Ontario
Cancer Care Ontario
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Cancer Risk Factors in Ontario

Genetic Susceptibility to Cancer

GENETIC SUSCEPTIBILITY TO CANCER

Cancer	Major familial susceptibility syndromes	Major genes	Gene function	Mode of inheritance*
Breast and ovary	Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*	Tumour suppressor	Dominant
	Li-Fraumeni syndrome (breast)	*p53, CHEK2*	Tumour suppressor	Dominant
	Cowden syndrome (breast)	*PTEN*	Tumour suppressor	Dominant
	HNPCC/Lynch syndrome (ovary)	*MLH1, MSH2, MSH6, PMS2*	DNA repair	Dominant
	Ataxia telangiectasia (breast and ovary)	*ATM*	DNA repair	Recessive
	Peutz-Jeghers syndrome (breast and ovary)	*STK11*	Tumour suppressor	Dominant
Colon and rectum	HNPCC/Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	DNA repair	Dominant
	Familial adenomatous polyposis (FAP), including attenuated FAP	*APC*	Tumour suppressor	Dominant
	MYH-associated polyposis	*MYH*	DNA repair	Recessive
	Peutz-Jeghers syndrome	*STK11*	Tumour suppressor	Dominant
	Juvenile polyposis	*SMAD4/DPC4*	Tumour suppressor	Dominant
Prostate	Hereditary prostate cancer[†]	…	…	…
	Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*	Tumour suppressor	Dominant
	Li-Fraumeni syndrome	*p53, CHEK2*	Tumour suppressor	Dominant
Leukemia/lymphoma	Bloom syndrome	*BLM*	DNA repair	Recessive
	Ataxia telangiectasia	*ATM*	DNA repair	Recessive
	Fanconi anemia	*FANCA,B,C,D,E,F,G*	DNA repair	Recessive
	Down syndrome	Chromosome 21[‡]	…	…
Pediatric cancers	Retinoblastoma	*RB1*	Tumour suppressor	Dominant
	Wilms tumour syndromes[§]	*WT1*	Tumour suppressor	Dominant

* Dominant inheritance refers to a gene variant on any non-sex chromosome that will always be expressed, regardless of the other variant of that gene present. Recessive inheritance refers to a gene variant that will only be expressed when two copies of that variant are present.
[†] Several susceptibility loci have been identified but associated genes unknown.
[‡] Down syndrome involves aneuploidy, specifically an extra copy of chromosome 21, instead of a mutation on a single major gene.
[§] Includes Beckwith-Wiedemann syndrome and familial Wilms tumours not associated with a *WT1* germline mutation.

Introduction: cancer genetics

- Clustering of cancer in families is not uncommon and may be due to shared environmental exposures and/or inherited genetic factors, including complex interactions between the two.
- Several clinical features suggest an underlying hereditary/genetic basis for cancer, including:

Features in the individual patient	Features in the patient's family
• multiple primary tumours in the same organ • multiple primary tumours in different organs • bilateral primary tumours in paired organs • multifocality within a single organ • younger-than-usual age at diagnosis • unusual histology • in the sex not usually affected • associated with other genetic traits • associated with congenital defects • associated with an inherited precursor lesion • associated with another rare disease • associated with cutaneous lesions known to be associated with cancer susceptibility disorders	• 1 first-degree relative with the same or a related tumour and at least one individual feature • ≥ 2 first-degree relatives with tumour of the same site • ≥ 2 first-degree relatives with tumour types of a known familial cancer syndrome • ≥ 2 first-degree relatives with rare tumours • ≥ 2 relatives in two generations with tumour of the same site or etiologically related sites

Source: Modified from Weber et al., 2003[219]

- Most known hereditary cancer susceptibility genes are rare and have a high penetrance (the proportion of individuals carrying a given variant of a gene [allele or genotype] that also express its associated trait). However, such genes likely account for only a small proportion of cancers, with a larger proportion due to common variation in one or several low penetrance genes that interact with other genes or environmental factors (e.g., tobacco smoke, alcohol).[64]
- Information on potential genetic modifiers for cancer is rapidly emerging, but remains of little clinical value at the present due to methodological challenges in identifying and validating such genes. This summary therefore focuses on well-established familial cancer susceptibility syndromes for common cancers. A comprehensive overview of all cancer susceptibility syndromes and their associated cancers is outlined in other reviews, including Lindor et al.[99]

BREAST AND OVARIAN CANCER

Family history is a well-established risk factor for breast and ovarian cancer. It is estimated that 5%–10% of all breast and ovarian cancers are due to highly penetrant germline mutations in a single cancer susceptibility gene.[64] Several breast and ovarian cancer susceptibility genes have been identified to date, most of which are inherited in an autosomal dominant manner.

Hereditary breast/ovarian cancer syndromes (BRCA1/BRCA2 associated)

- Hereditary breast and ovarian cancer syndromes, involving germline mutations to the *BRCA1* or *BRCA2* gene, account for most hereditary breast and ovarian cancers.[99] Certain populations, including those of Ashkenazi Jewish descent, have particularly high prevalence of *BRCA1* or *BRCA2* mutations.[99]
- *BRCA2*-related breast cancers appear clinically similar to sporadic cancers. *BRCA1*-related breast cancers, in contrast, have higher than expected frequencies of medullary histology, high histologic grade, and a greater likelihood of having the "triple-negative" phenotype (i.e., estrogen receptor negative, progesterone receptor negative and negative for HER 2/neu overexpression). *BRCA1*- and *BRCA2*-associated ovarian cancers are more likely than sporadic cancers to be serous adenocarcinomas and less likely to be mucinous and borderline.[99]

- The penetrance of *BRCA1* and *BRCA2* mutations is high in both breast and ovarian cancer, although estimates vary widely depending on the population.[220] Two large meta-analyses estimated the cumulative risk of breast cancer by age 70 as 55%–65% for BRCA1 and 45%–49% for *BRCA2*.[221,222] The cumulative risk of ovarian cancer by age 70 in these studies was 39% for BRCA1 and 11%–18% for *BRCA2*.[221,222]
- Breast and ovarian cancer risk among *BRCA1* and *BRCA2* carriers can likely be modified by other factors. Surgical removal of the ovaries and oral contraceptives, for example, reduce the risk of ovarian cancer among *BRCA1* or *BRCA2* mutation carriers.[223,224] Other potential modifiers, including reproductive and genetic factors, remain unclear.[225]
- *BRCA1* and *BRCA2* mutations are most strongly associated with breast and ovarian cancer, but also increase the risk of several other cancers, including cancer of the fallopian tubes and primary peritoneum. They are also consistently associated with cancer of the prostate, pancreas and male breast, although the evidence for these cancers is stronger for *BRCA2*.[99]

Li-Fraumeni syndrome

- Li-Fraumeni syndrome (LFS) is a rare cancer predisposition syndrome characterized by pre-menopausal breast cancer, sarcoma (soft tissue and bone), leukemia and adrenocortical carcinoma.[99]
- LFS is associated with a high lifetime risk of developing cancer. Cancer-specific risks cannot be estimated since LFS is so rare; however, individuals with LFS have a 50% chance of developing any type of cancer before age 30 and a 90% chance by age 70.[226] The risk of cancer is particularly high in females with LFS, compared to males.[227]

Cowden syndrome

- Cowden syndrome is an autosomal dominant disorder, characterized by multiple hamartomas (benign malformations of tissues that resemble tumours) and an increased risk of female breast cancer, thyroid cancer (non-medullary) and endometrial cancer. Cowden syndrome may also increase the likelihood of developing other cancers such as gastrointestinal malignancies.[99]
- The lifetime risk of cancer associated with Cowden syndrome is highest for breast cancer, estimated to be as high as 85%, with a 50% risk by age 50.[228] Penetrance for thyroid and endometrial cancer ranges from nearly 30% to 35%.[228]

Other genetic syndromes associated with breast and/or ovarian cancer

- Hereditary breast cancer may be caused by Peutz-Jeghers syndrome and ataxia-telangiectasia. Peutz-Jeghers syndrome is also associated with hereditary ovarian cancer, as is hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome. These syndromes are outlined below.

COLORECTAL CANCER

Hereditary non-polyposis colorectal cancer (HNPCC)

- Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is the most common type of hereditary colorectal cancer.[99] It is caused by germline mutations in at least one of four genes involved in mismatch repair (see table on page 55).
- The majority of HNPCC cases are caused by mutations in the *MLH1* and *MSH2* genes.[229] The risk of developing colorectal cancer before age 70 among *MLH1* and *MSH2* heterozygotes is estimated to range from 52% to as high as 82%.[229] Substantially lower risk estimates have consistently been shown for both *MSH6* and *PMS2* mutations.
- HNPCC is characterized by early onset of colorectal cancer (mean diagnosis age 44–61),[229] a predisposition for multiple colorectal tumours, a predominance of proximal colon (right-sided) tumours and predisposition for poorly differentiated tumours.[230]
- HNPCC is also associated with an increased risk of several other cancers, including cancer of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain and skin. Endometrial cancer risk among women with HNPCC is estimated as 25%–60% before age 70; the associated risk for all other HNPCC-related cancers is much lower.[229]

Familial adenomatous polyposis (FAP) and attenuated FAP

- Familial adenomatous polyposis (FAP) and attenuated FAP are autosomal dominant disorders characterized by the development of clusters of precancerous polyps in the colon (hundreds to thousands in FAP and less than 100 in attenuated FAP).[230]
- If left untreated, individuals with classical FAP have almost a 100% chance of developing colorectal cancer in their lifetime, with an average age at diagnosis of 39.[231] Lifetime colorectal cancer risk is slightly lower in people with attenuated FAP (approximately 70% by age 80) and the average age of diagnosis is 10–15 years later than in classical FAP.[231]
- Colorectal cancer is the predominant malignancy associated with FAP, but individuals with FAP also have an increased risk of cancer of the small intestine as well as several extraintestinal malignancies, such as thyroid cancer (non-medullary), hepatoblastoma, brain cancer (particularly medullablastoma), stomach cancer and pancreatic cancer.[231] The absolute lifetime risks for these cancers resulting from FAP are, however, lower than the FAP-associated risk of colorectal cancer (< 1%–12%).[231]

MYH-associated polyposis (MAP)

- *MYH*-associated polyposis (MAP) is an autosomal recessive syndrome resulting from inherited mutations in the *MYH* gene. MAP frequently has a clinical presentation that resembles attenuated FAP, including the presence of multiple colorectal polyps appearing before age 30, but may present with a broad spectrum of clinical features.[230]
- Individuals with MAP have a high risk of colorectal cancer. The risk of developing this cancer by age 70 in patients with mutations in both copies of the *MYH* gene (homozygous or biallelic carriers) has been estimated to be as high as 80%.[232] Risk in patients with mutations in one copy of the *MYH* gene (heterozygous or monoallelic carriers), however, remains somewhat unclear.

- Evidence for tumours outside of the colon in patients with MAP is somewhat limited, although cancers of the stomach, small intestine, endometrium and several other body sites have been reported.[99]

Peutz-Jeghers syndrome (PJS)

- Peutz-Jeghers syndrome (PJS) is a rare genetic disorder characterized by multiple gastrointestinal hamartomous polyps, hyperpigmentation of the lips and buccal mucosa, and an increased risk of several gastrointestinal and extraintestinal cancers.[233]
- Individuals with PJS have a high lifetime risk of developing cancers, the majority of them gastrointestinal. A recent systematic review and meta-analysis estimated the lifetime risk of any cancer to be as high as 93% in patients with PJS, with a nearly 70% lifetime risk of developing any gastrointestinal cancer and a 39% chance of colorectal cancer.[234]
- Extraintestinal cancers occurring in excess in PJS include cancers of the pancreas, lung, breast, uterus, ovary, cervix and testes. Of these, breast cancer and pancreatic cancer have the highest lifetime risk in PJS patients.[99]

Other genetic syndromes associated with colorectal cancer

- Juvenile polyposis is a rare genetic syndrome, characterized by childhood-onset hamartomatous polyposis in the gastrointestinal tract, which can cause hereditary colorectal cancer.[99]

PROSTATE CANCER

Familial clustering of prostate cancer is well documented.[235] Although familial clustering may occur due to shared environmental exposures or by chance due to the high incidence of prostate cancer, results of early twin studies support a hereditary basis.[235] Similar to breast and ovarian cancer, an estimated 5%–10% of all prostate cancer diagnoses are attributed to inherited genetic factors or susceptibility genes.[235]

Hereditary prostate cancer syndromes

- Hereditary prostate cancer appears to be complex and heterogeneous. Several segregation analyses of high-risk families support the existence of one or several highly penetrant prostate cancer susceptibility genes.[236] An autosomal dominant mode of inheritance is supported by most studies, although one study found an autosomal recessive inheritance pattern[237] and another suggested an X-linked pattern that was most apparent for older ages at diagnosis.[238]
- Several prostate cancer susceptibility loci have been identified in linkage analyses, including hereditary prostate cancer (HPC) 1, HPC2, PCAP, HPCX, CAPB, HPC20, 8p and 8q.[99] The specific genes at these loci that are responsible for prostate cancer susceptibility are yet to be identified. The *RNASEL* gene has been proposed as a candidate for HPC1[239,240] and the *MSR1* gene has been proposed as a candidate for the 8p loci[241,242] but additional research is needed to confirm these findings.

Other genetic syndromes associated with prostate cancer

- As mentioned above, *BRCA1* and *BRCA2* mutations are associated with increased susceptibility to prostate cancer.

LEUKEMIA/LYMPHOMA

Several hematopoietic cancers are associated with genetic predisposition syndromes, although inherited syndromes account for a small percentage of hematopoietic tumours.[243] These disorders primarily involve genes involved in DNA repair, cell cycle regulation, and promotion of apoptosis or cell proliferation.

Bloom syndrome

- Bloom syndrome is a rare autosomal recessive disorder characterized by a short stature, but primarily normal body proportions, hypersensitivity to the sun on the face resulting in a butterfly rash, sterility in males or reduced fertility in females, and immunodeficiency.[99]
- Individuals with Bloom syndrome have an increased risk of several cancer types. Before age 20, leukemia (acute myeloid and acute lymphoid) and lymphoma are the most common types of cancer diagnosed, but carcinomas of the tongue, larynx, lung, esophagus, colon, skin, breast and cervix become more common during the mid-20s to early-30s.[99]

Ataxia-telangiectasia

- Ataxia-telangiectasia (AT) is a rare autosomal recessive disorder characterized by cerebellar ataxia (lack of coordinated muscle movement) that begins early in childhood and progresses over time, and telangiectasias (small blood vessels near the surface of the skin) on areas of the skin exposed to sun and the conjunctiva.[99]
- AT patients have a 38% chance of developing any cancer, with lymphoid malignancies, particularly non-Hodgkin lymphoma and acute or chronic lymphocytic leukemia, accounting for roughly 85%.[244] Several other cancers, such as breast, ovary, stomach and skin, have also been reported in AT.[99] In addition, AT patients also have an increased risk of secondary brain cancers following radiotherapy for a first cancer due to a hypersensitivity to ionizing radiation.[244]

Fanconi anemia

- Fanconi anemia is a rare autosomal recessive disease, caused by mutations in up to 15 genes involved in DNA repair/stability. It is most frequently characterized by physical abnormalities (e.g., short stature, deformities of the limbs and extremities), bone marrow failure and increased cancer susceptibility.[245]
- Fanconi anemia is predominantly associated with an increased susceptibility to leukemia, primarily acute myeloid leukemia. Fanconi anemia patients have a roughly 500-fold greater risk of acute myeloid leukemia compared to the general population.[245] An increased risk of squamous cell carcinoma of the head and neck, esophagus, and gynecologic system is also seen in Fanconi anemia patients.[245] Fanconi anemia patients have an increased sensitivity to chemotherapy and radiation and therefore have a high risk of morbidity following cancer treatment.[99]

Down syndrome

- Down syndrome, often referred to as trisomy 21, is a condition involving aneuploidy (an abnormal number of chromosomes); specifically, an extra copy of chromosome number 21. It is characterized by several craniofacial dysmorphisms, a variety of congenital defects, mental retardation, decreased muscle tone at birth and early dementia.[246]
- An increased risk of leukemia in children with Down syndrome is well established, with most contemporary studies estimating a 10- to 20-fold higher risk of acute leukemia in children with Down syndrome compared to the general population.[246–248] The magnitude of the increased risk of childhood leukemia appears to wane with age, with a much higher risk observed in children younger than 5 years old, and is particularly high for acute megakaryocytic leukemia (AMKL), a rare form of acute myeloid leukemia (AML).[249]
- Patients with Down syndrome, however, have a significantly lower risk of solid tumours in both childhood and adulthood, compared to the general population.[248,249]

Other inherited leukemia/lymphoma predisposition syndromes

Several other genetic susceptibility syndromes are associated with increased risk of leukemia and/or lymphoma but are not outlined here in detail. Examples of these include syndromes involving deficiencies in DNA damage repair, such as Nijmegen breakage syndrome; syndromes involving defects in cell cycle regulation and differentiation such as Li-Fraumeni syndrome, neurofibromatosis type 1 and Noonan and Noonan-like syndrome; syndromes involving genes that encode transcription factors, such as familial platelet disorder and CEBPA-dependent familial acute myeloid leukemia; and syndromes involving aneuploidy.[246]

FAMILIAL SUSCEPTIBILITY SYNDROMES RELATED TO PEDIATRIC CANCERS

Retinoblastoma

- Retinoblastoma is a malignant tumour of the retina in the eye that occurs early in childhood, with the majority of cases diagnosed before age 5. It occurs when there are deleterious mutations to both copies of the *RB1* gene; the heritable form involves germline mutations to at least one copy of the *RB1* gene.[250]
- People with a hereditary predisposition to retinoblastoma due to *RB1* mutations have over a 90% risk of developing this cancer.[99] Absolute risk, including the laterality of the tumour (i.e., if one or both eyes are affected), likely depends on the mutation type and other genetic modifiers.[251]
- Individuals with germline *RB1* mutations are also at an increased risk of second primary cancers, particularly osteosarcoma, other sarcomas and melanoma, following treatment with radiotherapy.[250]

Wilms tumour

- Wilms tumour is a childhood malignancy of the kidney cell progenitors that usually occurs before age 5. An estimated 10%–15% of Wilms tumours are heritable, although the genetic causes appear to be heterogeneous and complex.[252]

- Several congenital syndromes are associated with a predisposition for Wilms tumour. These include syndromes involving germline mutations to the *WT1* gene (chromosome 11p13), including Wilms tumour, anidria, genital anomalies, retardation (WAGR) syndrome, Denys-Drash syndrome and Frasier syndrome. Beckwith-Wiedemann syndrome, which is caused by abnormal regulation of gene transcription on chromosome 11p15, is also associated with Wilms tumour.[252]
- In addition, germline *WT1* mutations may predispose children to Wilms tumour in the absence of a congenital anomaly or congenital syndrome. These mutations may be passed down from a family member or may develop *de novo* during germ cell formation.[253]
- Only a small proportion of Wilms tumour patients with a family history of this tumour have germline *WT1* mutations.[252] Other familial predisposition genes have been mapped to genetic loci on chromosome 17q (called FWT1) and 19q (called FWT2), but the specific genes involved have not been identified.[252]

OTHER HEREDITARY CANCER SYNDROMES

Several other hereditary cancer predisposition syndromes are associated with less common cancers than those outlined above. The 54 known hereditary cancer syndromes are described in detail by Lindor et al.;[99] some examples of these include the following:

- **Genodermatoses**, such as familial melanoma syndromes, most strongly associated with increased risk of cutaneous melanoma; Gorlin syndrome/nevoid basal cell carcinoma syndrome, which is associated with an increased risk of basal cell carcinoma; and xeroderma pigmentosum, which is associated with hypersensitivity to sunlight and a corresponding increased risk of all types of skin cancer (melanoma, basal cell carcinoma, squamous cell carcinoma).
- **Endocrine tumour syndromes**, such as multiple endocrine neoplasia type 1 (MEN 1), which is most frequently associated with parathyroid adenomas, pancreatic islet cell tumours and pituitary adenomas; multiple endocrine neoplasia type 2 (MEN 2), which is strongly associated with medullary thyroid cancer; and familial papillary thyroid cancer.
- **Hereditary pancreatic cancer syndromes**, such as hereditary pancreatic adenocarcinoma and hereditary pancreatitis, as well as several other syndromes outlined above, including hereditary breast and ovarian cancer syndrome (*BRCA1/BRCA2* associated) and Peutz-Jeghers syndrome.