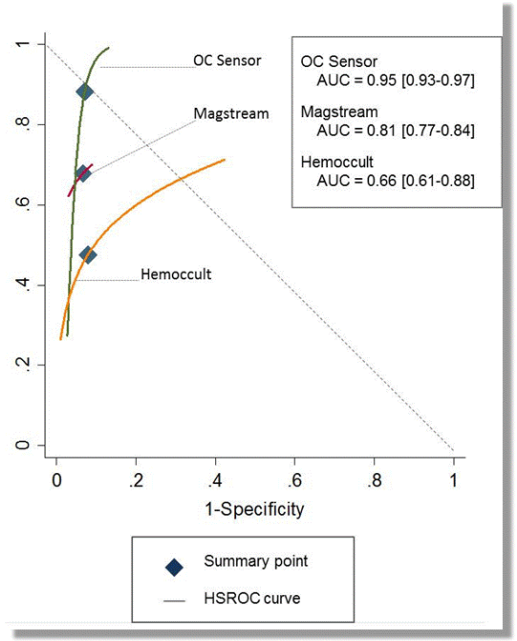
Bivariate summary estimates



- We observe a clear difference in CRC screening between the sensitivity and specificity of OC Sensor compared to Hemoccult: OC Sensor is significantly more accurate than Hemoccult.
- We did not find strong evidence for differences in accuracy between Magstream and Hemoccult or between OC Sensor and Magstream.

Hierarchical summary ROC plots

- When used in CRC screening, the AUC analysis reveals that OC-Sensor has a high accuracy, Magstream a moderate accuracy and Hemoccult a low accuracy.
- Credibility intervals of the AUC show that OC Sensor's screening accuracy is significantly higher than that of Magstream and Hemoccult.



Discussion

- Our findings support the use of OC Sensor for colorectal cancer detection.
- The bivariate ellipse analysis revealed the clear dominance of OC Sensor vis-à-vis Hemoccult, while the AUC analysis demonstrated its high global test performance.
- We did not reveal significant accuracy differences between Magstream and Hemoccult nor between Magstream and OC Sensor, pointing to the need for new diagnostic data to narrow credibility intervals.
- The diagnostic estimates obtained herein may be extended to derive model parameters for economic decision making, as well as, to offer insight for future clinical practice.
- Our findings bear the potential to influence the near and longstanding future of iFOBT and gFOBT tests as part of the colorectal cancer screening arsenal.

References

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