2016

Lynch Syndrome

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Introduction

- Lynch Syndrome (LS) is a cancer susceptibility syndrome
- Formerly known as Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC)
- Autosomal dominant inherited trait
- High penetrance, due to defects in repairing base mismatches during DNA replication (Shulman, 2015, p. 33)
- Significantly more susceptible to colorectal (CRC), endometrial and many other types of cancer
- 50% chance of inheritance if one parent affected
- Four genes become mutated, called mismatch repair (MMR) genes, these mutations can lead to replication of cancer causing cells (Mange et al., 2015, p. 421-2)
- New recommendations within the last five years include screening for LS in all newly diagnosed CRCs
- Universal screening reduces mortality and increases surveillance for those with a familial history of LS (Vindigni & Kaz, 2016, p. 975)
- CRC incidence has declined in the Unites States due to increased screening methods including occult blood tests and colonoscopies (Wanebo et al., 2012, p. 822)
- CRC is the third most common cancer worldwide, and second leading cause of cancer-related death
- LS accounts for 1-3% of these tumors (Moreira et al., 2012, p. 1555)

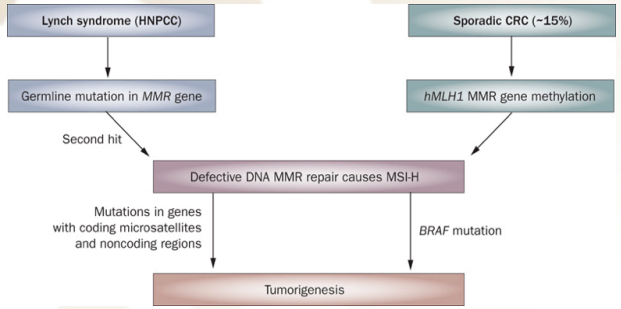
Topic Selection

- Advancing cancer technology is relevant to advanced practice nursing
- Knowledge of current recommendations is essential to evidence based practice

Pathophysiology

- Mismatch repair mutation (MMR) occurs in one of the following genes: MLH1, MSH2, MSH6, PMS2
- Mismatch repair corrects DNA replication mistakes
- Loss of function in the MMR gene means two hits must occur, one hit to each allele
- Germline mutations are transmitted to offspring
- Mutation leads to loss of original function or expression, which leads to pathogenesis (Liu et al., 2016, p. 417-18)
- Errors accumulate during DNA replication easily in repetitive sequences of DNA called microsatellites, this is called microsatellite instability (MSI) or loss of MMR protein expression, which defines LS (Moreira et al., 2012, p. 1556)
- See difference in mutation type for LS compared to spontaneous CRC (Sinicrope, 2010, figure 1)

Figure 1. Lynch Syndrome compared to sporadic colorectal cancer, differences in mutations illustrated, both leading to cancer



Significance of Pathophysiology

- Pathology plays a major impact in how to screen individuals and families
- Updated recommendations
- Old screening tools (Amsterdam I, Amsterdam II, and revised Bethesda guideline) determined if an individual was at high risk for LS based on personal and family history
- Still sometimes used but these tools can miss patients who should be tested for LS
- Tumor-based screening protocols better identify those with LS according to the CDC (Mange et al., 2015, p. 422)
- Experts recommend that every person newly diagnosed with CRC or endometrial cancer be screened for LS, this is referred to as universal screening (Vindigni & Kaz, 2016, p. 971)
- The Lynch Syndrome Screening Network (LSSN) created in 2011 promotes universal screening, website is http://www.lynchscreening.net (Mange et al., 2015, p. 421 & 424)
- *Figure 2* is a sample algorithm for universal CRC screening (Vindigni & Kaz, 2016, figure 1)
- Testing is by immunohistochemistry (IHC), which determines whether or not the four types of repair genes are present on a tissue sample (Shulman, 2015, p. 35)
- The other form of testing looks for microsatellite instability which are errors in repetitive DNA sequences (see *Figure 3*)
- Testing for both IHC and MSI reduces the likelihood of missing a diagnosis of LS
- If LS is positive, recommendations also involve screening family members (Vindigni & Kaz, 2016, p. 970)

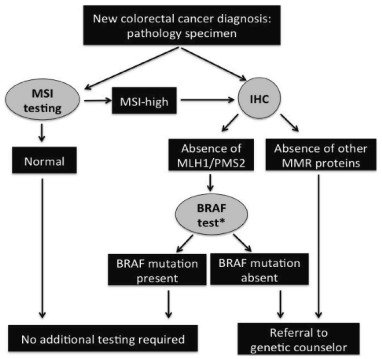
Figure 3. http://kintalk.org/whats-lynch-syndrome/diagnosing-lynch-syndrome/

Signs and Symptoms

- Treatment depends on cancer location and metastasis
- Liver metastasis results in significant mortality (Wanebo et al., 2012, p. 834)
- Individuals develop cancer at an earlier age than sporadic cancers, average age of onset is 45 (Liu, Thompson, Ward, Hesson, & Sloane, 2016, p. 417)
- Colorectal and endometrial cancer are the two main cancers seen, but LS also increases risk for ovarian, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin cancers (Ten Broeke et al., 2015, p. 325)
- Signs and symptoms vary according to the type of cancer
- Cancer risks:

LS -	4-5% CRC
LS +	20-60% CRC
LS -	2-3% Endometrial CA
LS +	20-60% Endometrial CA

Figure 2. Universal testing algorithm for colorectal cancer



Significance to Nursing

- Important to educate and guide patients
- Emotional burdens are associated with hereditary cancer and associated knowledge
- Psychological effects have focused on family genetic testing and screening related to Huntington's disease and the BRCA1/2 gene associated with breast cancer
- Most studies focus on immediate family and not extended family
- Cancer distress, cancer worry, and depression all need to be further researched when considering familial genetic testing (Eliezer, Hadley, & Koehly, 2014, p. 1293)
- Practice with empathy and awareness to empower patients and decide what to do with the knowledge they are able to uncover through genetic testing
- Preventative medicine and primary prevention is far more effective than tertiary prevention interventions, and the information behind LS allows more opportunities to prevent cancer rather than treat

Conclusions

- Genetic advances will continue to evolve and screening recommendations for individuals and families will continually change
- Knowledge is power: current knowledge must be used in a way to benefit the general population
- Increasing awareness is essential, providers must be informed about new screening guidelines
- LS poses a significant risk for developing cancer but screening tools are causing decline in colorectal cancer mortality (Wanebo et al., 2012, p. 822)

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