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Lynch Syndrome and Breast Cancer
Association or Incidental Finding?

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Disclosures

- Jessica Stoll and Sonia Kupfer have nothing to disclose.

- Shelly Cummings, Eric Rosenthal, Krystal Brown, Jamie Willmott, and Ryan Bernhisel are employed by and own stock in Myriad Genetics, Inc.

Background

- Increased risk of breast cancer in women with Lynch syndrome (LS) is debated
- Estimates from prior studies range from no increased risk to 14-fold relative risk[1]
- Prospective studies[2,3]:
  - Win *et al* 2012: 3.95 SIR for all mutation carriers
  - Moller *et al* 2017: risks similar to general population for *MLH1, MSH2, MSH6*

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[1]Win *et al. Breast Cancer Research.* 2013
[2] Win *et al*. *J Clin Oncol*. 2012
[3] Moller *et al*. *Gut* 2017

Clinical Laboratory Retrospective Cohort Study

- Roberts *et al* 2018
  - 423 female mutation carriers
  - Increased risks for *MSH6* and *PMS2*
    - *MSH6*: SIR = 2.11, 95% CI 1.56-2.86
    - *PMS2*: SIR = 2.92, 95% CI 2.17-3.92
  - No association for *MLH1* or *MSH2*
  - Limitations: moderate sample size, potential for selection bias

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Roberts M *et al. Genet Med*. 2018

Aim

- To determine if women who carry a LS pathogenic variant (PV) have an increased risk for breast cancer using data from a large clinical laboratory cohort.

Methods

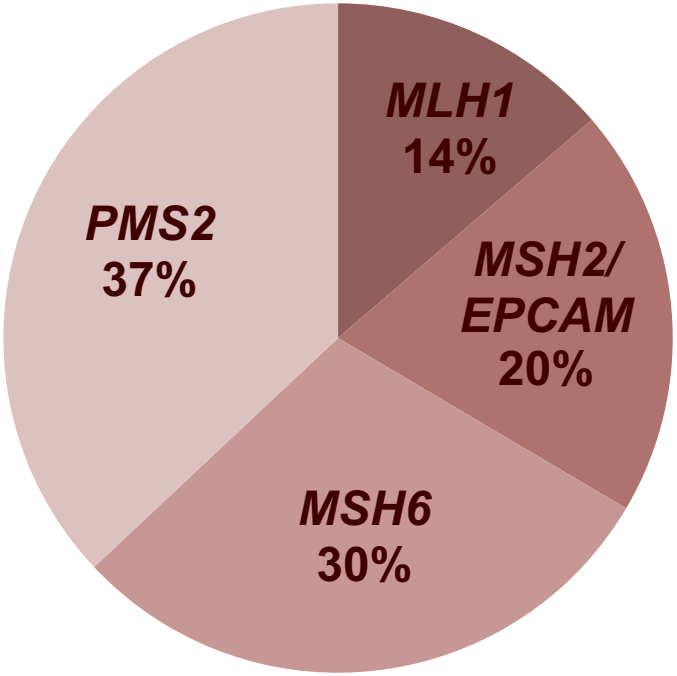
- Clinical laboratory database queried for PVs in LS genes (*MLH1, MSH2, MSH6, PMS2, EPCAM)* in women tested with a 25-28 multigene pan-cancer panel from 2013-2018
  - PVs defined as variants with a laboratory classification of Deleterious or Suspected Deleterious
  - Women excluded if found to carry a PV in more than one gene
  - Clinical information obtained from provider-completed test requisition forms (TRFs)
  - Women excluded if from a state prohibiting use of de-identified genetic/clinical information

Methods

- Standardized incidence ratios (SIR) of breast cancer calculated using breast cancer rates in:
  - General US population (SEER)
  - All women tested with the multigene panel from 2013-2018, based on ascertainment for suspicion of hereditary breast and ovarian cancer (HBOC) or LS

Demographics

- 405,601 women tested
- 2,942 carriers of PVs in LS genes (0.7%)



- 17% LS carriers with history of breast cancer
  - Average age at diagnosis: 51.3 years (range 19-90 years)

Breast cancer risk in women with LS compared to *women in the general US population*

	N	Observed	Expected	SIR	95% CI
Total	2942	501	538.6	0.93	(0.85-1.02)

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Total	**2942**	**501**	**538.6**	**0.93**	**(0.85-1.02)**
MLH1	402	46	63.0	0.73	(0.53-0.97)
MSH2/EPCAM	583	70	105.0	0.67	(0.52-0.84)

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MSH2/EPCAM	583	70	105.0	0.67	(0.52-0.84)
MSH6	869	161	170.0	0.95	(0.81-1.11)
PMS2	1088	224	200.7	1.12	(0.97-1.27)

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Breast cancer risk in women with LS compared to *women ascertained for suspicion of HBOC* (n = 371,323)

	N	Observed	Expected	SIR	95% CI
Total	**1831**	**441**	**489.5**	**0.90**	**(0.82-0.99)**
MLH1	148	32	33.4	0.96	(0.66-1.35)
MSH2/EPCAM	248	56	63.3	0.88	(0.67-1.15)
MSH6	561	138	154.3	0.89	(0.75-1.06)
PMS2	874	215	238.6	0.90	(0.78-1.03)

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Breast cancer risk in women with LS compared to *women ascertained for suspicion of LS* (n = 34,278)

	N	Observed	Expected	SIR	95% CI
Total	**1111**	**60**	**60.1**	**1.00**	**(0.76-1.28)**
MLH1	254	14	10.9	1.28	(0.70-2.15)
MSH2/EPCAM	335	14	17.0	0.83	(0.45-1.39)
MSH6	308	23	20.2	1.14	(0.72-1.71)
PMS2	214	9	12.1	0.75	(0.34-1.42)

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Strengths & Limitations

- Strengths
  - Large sample size
  - Correction for selection bias in analyses
- Limitations
  - Breast cancer history obtained from test requisition forms
  - Inclusion of only women who underwent genetic testing

Conclusions

- No evidence for increased risk of breast cancer in women with LS in this large testing cohort
- Wide variation in breast cancer risk estimates likely due to study designs and methodology
- Insufficient evidence to change breast cancer screening recommendations for LS

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Thank You