Ontario
Cancer Care Ontario
Action Cancer Ontario

Cancer Risk Factors in Ontario

Medical Conditions and Treatments

MEDICAL CONDITIONS AND TREATMENTS

Risk factor/exposure	Cancer	Direction of association
Inflammatory and autoimmune conditions		
Inflammatory bowel disease	Colon and rectum, small intestine	↑
Celiac disease and dermatitis herpetiformis Rheumatoid arthritis and systemic lupus erythematosus Sjoren syndrome Hashimoto thyroiditis	Lymphoma	↑
Diabetes	Liver, pancreas, colon and rectum, endometrium, breast, bladder	↑
	Prostate	↓
Other medical conditions		
GERD and Barrett esophagus	Esophagus*	↑
Cryptorchidism	Testis	↑
Benign breast disease	Breast	↑
Medical radiation (therapy and diagnostics)		
X-radiation and gamma radiation	Esophagus, bone and connective tissue, brain and central nervous system, bladder, kidney, leukemia, thyroid	↑
Radioiodines, including iodine-131	Thyroid	↑
Phosphorus-32	Acute leukemia	↑
Antineoplastic drugs		
Busulfan, chlorambucil, melphalan, semustine (methyl-CCNU), treosulfan, etoposide (in combination with cisplatin and bleomycin)	Acute myeloid leukemia	↑
Cyclophosphamide	Acute myeloid leukemia, bladder	↑
Thiotepa	Leukemia	↑
MOPP combined chemotherapy	Acute myeloid leukemia, lung	↑
Chlornaphazine	Bladder	↑
Tamoxifen	Endometrium	↑
Other medications		
Methoxsalen + UVA (PUVA)	Skin (SCC)	↑
Immunosuppressive drug: azathioprine	Non-Hodgkin lymphoma, skin	↑
Immunosuppressive drug: cyclosporine	Non-Hodgkin lymphoma, skin, multiple others	↑
Non-steroidal anti-inflammatory drugs	Colon and rectum, other digestive tract (esophagus, stomach)	↓

Abbreviations: MOPP= chlormethine (mechlorethamine), vincristine (oncovin), procarbazine, and prednisone; GERD= gastroesophageal reflux disease; SCC= squamous cell carcinoma; UVA= ultraviolet A

*Association is for adenocarcinoma only.

MEDICAL CONDITIONS

Inflammatory and autoimmune conditions

- There is strong evidence that inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis (UC), increase the risk of cancer of the colon and rectum and of the small intestine.[64] Emerging evidence suggests that IBD, particularly Crohn's disease, may also cause certain extra-intestinal cancers and lymphoma.[254]
    - Meta-analyses have estimated colorectal cancer risk to be 1.5–2.5 times greater among people with Crohn's disease[255–257] or UC.[258] Crohn's disease is associated with an approximately 30 times greater risk of cancer of the small intestine,[255–257] although the absolute individual risk remains low since this cancer is quite rare. UC is also associated with a significantly elevated risk of small intestinal cancer but the magnitude appears lower than for Crohn's disease.[259]

- Colorectal cancer risk is particularly high among people with an early age of IBD onset, longer duration of disease, more extensive disease and more severe inflammation.[260] Males with UC appear to have a higher risk than females.[258]

- Several other autoimmune and other chronic inflammatory conditions, including rheumatoid arthritis, Sjogren syndrome, systemic lupus erythematosus, chronic Hashimoto thyroiditis, and celiac disease and its cutaneous manifestation dermatitis herpetiformis, show a consistent association with increased risk of malignant lymphomas, most often non-Hodgkin lymphoma.[261] Lymphoma risk may also be associated with psoriasis, systemic sclerosis and sarcoidosis.

  - Results from the largest studies suggest the association is weakest for rheumatoid arthritis and strongest for Sjogren syndrome, with more moderate associations for systemic lupus erythematosus, celiac disease and Hashimoto thyroiditis.[261]

- Autoimmune and inflammatory conditions promote the development of cancer through their associated chronic inflammatory response.

Diabetes

- Diabetes consistently shows a strong positive association with the development of cancers of the liver, pancreas, colon and rectum, bladder, endometrium and breast. Prostate cancer risk is inversely associated with diabetes.[262]

- Diabetes appears to be most strongly associated with cancer of the liver and pancreas, the two organs directly involved in diabetes.[263] Meta-analyses demonstrate a 2- to 2.5-fold increased risk of these cancers, as well as endometrial cancer among people with diabetes,[264–269] although pancreatic cancer may be overestimated, since some diabetes cases may be caused by this cancer itself. A more modest increase in risk is observed for colorectal, bladder, and breast cancer, with risk of these cancers estimated to be 1.2- to 1.5-fold higher among diabetics.[270–276]

- Several aspects of the relationship between diabetes and cancer risk remain uncertain. The effect of diabetes type, for example, is unknown, since most studies have included type 2 diabetes patients only or have not distinguished between types.[263] Several diabetes medications (e.g., metformin, exogenous insulin) have been implicated in affecting cancer risk and progression among diabetes patients, but the evidence for specific drugs remains limited.[262]

- It is unclear if diabetes is associated with cancer *indirectly* due to shared risk factors (e.g., obesity) incompletely controlled for in existing studies or if diabetes has a direct causal relationship with these cancers.[262] Biologic mechanisms of action proposed for a potential direct link involve the role of circulating insulin (hyperinsulinemia) and/or chronic inflammation characteristic of diabetes, both of which may directly stimulate cell signalling pathways involved in carcinogenesis. Hyperinsulinemia may influence levels of other hormones associated with cancer development, while oxidative stress from chronic inflammation can damage cellular DNA or interfere with DNA repair.[263]

Gastroesophageal reflux disease and Barrett esophagus

- Gastroesophageal reflux disease (GERD) and Barrett esophagus are both established risk factors for cancer of the esophagus (adenocarcinoma), with most cases of Barrett esophagus arising from long-term GERD.[277]
- People with recurrent GERD symptoms have an overall 5- to 8-fold increased risk of esophageal adenocarcinoma.[278–280] A positive dose-response with both duration and severity (including frequency) of GERD symptoms is apparent,[278,280] with risk rising to upwards of 40-fold greater among people with the longest lasting and most severe symptoms.[281]
- Barrett esophagus is the precursor to esophageal adenocarcinoma. Relative to the general population, Barrett esophagus is associated with a high risk of esophageal adenocarcinoma, although the precise risk magnitude is debateable as older studies have reported much higher estimates than more recent, higher quality studies.[277,282] The absolute risk of developing esophageal adenocarcinoma for any given individual with Barrett esophagus is, however, very low.[278,282–287] The risk of progression from Barrett esophagus to cancer likely depends on factors such as the severity of dysplasia and the length of the esophagus affected.[282,286]
- Treatments for GERD and Barrett esophagus (e.g., proton pump inhibitors, hydrogen receptor antagonists, surgical methods) are effective at relieving reflux symptoms, but there is insufficient evidence to support their ability to prevent esophageal adenocarcinoma.[277,288]
- Esophageal adenocarcinoma is thought to develop through a sequence of progressive steps, but the mechanisms that drive this progression from GERD and Barrett esophagus remain unclear.[279] Potential mechanisms include the direct promotion of tumour development in response to esophageal epithelium that has been damaged by acid, pepsin and/or bile salts contained in gastroesophageal reflux; induction of an inflammatory response following damage to the esophageal epithelium; and the acquisition of multiple genetic and epigenetic changes during the progression from metaplasia to cancer.[279]

Cryptorchidism

- Cryptorchidism (a congenital abnormality of the genitourinary tract in which one or both testes fail to descend into the scrotum before birth) is the most well established risk factor for testicular cancer.[64]
- Cryptorchidism is associated with a 2.75- to 8-fold greater risk of testicular cancer overall.[289] This increased risk is restricted to the undescended testis in males with only one undescended testis and is attenuated in males who undergo orchiopexy (a surgical procedure to move the undescended testicle into the scrotum) before age 12.[289]

Benign breast disease

- Benign breast disease is a well-established risk factor for breast cancer. Women with non-proliferative lesions have a minimal increase in breast cancer risk compared to the general population. Proliferative lesions without atypia are associated with a small (1.5- to 2-fold) increase in breast cancer risk and proliferative lesions with atypia (i.e., atypical ductal hyperplasia and atypical lobular hyperplasia) are associated with a moderate increase (3.5- to 6-fold).[290]
- Breast cancer risk among women with benign breast disease may be modified by other factors, such as age at diagnosis for benign breast disease and family history of breast cancer; risk appears particularly high among women diagnosed with benign breast disease before menopause and some studies have reported particularly high risks among women with both benign breast disease and a family history.[290,291]

MEDICAL RADIATION (DIAGNOSTICS AND THERAPY)

X-radiation and gamma radiation

- Medical exposures to X- and gamma radiation include diagnostic tests, such as traditional radiography (e.g., X-rays), fluoroscopy (e.g., angioplasty) and computed tomography, as well as exposures from treatments, such as radiation therapy to treat cancer or benign conditions. The epidemiologic evidence supporting the association between medical X- and gamma radiation and cancer is outlined in the "Other Radiation" section (see page 29).

Radioiodines, including iodine-131

- Radioiodines, including iodine-131(^{131}I), are carcinogenic to humans (Group 1), causing cancer of the thyroid.[91] Associations have also been observed between radioiodines and leukemias as well as cancers of the digestive tract, salivary gland, bone and soft tissue.[91]
- A significantly higher risk of primary thyroid cancer has been seen among people being treated for hyperthyroidism with ^{131}I and people exposed to ^{131}I for diagnostic purposes. Although most studies have been based on small numbers of cases and have lacked detailed information on ^{131}I dose, people exposed to ^{131}I for medical purposes are estimated to have a 1.3- to 3.9-fold greater risk of thyroid cancer than the general population.[91] Childhood medical exposure has not been directly examined, but studies on exposures to radioactive iodines from the Chernobyl accident suggest that exposure during childhood and adolescence is particularly harmful.[91,292]

Phosphorus-32

- Therapeutic phosphorus-32 (^{32}P), administered as phosphate, is carcinogenic to humans (Group 1), causing acute leukemia in patients with *polycythaemia vera* (a blood disorder in which the bone marrow produces too many red blood cells).[91]
- A positive dose-response has been demonstrated between ^{32}P dose and acute leukemia risk among patients being treated for *polycythaemia vera*. While interpretation is difficult due to the potential for concomitant administration of other potentially carcinogenic treatments,[91] the largest study to date estimated a nearly 9-fold greater risk of acute myeloid leukemia/myelodysplatic syndrome among *polycthaemia vera* patients treated with ^{32}P compared to patients receiving traditional non-carcinogenic therapy.[293]

Biologic mechanisms

- All types of ionizing radiation damage DNA and may induce cancer through several mechanisms, including epigenetic changes resulting in genome instability, changes to the content and number of chromosomes and regulation of apoptosis, as well as the transformation of normal healthy cells through a bystander effect of being beside carcinogenic cells.[91]

PHARMACEUTICALS

Antineoplastic drugs

- The International Agency for Research on Cancer (IARC) has classified 11 antineoplastic drugs (busulfan, chlorambucil, cyclophosphamide, melphalan, semustine [methyl-CCNU], thiotepa, treosulfan, MOPP combined chemotherapy, etoposide (in combination with cisplatin and bleomycin), chlornaphazine, tamoxifen) as Group 1 carcinogens in humans.[80] Their use in treating primary cancers most commonly causes secondary leukemia, particularly acute myeloid leukemia (AML). The exceptions are chlornaphazine and tamoxifen, which cause secondary cancer of the bladder and endometrium, respectively. Cyclophosphamide and MOPP combined chemotherapy respectively cause cancer of the bladder and lung (in addition to AML).[80]
- Antineoplastic drugs can induce carcinogenesis through distinct mechanisms, depending on the class of the drug:[80]
    - Alkylating agents and antineoplastic drugs that are metabolized to alkylating agents (all carcinogenic antineoplastics except for MOPP combined chemotherapy, etoposide, and tamoxifen) can bind to DNA and potentially induce mutations in normal healthy cells.
    - Topoisomerase II inhibitors, such as etoposide, interfere with the ability of the enzyme DNA polymerase to replicate a DNA strand, leading to mutations, chromosomal aberrations and/or an abnormal number of chromosomes (aneuploidy).
    - Tamoxifen, a hormonal treatment for breast cancer, may promote cancer development through an estrogen receptor-dependent pathway. Tamoxifen is a selective estrogen receptor modulator that acts as an estrogen receptor antagonist in the breast but an estrogen receptor agonist in the bones and uterus, stimulating endometrial epithelial cell proliferation.

Methoxsalen plus ultraviolet A radiation photochemotherapy (PUVA)

- Methoxsalen is a naturally derived psoralen and photosensitizer, primarily used together with ultraviolet A radiation (PUVA photochemotherapy) to treat psoriasis and other skin conditions, such as vitiligo.[80] PUVA may also be used to prevent rejection and graft versus host disease following organ transplantation. PUVA is classified as carcinogenic to humans (Group 1), with sufficient evidence that it causes cutaneous squamous cell carcinoma.[80]

- Several studies of psoriasis patients have consistently demonstrated the carcinogenic effect of PUVA therapy, with the risk of cutaneous squamous cell carcinoma approximately 5–10 times greater than in the general population.[80] These may, however, be overestimates, since psoriasis patients are frequently exposed to other potentially carcinogenic agents.
- Methoxsalen can promote carcinogenesis through several genotoxic events following photo-activation by UVA radiation. Photoproducts of methoxsalen can also bind to DNA (i.e., form DNA adducts), potentially interfering with DNA repair and replication.[80]

Immunosuppressive drugs

- An increased risk of cancer in organ transplant recipients is well established,[64] with particularly high risks of cancer types that are causally associated with viral infections, including lymphomas, Kaposi sarcoma, anogenital cancers and liver cancer.[294,295] The excess risk is primarily due to therapeutic immunosuppression used to prevent organ rejection and graft versus host disease.[295]
- Azathioprine and cyclosporine, two immunosuppressive drugs commonly used in organ transplant recipients or for the treatment of autoimmune disorders, are classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1).[80] Both cause non-Hodgkin lymphoma and skin cancer (squamous cell carcinoma). Cyclosporine has also been shown to cause many other cancers (i.e., Kaposi sarcoma and cancers of the oral cavity, cervix, colon and rectum and liver).[80]
- Epidemiologic evidence supporting the carcinogenicity of azathioprine and cyclosporine in humans has largely come from studies of organ transplant recipients and people with autoimmune disorders. The individual effect of these drugs is difficult to ascertain, since they are often used in combination with other drugs or for varying periods of time.[296]
- Azathioprine and cyclosporine can induce cancer through two primary mechanisms:[80]
    - As immunosuppressants they may allow for the development of lymphoproliferative disorders and malignancies, predominantly of viral origin, due to compromised immune surveillance.
    - They may directly promote cancer development through their effect on cellular DNA. Azathioprine, for example, causes 6-thioguanine to accumulate in DNA, while cyclosporine can induce oxidative stress pathways, both resulting in DNA damage.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, may protect against cancer. Aspirin is consistently associated with a reduced risk of colorectal cancer and other cancers of the digestive tract, including the esophagus and stomach. Aspirin may also possibly protect against cancers of the breast and prostate, while the relationship with lung cancer is inconsistent.[297]
- Meta-analyses of observational studies and pooled results of multiple European randomized control trials of aspirin use for the prevention of cardiovascular disease have estimated that regular aspirin use (at least 1–2 tablets/week) reduces the risk of colorectal cancer by 20%–30%.[297,298]

- Strong reductions (30%–40%) in the risk of esophageal and stomach cancer have also been associated with regular aspirin use, while the risk reduction for cancers of the breast and prostate appears to be more modest.[297]
- The dose and duration of aspirin use required for a protective effect against cancer is uncertain. For colorectal cancer, observational studies differ in their definition of regular aspirin use and few have examined the effect of dose,[297] while results of randomized control trials are inconsistent; the European randomized control trials show a beneficial effect on colorectal cancer for any dose over 75 mg/day after treatment for at least 5 years and a latency of about 10 years,[298,299] while two US randomized control trials of low-dose (75–300 mg) aspirin with average follow-up of 10 years showed no reduction in colorectal cancer risk.[300,301]
- Several mechanisms have been proposed through which NSAIDs reduce cancer risk; they can inhibit the cyclooxygenase (COX) enzyme, which is abnormally expressed in cancer cells and has been implicated in cancer development, tumour growth and apoptosis. Aspirin and other NSAIDs may also limit cell proliferation and activate tumour suppressor genes, independent of the COX pathway.[297]