Incident Testing for Lynch Syndrome in Colorectal Cancer Under 50 in British Columbia

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Background

- Lynch syndrome (HNPCC) is the most common form of inherited colorectal cancer
  - 2-5% of all colorectal cancers
  - High life-time risk of colon and other cancers

Cancer	General population risk	HNPCC risk	Mean age of onset
Colon	6%	80%	44 yrs
Endometrial	3%	20-60%	46 yrs
Stomach	~1%	10-19%	56 yrs
Ovary	2-3%	10-12%	42 yrs
Hepatobiliary tract	<1%	2-7%	not reported
Urinary tract	<1%	4-5%	~55 yrs
Small bowel	<1%	1-4%	49 yrs
Brain/CNS	<1%	1-3%	~50 yrs

Adapted from Genereviews

Background

- Underlying mutations in DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2
- Microsatellite instability (MSI) in up to 90% of Lynch colorectal tumors
- Intensive cancer screening and prophylactic surgery shown to reduce incidence and mortality of colorectal cancer and endometrial cancer
- Optimal method of identifying individuals with Lynch syndrome is currently under debate

Background

- Genetic counselling and testing for Lynch syndrome have been available on a clinical basis
  - Amsterdam I or II or revised Bethesda criteria
- Previous work has shown:
  - Overall yield of Lynch mutations differs based on ascertainment method
    - Colorectal cancer <50 years of age was 14% (Hampel et al. 2008)
    - Clinic based approach at BCCA (including individuals with and without cancer) is 3.4% (Cremin et al. 2009)
- Evaluation of Genomic Applications in Practice and Prevention Working Group recommended removal of family history from consideration as a preliminary test in newly diagnosed colorectal cancer (Palomaki et al. 2009)

Clinical Criteria - Amsterdam

- Amsterdam I
  1. ≥3 relatives with colorectal cancer (CRC) plus
  2. One affected patient should be a first degree relative of the other two
  3. ≥2 successive generations affected
  4. At least one case of CRC dx <50
  5. FAP excluded
  6. Pathology confirmation

- Amsterdam II
  1. ≥3 relatives with Lynch-associated cancers plus
  2. One affected patient should be a first degree relative of the other two
  3. ≥2 successive generations affected
  4. One or more cases of CRC dx <50
  5. FAP excluded
  6. Pathology confirmation

Clinical Criteria – Bethesda and HCP

- **Revised Bethesda**

1. CRC dx <50
2. Synchronous, metachronous CRC or other Lynch-associated tumor
3. CRC <60 with tumor infiltrating lymphocytes, crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern
4. CRC dx in patients with ≥1 first degree relative with Lynch-associated tumor with ≥1 dx <50
5. CRC dx in patient with ≥2 first or second degree relatives with Lynch-associated tumor regardless of age

- **HCP**

1. Carrier testing
2. Isolated CRC ≤40
3. ≥2 HNPCC primaries, one being colon, one dx ≤50
4. Amsterdam I
5. 2 first degree relatives with HNPCC-related cancers, one being colon, both dx ≤50
6. ≥3 HNPCC-related cancers, one being colon, one dx ≤50 and more than one generation affected
7. Isolated case CRC ≤50 with MSI-H result

Lynch syndrome identification in BC

- In BC a combination approach to identify patients at increased risk for Lynch syndrome has been used since June 2008

- Patients identified in two ways:

  - Clinic-based: Referral to the HCP due to personal and/or family history of colorectal and other Lynch-related cancers

  - Incident-case based: MSI analysis in patients ≤50 diagnosed with colorectal cancer.

Referral to BCCA vs. HCP

- Referral to BCCA includes referral for
  - Oncological consult and care
  - Cancer drug therapy
  - Radiation therapy
  - MSI, IHC, Germline mutation testing
  - Referral to HCP

- Referral to HCP
  - Appointment with a Geneticist/ Genetic Counsellor due to personal or family cancer history that might indicate an inherited gene mutation
  - Further investigation for Lynch syndrome

Hypothesis

Direct referral for MSI analysis on incident colorectal cancer (CRC) ≤50 will generate a different rate of ascertainment of Lynch syndrome than referrals based on Amsterdam and revised Bethesda guidelines.

What is MSI?

- Microsatellite instability (MSI) refers to difference between the size of microsatellites in DNA from tumor tissue compared to normal tissue from the same person

- A panel of five mononucleotide and dinucleotide markers recommended by National Cancer Institute in 1998 is used in assessing MSI
  - BCCA lab currently uses a panel of 7 markers

- **MSI-high** - ≥30% of the markers show instability
- **MSI-low** - <30% of the markers show instability
- **MSI-stable** - 0% of the markers show instability

Data Set

- Cases of colorectal cancer ≤50 diagnosed between June 1, 2008 – August 30, 2009 referred to the BC Cancer Agency*

- 169 cases
  - 60 (36%) referred to HCP
  - 91 female
  - 78 male

*An additional 103 non-referred cases were identified from the BC Cancer Registry but are not included in this preliminary report

Data request specifications

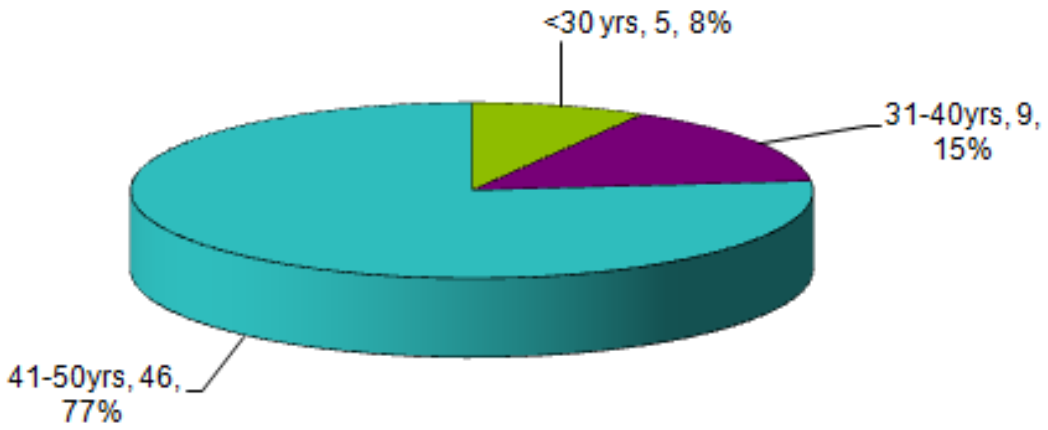
Some demographic and clinicopathologic information:

- Date of birth
- Date of death
- Sex
- Age at diagnosis
- Tumor site
- TNM stage and grade classification
- Health authority at time of diagnosis
- Referral status to HCP

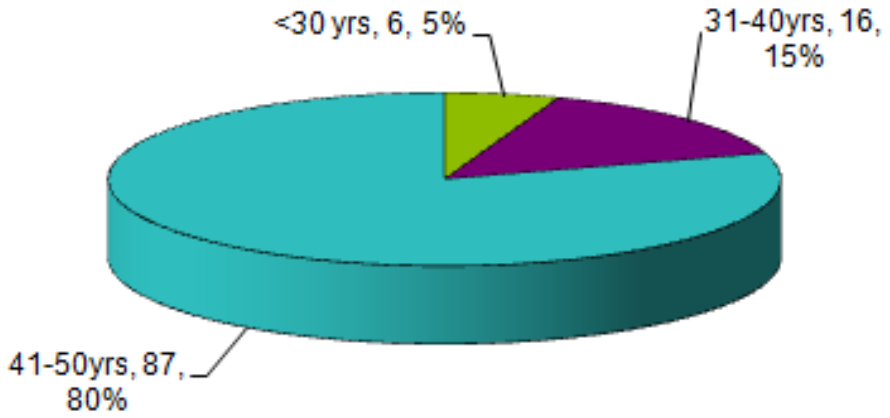
Age Distribution (n=169)

Median age at diagnosis – 46

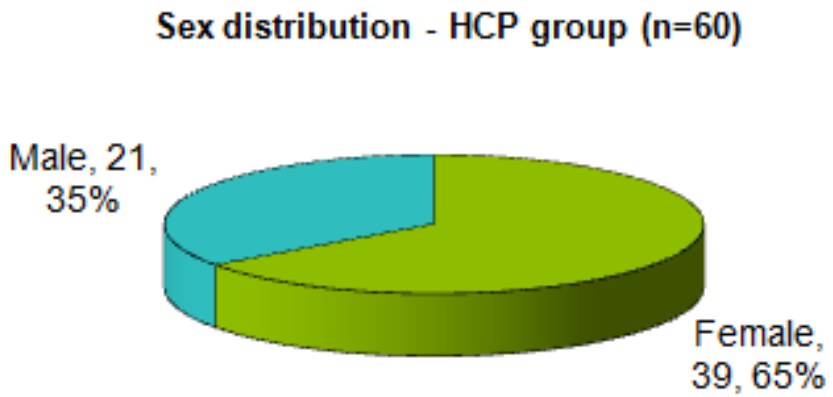
Age distribution - HCP group (n=60)

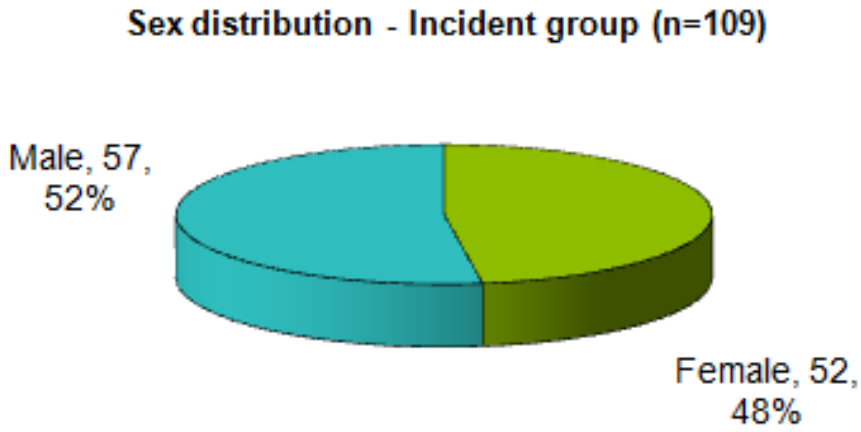


Age distribution - Incident group (n=109)



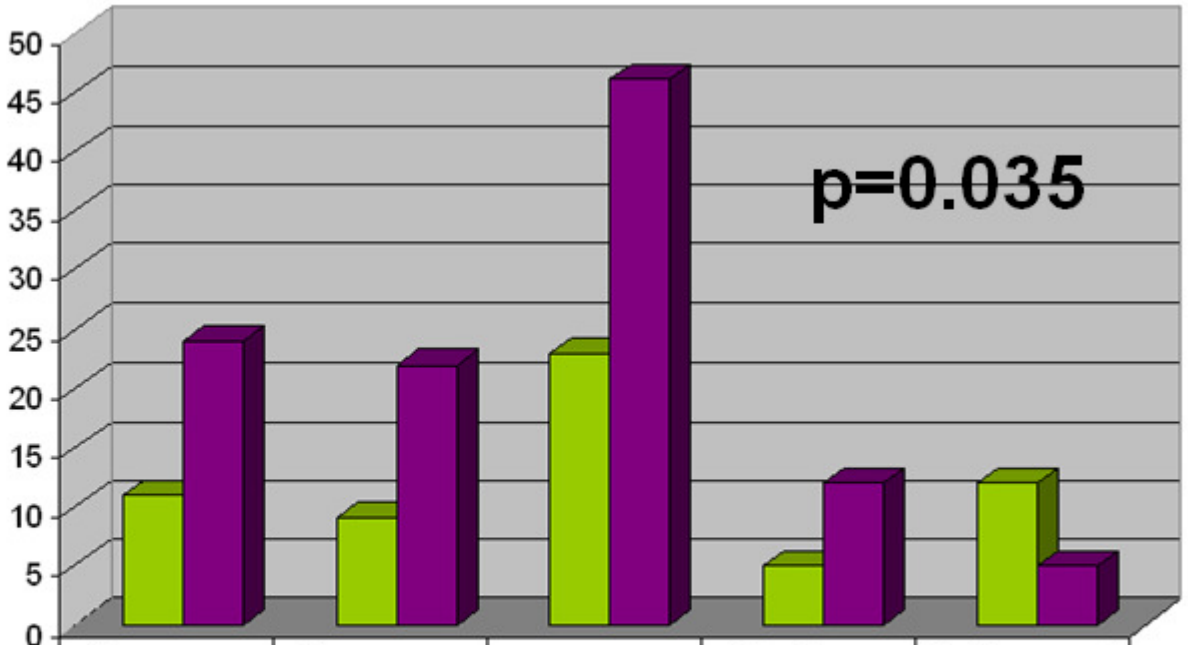
Sex Distribution (n=169)





p=0.037

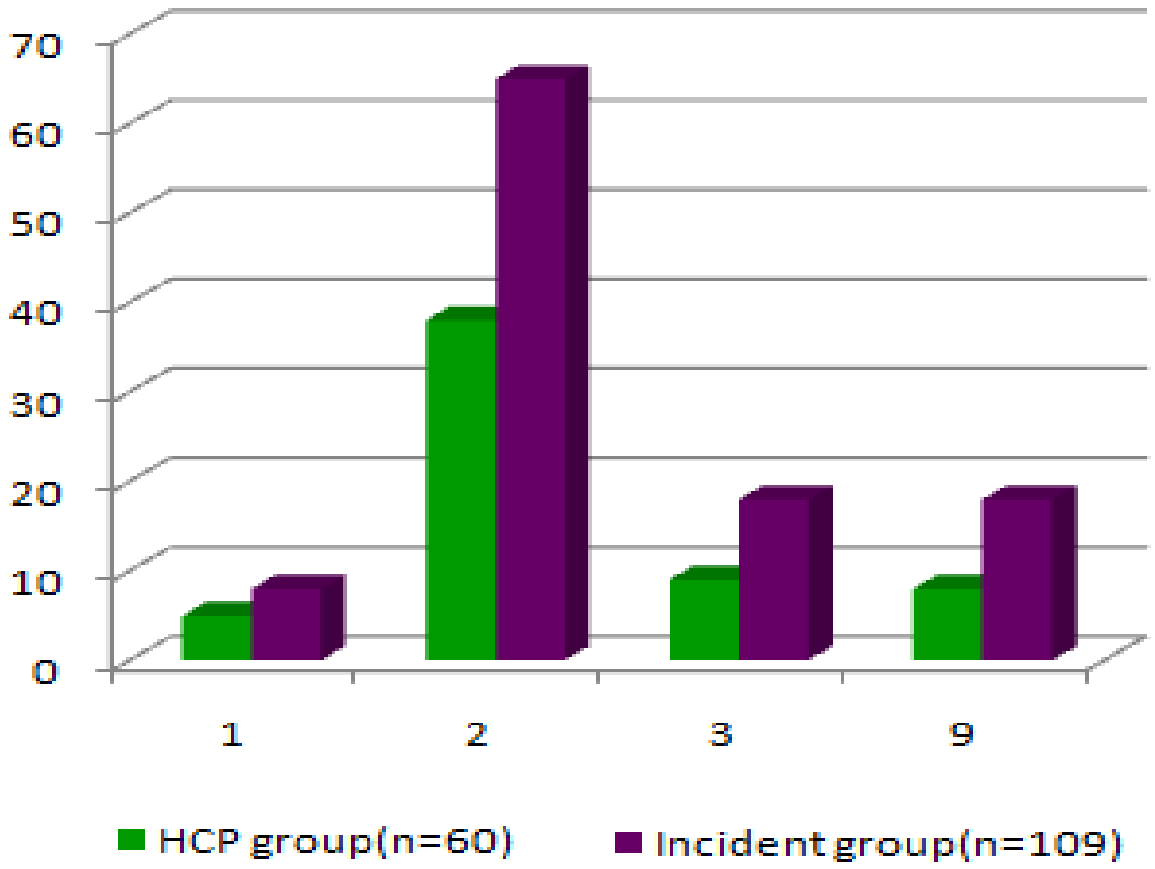
Health authority distribution at time of diagnosis (n=169)



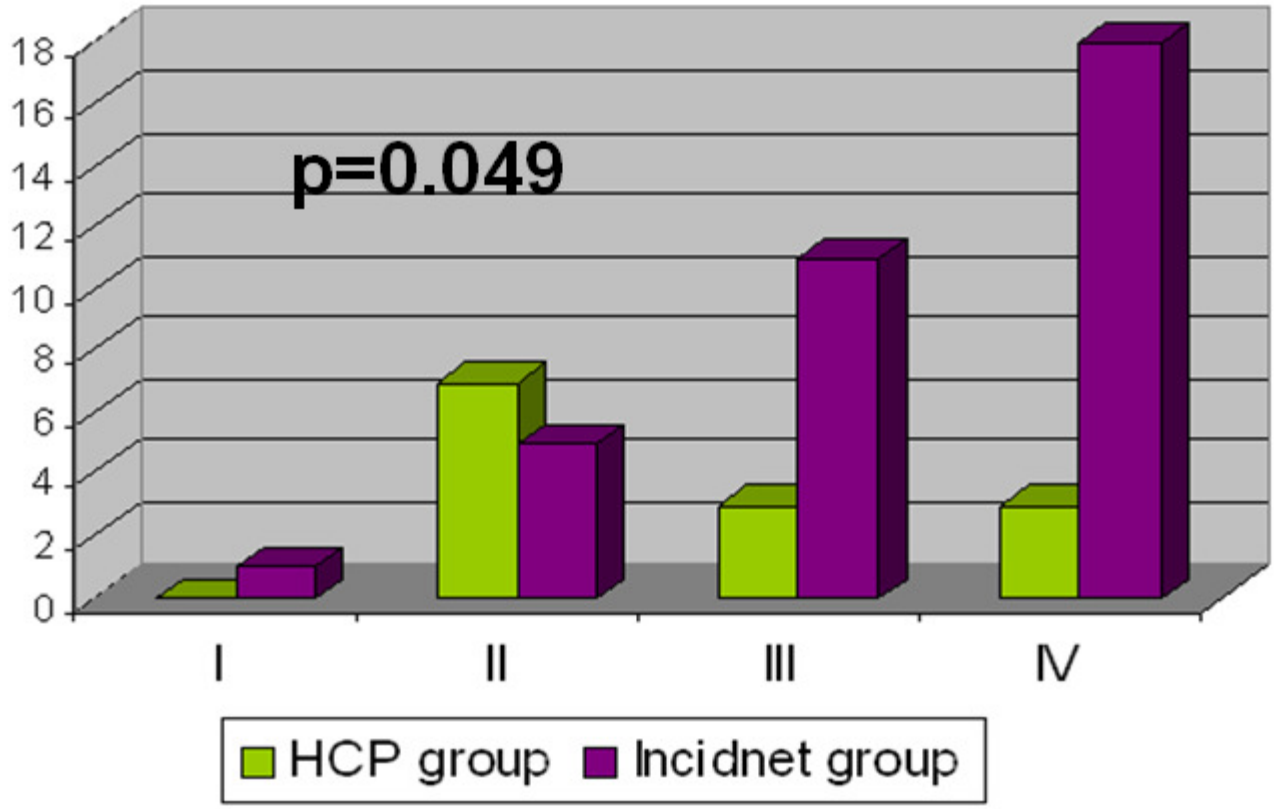
	Vancouver Coastal	Vancouver Island	Fraser Valley	Southern Interior	Northern and Other
HCP group (n=60)	11	9	23	5	12
Incident group (n=109)	24	22	46	12	5

Tumor site distribution (n=169)

Tumor surgical grade (n=169)



Tumor surgical stage (n=169)



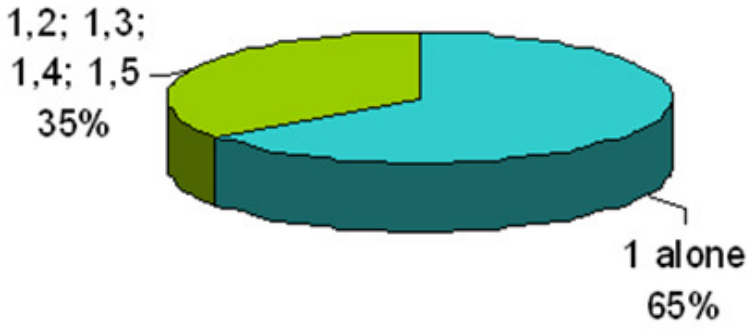
Patient distribution by Clinical criteria

Clinical criteria met	Number of patients (n=176)
Revised Bethesda	169
Amsterdam I	2
Amsterdam II	4
HCP	72
Family history not taken or incomplete	24
Adopted	6

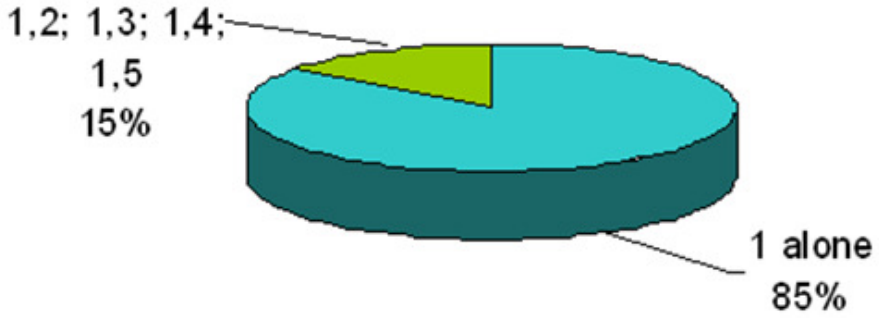
Each patient may qualify for one or more criteria
Patients diagnosed at 50 were considered to fulfill Revised Bethesda criteria

Patient distribution by clinical criteria (n=169)

HCP group (n=60)

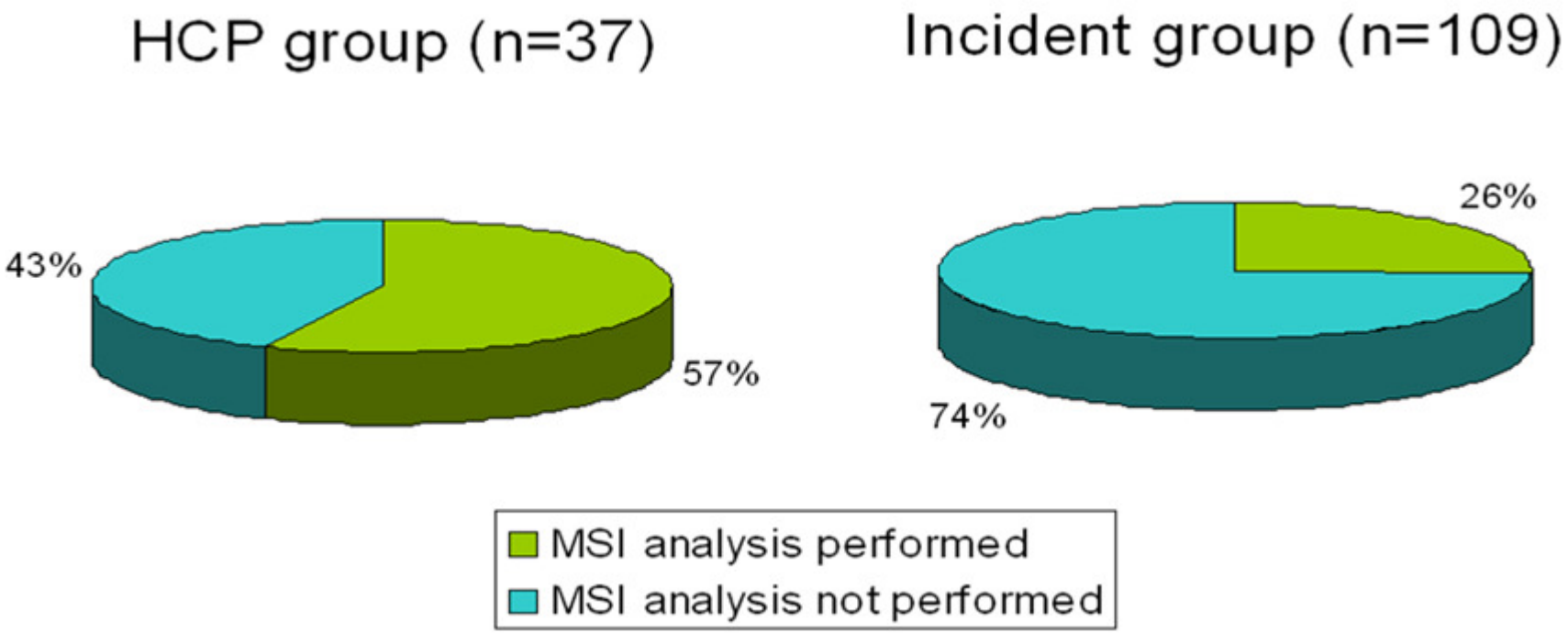


Incident group (n=109)



p=0.003

MSI analysis in patient population (n=146)



p=0.001

23 patients did not have genetic counselling

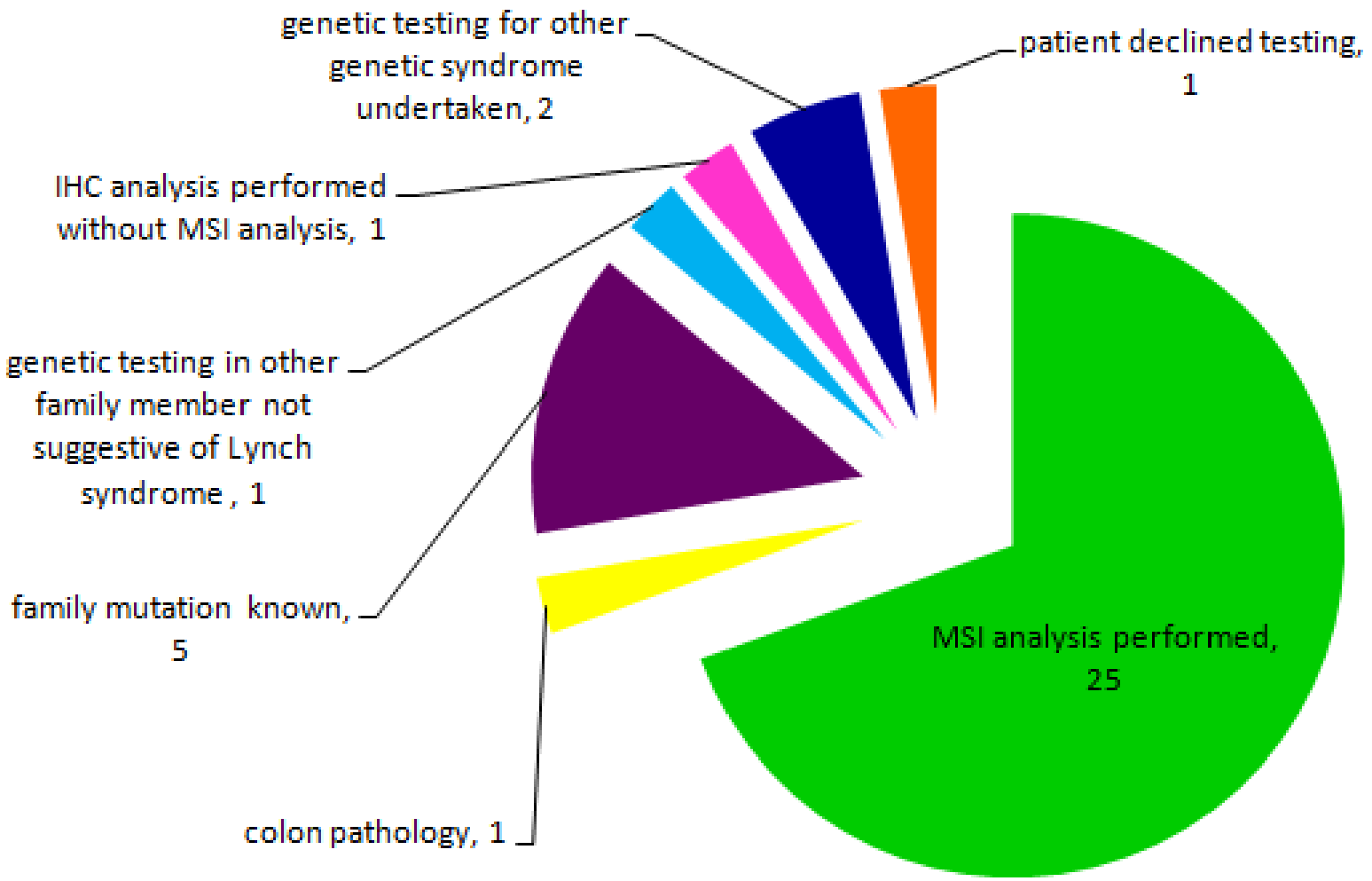
Patient deceased	2
Patient did not wish to attend appointment	1
No appointment offered - personal or family history not suggestive of Lynch syndrome	7
No appointment offered - Patient referred to Oncologist for MSI analysis	1
Personal or family history or genetic testing suggestive of other cancer syndrome (FAP, HBOC, NHL)	3
Patient awaiting appointment	4
Unknown	5

MSI utilization rate and results

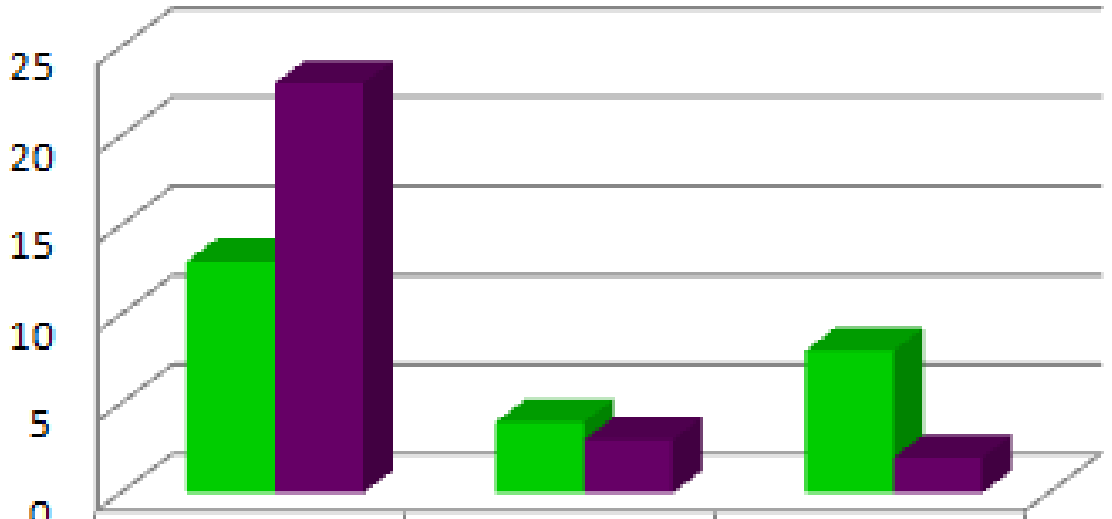
	HCP group (n=37)	Incident group (n=109)
MSI utilization rate	25/37 = 67%	28/109 = 26%
MSI-H rate	48%	18%

- 37 of the 60 patients in the HCP group received genetic counselling
- MSI analysis was offered to 25 of 37 patients in the HCP group
- Overall 53 patients underwent MSI analysis
- 32% of patients receiving MSI analysis showed microsatellite instability

MSI analysis in HCP group (n=37)

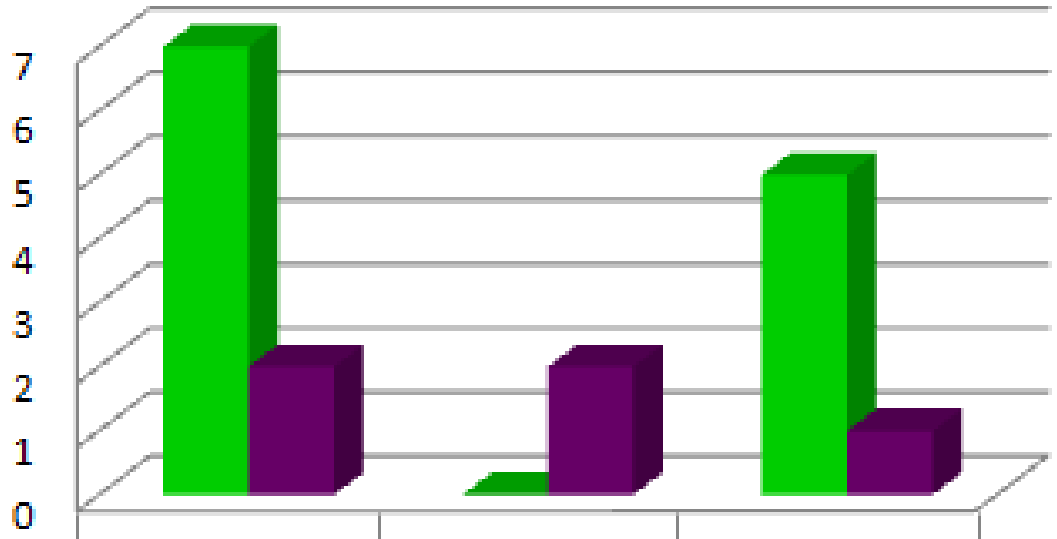


MSI analysis results in HCP and Incident groups



	MSS	MSI-L	MSI-H
HCP group (n=25)	13	4	8
Incident group (n=28)	23	3	2

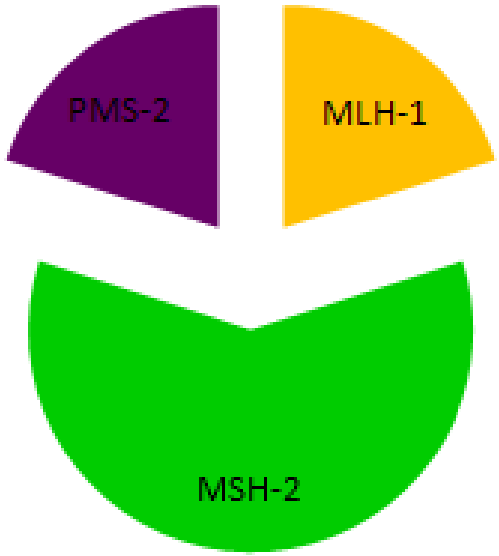
IHC analysis based on MSI results (n=17)



	MSS	MSI-L	MSI-H
HCP group (n=12)	7	0	5
Incident group (n=5)	2	2	1

Germline mutation analysis results (n=6)

HCP group (n=5)



	HCP group (n=5)
MLH-1	1
MSH-2	3
MSH-6	0
PMS-2	1

Demographic & clinicopathologic features of CRC in individuals whose tumors showed microsatellite instability (n=17)

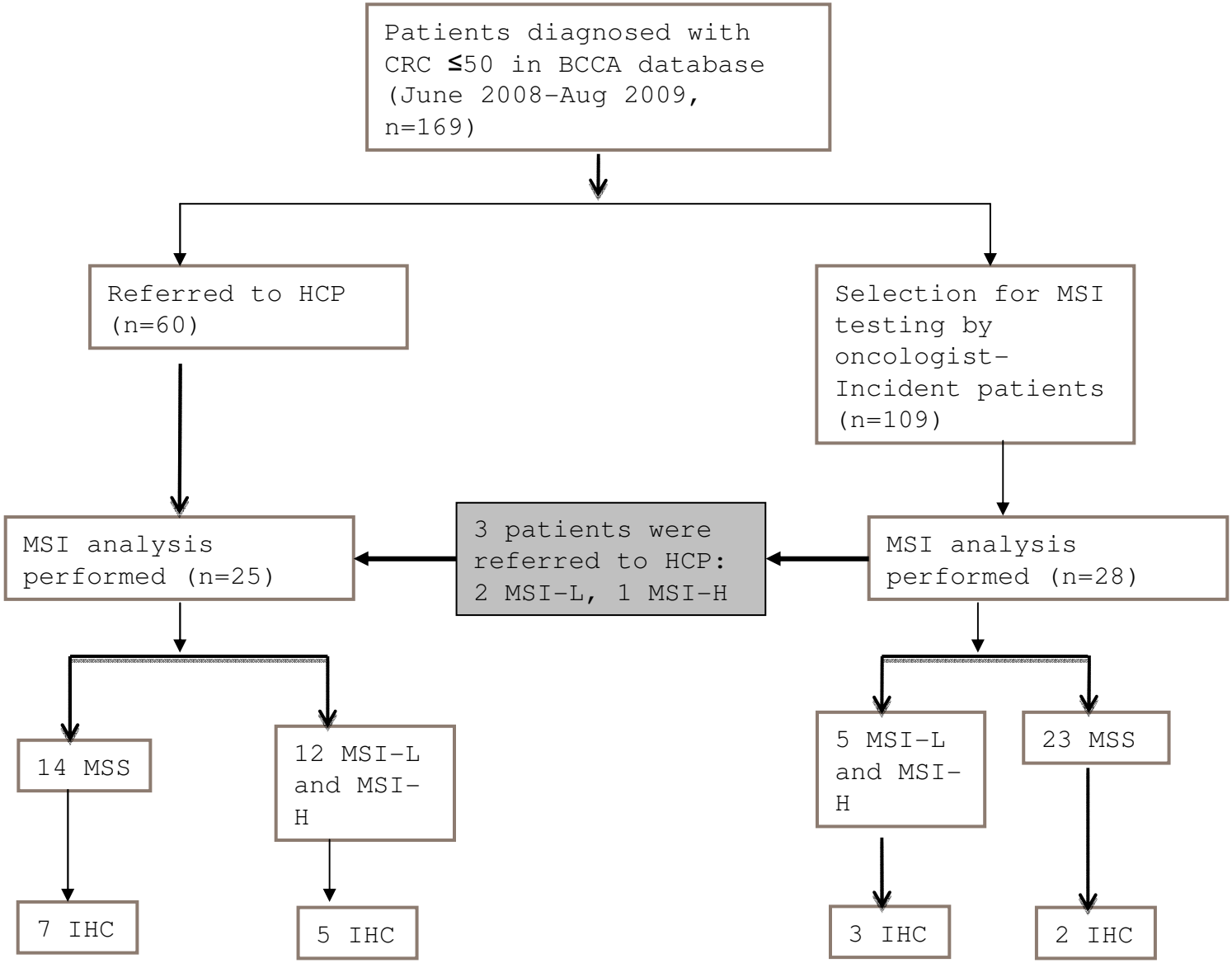
Age at diagnosis	Geographic location at diagnosis	Tumor location	Tumor surgical stage	Tumor surgical grade	Clinical criteria met	MSI results	Genetic testing results
49	Fraser	RECTUM, NOS	3A	3	RB-1	MSI-L 1/6	
40	Fraser	SPLENIC FLEXURE OF COLON	2A	2	RB-1,4; AMS-I	MSI-H 7/7	MLH1
47	Vancouver Island	ASCENDING COLON	4	9	RB-1	MSI-L - 3/7	
43	Fraser	CECUM	2A	2	RB-1	MSI-H 7/7	PMS2-biallelic
43	Fraser	CECUM	2A	2	RB-1	MSI-H 7/7	
49	Fraser	APPENDIX	4	1	RB-1	MSI-L 1/6	
43	Fraser	CECUM	2A	2	RB-1	MSI-H 7/7	
49	Fraser	APPENDIX	4	1	RB-1	MSI-L 1/6	
37	Fraser	SIGMOID COLON	4	1	RB-1	MSI-H 7/7	
44	Vancouver Island	RECTUM, NOS	3B	2	RB-1	MSI-L 3/7	
43	Northern	RECTUM, NOS	1	2	RB-1	MSI-H 7/7	
37	Fraser	CECUM	2A	2	RB-1,4; AMS-II	MSI-H 7/7	
43	Fraser	COLON, NOS	3B	2	RB-1,4	MSI-H 4/7	MSH2
49	Fraser	TRANSVERSE COLON	3C	2	RB-1	MSI-L 1/6	MSH2
38	Vancouver Coastal	TRANSVERSE COLON	3A		RB-1, 5	MSI-H 5/5	MSH2
41	Southern Interior	HEPATIC FLEXURE	3A		RB1	MSI-H 7/7	
38	Vancouver Coastal	RECTUM, NOS	3A		RB 1	MSI-L 1/6	

Conclusions

- Low overall MSI utilization rate especially in the incident group
  - High uptake of MSI testing among those to whom it was offered in the HCP group
- Difficult to make conclusions about effectiveness of MSI testing given low utilization rate
  - 18% microsatellite instability in those having MSI analysis
- Germline mutations identified in HCP group only

Conclusions

- Both approaches have advantages and disadvantages
- Possible reasons for low MSI utilization rate
  - Lack of knowledge about availability and criteria for MSI analysis
  - Perhaps pathologists are better able to utilize MSI
- Further education regarding MSI analysis availability and criteria
- Analysis of data from patients with CRC ≤50 from September 2009-May 2010


Patients diagnosed with CRC ≤50 in BCCA database (June 2008-Aug 2009, n=169)
Referred to HCP (n=60)
Selection for MSI testing by oncologist- Incident patients (n=109)
MSI analysis performed (n=25)
3 patients were referred to HCP: 2 MSI-L, 1 MSI-H
MSI analysis performed (n=28)
14 MSS
12 MSI-L and MSI-H
5 MSI-L and MSI-H
23 MSS
7 IHC
5 IHC
3 IHC
2 IHC

Thank You!