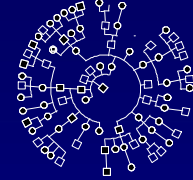


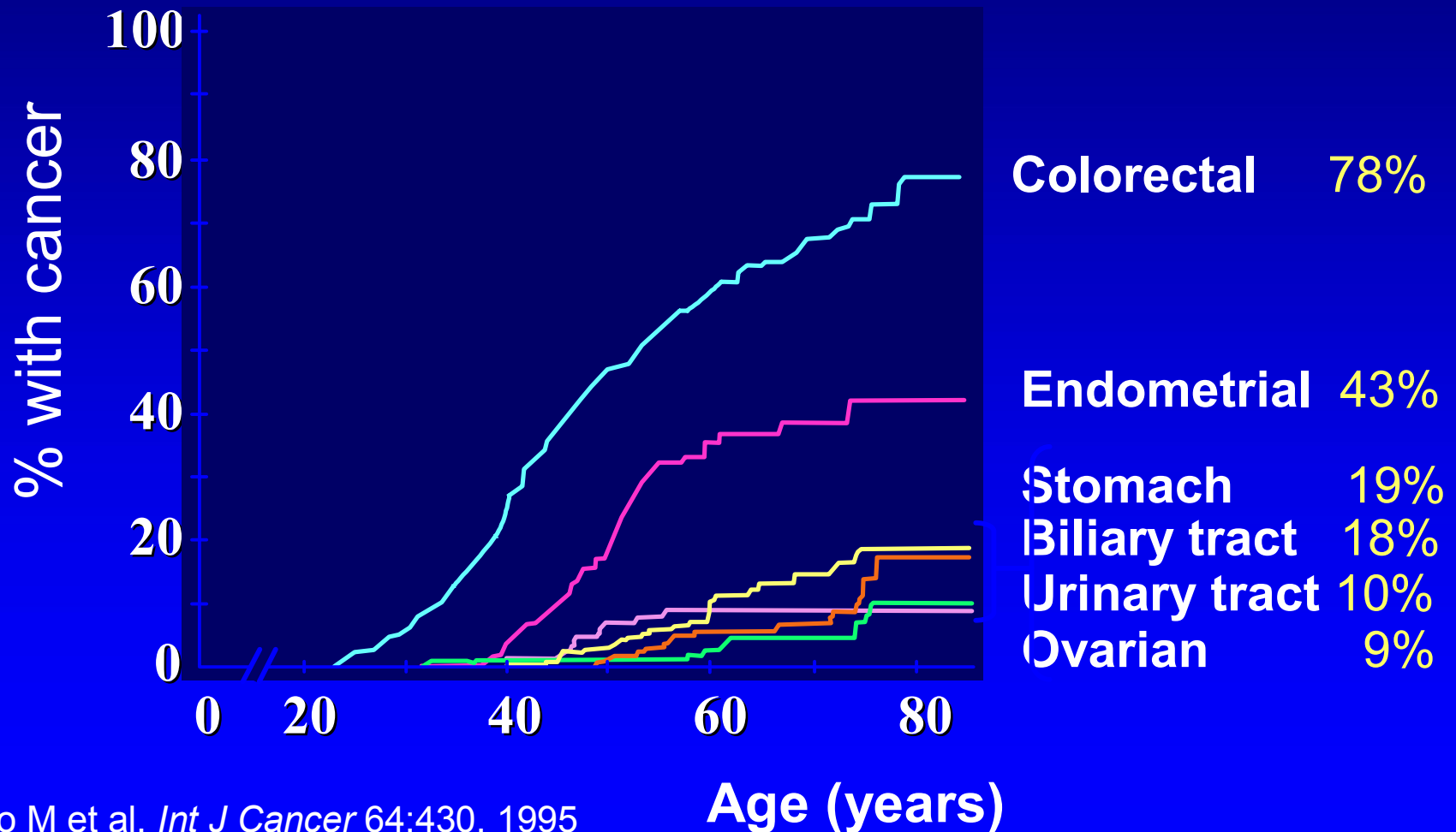
Mortality in Families with the Lynch Syndrome

Andrea de Jong, Yvonne Hendriks, Sybrand de Boer,
Annemieke Cats, Gerrit Griffioen, Jan Kleibeuker, Fokko
Nagengast, Frits Nelis, Matti Rookus, Hans Vasen

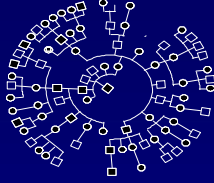
The Netherlands Foundation for the Detection of Hereditary Tumours



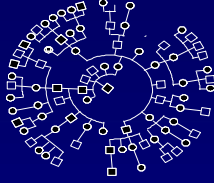
Cancer Risks in HNPPCC



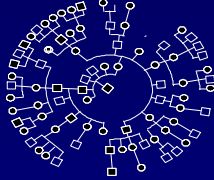
Mortality Risks in HNPPC



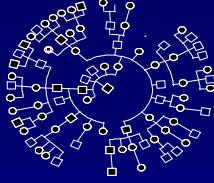
???



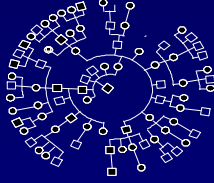
1. Evaluation of causes of death in families with Lynch syndrome
2. To examine the effectiveness of the surveillance program for CRC by assessing the mortality over time
3. To compare mortality due to all cancers (except CRC/EC) with general population



- Dutch HNPCC Registry
- 146 mutation families (1 april 2004): 55 *hMLH1*, 67 *hMSH2*, 24 *hMSH6*
- Selection: (putative) carriers, FDR:
alive > 1960, born between 1880 – 1984
- non-carriers were excluded

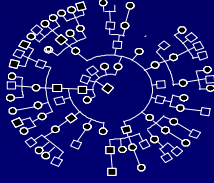


- Dates of birth were estimated if missing (10%)
- Exclusion: Individuals with loss of follow-up (n=20) and with unknown gender (n=40)



O/E ratio on basis of age, gender and calender – period specific cancer mortality rates in the Dutch General Population.

(computer program, developed at the Netherlands Cancer Institute (van Leeuwen et al. J. Clin. Oncol., 1994))



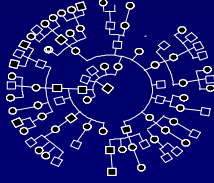
Selection bias:

HNPPC families: mainly due to diagnosis of CRC / EC in family.

Testing bias:

Subjects probably opt for DNA-test more often when CRC / EC in past.

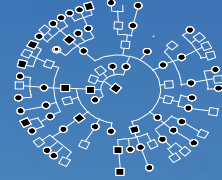
Testing bias other tumours?



	N	Tested	% tested
Affected *	117	56	47.9
No cancer **	2139	915	42.8

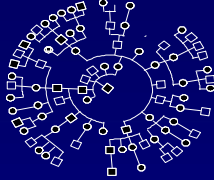
* Subjects with a non CRC / EC carcinoma

** Subjects without any cancer or with CRC/ EC
> age 60



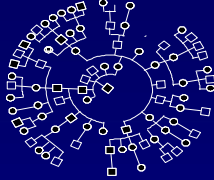
Results





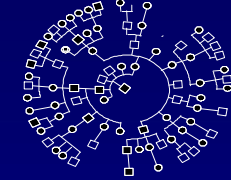
Characteristic	No. of subjects	Person years	(%)
All	2788	92196.18	
Cause of death			
Cancer	445		(61)
No cancer	206		(28)
Unknown	82		(11)
Gender			
Male	1413	46189.92	(50)
Female	1375	46006.26	(50)
Mutation status			
Carrier	882	31431.36	(34)
Putative carrier	310	9058.42	(10)
FDR	1596	51706.40	(56)
Mutation in family			
<i>hMLH1</i>	1088	36547.56	(40)
<i>hMSH2</i>	1351	43499.72	(47)
<i>hMSH6</i>	349	12148.89	(13)
Period alive			
1960 - 1975	2532	38772.37	(42)
1976 - 1990	2532	33518.25	(36)
1991 - 2004	2200	19905.57	(22)
Surveillance			
yes	897	35579.33	(38)
no	1073	25472.61	(28)
unknown	818	31144.24	(34)

Descriptive characteristics of the study cohort



Causes of death due to carcinoma

All (n = 445)	Male (n = 240)	Female (n = 205)
CRC (50.3%)	CRC (56.3%)	CRC (43.4%)
EC (6.7%)	Lung (7.5%)	EC (14.6%)
Brain (6.7%)	Brain (7.5%)	Brain (5.9%)
Lung (4.5%)		
Stomach (4.1%)		



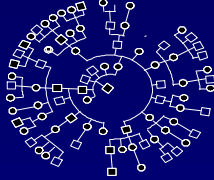
Standard Mortality Rate (SMR) for Colorectal (CRC) and Endometrial Cancer (EC) in three successive time periods

Cancer site	1960-1975			1975 - 1990			1990 - 2004		
	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
CRC ¹	86	2.66	32.3	84	4.39	19.1	54	5.36	10.1
EC ²	10	0.43	23.4	14	0.43	32.6	6	0.43	14.1

Obs.: observed; Exp.: expected

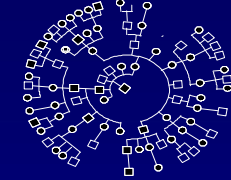
¹statistical significance between periods 1960-1975 and 1990-2004; $P < 0.001$, Hazard ratio = 3.2, 95% CI = 2.3 – 4.6

²no statistical significance between periods 1960-1975 and 1990-2004; Hazard ratio = 1.7, 95% CI = 0.6 – 5.6



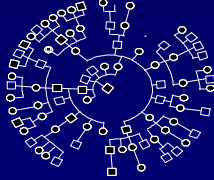
Effect of surveillance on mortality due to CRC

	Surveillance	No surveillance
N	897	1073
Person years	25758.77	26719.76
Observed	14	200
Expected	2.2	8.4
RR	6.5	23.9
<i>P</i>	<0.001	
95% CI	2.2 – 6.9	



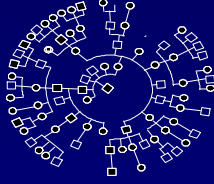
Observed (Obs.) and expected (Exp.) numbers of cancers, standardized mortality ratio's (SMR) and Absolute Excess Risks (AER) in 146 families with Lynch syndrome

Cancer site	Obs.	Exp.	SMR	95% CI	<i>P</i>	AER
Brain	30	3.29	9.11	6.2 – 13.0	<0.001	2.9
Kidney / ureter	17	2.89	5.88	3.4 – 9.4	<0.001	1.5
Stomach	18	8.46	2.13	1.3 – 3.4	0.01	1.0
Bladder	5	2.92	1.71	0.6 – 4.0	NS	0.2
Small Bowel	6	0.33	18.3	6.7 – 39.6	<0.001	0.6
Pancreas	12	5.55	2.16	1.1 – 3.8	0.02	0.7
Oesophagus	4	2.53	1.58	0.4 – 4.0	NS	0.2
Prostate	6	4.56	1.32	0.5 – 2.9	NS	0.2
Liver	15	0.98	15.3	8.6 – 25.2	<0.001	1.5
Ovarium	9	3.97	2.27	1.0 – 4.3	0.04	0.5
Non specified	16	5.29	3.03	1.7 – 4.9	<0.001	1.2
Lung	20	31.60	0.63	0.4 – 1.0	0.04	-1.3
Breast	6	12.8	0.47	0.2 – 1.0	0.06	-0.7



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A significant decrease in SMR due to CRC was observed over time.

Lynch syndrome family members have a significantly increased risk of dying from cancer of the brain and kidney / ureter.