BC CANCER HEREDITARY CANCER
Provincial Health Services Authority

Lynch Syndrome – *PMS2* Cancer Risks and Management

Overview

Lynch syndrome is an inherited condition that increases the risk of certain cancers. It is caused by pathogenic variants in one of several genes involved in repairing DNA. One of these genes is *PMS2*.

People with a pathogenic variant in the *PMS2* gene have a higher chance of developing certain types of cancer, often at younger ages than the general population. These include colorectal and endometrial cancer.

This page summarizes the cancer risks and management recommendations for individuals with a pathogenic variant in the *PMS2* gene. These may be adjusted depending on a person's personal or family history of cancer.

Cancer Risks Associated with *PMS2*

Cancer Type	**Average Age** (years)	***PMS2*** (risk to age 75 years)	**General Population Risks**
Colorectal	61 to 66 years	10-20%	6 to 7%
Endometrial	49 to 50 years	13%	2.6%

There is no clear evidence that people with a *PMS2* pathogenic variant are at increased risk for cancers associated with Lynch syndrome caused by pathogenic variants in other genes, such as ovarian, ureter/renal pelvis, stomach, hepatobiliary tract, small intestine, pancreas and brain. We expect to learn more about *PMS2* cancer risks in the future and our recommendations for screening and prevention may change.

Cancer Screening and Risk Reduction

Colorectal Cancer

Screening:

- Colonoscopy every 1–3 years is recommended starting at age 35, or 2–5 years before the youngest colorectal cancer diagnosis in the family if that diagnosis occurred before age 35.

Risk Reduction:

- Daily low-dose aspirin (81 mg) is recommended, unless contraindicated, to reduce colorectal cancer risk in individuals with Lynch syndrome, with a double dose for those with a BMI of 30 or greater. Aspirin can be initiated five years prior to the start of colonoscopy screening and stop by age 70 (if the sole indication is colorectal cancer prevention). H. pylori testing and eradication as well as blood pressure control reduce the risk of aspirin-related adverse effects.
- Prophylactic colectomy is generally not recommended, except in specific situations outlined below. Surveillance of all remaining colonic mucosa should continue every 1–2 years, even after surgery.
    - Individuals not undergoing regular colonoscopic surveillance may benefit most
    - Segmental or extended colectomy may be considered in cases of adenomas not amenable to endoscopic removal or if high-grade dysplasia is present
    - Colectomy at the time of cancer diagnosis lowers the risk of a second primary colorectal cancer but has not been shown to improve overall survival.

Endometrial and Ovarian Cancer
Screening:

Endometrial and Ovarian Screening:

- Transvaginal ultrasounds (TVUs), annual endometrial biopsies, pelvic exams, and/or CA-125 blood tests are not recommended in British Columbia, as they are either proven ineffective or lack sufficient evidence to support their use for screening purposes.
- Prompt evaluation by a physician is recommended for any unusual uterine bleeding (e.g., bleeding between menstrual periods or any postmenopausal bleeding), or for persistent symptoms such as pelvic or abdominal pain, bloating, increased abdominal girth, early satiety, difficulty eating, or urinary urgency/frequency that are a change from baseline.

Prevention:

- Recommend consultation with a gynecologic oncologist or gynecologist in community to discuss prevention strategies such as hysterectomy from age 50.
- Bilateral salpingo-oophorectomy (BSO) may be considered at the time of hysterectomy - particularly with a family history of ovarian cancer. However, current evidence does not suggest a significantly increased risk for ovarian cancer with PMS2 pathogenic variants. Menopausal hormone therapy is recommended at the time of risk-reducing BSO and should continue until the usual age of menopause.
- There may be a potential benefit to using the oral contraceptive pill (OCP) or Mirena IUD. In the general population, OCP use for at least 5 years reduces the risk of ovarian and endometrial cancer by 50% or more. This protective effect increases with longer duration of use and can persist for at least 20 years after

discontinuation. However, it is unclear whether the same level of risk reduction applies to individuals with Lynch syndrome.

The Gynecologic Cancer Prevention and Survivorship Program provides menopause management, and surgical decision support for individuals considering risk-reducing surgery.

Gastric and Small Bowel Cancer
There is currently limited scientific evidence to recommend gastric and small bowel cancer surveillance for people with Lynch syndrome. The surveillance below can be considered if there is a family history of gastric/small bowel cancer, additional risk factors, or at the discretion of the gastroenterologist.

High-quality esophagogastroduodenoscopy (EGD) every 2-4 years preferably at time of colonoscopy, beginning at age 30-40 years.

Screen for *Helicobacter pylori* and gastritis at the time of EGD, or as one-time noninvasive test if not undergoing endoscopy. Treat *H. pylori* if detected.

Pancreatic Cancer
The Cancer of the Pancreas Screening Consortium (CAPS; Goggins et al., 2020) does not currently recommend pancreatic cancer screening for *PMS2* carriers. However, screening may be considered on a case-by-case basis for individuals with a significant family history of pancreatic cancer.

To lower the risk, avoid or quit cigarette smoking, exercise regularly, limit alcohol, maintain a weight that supports overall health and choose healthy foods and drinks.

Breast and Prostate Cancer
General population screening is sufficient unless there is a close family history.

Family and Reproductive Considerations

Inheritance

Lynch syndrome follows an autosomal dominant pattern. Each child of someone with a *PMS2* pathogenic variant has a 50% chance of inheriting the variant.

Family members are encouraged to contact their local genetics clinic to learn more about whether genetic testing or cancer screening may be helpful for them. Family members who live in British Columbia or the Yukon can contact our program directly at hereditarycancer@bccancer.bc.ca. In BC/Yukon, genetic testing is generally available starting at age 19.

CMMRD (constitutional mismatch repair deficiency):

CMMRD is a rare condition that happens when a child inherits two pathogenic variants (one from each parent) in the same Lynch gene (e.g. *PMS2*). It causes a high risk of childhood cancers, such as leukemia, brain, and intestinal cancers, usually diagnosed around age 10. If an individual with an *PMS2* pathogenic variant is planning a family, a review of their partner's family history of cancer may be helpful. Genetic counselling may be offered if there is a concern for the risk of CMMRD in children.

Note: In the information above, male/female refers to sex assigned at birth.