

# **DNA MISMATCH REPAIR GENE MUTATIONS IN EARLY ONSET COLORECTAL CANCER**

**Genotypic Impact on Outcome**

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# MMR Gene Mutation Carrier Identification in General Population

Current mutation analysis is targeted by FH criteria

Predicates against low penetrance mutations & small families

MSI pre-screening prejudices functional effects of mutations

HNPCC family members develop early onset cancer

Need for systematic mutation detection in general population

# COGS study

Aims to define genetic contribution to colorectal cancer

Recruit all colorectal cancer patients in Scotland diagnosed <55 years, regardless of family history

Systematic recruitment soon after diagnosis

# Methodology

Subject materials	Blood sample for DNA Detailed family history Tumour material
Mutation analysis	All exons of MSH2, MLH1, MSH6 by dHPLC/sequencing MLPA for MSH2/MLH1 deletions
Survival analysis	Kaplan-Meier

# Assembly of Colorectal Cancer Patient Series

May 2005

Recruitment	1148
Subject concordance (since 1999)	90%
Total disease burden coverage (<55 yrs)	74%
Mean time from diagnosis to recruitment	17 wks

# Mutation prevalence in COGS recruits

Pathogenic mutation frequency (38/876) 4.3%

(only 34% of carriers are AMST II positive)

Male (27/466)

Female (11/410)

MLH1

39%

5.8%

MSH2

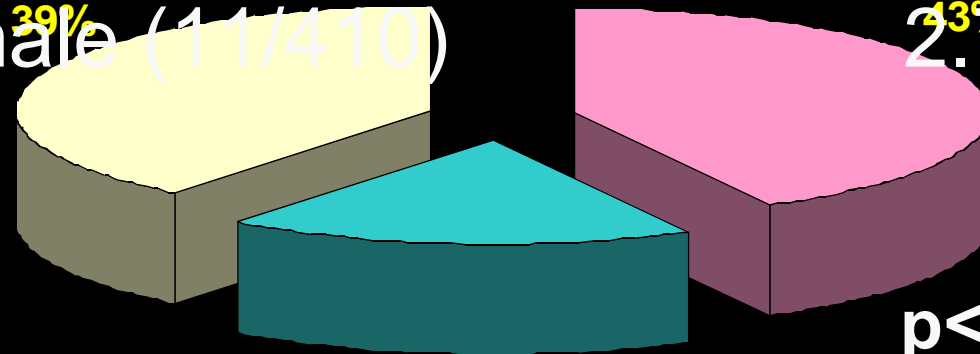
43%

2.7%

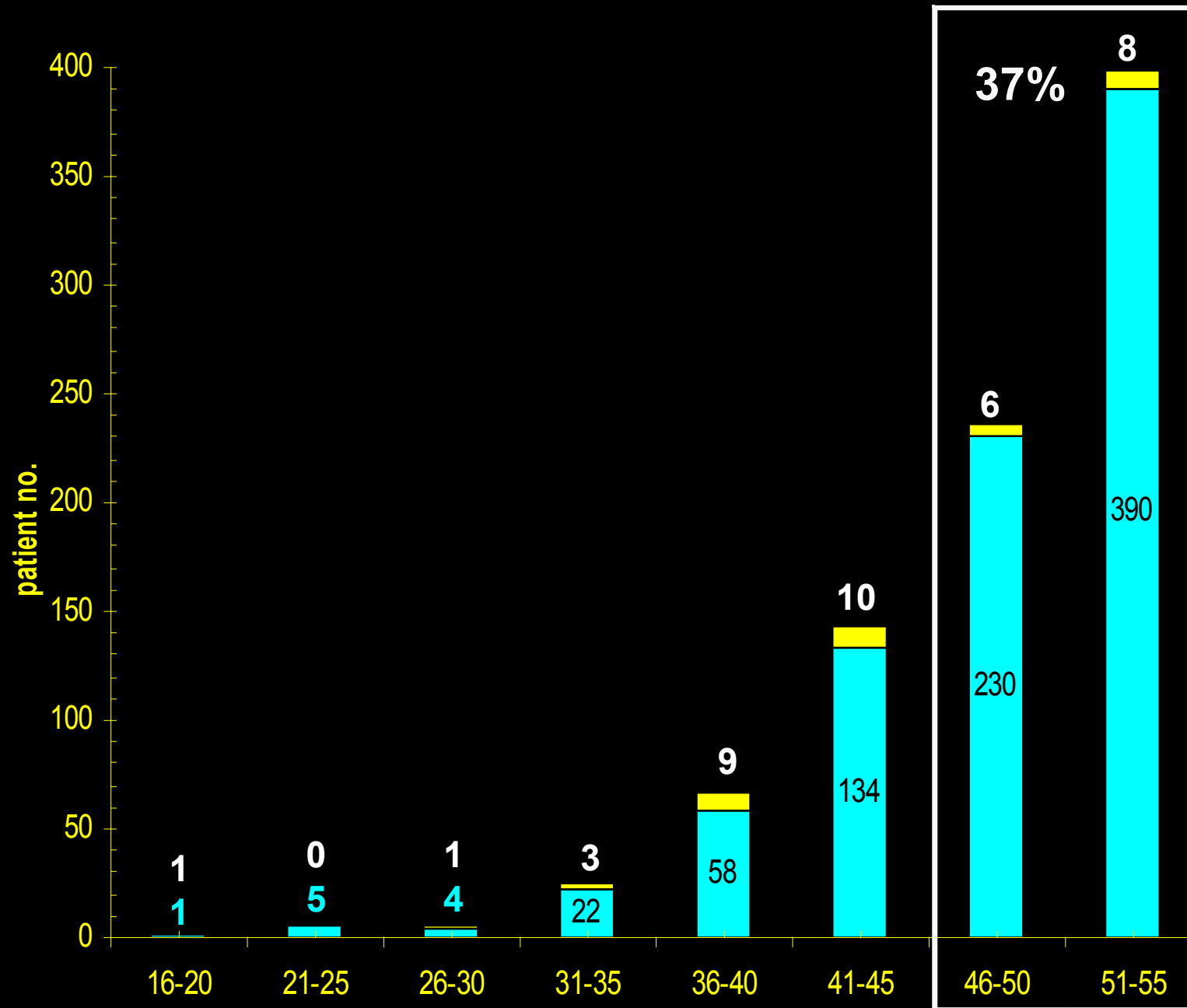
MSH6

18%

$p < 0.037^*$



# MMR Mutation Status by Age Group

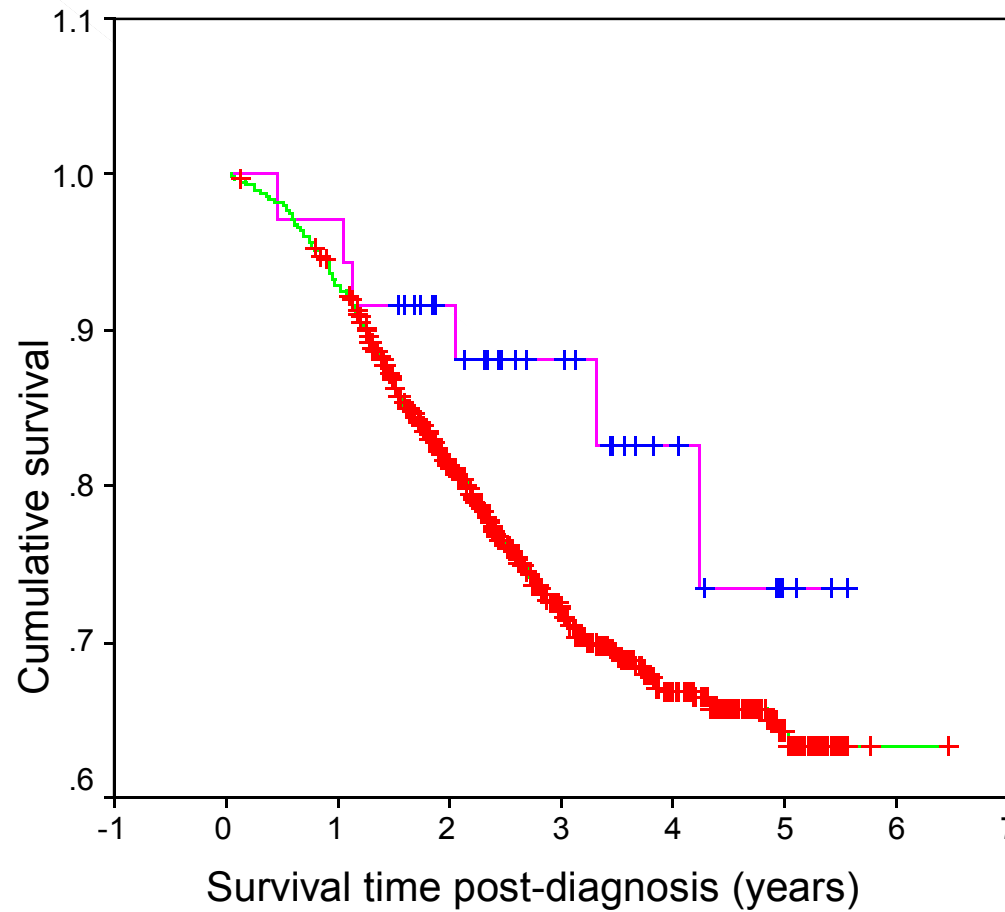


	<b>Carriers (%)</b> <b>n=38</b>	<b>Non-carriers (%)</b> <b>n=838</b>	
<b>Mean age</b>	42.7 years	48.2 years	<0.0001*
<b>Tumour location</b>			
Proximal colon	22 (58)	169 (26)	
Distal colon	16 (42)	493 (74)	<0.0001*
<b>Histology</b>			
Mucinous	13 (38)	108 (17)	
Standard	21 (62)	540 (83)	0.004*

No significant differences

Duke's stage  
 Histological differentiation  
 Presence of metastases

# Survival by MMR genotype



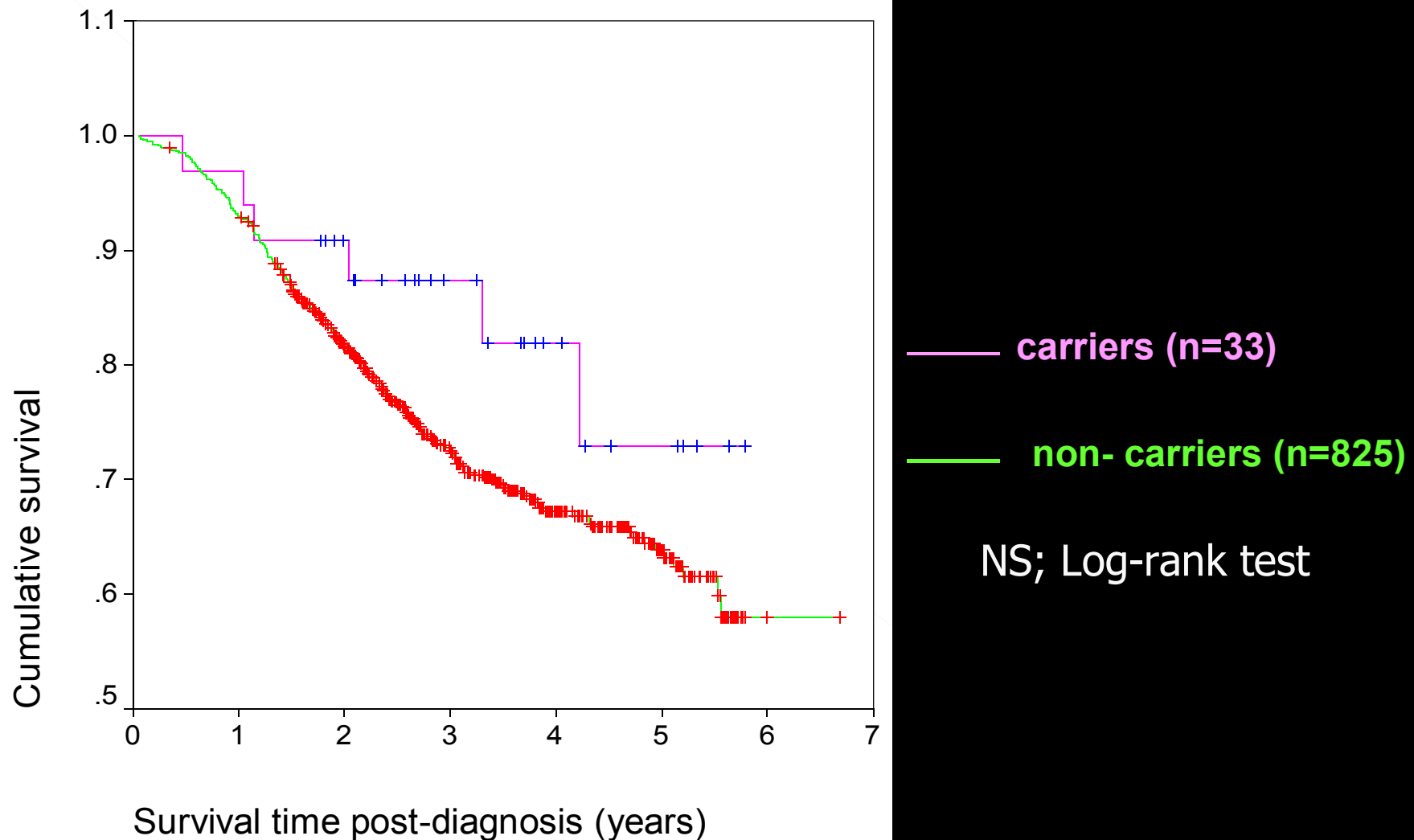
— carriers (n=38)

— non-carriers (n=838)

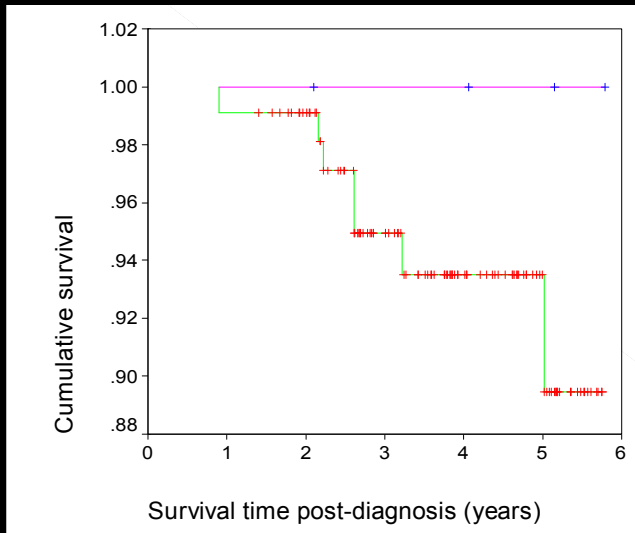
NS; Log-rank test

# Survival by MMR genotype

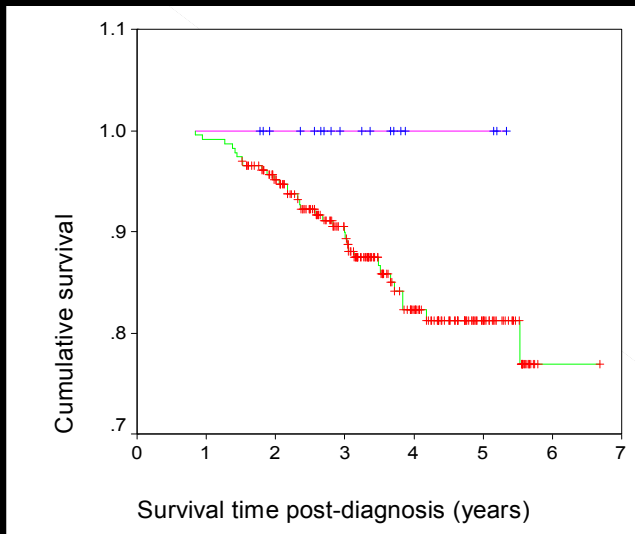
Excluding surveillance detected tumours and previous cancer



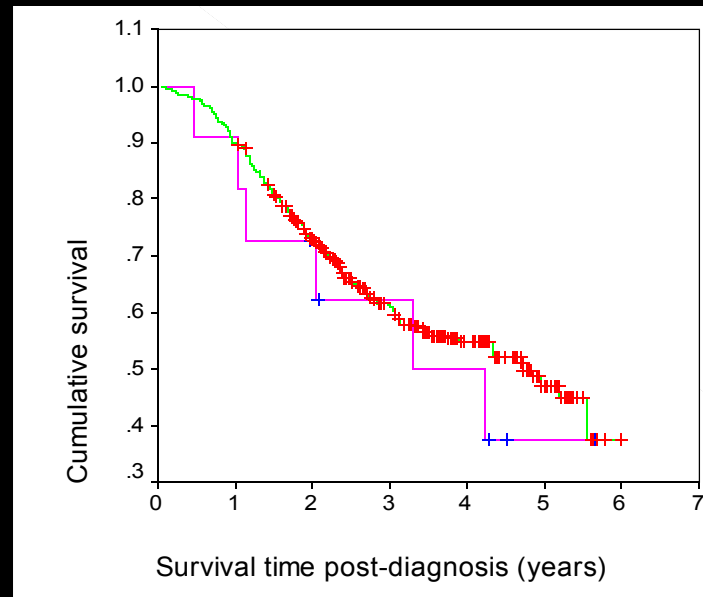
# Dukes A



# Dukes B



# Dukes C



— carriers

— non-carriers

# Conclusions

MMR mutation prevalence in CRC <55yrs was 4.3%

Two-fold excess prevalence of mutations in males

Age at onset selection enriches for mutation carriers

Most MMR mutation carriers do not fulfil AMS II criteria

Survival and tumour stage is not influenced by MMR mutation status

# Colon Cancer Genetics Group

## Genetic Susceptibility

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