

Cancer risk in MMR mutation carriers

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Problem: How do we estimate cancer penetrance (age-specific cumulative risk) in individuals who carry a germline MMR mutation?

Issue 1. Heterogeneity of risk. May depend on:

- mutation
- gene
- environmental exposures
- other genetic mutations

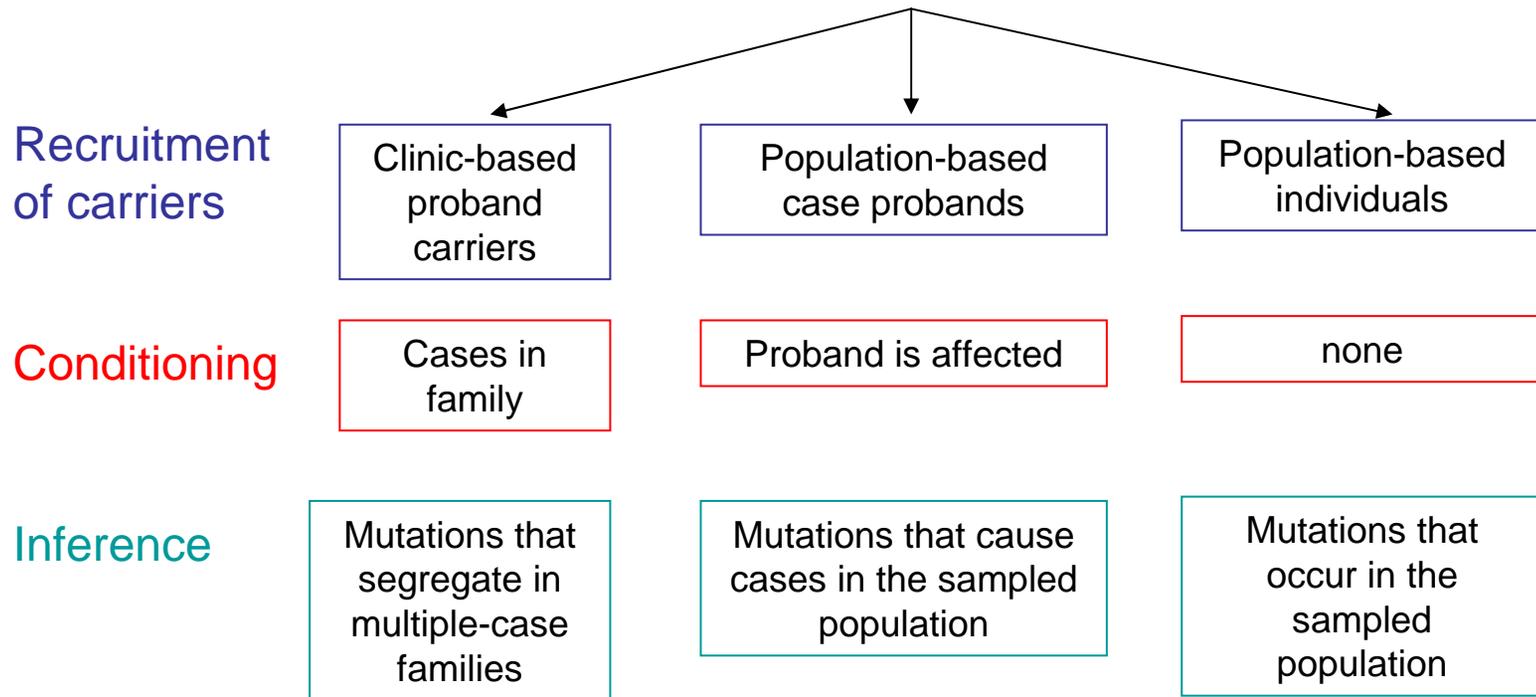
There may not be 'a' penetrance!

Issue 2. How to estimate penetrance – not straightforward

Designs to estimate penetrance

Not case-control study - mutations are too rare

Need family designs – study relatives of known carriers



Question: Does penetrance differ by setting? – Need valid estimates and SEs

Clinic-based
(six studies of 1,681
carriers)

Mitchell et al 2002

Clinic-based
84 families

Quehenberger,
Vasen et al, 2005

Population-based
6 families
of CRC < 35

Dunlop et al, 1997

Estimates of cumulative CRC risk to age 70

Males: 81%
Females: 63%

27% (13-51)
23% (11-44)

74% (approx 55-95)
30% (approx 10-50)

Estimates of Hazard ratio

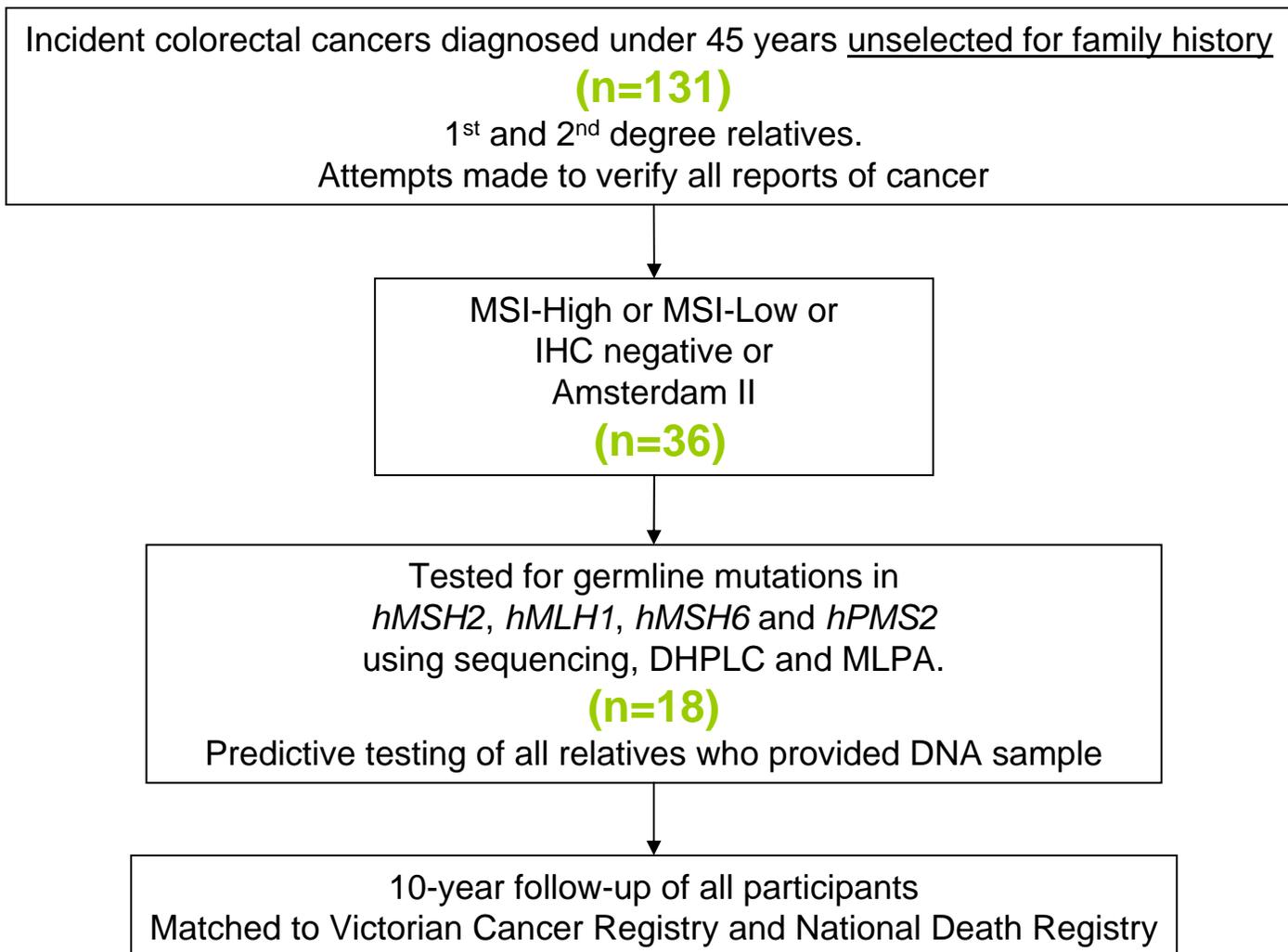
Approx 25

<50 years, approx 25
>50 years, approx 4

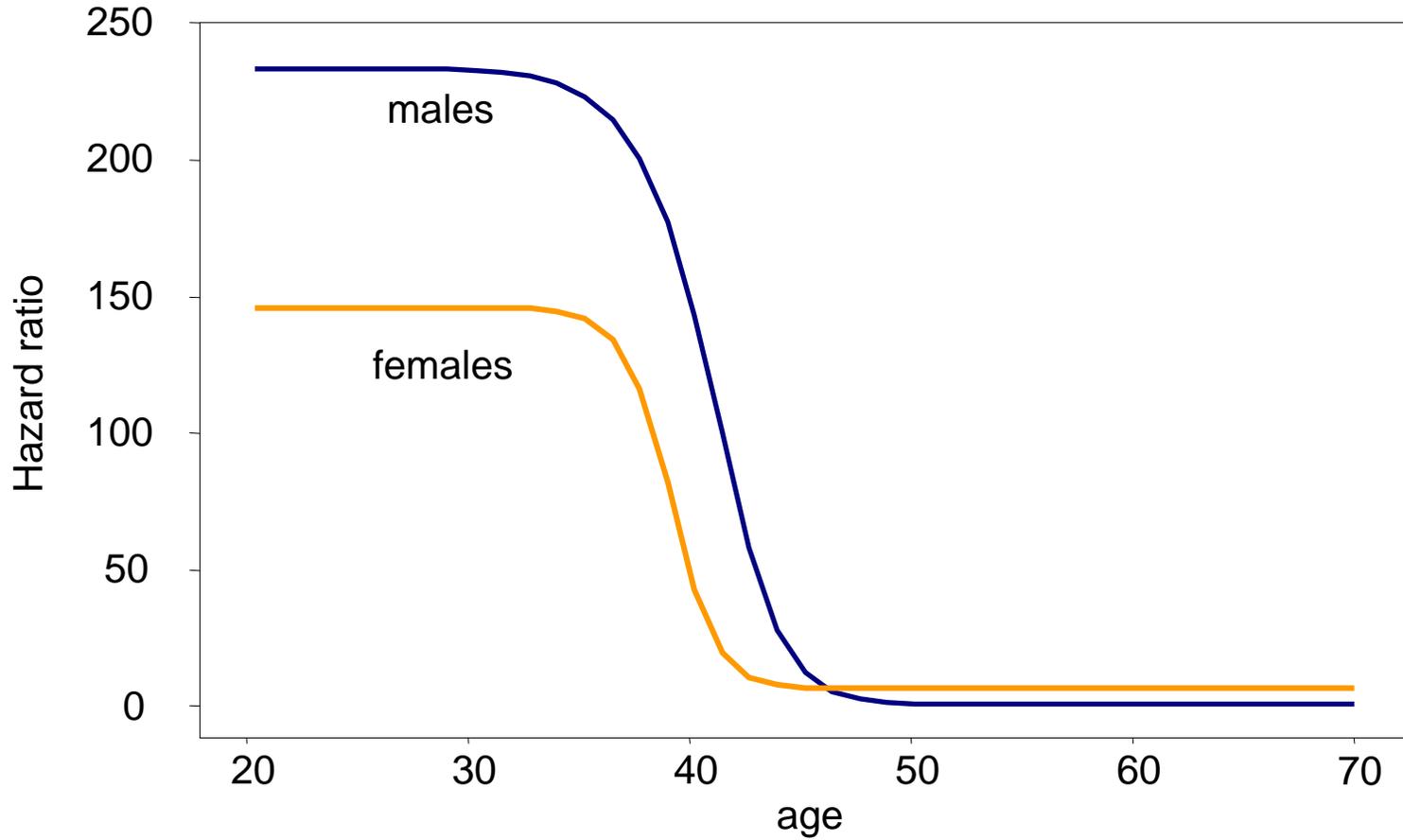
males 29
females 18

Incorrect!
(inadequate conditioning
on ascertainment)

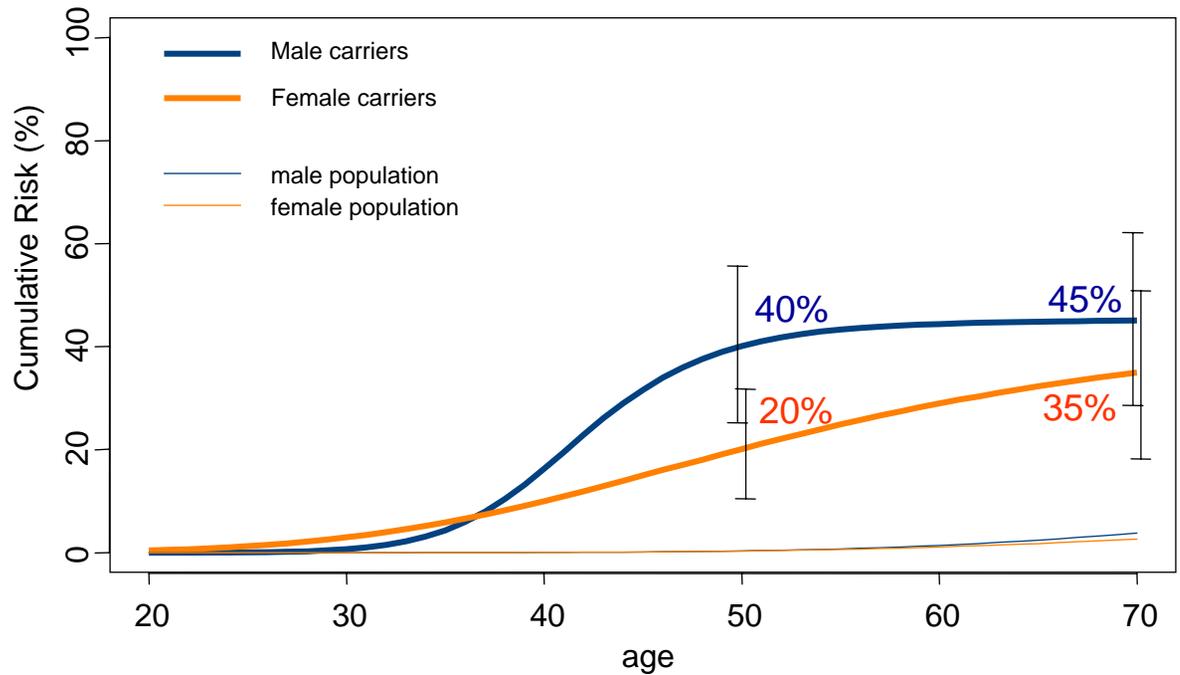
Victorian Colorectal Cancer Family Study



Hazard ratio (risk in carriers compared to risk in the population) for CRC in MMR mutation carriers



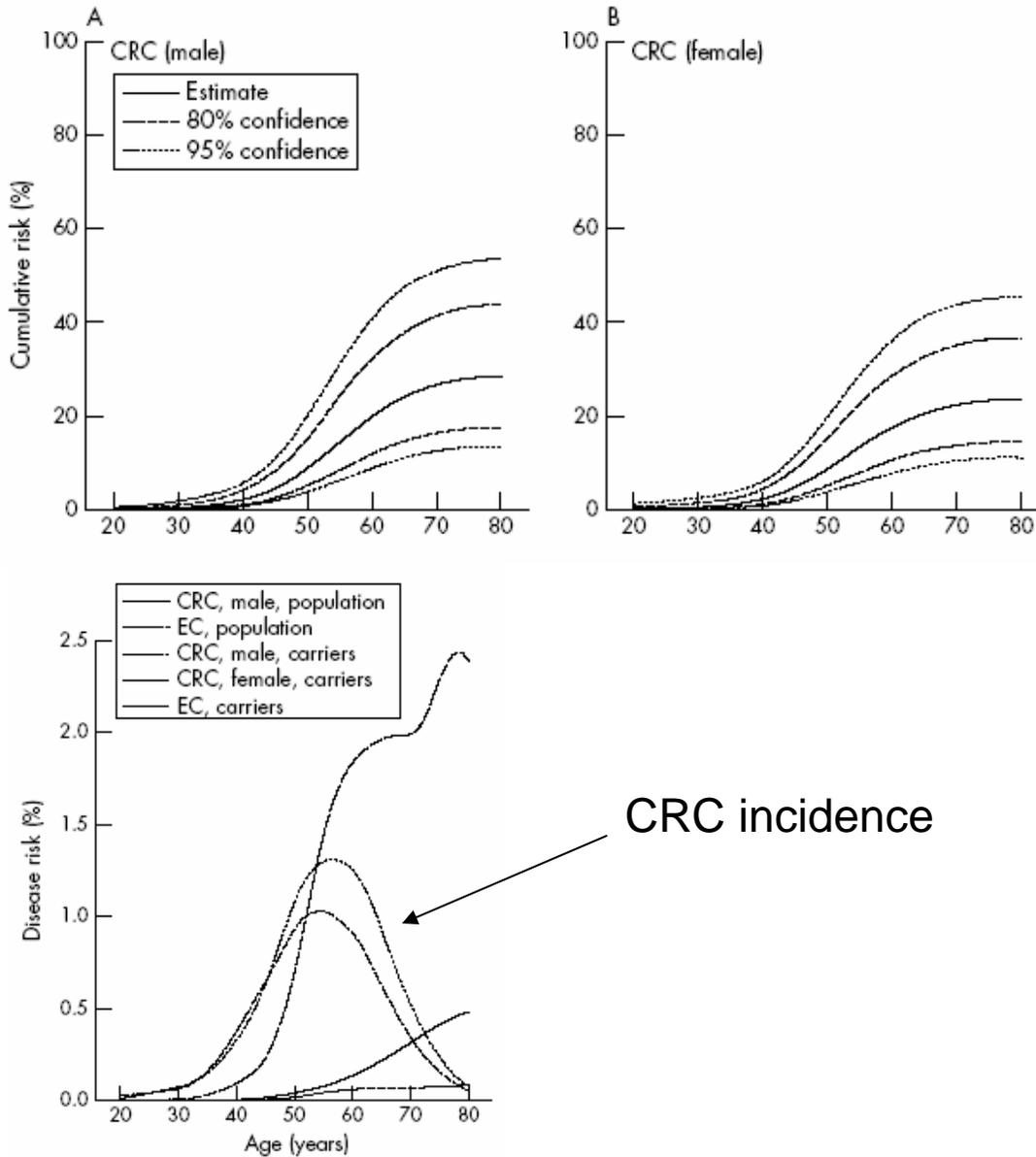
Cumulative risk of CRC in MMR mutation carriers



10-year risks of CRC given no disease at beginning of age period

	Male carriers	Male pop'n	Female carriers	Female pop'n
40 to 50 yrs	28%	0.3%	11%	0.2%
50 to 60 yrs	7%	1.0%	11%	0.8%
60 to 70 yrs	2%	2.4%	14%	1.6%

Quehenberger et al, 2005



Colon Cancer Family Registry

Hundreds of families identified with definite MLH1, MSH2 or MSH6 mutations

Clinic-based and population-based with different ages at diagnosis

- Modified segregation analyses provide
Hazard ratios
penetrance, and
standard errors
- Valid estimates despite incomplete mutation testing of relatives
- More precision will increase with more complete testing of relatives

Colon Cancer Family Registry

Potential to estimate penetrance by:

Gene	MLH1, MSH2, MSH6
Type of variant	PTT, missense
Sex	male, female
Setting	clinic-based, population-based
Cancer specific	CRC, extra-colonic, endometrial, other

These analyses will inform us on the sample sizes needed to test for differences by gene etc...