


OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING

Saturday, May 1, DDW New Orleans, 2010

Presenter: Gerrit Meijer



**World Organisation of
Digestive Endoscopy**


Colorectal Screening Committee

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**No polyp, no cancer
Is it that simple?**


Outline

- Semantics
- What should we hunt for?
- High risk adenomas
 - Adenoma carcinoma sequence
 - Tumor biology
- Alternative pathways

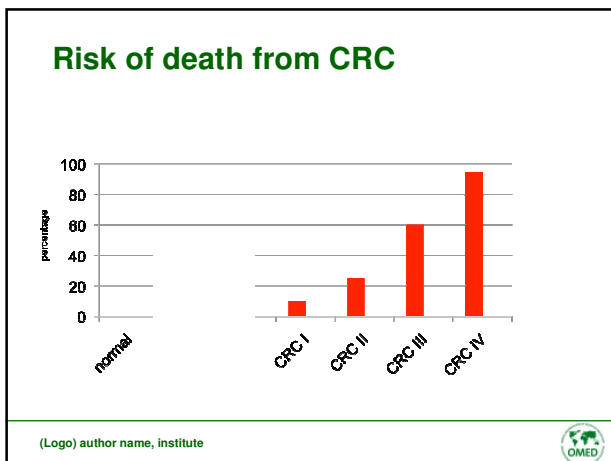
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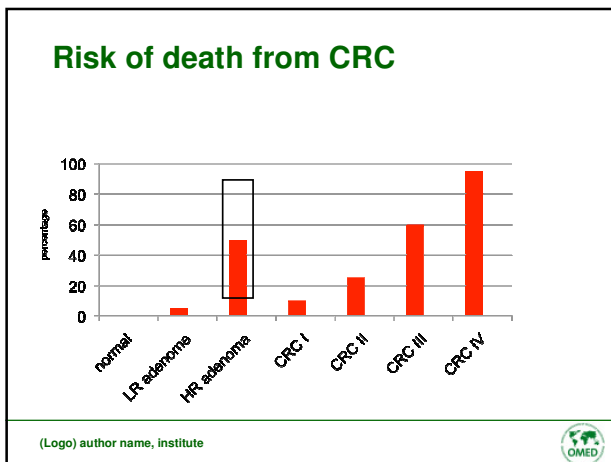
**No polyp, no cancer
Semantics***

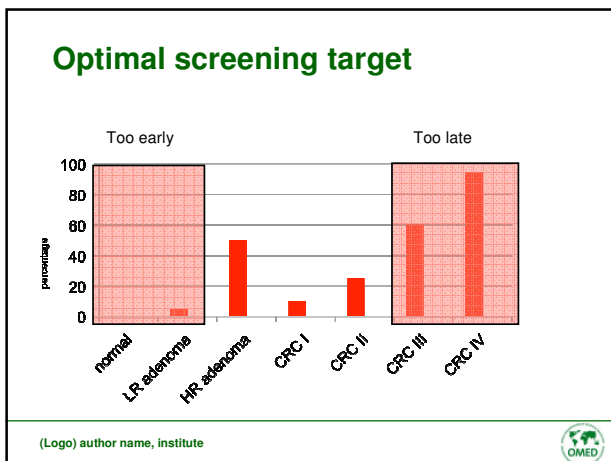
- Polyp
 - Tumorous mass that protrudes into the lumen of the gut
- Neoplasia
 - Clonal growth with genetic changes being passed on to next generations of cells constituting the neoplasm
- Adenoma
 - Benign epithelial neoplasm that forms glandular patterns or that originates from glands
- Dysplasia
 - Disordered growth; cellular and architectural changes that mark the morphology of epithelium at the stage between normal and cancer

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What defines High Risk adenomas ?

- No evidence from longitudinal studies
- Evidence from cross sectional studies not straight forward
 - Size, histological type, dysplasia
 - Biological features

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Which adenomas are relevant?

Size

	total number	number with malignancy	% with malignancy
< 1 cm	1479	19	1.3
1-2 cm	580	55	9.5
> 2cm	430	169	39.3

THE EVOLUTION OF CANCER IN THE COLON AND RECTUM

T. MUTO, H. J. R. BUSSEY, AND B. C. S.

Unlikely that > 20% will progress

Size may be overestimated as risk factor



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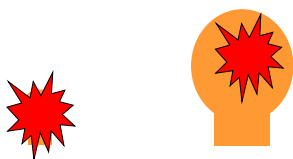
Size may be overestimated as risk factor



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Size may be overestimated as risk factor



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Which adenomas are relevant?

Dysplasia

	total number	number with malignancy	% with malignancy
mild	1734	99	5.7
moderate	549	99	18.0
severe	223	77	34.5

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Cancer: 1975/36/2251-70



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Which adenomas are relevant?

Dysplasia

	total number	number with malignancy	% with malignancy	% of cancers
mild	1734	99	5.7	36.0
moderate	549	99	18.0	36.0
severe	223	77	34.5	28.0

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Cancer: 1975:36:2251-70



Which adenomas are relevant?

Histological type

	total number	number with malignancy	% with malignancy
tubular	1880	90	4.8
tubulovillous	383	86	22.5
villous	243	99	40.7

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Cancer: 1975:36:2251-70



Which adenomas are relevant?

Histological type

	total number	number with malignancy	% with malignancy	% of cancers
tubular	1880	90	4.8	32.7
tubulovillous	383	86	22.5	31.3
villous	243	99	40.7	36.0

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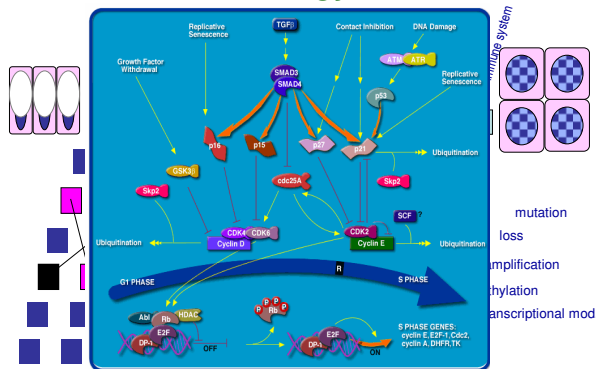
Which adenomas are relevant?

Traditional phenotypic variables are imprecise indicators of the risk that an adenoma will progress to cancer

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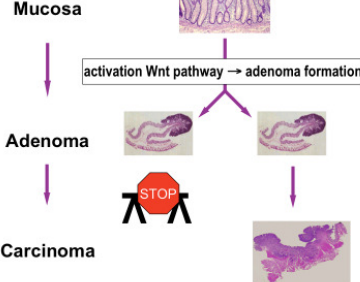
Biology



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Normal Mucosa



No progression 95% **Progression 5%**

Affected

Biological Processes

- Proliferation
 - Differentiation
 - Apoptosis
 - Hypoxia
 - Glycolysis and associated metabolic pathways
-
- Senescence
 - Proliferation
 - Differentiation
 - Chromosomal instability
 - Angiogenesis
 - Invasion
 - Stroma activation
 - Fatty acid metabolism

Sillars-Hardebol AH, Tumour Biol. 2010 Apr;31:89-96.

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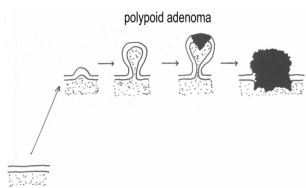
Which adenomas are relevant?

Biological variables can be adequate indicators of the risk that an adenoma will progress to cancer

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Alternative pathways: flat adenoma



- Easier missed on endoscopic screening
- More aggressive behaviour
- More frequent p53, less frequent k-ras mutations

JAMA, March 5, 2008 - Vol 299, No. 9 1027

Prevalence of Nonpolypoid (Flat and Depressed) Colorectal Neoplasms in Asymptomatic and Symptomatic Adults

Elia M. Sostres, MD, MS
Tanya Kubrakova, MD, MS
Robert V. Boush, MD
Suhail Park, MD
Srinivas Mahalingam, MD
John Sato, MD
Norman Meritt, MD
Sha Fu-Rong, MD, MS

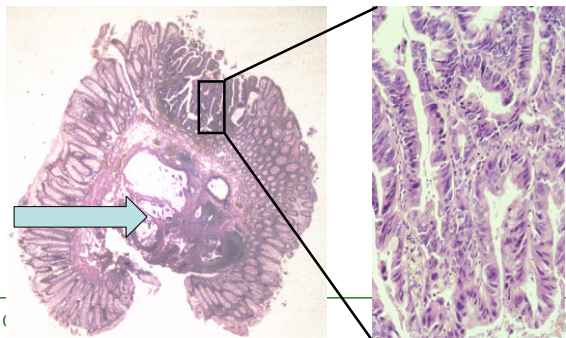
Results The overall prevalence of NP-CRNs was 9.35%

NP-CRNs were more likely to contain carcinoma (odds ratio, 9.78; 95% CI, 3.93-24.4) than polypoid lesions, irrespective of the size.

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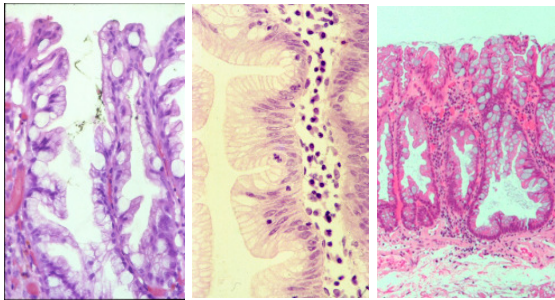


Flat carcinoma



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**Alternative pathways:
serrated adenoma**



Hyperplastic polyp Serrated adenoma Sessile serrated adenoma/...

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J Clin Pathol. 2004 July; 57(7): 662-666. PMID: 151770565
doi: 10.1136/jcp.2003.015230.
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My approach to serrated polyps of the colorectum

T Higuchi¹ and J R Jass²

Diagnosis	RC	LC/R	Un site	Total	%
TA	186	402	125	713	50
TVA	38	128	33	199	14
VA	1	11	1	13	1
HP	39	233	30	302	21
SSA	12	18	1	31	2
MP	5	9	2	16	1
SA	1	16	1	18	1
Other				144	10
				1436	100

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Alternative pathways

- May constitute around 10% of adenomas
- Atributable risk uncertain

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Conclusions

- The vast majority of adenomas do not progress to cancer and should not be screened for
- High risk adenomas and early stage cancers are the optimal screening targets
- Advanced adenoma is a suboptimal surrogate marker for high risk adenomas, and consequently a suboptimal intermediate endpoint
- Molecular characteristics of adenomas are potentially better outcome measures
- Alternative pathways do matter, how much we don't exactly know

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Bottom line

- Of most of the > 1.000.000 colorectal cancers annually world wide we do not know whether they arose
 - from a small or large precursor
 - via the traditional or an alternative pathway
 - from a flat or a polypoid precursor
 - through slow or rapid progression

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