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Cancer Risk Factors in Ontario

Evidence Summary

Prepared by Prevention and Cancer Control staff: Elisa Candido, Beth Theis, Loraine Marrett (Prevention and Surveillance); Garthika Navaranjan, Ann Del Bianco, Paul A. Demers (Occupational Cancer Research Centre).

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FOREWORD

Cancer Risk Factors in Ontario: Evidence Summary is the first report in our *Cancer Risk Factors in Ontario* series, which supports one of Cancer Care Ontario's key priorities to reduce chronic disease through prevention.

It builds on the work described in the report we released in partnership with Public Health Ontario in 2012, called *Taking Action to Prevent Chronic Disease*, which provided advice to the Ontario government. This document reflects a commitment to the widespread implementation of population-based interventions by addressing four common risk factors—tobacco, alcohol, physical inactivity and unhealthy diet—shared by cancer and other chronic diseases.

Cancer Risk Factors in Ontario: Evidence Summary goes a step further by providing a summary of the epidemiologic evidence for a wider range of cancer risk factors important to Ontarians. The unusually large breadth of risk factor domains explored in this report spans more than just behavioural, occupational and environmental risks; it also reviews infectious agents, genetic predispositions, medical conditions and treatments, and reproductive and hormonal factors that are central to breast and gynecological cancers.

We have relied on respected expert panels for assessments of evidence strength wherever possible, and supplemented with findings from large meta-analyses, reviews and prospective studies, many of which have been very large national cohort studies or international collaborations.

It is our intent that this report will serve as a valuable reference and foundation for future prevention efforts, especially for planning and reporting on cancer prevention actions. To ensure that it is user-friendly, we have showcased information in many forms and at many different levels, and provided a glossary and extensive referencing so that readers can pursue in more detail specific areas of interest. Users can also download the complete report or individual sections that are relevant to their needs.

Subsequent *Cancer Risk Factors in Ontario* reports will focus on individual risk factor domains and, where possible, provide prevalence estimates of these factors or highlight gaps in data on cancer risk factors in Ontario.

Linda Rabeneck, MD, MPH, FRCPC
Vice President, Prevention and Cancer Control
Cancer Care Ontario

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INTRODUCTION

Cancer Risk Factors in Ontario: Evidence Summary summarizes the epidemiologic evidence linking risk factors to various types of cancer. A wide range of risk factor domains is addressed here (see table on page 6), including not only those traditionally considered modifiable, such as tobacco use, but also those usually considered non-modifiable, such as reproductive factors. The epidemiologic evidence for these domains is addressed in short summary chapters, each of which can stand alone and contains a summary table linking risk factors/exposures and cancers, followed by more detailed text. Shaded boxes in many chapters give definitional and measurement information. Users are referred to the extensive bibliography for further detail on specific cancer-risk factor associations.

This report includes only associations between risk factors and cancer types judged causal or probably causal by large expert panel reviews and/or systematic analyses. Classifications of strength of evidence have been adopted from two respected expert panels. The occupational and environmental risk factors, as well as several others, are classified by the International Agency for Research on Cancer (IARC) as carcinogenic[a] (Group 1) to humans. IARC describes well-established *causal* relationships in humans as "sufficient," and probable relationships as "limited"; the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) expert panel report uses the terms "convincing" and "probable" for these two categories. A full description of the rating system applied by each expert panel and the associated criteria can be found in Appendix A.

This report does not include risk factors/exposures or associations between risk factors/exposures and cancer sites described as "possible" or those that have not yet achieved strong enough levels of evidence (e.g., radiofrequency electromagnetic fields from wireless phone use).

Cancer Risk Factors in Ontario: Evidence Summary follows the publication of our surveillance report, *Cancer in Ontario: Overview*, which demonstrated the substantial burden of cancer on the health of Ontarians. The next *Cancer Risk Factors in Ontario* series report will focus on tobacco use, followed by a report on alcohol use.

[a]Terms in blue are defined in the glossary

Table. Risk factors included in the *Cancer Risk Factors in Ontario* report series

Risk factor domain	Description
Tobacco use	Active smoking, second-hand smoke, preconception/pregnancy exposure, smokeless tobacco
Alcoholic drinks	Alcoholic beverage consumption
Diet	Red meat, processed meat, salt and salty/salted foods, dietary fibre, vegetables and fruit
Body composition	Body fatness, abdominal fatness, adult weight gain, adult attained height
Physical activity	Physical activity
Reproductive and hormonal factors (female)	Parity, breastfeeding, age at first birth, age at menarche, age at menopause, oral contraceptive use, hormone replacement therapy for menopause
Ultraviolet (UV) radiation	Solar ultraviolet radiation, UV-emitting indoor tanning devices
Other radiation	Radon-222 and its decay products, X- and gamma radiation
Dusts and fibres	Asbestos (all forms), silica dust (crystalline), wood dust
Metals	Arsenic and inorganic arsenic compounds, nickel compounds, beryllium and beryllium compounds, cadmium and cadmium compounds, chromium (VI) and chromium compounds
Industrial chemicals	Acid mists (strong, inorganic), benzene, 1,3-butadiene, formaldehyde, mineral oils (untreated or mildly treated)
Complex mixtures	Diesel engine exhaust, polycyclic aromatic hydrocarbons (PAHs), particulate matter < 2.5 µm in diameter ($PM_{2.5}$)
Infectious agents	Epstein-Barr virus, hepatitis B virus, hepatitis C virus, human herpes virus 8, human immunodeficiency virus type 1, human papillomavirus, human T-cell lymphotrophic virus type 1, *Helicobacter pylori*, liver flukes, schistosomes
Genetic susceptibility	Major familial susceptibility syndromes for cancers of the breast, ovary, colon and rectum and prostate as well as for leukemia/lymphoma and pediatric cancers
Medical conditions and treatments	Inflammatory and autoimmune conditions, diabetes, gastroesophageal reflux disease and Barrett esophagus, cryptorchidism, benign breast disease, medical radiation (therapy and diagnostics), antineoplastic drugs, other medications

TOBACCO USE

Risk factor/exposure	Cancer	Direction of association	Magnitude of risk*	Strength of evidence[a]
Active smoking	Oral cavity and pharynx	↑	3.4–6.8[b]	Sufficient
	Nasopharynx, nasal cavity and paranasal sinuses	↑	2.0[b]	
	Esophagus	↑	2.5[b]	
	Stomach	↑	1.53–1.65[b,c]	
	Colon and rectum	↑	1.07–1.20[d,e,f,g]	
	Liver	↑	1.5–1.6[b,h]	
	Pancreas	↑	1.7[b]	
	Larynx	↑	7.0[b]	
	Lung	↑	9.0[b]	
	Cervix†	↑	1.8[b]	
	Ovary‡	↑	2.1[i]	
	Kidney, bladder, other urinary§	↑	1.5–2.8[b]	
	Leukemia, myeloid	↑	1.09[b]	
	Endometrium	↓	0.5–0.7[a]	
	Female breast	↑	…	Limited
Second-hand smoke	Lung	↑	1.2–1.4[j,k,l]	Sufficient
	Pharynx	↑	…	Limited
	Larynx	↑	…	
Preconception/ pregnancy exposure	Hepatoblastoma	↑	1.86–4.74[m]	Sufficient
	Childhood leukemia‖	↑	…	Limited
Smokeless tobacco	Oral cavity	↑	1.36–1.80[n,o]	Sufficient
	Esophagus	↑	1.13–1.60[n,o]	
	Pancreas	↑	1.07–1.60[n,o]	

Sources: [a]IARC, 2012; [b]Gandini et al., 2008 ; [c]Ladeiras-Lopes et al., 2008; [d]Botteri et al., 2008; [e]Tsoi et al., 2009 ; [f]Liang et al., 2009; [g]Huxley et al., 2009; [h]Lee et al., 2009; [i]Jordan et al., 2006 ; [j]IARC, 2004; [k]Taylor et al., 2007; [l]Stayner et al., 2007; [m]Pang et al 2003; [n]Boffetta et al., 2008; [o]Lee et al., 2008

*Relative risk (RR) comparing current cigarette smokers to (lifetime) never-smokers, never-smokers exposed to second-hand smoke to never-smokers not exposed to second-hand smoke, or ever-users of smokeless tobacco (oral use) to never-users.

… Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."

† Tobacco acts as a co-factor with human papillomavirus (HPV) infection.

‡ Association is restricted to cancers with a mucinous morphology.

§ Tobacco is a cause of cancers of both the body and pelvis of the kidney; other urinary includes ureter.

‖ Association is most apparent for acute lymphocytic leukemia in offspring of parents who smoked during preconception and/or pregnancy.

ACTIVE SMOKING

Background

» Tobacco use is the largest cause of cancer worldwide.[1]

» Cigarettes (manufactured, hand-rolled, filtered, un-filtered, and flavoured) are the main form of tobacco smoked worldwide; other types of smoked tobacco products include cigars and pipes.[1]

» Tobacco smoke contains over 70 known carcinogens, including polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, aldehydes, phenols, volatile hydrocarbons, other organics and inorganic compounds.[1]

- Tobacco smoke is a multi-organ carcinogen (Group 1). There is sufficient evidence that tobacco smoking causes cancers of the oral cavity and pharynx, nasopharynx, nasal cavity and paranasal sinuses, esophagus, stomach, colon and rectum, liver, pancreas, larynx, lung, cervix, ovary, kidney, bladder and other urinary (including ureter) and bone marrow (myeloid leukemia). Tobacco smoking is inversely related to endometrial cancer risk.[1]
- According to the International Agency for Research on Cancer (IARC), limited evidence suggests a causal association between active tobacco smoking and female breast cancer,[1] although several other consensus reviews have drawn different conclusions.[1–4]
- Tobacco smoking is most strongly related to cancers of the respiratory tract, particularly of the lung, larynx and upper digestive tract. A recent meta-analysis reported that current smokers have an approximately 7 times greater risk of laryngeal cancer and a 9 times greater risk of lung cancer than never-smokers,[5] although lung cancer risk has been estimated in some studies to be as much as 20 times greater among smokers than lifetime never-smokers.[6] The tobacco smoke-related risk of upper digestive tract cancers (i.e., oral cavity, nasopharynx, hypopharynx, pharynx, esophagus) associated with tobacco smoke is approximately 3.6 times greater among current smokers.[5] Tobacco smoking increases the risk of colorectal cancer by 7%–20%.[7–10]
- Most cancer sites show a strong positive dose-response relationship, with cancer risk increasing with both intensity (e.g., number of cigarettes per day) and duration of smoking.[1] For lung cancer, smoking duration appears to be a stronger determinant of risk than intensity.[6]
- Actively smoking cigars and pipes is also causally associated with higher risk of cancers of the lung, upper aerodigestive tract (i.e., oral cavity, pharynx, larynx), esophagus, pancreas, stomach and bladder.[6]
- Quitting smoking reduces the risk of tobacco-related cancers, compared to not quitting. Risk generally decreases with both increasing time since cessation and decreasing age at cessation. For some cancers, such as lung and laryngeal, risk declines rapidly,[11] while for others, such as esophageal cancer, risk reductions only occur many years after cessation.[12]
- For some cancers, particularly those of the oral cavity, pharynx, larynx and esophagus (squamous cell carcinoma),[1,13] there is a synergistic interaction between tobacco smoking and alcohol consumption, whereby the increased risk for these cancers associated with tobacco is greater in people who drink alcohol than in non-drinkers.

- Tobacco smoking also interacts synergistically with radon exposure to influence lung cancer risk; the increased risk of lung cancer among smokers is substantially higher among those who smoke and are exposed to radon than those without radon exposure.[1,14]
- In addition, an interaction between tobacco smoking and infectious agents is likely. A recent meta-analysis concluded that tobacco smoke seems to interact with both hepatitis B and C infections to influence liver cancer risk, with risk particularly high among smokers.[15] For cervical cancer, tobacco smoke acts as a co-factor with human papillomavirus (HPV) infection.[1]
- Potential gene-tobacco smoke interactions that could influence susceptibility to tobacco-related cancers remain largely unclear. The strongest evidence of an interaction is for a variant of the N-acetyltransferase gene (NAT2) in bladder and breast cancer risk and for the GTSM1 gene variant alone or in combination with the CYP1A1 variant in lung cancer.[1]

SECOND-HAND SMOKE

Background

» Second-hand smoke (also known as involuntary or passive smoking, or environmental tobacco smoke) consists of sidestream smoke (released from the burning tip of a cigarette between puffs) and mainstream smoke (released from the mouth end of a cigarette during smoking) exhaled by the smoker.[1]

» Second-hand smoke has a similar composition as mainstream smoke that is actively inhaled, but the concentration of individual chemicals and compounds differs.[1]

» Second-hand smoke exposure can occur in all places where smoking is present (e.g., the home, workplace, bars, restaurants, public buildings and other public spaces).

- There is sufficient evidence that second-hand smoke exposure causes lung cancer.[1] Limited evidence also suggests an association between second-hand smoke and cancers of the larynx and pharynx.[1]
- Several meta-analyses have demonstrated a 20%–40% increased risk of lung cancer among non-smoking adults exposed to second-hand smoke at home or work.[6,16,17] Emerging evidence suggests that exposure to second-hand smoke during childhood may also increase the risk of lung cancer in adulthood.[1]
- For lung cancer, evidence of a positive dose-response exists for both duration and intensity of exposure to second-hand tobacco smoke.[6]
- Few studies have examined the possible association between second-hand smoke exposure and cancers of the upper aerodigestive tract but the risk of laryngeal and pharyngeal cancer may be increased in response to long duration (>15 years) of exposure to second-hand smoke at home and/or work.[18]

PRECONCEPTION/PREGNANCY EXPOSURE

- There is now sufficient evidence that parental tobacco smoking (by the father and/or mother during the preconception period and during pregnancy) causes hepatoblastoma, a rare embryonic cancer.[1,19] Parental tobacco smoking has also been associated with increased risk of childhood leukemia (particularly acute lymphocytic leukemia).[1]

SMOKELESS TOBACCO

Background

» Smokeless tobacco products are tobacco products that are consumed without burning, including products intended for oral use that are placed in the mouth and are sucked (dipped), chewed, gargled or applied to the gums or teeth, and products inhaled through the nasal passages.[1]

» Smokeless tobacco products most commonly used in North America include chewing tobacco and snuff.[20]

» Smokeless tobacco products contain multiple carcinogens, including tobacco-specific N-nitrosamines, N-nitrosamino acids, volatile N-nitrosamines, polycyclic aromatic hydrocarbons (PAHs), formaldehyde and acetaldehyde.[1]

- Smokeless tobacco (e.g., chewing tobacco, snuff, snus) causes cancer of the oral cavity, esophagus and pancreas.[1]
- Smokeless tobacco increases the risk of oral cancer by approximately 36%–80%[20,21] after adjusting for tobacco smoking. Smokeless tobacco-related oral cancers generally appear to occur more frequently in areas directly in contact with tobacco, including the gums and buccal mucosa.[22]

BIOLOGIC MECHANISMS

- Tobacco smoke may induce cancer through several mechanisms when ingested (either directly through tobacco smoke or indirectly by dissolving in saliva):[23]
  - Tobacco carcinogens can form DNA adducts, which can lead to DNA damage.
  - Nicotine and tobacco-specific nitrosamines (e.g., 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone [NNK]) may activate signal transduction pathways and allow damaged epithelial cells, which would normally die, to survive.
  - Co-carcinogens and tumour promoters in tobacco smoke can lead to methylation of key tumour suppressor genes, interfering with mechanisms that regulate normal cell growth.
- Smokeless tobacco may induce cancer through tobacco-specific nitrosamines such as *N*'-nitrosonornicotine (NNN) and NNK, which are considered "carcinogenic to humans." Once ingested by smokeless tobacco users, these may form DNA adducts and/or interfere with signal transduction pathways.[22]

ALCOHOLIC DRINKS

Risk factor/exposure	Cancer	Direction of association	Magnitude of risk*	Strength of evidence[a]
Alcohol consumption	Oral cavity and pharynx	↑	1.75–1.86[b,c]	Sufficient
	Esophagus[†]	↑	1.4–1.5[b,c]	
	Colon and rectum	↑	1.18–1.20[d]	
	Larynx	↑	1.38–1.43[b,c]	
	Breast	↑	1.25–1.31[b,c]	
	Liver	↑	1.18–1.19[b,c]	
	Pancreas	↑	…	Limited

Sources: [a]IARC, 2012; [b]Bagnardi et al., 2001; [c]Corrao et al., 2004; [d]Fedirko et al., 2011

[*] Relative risk (RR) estimate comparing 25 g/day (approximately two drinks) of alcohol intake to non-drinking.
… Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."
[†] Association is primarily restricted to squamous cell carcinoma. The association, if any, with adenocarcinoma is weak.

Background

» Alcoholic beverages contain ethanol (commonly referred to as alcohol) produced through the fermentation of sugars by yeasts.[24]

» Beers, wines and spirits are the most common alcoholic drinks commercially produced; other alcoholic beverages, such as fermented milks, fermented honey-water (mead) and fermented apples (cider), may be particularly important in some populations or geographic areas.[24]

» Alcohol content differs among types of alcoholic drinks, usually ranging from 3%–7% in beers, 9%–15% in wines and 35%–50% in spirits or liquors.[24]

» Standard serving sizes for alcoholic beverages vary among countries but one drink usually contains 12–15 g of alcohol.[25] In Canada, one standard drink is usually defined as: a 341 ml or 12 oz bottle of regular strength beer (5%), a 142 ml or 5 oz glass of wine (12%), or a 43 ml or 1.5 oz shot of distilled liquor.[26]

- Alcoholic beverages have been classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1), causing cancers of the oral cavity, pharynx, larynx, esophagus (primarily squamous cell carcinoma), colon and rectum, female breast, and liver.[1,24] There is limited evidence that alcohol consumption may also cause cancer of the pancreas.[1]
- Meta-analyses have estimated that compared to non-drinkers, people who drink 25 g (~ 2 drinks) of alcohol/day have a 75%–86% increased risk of cancers of the oral cavity and pharynx, a 40%–50% increased risk of esophageal cancer, a roughly 40% increased risk of laryngeal cancer, a 25%–31% increased risk of breast cancer, and a roughly 20% greater risk of colorectal cancer.[27,28] The risk of developing these cancers increases substantially with alcohol intake equivalent to 4 or more drinks/day.[29–34]

- The risk of liver cancer is estimated as 18%–19% higher in people who drink 25 g/day of alcohol compared to non-drinkers;[27,28] however, these estimates should be interpreted cautiously because alcohol-related liver cancers generally follow cirrhosis, which often leads to a reduction of alcohol consumption. For this reason, a large expert panel report by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) acknowledges that alcohol is causally related to cirrhosis of the liver but has classified the evidence for an association between alcohol consumption and liver cancer as "probable."[24]
- Despite a protective effect of light to moderate alcohol consumption for other chronic diseases, such as cardiovascular disease, no clear "safe limit" of alcohol intake to prevent an increased risk of cancer has been determined.[24]
    - A dose-response relationship exists between alcohol consumption and cancer risk. For most cancers, the increase in risk is continuous and is apparent even at low levels of intake. For example, each 10 g/day (< 1 drink) increase in alcohol consumption is associated with a 21% increase in oral cavity and pharyngeal cancer risk [29] and a 7%–10% increase in female breast cancer risk.[24,32,35] For colorectal cancer, a dose-response is evident, but it is unclear whether there is a lower threshold below which no increased risk of colorectal cancer is observed.[1]
- Increased cancer risk exists regardless of the type of alcoholic drink consumed, suggesting that the risk is due to ethanol, another IARC Group 1 carcinogen.[1] The effects of duration and cessation of the consumption of alcoholic beverages and the lifetime period of exposure on cancer risk remain uncertain.
- Alcohol consumption interacts synergistically with tobacco smoking to influence the risk of some cancers, particularly of the oral cavity, pharynx, larynx and esophagus[1,13] (see tobacco section on page 7).
- Susceptibility to alcohol-related cancers may be higher among individuals with certain functional variants in the genes involved in alcohol metabolism, including those that encode the major alcohol-metabolizing enzymes, alcohol dehydrogenases and aldehyde dehydrogenases (ALDH). The variant allele ALDH*2 is prevalent in Asian populations and has been shown to increase the risk of upper aerodigestive tract cancers in moderate and heavy drinkers.[1,36]
- Evidence suggests several ways that alcohol may increase cancer risk,[37] including:
    - Reactive metabolites of alcohol may be carcinogenic. Acetaldehyde has been identified as a carcinogen by IARC and has been shown to form DNA adducts. The resulting genetic damage may lead to increased proliferation of tumour cells.
    - Alcohol may act as a solvent, allowing other carcinogens to penetrate cells more easily. This may contribute to the observed synergistic effect between alcohol and tobacco smoking.
    - The production of prostaglandins, lipid peroxidation and the generation of free radical oxygen through the metabolism of alcohol may mediate the effects of alcohol.
    - In the case of breast cancer, evidence suggests that the carcinogenic effect is due to increased estrogen production in response to alcohol consumption.
    - The diets of people who are heavy alcohol consumers may be lacking essential nutrients, which may make body tissues more susceptible to carcinogenesis.

DIET

Risk factor/exposure	Cancer	Direction of association	Magnitude of risk*	Strength of evidence[a]
Red meat	Colon and rectum	↑	1.17[b]	Convincing
Processed meat	Colon and rectum	↑	1.18[b]	Convincing
Salt and salted/ salty foods[†]	Stomach	↑	…	Probable
Dietary fibre	Colon and rectum	↓	0.90[b]	Convincing
Vegetables and fruit[‡]	Oral cavity, pharynx, larynx	↓	…	Probable
	Esophagus	↓	…	
	Stomach	↓	…	
	Lung[§]	↓	…	

Sources: [a]WCRF/AICR, 2007; [b]WCRF/AICR, 2011

* Relative risk (RR) estimate for: every 100 g/day increase in red meat consumption; every 50 g/day increase in processed meat consumption; and every 10 g/day increase in dietary fibre intake.
…Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."
[†] Salt refers to total salt consumption (usually measured in g/day), from processed foods, as well as salt added in cooking and at the table. Salted/salty foods refers to the consumption of foods containing salt, including processed and salt-preserved foods.
[‡] Vegetables refer to non-starchy vegetables and allium vegetables (e.g., onions, garlic, leeks), but exclude roots and tubers, such as potatoes, sweet potatoes and yams.
[§] Probable evidence supports only fruit (not vegetables) as protective for lung cancer.

Introduction: food or nutrients?

Dietary factors are thought to account for a large proportion of certain cancers. Individual diets are dynamic and complex, consisting of a large number of factors, including micronutrients (e.g., vitamins and minerals), macronutrients (e.g., proteins, fats, carbohydrates), whole food items and processed foods, present in countless combinations.

This evidence summary takes a food-based approach, which is the most useful from a prevention standpoint because people consume whole foods rather than individual nutrients. Although convincing or probable evidence from good-quality randomized control trials supports supplementation of some micronutrients (e.g., calcium, selenium) for the prevention of certain cancers, it is difficult to determine whether any given constituent of a particular food is causally associated with a decreased or increased cancer risk, or is simply a marker for some other constituent of the food or of the whole food itself.

A food-based approach is still faced with challenges in determining whether a particular food is a causal risk or protective factor for a given cancer, since individuals eat many different kinds of foods, more than one of which can contain similar types of dietary constituents. Dietary fibre, for example, is found in cereals and grains, as well as in vegetables and fruit. Similarly, salt or sodium is found in processed meats, but also occurs in non-meat processed food items.

RED MEAT AND PROCESSED MEAT

Background

» Red meat comes from animals with more red than white muscle fibres and includes beef, pork, lamb and goat. Processed meat generally refers to meats preserved by smoking, curing or salting, or the addition of chemical preservatives (e.g., ham, bacon, sausages, hot dogs), although there is no standard processed meat definition.[24]

» Consumption of red and processed meat is generally highest in high-income countries, such as the United States and Canada.[24]

» Since processed meat is generally red meat, it is difficult to disentangle the cancer risk associated with each of these factors in epidemiologic studies.[24]

- Red meat and processed meat consumption are both convincing causes of colorectal cancer.[24,38]
- Substantial evidence from prospective studies demonstrates a positive dose-response relationship between colorectal cancer risk and both red and processed meat consumption. A World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) meta-analysis estimated a 17% increase in risk for every 100 g/day increase in red meat consumption and an 18% increased risk of colorectal cancer for every 50 g/day increase in processed meat consumption.[38] Results of another meta-analysis suggests that elevated risk associated with red meat consumption levels off above 140 g/day.[39]
- The lowest intake of red meat consumption associated with increased risk of colorectal cancer remains unclear.[24]
- The associations with red and processed meat appear to be of similar magnitude for both colon and rectal cancer, although results have more often reached statistical significance for colon cancer.[39] Some studies show a positive association with red meat consumption for men, but not for women.
- Red and processed meat may increase colorectal cancer risk through several plausible biologic mechanisms:[38]
  - Heme iron in red meat can promote the formation of potentially carcinogenic *N-nitroso* compounds and other harmful substances in response to oxidative degradation of fats.
  - Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) from cooking red meat at high temperatures can promote colorectal cancer in people with a genetic predisposition.
  - Processed meats frequently contain nitrates and/or nitrite-fortified salts, which can promote carcinogenesis in the stomach via the formation of *N-nitroso* compounds.

SALT AND SALTED/SALTY FOODS

Background

» "Salt," which commonly refers to sodium chloride, is used to preserve and enhance the flavour of many foods.[24]

» Although the use of salt as a preservative has become less common with the increased availability of refrigeration, several traditional diets still include large amounts of salt-preserved foods, including salted meat and fish. Processed foods are the main source of dietary salt intake in most industrialized countries, with only a small amount added during cooking or at the table.[24]

» Assessing salt intake in epidemiologic studies is difficult. Although measuring the amount of sodium excreted in the urine provides the most reliable estimate,[24] most studies rely on self-reported intake of salty, salted and salt-preserved foods.

- The WCRF/AICR concluded that salt and salted/salty foods probably cause stomach cancer.[24]
- Stomach cancer incidence rates are highest in areas of the world where traditional diets are high in salt (e.g., parts of Asia, Latin America).[40]

- Cohort studies show a positive dose-response relationship between total salt intake (from all sources, including processed foods, salt-preserved foods, and salt added during cooking and at the table) and stomach cancer, and several case-control studies have shown increased risk of stomach cancer with high levels of salt intake.[24] The WCRF/AICR meta-analysis of two cohort studies indicates an 8% increase in stomach cancer risk for every 1 g/day intake of salt.[24]
- Intake of salty/salted foods has also been associated with increased risk of stomach cancer. Case-control studies show a positive dose-response, with a 5.2-fold increased risk of stomach cancer for each additional serving of salty/salted food per day.[24]
- Evidence suggests that salt and salty/salted foods may interact synergistically with *Helicobacter pylori* infection, an established risk factor for stomach cancer, to promote stomach cancer.[41]
- High salt intake can damage the stomach lining, which may promote the effect of gastric and food-derived carcinogens and cause inflammatory responses that increase epithelial cell proliferation.[40]

DIETARY FIBRE

Background

» Dietary fibre can be defined as the components of plant cell walls that cannot be digested in the small intestine.[24]

» Naturally occurring dietary fibre is derived from plant foods, including pulses (legumes), cereals (grains) that have undergone minimal processing, vegetables and fruit.

- There is now convincing evidence that foods containing dietary fibre have a protective effect against the risk of cancer of the colon and rectum.[38]
- Colorectal cancer risk shows an inverse dose-response to dietary fibre intake, with a 10% decreased risk of colorectal cancer for every 10 g/day intake of total dietary fibre.[38] Similar findings have been observed for colon and rectal cancer, although the results for rectal cancer have generally not reached statistical significance.[38]
- Colorectal cancer risk is reduced in response to total dietary fibre intake and to fibre derived from cereals (grains) and whole grains. Fibre from other sources (e.g., vegetables and fruit) also appears to be protective, although results are not statistically significant.[38]
- Several biologic mechanisms have been proposed for the protective effect of fibre, including diluting fecal carcinogens, reducing transit time through the colon, increasing stool weight, altering bile acid metabolism, reducing colonic pH and/or increasing the production of short-chain fatty acids, which may induce apoptosis following fermentation of fibre by the gut flora.[42]

VEGETABLE AND FRUIT CONSUMPTION

Background

» Vegetables can be classified as starchy (e.g., potatoes, yams and other root vegetables) or non-starchy (e.g., green leafy, cruciferous and allium vegetables). Fruit are the edible seed-containing part of a plant (e.g., apples, bananas, berries).[24]

» Vegetables and fruit are rich sources of vitamins, minerals, dietary fibre, and other micronutrients and bioactive compounds, such as phytochemicals.

» Epidemiologic studies of vegetable and fruit consumption generally rely on self-reported intake and differ in the definition and groupings of vegetables and fruit.

- Consumption of non-starchy vegetables and of fruit has been classified by the WCRF/AICR as probably protective against of cancers of the oral cavity, pharynx, larynx, esophagus and stomach. Fruit consumption also probably protects against lung cancer.[24]
- Risk reductions of 30%–50% have been estimated for cancers of the mouth, pharynx and larynx with higher versus lower intakes of vegetables and fruit.[24,43,44]
- Evidence suggests an inverse dose-response between vegetable consumption and cancer of the oral cavity, pharynx, larynx and esophagus (raw vegetable consumption) and between fruit consumption and cancers of the esophagus, stomach and lung. Case-control studies but not cohort studies support inverse dose-response relationships with vegetable consumption and stomach cancer and with fruit consumption and cancer of the mouth, pharynx and larynx.[24]
- It is unclear whether all vegetables and fruit confer a protective effect, although it is likely that a few vegetables or fruits have an important effect on certain cancers (e.g., foods containing lycopene probably protect against prostate cancer; foods containing carotenoids protect against cancers of the mouth, pharynx, larynx and lung cancer; and foods containing vitamin C protect against esophageal cancer).[24]
- Vegetables and fruit may confer a protective effect through several generic and cancer-specific biologic mechanisms by, for example, preventing nutrient deficiencies.[45] Fruit and vegetables also contain specific potentially cancer-preventive components, including antioxidants (e.g., carotenoids, vitamin C, lycopene), dietary fibre and phytochemicals (e.g., phytoestrogens). These substances may reduce cancer risk through antioxidant activity, modulation of detoxification enzymes, stimulation of the immune system, antiproliferative activities, and/or modulation of steroid hormone concentration and hormone metabolism.[24]
- The low energy density and high fibre content of vegetables and fruit may indirectly protect against certain cancers by preventing weight gain, overweight and obesity.[24]

BODY COMPOSITION

Risk factor/exposure	Cancer	Direction of association	Magnitude of risk*	Strength of evidence[a]
Body fatness	Esophagus[†]	↑	1.55[a]	Convincing
	Colon and rectum	↑	1.10–1.15[a,b]	
	Pancreas	↑	1.14[a]	
	Breast (post-menopausal)	↑	1.13[c]	
	Endometrium	↑	1.52[a]	
	Kidney	↑	1.31[a]	
	Gallbladder[‡]	↑	…	Probable
	Breast (pre-menopausal)	↓	…	
Abdominal fatness	Colon and rectum	↑	1.02[b]	Convincing
	Pancreas	↑	…	Probable
	Breast (post-menopausal)	↑	…	
	Endometrium	↑	…	
Adult weight gain	Breast (post-menopausal)	↑	…	Probable
Adult attained height[§]	Colon and rectum	↑	1.05[b]	Convincing
	Breast (post-menopausal)	↑	1.10[c]	
	Pancreas	↑	…	Probable
	Breast (pre-menopausal)	↑	…	
	Ovary	↑	…	

Sources: [a]WCRF/AICR, 2007; [b]WCRF/AICR, 2011; [c]WCRF/AICR, 2010

* Relative risk (RR) estimate for each: 5 kg/m^2 increase in body mass index (body fatness indicator); 2.5 cm increase in waist circumference (abdominal fatness indicator); 5 cm increase in adult attained height.

…Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."

[†] Adenocarcinoma only.

[‡] Directly, and indirectly through the formation of gallstones.

[§] Unlikely to directly modify cancer risk.

BODY FATNESS

Background

» Body fatness is typically assessed using body mass index (BMI), a measure of weight adjusted for height that is calculated as weight in kilograms divided by height in metres squared (kg/m^2).

» Adult body fatness is frequently classified by the World Health Organization into four broad categories based on the following BMI cut-offs:[46]

Classification	BMI (kg/m^2)
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	≥ 25.00
Obese	≥ 30.00

» Fat is not equally distributed around the body, but rather accumulates subcutaneously in certain parts of the body such as the abdomen. Intra-abdominal fat stores may be a better predictor of chronic disease risk than overall body fatness.[24]

- The evidence is convincing that greater body fatness increases the risk of cancers of the esophagus (adenocarcinoma), colon and rectum, pancreas, breast (post-menopausal), endometrium and kidney, and probable that it increases the risk of gallbladder cancer.[24,38,47] Greater body fatness probably reduces the risk of pre-menopausal breast cancer.[47]
- A positive dose-response relationship is generally apparent for cancers associated with body fatness in adults, even within the range usually considered healthy.
    - For every 5 kg/m^2 increase in BMI within the range considered "normal" and above, risk increases by 50%–55% for esophageal adenocarcinoma and endometrial cancer, roughly 30% for kidney cancer, and 10%–15% for colorectal, post-menopausal breast and pancreatic cancer.[24,38,47]
- For certain cancers, existing evidence suggests that the relationship with body fatness differs by subtype. For example:
    - Cancer of the esophagus: an association is apparent for adenocarcinoma only, while evidence for all types of esophageal cancer combined or squamous cell carcinoma is inconsistent.[24]
    - Cancer of the colon and rectum: the evidence is more consistent and shows a larger increase in risk for colon cancer than for rectal cancer.[38,48,49]
    - Cancer of the breast (pre- and post-menopausal): results from a large meta-analysis[50] and subsequent prospective studies[51–53] suggest that the relationship with body fatness depends on the hormone receptor (estrogen and progesterone) status of the tumour.
- For some cancer sites there is some evidence to suggest that associations with body fatness may differ by sex. For example, a stronger association with BMI for colon and rectal cancers is apparent in men.[38,48] The association between BMI and kidney cancer, on the other hand, appears to be stronger in women.[48,54]
- Evidence suggests that hormone replacement therapy (HRT) used during and/or following menopause modifies the association between body fatness and both post-menopausal breast cancer and endometrial cancer; greater body fatness increases the risk of cancer of the breast (post-menopausal) and endometrium among women who have never used HRT, but the association is generally weaker or null among ever-users.[47,55]

ABDOMINAL FATNESS

- According to the comprehensive World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) review, abdominal fatness is a cause of colorectal cancer and probably causes cancers of the pancreas, breast (post-menopausal) and endometrium.[24,38,47]
- For colorectal cancer, a consistent and clear dose-response relationship is observed with both measures of abdominal obesity (waist circumference and waist-to-hip ratio). Colorectal cancer risk is estimated to increase by approximately 2% for every 2.5 cm (1 inch) increase in waist circumference and by roughly 17% for every 0.1 increase in waist-to-hip ratio.[38]

ADULT WEIGHT GAIN

- Existing epidemiologic evidence suggests that weight gain during adulthood is a probable cause of post-menopausal breast cancer.[47]
- There is consistent evidence of a dose-response relationship such that the risk of post-menopausal breast cancer rises with increases in the amount of weight gained during adulthood.[24]

ADULT ATTAINED HEIGHT

- Greater adult attained height is a convincing cause of cancers of the colon and rectum, as well as breast cancer (post-menopausal). It is also probably a cause of cancer of the pancreas, breast (pre-menopausal) and ovary.[24,38,47]
- For cancer sites that have a convincing association with adult attained height, abundant and consistent evidence demonstrates a positive dose-response; each 5 cm (approximately 2 inches) increase in adult attained height increases colorectal cancer risk by 5%[38] and post-menopausal breast cancer risk by 10%.[47]
- The relationship with attained height is stronger for colon cancer than rectal cancer. It is also stronger in men than in women.[38]

BIOLOGIC MECHANISMS

- Several potential mechanisms have been proposed to explain the relationship between body composition and increased cancer risk:[24]
    - Abdominal fatness and obesity are associated with insulin resistance, resulting in excess circulating insulin (hyperinsulinemia) and insulin-like growth factor-1 (IGF-1), which can promote the development of certain cancers.
    - Adipose cells produce hormones, known as adipokines, such as leptin and adiponectin, which may stimulate cell growth.
    - Adipose tissue is the main site of estrogen synthesis in men and post-menopausal women. Excess sex steroids are strongly associated with risk of endometrial and post-menopausal breast cancer.
    - Obesity is characterized by low-grade chronic inflammation, which can promote the growth of cancer cells.
- The biologic mechanisms responsible for a decreased risk of pre-menopausal breast cancer with increasing body fatness are unclear, although various explanations, mostly focusing on endogenous hormone levels, have been proposed.[24]
- Adult attained height is unlikely to directly modify cancer risk. Instead, it is probably a marker for genetic, environmental, hormonal, and/or nutritional factors that affect growth from preconception until adulthood.[24]

PHYSICAL ACTIVITY

Risk factor/exposure	Cancer	Direction of association	Magnitude of risk*	Strength of evidence[a]
Physical activity	Colon	↓	0.92[b]	Convincing
	Breast (post-menopausal)	↓	…	Probable
	Endometrium	↓	…	

Sources: [a]WCRF/AICR, 2007; [b]WCRF/AICR, 2011

* Relative risk (RR) for every 5 METs-hour/day increase in physical activity.
…Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."

Background

» Physical activity is any movement using skeletal muscles. It can be classified according to type (occupational, household, active transportation, recreational/leisure-time), and by intensity based on energy expenditure (vigorous, moderate, light or sedentary).[24]

» Total physical activity levels are determined by frequency, intensity and duration; one hour of light physical activity may therefore result in the same amount of total energy used as 20 minutes of vigorous activity.[24]

» Sedentary behaviour describes activities involving prolonged sitting, reclining or lying down that are characterized by low energy expenditure (e.g., watching television or using a computer). It is considered distinct from physical inactivity, which represents the absence of physical activity;[56] therefore, a person may be physically active but still have prolonged periods of sedentary time.

- The evidence is now convincing that physical activity reduces the risk of colon cancer and probably cancer of the breast (post-menopausal) and endometrium, independently of other factors, such as body fatness.[24,38,47,57]
- In reviews and meta-analyses, risk was reduced by 20%–25% for colon cancer,[10,58,59] 20%–30% for breast cancer,[60] and 20%–30% for endometrial cancer[61–63] when comparing those with the highest levels of physical activity to those with the lowest levels.
- Epidemiologic evidence demonstrates an inverse dose-response relationship between physical activity and cancer risk, with higher levels of physical activity (within the range of activity examined) associated with decreasing cancer risk.[24]
- All types of physical activity (occupational, household, transport, recreational) appear to reduce cancer risk.[24]
- The minimum amount of physical activity for cancer protection is difficult to determine because of differences in measurement and classification among studies. Most studies have examined physical activity with respect to energy expenditure or duration, but few provide sufficient details to evaluate the effect of intensity.[24]

- The relationship between physical activity and cancer risk may be modified by several factors:
    - For breast cancer, a greater relative benefit of physical activity is observed for women without a family history of breast cancer, women with a normal body mass index (although benefits are seen within all levels of body mass index), parous women and non-Caucasian women.[60]
    - For colon cancer, some evidence suggests that physical activity may have a stronger effect for men than for women.[38]
- Interest in the potential risk of cancer associated with sedentary behaviours, independent of being physically inactive, is emerging. The few studies that have examined a potential association between sedentary behaviours and cancer risk have generally shown positive associations with colorectal, endometrial, ovarian and prostate cancer.[56]

BIOLOGIC MECHANISMS

- Physical activity may directly protect against cancer through several biologic mechanisms, including promoting healthier levels of circulating hormones and a healthy body weight.[57] Specifically:
    - Physical activity may protect against colorectal cancer by decreasing inflammation, reducing insulin levels, reducing insulin resistance, improving endogenous steroid hormone metabolism and reducing transit time through the gastrointestinal tract.
    - Physical activity may protect against breast cancer by improving endogenous steroid hormone metabolism, possibly strengthening the immune system, and reducing levels of circulating estrogens and androgens.
- Physical activity may also indirectly protect against cancers associated with body fatness, including colorectal cancer and post-menopausal breast cancer, through its role in maintaining energy balance and body fatness.[24]

REPRODUCTIVE AND HORMONAL FACTORS (FEMALE)

Risk factor/exposure	Cancer	Direction of association	Magnitude of risk*	Strength of evidence
Parity	Cervix	↑	1.07[a]	Established
	Breast	↓	0.89–0.92[b]	
	Endometrium	↓	0.65[c]	
	Ovary	↓	0.92[d]	
Breastfeeding	Breast	↓	0.98[e]	Established
Later age at first birth/full-term pregnancy	Breast	↑	1.10–1.23[b]	Established
	Cervix	↓	0.95[a]	
Later age at menarche	Breast	↓	0.65–0.93[b]	Established
	Endometrium	↓	0.72–0.76[c,f]	
Later age at menopause	Breast	↑	1.20–1.32[b]	Established
	Endometrium	↑	1.53–2.20[c,f]	
Oral contraceptive use	Liver†	↑	1.45–1.57[g]	Sufficient
	Breast‡	↑	1.24[h]	
	Cervix‡	↑	1.65[i]	
	Endometrium	↓	0.50–0.65[c,j]	
	Ovary	↓	0.73[k]	
Hormone replacement therapy for menopause	Breast	↑	1.21[l]	Sufficient
	Endometrium	↑	1.44–1.75[f,m]	

Sources: [a]International Collaboration of Epidemiological Studies of Cervical Cancer, 2006; [b]Reeves et al., 2009; [c]Dossus et al., 2010; [d]Tsilidis et al., 2011; [e]WCRF/AICR, 2007; [f]Kerageorgi et al., 2010; [g]Maheshwari et al., 2007; [h]Collaborative Group on Hormonal Factors in Breast Cancer, 1996; [i]International Collaboration of Epidemiological Studies of Cervical Cancer, 2007; [j]IARC, 2007; [k]Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; [l]Collaborative Group on Hormonal Factors in Breast Cancer, 1997; [m]Allen et al., 2010

* Risk estimates are relative risks (RRs). The groups for comparison and measures of exposure differ between risk factor/exposures and in some cases between cancers for a given exposure. See text for details.
† In populations at low risk for hepatitis B infection.
‡ Current and recent oral contraceptive use.

Background

» Reproductive factors, such as parity, age at menarche and age at menopause, are closely related and influence the levels of sex hormones (e.g., estrogen, progesterone) circulating in the body.[64]

» Endogenous female sex hormones are produced by the ovaries. Among other functions, estrogen stimulates the development of the breasts and the growth of endometrial tissue. Progesterone plays a key role in preparing the endometrium for pregnancy and also regulates the effect of estrogen.[64]

» The strong connections between reproductive factors, endogenous hormones and exogenous hormones, such as oral contraceptives, make it difficult to disentangle the individual effect of each factor on cancer risk in epidemiologic studies.

PARITY

- Parity is a well-established protective factor for cancer of the breast, endometrium and ovary.[65] In contrast, higher parity *increases* the risk of cervical cancer.
- An inverse dose-response relationship is seen for breast, endometrial and ovarian cancer, and a positive dose-response is observed for cervical cancer:
    - A large UK cohort study found an approximately 10% reduction in risk for each additional birth for the most common histologic types of breast cancer (unadjusted for age at first birth).[66] Several large studies have found an effect of parity independent of age at first birth.[67–69]
    - Compared to nulliparous women, women who had had at least one full-term pregnancy had a 35% reduced risk of endometrial cancer in a large European cohort;[70] risk decreases with increasing numbers of children.[70,71]
    - Ovarian cancer risk was 29% lower for women with at least one full-term pregnancy than for nulliparous women in a large cohort study, with an 8% lower risk per full-term pregnancy.[72]
    - A large international pooled analysis found cervical cancer risk increased 7% per additional full-term pregnancy after controlling for other factors, including age at first birth, age at first sexual intercourse and number of sexual partners.[73]
- For breast and ovarian cancer, some evidence suggests that risk varies depending on the histologic type of the tumour, with a reduced risk more consistently seen for estrogen receptor (ER)-positive than for ER-negative breast cancer[74] and for the most common histologic subtype of ovarian cancer and some rare subtypes.[75]

BREASTFEEDING

- A large meta-analysis conducted by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) found a 2% reduction in breast cancer risk for every 5 months of breastfeeding, additional to the risk reduction from number of births, and controlling for such other factors as age at first birth.[24]
- Some evidence is emerging that breastfeeding lowers the risk of ovarian cancer, although the WCRF/AICR panel concluded that the evidence for this cancer was only limited.[24,76]

LATER AGE AT FIRST BIRTH

- Older age at first birth is a well-established risk factor for breast cancer.[65] In a large UK cohort study, risk increased 10%–23%, depending on histologic type, per 5-year delay in age at first birth.[66] A large review found a more consistent increase in risk with delayed childbearing for estrogen receptor (ER)-positive than for ER-negative breast cancer.[74]
- Later age at first birth decreases the risk of cervical cancer. A large international pooled analysis estimated that risk decreased 5%/1-year increase in age at first full-term pregnancy after controlling for factors, including parity, age at first sexual intercourse and number of sexual partners.[73]

LATER AGE AT MENARCHE

- Later age at menarche has been consistently associated with a reduced risk of breast cancer.[65] A large UK cohort study estimated a 7%–35% decrease in breast cancer risk, depending on histologic type, with every 5-year increase in age at menarche.[66] A large review found older age at menarche more consistently associated with a reduced risk of estrogen receptor (ER)-positive/progesterone receptor (PR)-positive than with ER-negative/PR-negative breast cancer.[74]
- Later age at menarche is also a protective factor for endometrial cancer.[65] This has been confirmed in two large studies (one from the UK and one from the US), with decreases of more than 24% for menarche at age 15 or older compared with menarche at approximately age 12 or younger and decreasing risk with later ages at menarche; one study controlled for body mass index, which is related to both endometrial cancer risk and age at menarche.[70,71]

LATER AGE AT MENOPAUSE

- Late menopause is an established risk factor for breast cancer.[65] A large UK cohort study found a 20%–32% increase in risk, depending on histologic type, per 5-year delay in age at menopause in never-users of hormone replacement therapy.[66] A large international pooled analysis found an approximate 3% increase in breast cancer risk for each year increase in age at menopause.[77]
- Late menopause is a risk for endometrial cancer.[65] Two large cohort studies, one in the US and one in Europe, found risk increases of from 53% to more than 2-fold for menopause of age 55 or older compared with ages less than 45 or less than 50, the risk increasing with older ages at menopause.[70,71]
- For ovarian cancer the results are mixed, with contradictory findings from large cohort studies as to whether late menopause increases risk.[72,75,78]

ORAL CONTRACEPTIVES

- Combined oral estrogen-progestogen contraceptives are classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1), on the basis of increased risks for cancer of the breast (among current and recent users), cervix and liver (in populations at low risk for hepatitis B viral infection).[79,80]
- Large international pooled analyses have estimated current users of combined oral estrogen-progestogen contraceptives have a 24% increased risk of breast cancer and a 65% increased risk of cervical cancer compared to never-user.[81,82] Liver cancer risk may be increased by roughly 50% in long-term oral contraceptive users in populations at low risk for hepatitis B infection.[80,83]
- Cessation of oral contraceptive use reduces the associated risk of breast and cervical cancer in a dose-dependent manner, with risk declining over time to no excess risk by 10 years after cessation.[81]
- There is convincing evidence that oral contraceptives reduce the risk of cancer of the endometrium (with the risk for ever-users approximately halved)[79,80] and ovary (with a 27% lower risk among ever-users and further reductions with greater duration of use).[72,84]

HORMONE REPLACEMENT THERAPY FOR MENOPAUSE

IARC has concluded that combined estrogen-progestogen hormone replacement therapy (HRT) for menopause increases the risk of breast cancer, mainly in current or recent users. A large pooled analysis found a risk increase of approximately 2%/year for current or recent use;[77] risk magnitude varies with type of hormone therapy and histologic type of breast cancer.[85–87] HRT use increases the risk of endometrial cancer when progestogens are taken for less than 10 days/month, but not when progestogens are taken daily.[79,80] The broad range in magnitude of increased risk for endometrial cancer among current HRT users reflects different preparations and different durations of use, with risk estimates from less than 2-fold to more than 7-fold.[71,88]

BIOLOGIC MECHANISMS

- High levels of unopposed estrogen appear to be the common exposure in several risk factors considered here; reproductive factors increase total estrogen exposure by resulting in more lifetime menstrual cycles. Exact mechanisms, and whether estrogen is a causal or promoter agent, are not fully understood.[89,90] Breastfeeding may lower risk hormonally by lowering the number of menstrual cycles, and through developmental and other effects on breast epithelium.[24] Developmental effects on the breast may also contribute to reduction in breast cancer risk with higher parity.[89]
- The lowered risk of ovarian and endometrial cancers with oral contraceptive use appears to be associated with atrophic and antiproliferative effects in the endometrium and apoptosis of ovarian epithelial cells.[80]
- Methodologic issues complicate our understanding of the role of several factors associated with increased risk of cervical cancer: higher parity, earlier age at first birth, oral contraceptive use, sexual behaviour and human papillomavirus (HPV) infection. Higher parity and earlier age at first birth appear to have a role beyond simply serving as proxies for increased exposure to HPV. High parity may, for example, be a co-factor affecting the risk of HPV infection and/or its progression to cervical cancer.[73,82]

ULTRAVIOLET RADIATION

			Magnitude of risk*			
Risk factor/exposure	**Cancer**	**Direction of association**	Total exposure	Intermittent exposure	Chronic exposure	**Strength of evidence[a]**
Solar ultraviolet (UV) radiation	Skin (melanoma)	↑	1.34[b]	1.61[b]	0.95[b]	Sufficient
	Skin (BCC)	↑	0.98[c]	1.38[c]	1.19[c]	
	Skin (SCC)	↑	1.53[c]	0.91[c]	1.64[c]	
	Lip	↑	…	…	…	Limited
	Eye	↑	…	…	…	
UV-emitting indoor tanning devices	Skin (melanoma)	↑		1.15–1.22[d,e]		Sufficient
	Eye	↑		1.30–3.40[a]		
	Skin (SCC)	↑		…		Limited

Abbreviations: UV= ultraviolet; BCC= basal cell carcinoma; SCC=squamous cell carcinoma

Sources: [a]IARC, 2012; [b]Gandini S, 2005; [c]Armstrong, 2001; [d]International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer, 2006; [e]Hirst, 2009

*Relative risk (RR) estimate for: highest exposure category to lowest for estimates of solar ultraviolet radiation; ever vs. never-use of UV-emitting tanning devices.
...Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."

SOLAR ULTRAVIOLET RADIATION

Background

» Ultraviolet radiation (UVR) is a type of electromagnetic radiation that can be further subdivided into UVA, UVB and UVC.[91]

» Sunlight is the major source of human exposure to UVR and is comprised largely of UVA, with a small component of UVB by the time it reaches the earth's surface.[91]

» UVR exposure can be classified into three types, based on the pattern of sun exposure: intermittent exposure (i.e., periodic bursts of exposure received, for example, during recreational outdoor activities), chronic exposure (i.e., more continuous exposure, often synonymous with exposures received in outdoor occupations) and total exposure (i.e., the combination of intermittent and chronic exposures).

- Solar and UV radiation have been classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC).[91] According to IARC, there is sufficient evidence that solar UV radiation causes all major skin cancer types, including cutaneous melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Limited evidence suggests that solar UV radiation also causes cancer of the lip and eye (conjunctival squamous cell carcinoma and ocular melanoma).[91]

- The relationship between solar UVR and skin cancer is complex:
  - Total cumulative lifetime exposure influences risk, but the pattern of sun exposure may be particularly important for different types of skin cancer. Cutaneous melanoma risk appears most strongly related to intermittent UV exposure,[91–93] while chronic exposure appears most important for SCC.[91,94] BCC generally shows an association with intermittent and chronic exposure (measured by objective indicators of skin damage) that is more modest in magnitude than the relationship of these exposures with melanoma and SCC.[91,94]
  - Cutaneous melanoma risk appears to depend on the body part exposed,[91,95,96] and dose and timing of exposure, with indications that childhood exposure may be particularly important.[97,98]
- Personal characteristics and exposures can modify the relationship between solar UVR exposure and cancer risk:
  - People with certain phenotypic characteristics—fair skin, light eyes, blond or red hair, and a tendency to burn rather than tan when exposed to sunlight—have higher susceptibility to UVR damage and subsequent risk of all types of skin cancer.[91,94]
  - People with certain rare genetic conditions (e.g., xeroderma pigmentosum, basal cell nevus syndrome)[99] and those sensitive to UVR due to immunosuppression (e.g., organ transplant recipients, patients with acquired immunodeficiency syndrome [AIDS] or human immunodeficiency virus [HIV]) and/or those who use certain photosensitizing agents (e.g., psoralens)[91] have high susceptibility to UVR damage.
- Individuals with outdoor occupations typically have chronic solar UVR exposure and are therefore at particularly high risk of developing squamous cell carcinoma. Outdoor workers typically demonstrate a lower risk of melanoma, but this observation may reflect self-selection of people at low risk of melanoma to outdoor work.[91]

ULTRAVIOLET RADIATION EMITTING TANNING DEVICES

Background

» UV-emitting indoor tanning devices, including sunbeds and sunlamps, are the main source of deliberate exposure to artificial UVR and are primarily used for cosmetic purposes.[91]

» Indoor tanning devices may have a UV intensity as much as 10–15 times stronger than the midday sun.[91]

- UV-emitting tanning devices are classified by IARC as carcinogenic to humans (Group 1). There is sufficient evidence that UV-emitting tanning devices cause cutaneous and ocular melanoma. There is limited evidence that UV-emitting indoor tanning devices cause squamous cell carcinoma.[91]
- Ever-use of indoor tanning devices increases the risk of cutaneous melanoma by 15%–22%,[100,101] with evidence that risk increases with greater frequency of use.[102–104] The few studies that have examined ocular melanoma risk have shown from 30% to as much as 3 times the risk compared with non-users for the highest exposure categories.[91] There is also some indication of a positive dose-response relationship.[91]
- The use of UV-emitting indoor tanning devices during adolescence and young adulthood may be associated with a particularly high risk of cutaneous and ocular melanoma.[91,100,105,106]

OTHER ARTIFICIAL SOURCES OF ULTRAVIOLET RADIATION

- Other artificial sources of UV radiation include medical and dental applications, arc welding and industrial lamps.
- There is sufficient evidence in humans for the carcinogenicity of welding. Epidemiologic evidence supports a causal association between welding and ocular melanoma; whether this can be attributed to UV radiation is currently unknown.[91]

BIOLOGIC MECHANISMS

- UV radiation exposure can induce carcinogenesis in several ways:[64]
    - UV radiation can damage DNA, either directly through the absorption of UVB or indirectly through the generation of reactive oxygen and/or nitrogen species in response to UVA.
    - UV radiation may introduce DNA mutations, including mutations to genes controlling cell proliferation (oncogenes and tumour suppressor genes) or cell signalling, and genes that code for enzymes that can detoxify by-products of oxidative stress.
    - UV radiation can interact with the immune system to suppress local and systemic immune responses.

OTHER RADIATION

Risk factor/ exposure	Cancer	The context where high risks were reported	Magnitude of risk*	Strength of evidence[a]
Radon-222 and decay products	Lung	Occupational Environmental	1.2–3.2[b] 1.1–1.4[c]	Sufficient
	Leukemia	Occupational Environmental	… …	Limited
X-radiation, gamma radiation	Salivary gland	Atomic bomb survivors Medical	*1.4–3.8*[d] *0.8*[d]	Sufficient
	Esophagus	Atomic bomb survivors Medical	*0.4–1.4*[d] *0.17–0.3*[d]	
	Stomach	Atomic bomb survivors	*0.1–0.5*[d]	
	Colon	Atomic bomb survivors Occupational	*0.5–1.2*[d] *2.6*[e]	
	Lung	Atomic bomb survivors Medical Occupational	*0.3–1.5*[d] *0.1–0.4*[d] *0.1–0.6*[d]	
	Bone	Atomic bomb survivors Medical	*1.2–3.3*[d] *0.02–0.2*[d]	
	Skin (BCC)	Atomic bomb survivors	*0.9–1.5*[d]	
	Breast	Atomic bomb survivors Medical	*1.3–2.0*[d] *0.06–0.4*[d]	
	Bladder	Atomic bomb survivors Medical Occupational[†]	*0.8–1.4*[d] *0.07–0.4*[d] *1.4*[e]	
	Kidney	Atomic bomb survivors Medical	*0.2–1.2*[d] *0.1–0.7*[d]	
	Brain and central nervous system	Atomic bomb survivors Medical	*0.4–2.6*[d] *0.07–4.6*[d]	
	Thyroid	Atomic bomb survivors Medical exposures	*1.0–3.2*[d] *3.0–12*[d]	
	Leukemia (excluding chronic lymphocytic leukemia)	Atomic bomb survivors Medical Occupational	*3.0–6.3*[d] *0.1–0.7*[d] *1.0–16*[d]	
	Liver, multiple myeloma, non-Hodgkin lymphoma, ovary, pancreas, prostate, rectum	Atomic bomb survivors, medical, occupational	…	Limited

Abbreviations: BCC= Basal cell carcinoma

Sources: [a]IARC, 2012; [b]Lubin et al., 1995; [c]Krewski et al., 2005; [d]UNSCEAR Report, 2006; [e]Sont et al., 2001

* For occupational radon-222 and its decay products, risk estimates are relative risks (RR) for exposures of 100 working-level months; for environmental radon-222 exposure, the lower RR estimate displayed is for exposures of 25–75 Bq/m^3 and the higher RR estimate displayed in the range is for exposures ≥ 200 Bq/m^3; *for X- and gamma radiation, risk estimates are the excess relative risk (ERR) at 1 sievert (Sv).*

…Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."

[†] Excess relative risk estimate for males only.

RADON-222 AND ITS DECAY PRODUCTS

Background

» Radon is a colourless, odourless radioactive gas released from the decay of uranium and thorium and their radioactive products (called "daughters").[91]

» The most common isotope is radon-222, which emits (radioactive) alpha particles.[91]

» Highest levels of exposure occur in an occupational setting in mines where uranium and thorium are present. Naturally occurring radon can also accumulate in workplace and residential buildings, especially in basements.[107]

» The primary route of human exposure is inhalation into the lungs.[108]

- In 1987, the International Agency for Research on Cancer (IARC) first stated that radon causes lung cancer in humans,[109] based largely on studies of underground haematite miners with high exposures to radon (specifically radon-222 and its decay products).[110] There is now evidence from studies of residential radon exposure within the general population that further supports a causal association between radon exposure and an increased risk of lung cancer.[110] There is some, but not sufficient, evidence that radon-222 causes leukemia.[91]
- A pooled analysis of 11 cohort studies found a 1.2–3.2 times greater risk of lung cancer at 100 working-level months among radon-exposed underground miners; a consistent dose-response relationship with cumulative radon exposure was also apparent.[111] Residential exposure to radon has been associated with a 10%–40% increase in lung cancer risk, from lower through higher exposures,[112] with pooled analyses from North America,[112,113] Europe[114,115] and China[116] demonstrating a consistent dose-response relationship.
- An interaction between radon exposure and tobacco smoking is generally seen for lung cancer risk[14,91] (see tobacco section on page 7).

X-RADIATION, GAMMA RADIATION

Background

» X-rays and gamma rays are types of ionizing radiation that are mainly distinguished by their origin.[91]

» X-rays are used in many medical applications, including diagnostic imaging and in therapy, mainly in cancer treatments to destroy malignant cells. Gamma rays are used in medicine, the nuclear power industry and in the production of nuclear weapons.[108]

» Environmental sources of X- and γ-radiation exposure include background radiation from terrestrial and cosmic sources,[91] as well as atmospheric nuclear weapons tests and nuclear power accidents, such as the Chernobyl and Fukashima disasters.

» The main route of exposure for X- and gamma radiation is absorption by bones and surrounding tissue after they have penetrated the skin (e.g., during diagnostic imaging).[110] Ingestion of food or water contaminated with radionuclides in areas where radioactive materials have been released into the environment, such as nearby rivers, is also a possible exposure route.[91]

- IARC first classified X-radiation and gamma radiation as carcinogenic to humans in 1999.[110] It is now well recognized that X-radiation and gamma radiation are multi-organ carcinogens. The epidemiologic evidence for carcinogenicity comes from studies of atomic bomb survivors, of people exposed during medical procedures, and of occupational or environmental exposures.[110]

Detonation of atomic bombs

- Evidence for risk from atomic bomb detonation comes largely from the Life Span Study, a population-based study of survivors of the atomic bomb attacks on Hiroshima and Nagasaki. Survivors were mainly exposed to gamma radiation and had significant increases in the incidence of leukemia and cancers of the salivary gland, esophagus, stomach, colon, skin, thyroid, brain and central nervous system, bladder, kidney, breast, lung and bone and connective tissue.[91] Slightly elevated incidence of liver and ovarian cancer were also seen.[91]
- Excess relative risks as high as 6 at 1 sievert have been observed among atomic bomb survivors, with the greatest risks observed for leukemia.[117] A dose-response relationship is apparent between estimated exposure dose, and risk of leukemia[118] and cancer of the salivary gland.[119]

Medical exposures

- Strong evidence exists of increased risk from medical X- and gamma radiation exposure for cancers of the esophagus, lung, thyroid, breast, bone and connective tissue, brain and central nervous system, bladder, salivary gland, kidney and leukemia. This evidence comes from studies of patients exposed to X- or gamma radiation for medical treatment or diagnostic purposes.[110]
    - Patients may be treated with radiotherapy, predominantly X-radiation, for malignant diseases, including cancer of the breast, ovary, cervix and Hodgkin disease,[91,110] which may lead to second primary cancers later in life.
    - There is also evidence of cancer following radiotherapy for benign disease, such as benign breast disease, ankylosing spondylitis or peptic ulcer. Increased risk of certain cancers has also been associated with diagnostic X-radiation, including multiple adult chest fluoroscopies for pulmonary tuberculosis, multiple childhood X-rays for scoliosis and prenatal X-ray exposure, with lower doses than those used for treatment.[110]
- The cancers described above have mostly demonstrated excess relative risks up to 5 at 1 sievert from medical exposures to X- and gamma radiation.[117] The exception is thyroid cancer, for which excess relative risk estimates as high as 12 at 1 sievert have been observed.[117] Significant dose-response relationships are apparent at high doses of radiotherapy for many cancer sites including brain, thyroid and bone. Dose-response relationships have also been seen for cancer of the salivary gland in patients who received radiation therapy as children for conditions in the head and neck area[120] and for cancer of the breast.[91]

Occupational exposures

- The evidence for cancer comes from studies of medical personnel, such as radiologists and X-ray technologists, Chernobyl clean-up workers, and nuclear industry workers in the US and UK and in the Mayak nuclear complex in the Russian Federation.
- Occupational studies have not demonstrated significantly increased risk for most cancer sites.[91,110] The exception is leukemia, for which excess relative risks of 1–16/sievert have been observed across occupational studies, depending on the occupational groups examined.[117]
- Lung cancer had an excess relative risk of 0.1–0.6 at 1 sievert in occupational groups, such as the Chernobyl clean-up workers and US radiation workers.[117] A positive dose-response relationship was observed for lung cancer in a 15 country study of cancer risk among nuclear industry workers.[121] A Canadian cohort study of occupational exposure to ionizing radiation found a greater excess relative risk of 3/sievert.[122]

BIOLOGIC MECHANISMS

- All types of ionizing radiation, including X- and gamma radiation, and alpha-emitters, such as radon, transfer energy, leading to DNA damage. This is followed by repair responses, such as apoptosis, changes to the number or content of chromosomes to produce abnormal chromosomes (chromosomal aberrations), mutations or transformation of the cell, all of which can induce carcinogenesis.[107]

DUSTS AND FIBRES

Risk factor/exposure	Cancer	The context where high risks were reported	Magnitude of risk*	Strength of evidence[a]
Asbestos (all forms)	Larynx	Occupational	1.2[a]	Sufficient
	Lung	Occupational	2–5[a,b]	
		Environmental	…	
	Mesothelioma	Occupational	†	
		Environmental	†	
	Ovary	Occupational	1.3–1.8[c,d]	
	Colon and rectum	Occupational	…	Limited
	Pharynx	Occupational	…	
	Stomach	Occupational	…	
Silica dust, crystalline (in form of quartz or crystobalite)	Lung	Occupational	1.3–2.6[a]	Sufficient
Wood dust	Sinonasal	Occupational	2–50[e,f]	Sufficient
	Nasopharynx	Occupational	1.5–2.5[a]	

Sources: [a]IARC, 2012; [b]Lenters et al., 2011; [c]Reid et al., 2009; [d]Camargo et al., 2011; [e]Demers et al., 1995; [f]IARC, 1995

*Relative risk (RR) estimate for persons exposed vs. unexposed.
…Magnitude of risk not shown in table if strength of evidence could not be accurately estimated or is "limited."
† The vast majority of mesotheliomas are the result of occupational exposure to asbestos, the remaining cases are likely the result of the environment. The precise magnitude of risk is difficult to determine.

ASBESTOS (ALL FORMS)

Background

» Asbestos is a commercial term for a group of six fibrous minerals made of silicon and magnesium, including amphibole minerals (actinolite, amosite, anthophyllite, crocidolite, tremolite) and serpentine minerals (chrysotile), that are found naturally in soil and rocks.[108,123]

» Asbestos fibres have several desirable properties, including resistance to heat, durability and strength, that have led to their use in a wide range of industrial applications, most frequently involving insulation and friction materials (e.g., brake pads and shoes).[124]

» Asbestos fibres are released into the environment from the weathering or mining of natural asbestos deposits and when asbestos-containing products are worn down or damaged.[124] The primary route of human exposure is inhalation of these airborne asbestos fibres.[124]

» Exposure is most likely to occur in occupational settings. Workers in several industries may have been or are currently exposed to asbestos, including those involved in asbestos mining, manufacturing, construction and transportation, as well as in the maintenance and remediation of asbestos containing structures.[125]

- There is consistent evidence that exposure to asbestos causes mesothelioma, and cancers of the lung, larynx and ovary.[124]
- There is a clear dose-response relationship between asbestos exposure and lung cancer risk.[126] A meta-analysis has shown that people in the highest exposed groups of workers (e.g., miners and insulators) are between 2 and 5 times more likely to develop lung cancer.[126] The impact of different asbestos fibre types and sizes on lung cancer risk remains unclear.[124] It is uncertain whether there is an increased risk for lung cancer at low levels of asbestos exposure.[124] The magnitude of risk from environmental exposure is too difficult to determine based on the existing literature.
- Mesothelioma, in contrast, can occur at low levels of exposure to asbestos as demonstrated by cases that occur as a result of environmental exposures. This is also indicated by studies where household members of asbestos workers have been found to be at risk of mesothelioma from contact with asbestos carried into the home (i.e., via hair, shoes and clothing) from their household member's workplace.[127,128] The vast majority of mesothelioma cases are the result of occupational exposure to asbestos; many of the remaining cases are likely the result of environmental exposure.
- Exposure to materials that are contaminated with asbestos is also associated with an increased lung cancer risk. For instance, vermiculite mined in Libby, Montana was contaminated with amphibole fibres (asbestos) and caused increased mesothelioma and lung cancer rates.[124] This asbestos-contaminated vermiculite was shipped to other areas, including Ontario and other Canadian provinces.
- Smoking does not affect the risk of mesothelioma; however, smokers who are exposed to asbestos have a greatly increased risk of developing asbestos-related lung and laryngeal cancer.[124]
- A meta-analysis found that, after adjusting for alcohol and tobacco consumption, people exposed to asbestos have an approximately 20% higher risk of laryngeal cancer.[123] Higher risks of asbestos-related laryngeal cancer have also been observed in certain populations.[124] There is evidence of a dose-response relationship for cumulative asbestos exposure and laryngeal cancer.[124]
- A dose-response relationship exists between asbestos exposure and ovarian cancer risk;[124] some studies have found that women living near asbestos facilities have a higher risk of ovarian cancer.[128–130] Women with occupational asbestos exposure have an approximately 30%–80% increased risk of ovarian cancer.[130,131]
- There is limited evidence for an association between asbestos exposure and cancers of the colon and rectum, pharynx and stomach.[132] Individuals with any exposure to asbestos are 50% more likely to develop pharyngeal cancer and 10%–40% more likely to develop colorectal or stomach cancer[123,124] compared to people with no exposure.
- The biologic mechanisms by which asbestos can induce cancer include impaired fibre clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, and resistance to apoptosis.[132] A study has also found that the release of the HMGB1 protein triggers a chronic inflammatory response in human mesothelial cells, which can lead to carcinogenesis.[133]

SILICA DUST, CRYSTALLINE (IN THE FORM OF QUARTZ OR CRISTOBALITE)

Background

» Silica is one of the most common minerals, naturally occurring in both crystalline and amorphous forms.[124] The most common type of crystalline silica is α-quartz; other common types include cristobalite and tridymite.[124]

» Crystalline silica is found naturally in rocks, soil, sands, acid volcanic rocks, some bentonite clays and in diatomateous earth, and can be produced through the conversion of amorphous forms of silica in the presence of heat.[124]

» The main categories of commercial silica products are sand and gravel (used in manufacturing glass, ceramics, foundry and abrasives), quartz crystals (used in jewelry, electronics and optical components), and diatomateous earth (used in filtration as fillers in and as carriers for pesticides and other commercial products, such as cleaners).[124]

» Workers in industries and occupations involving the movement of earth (e.g., mining, farming), the disturbance of silica-containing products (e.g., demolition of concrete) and the handling or use of sand or other silica-containing products (e.g., foundry processes) are considered to be at high risk of silica exposure,[124] with inhalation the primary route of exposure.

» Exposure in the general population is most likely to occur during the use of commercial products containing quartz (e.g., cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, paint and mortar), with inhalation as the primary route of exposure.[124]

- There is consistent evidence demonstrating an association between crystalline silica (in the form of α-quartz and cristobalite dust) and lung cancer, with a clear dose-response relationship.[124] Exposure to silica dust increases lung cancer risk 1.3–2.6 fold,[124,134] with higher risks from higher exposure levels.[124]
- The established biologic mechanisms for carcinogenesis include impaired particle clearance leading to macrophage activation and persistent inflammation.[132]

WOOD DUST

Background

» Wood dust is generated during the processing of wood (e.g., via sawing, sanding). It can come from softwood trees, which are mainly conifers, or hardwood trees, which are primarily deciduous trees in North America.[124]

» Wood dust exposure is generally highest during the manufacturing of wood furniture and cabinets, especially during the process of machine-sanding.[124] The primary route of exposure is inhalation of the dust.

» Since the industrial revolution, woodworking machines have increased in efficiency, increasing both production, and the generation of more and finer wood dust.[124]

- There is consistent evidence that exposure to wood dust causes sinonasal and nasopharyngeal cancer.[124]
- For sinonasal adenocarcinoma, there is strong evidence for a dose-response relationship. Depending on exposure level and wood dust type, risk ranges from 2–50 times that of the general population.[135,136] The highest risks for sinonasal adenocarcinoma have been observed for people exposed to high levels of hardwood dust and very high relative risks have been primarily observed in European studies.[124,135]
- People in wood-related occupations or who are exposed to wood dust are at 1.5–2.5 times increased risk of nasopharyngeal cancer, with insufficient evidence for a dose-response relationship.[124]
- The biologic mechanisms by which wood dust causes cancer have not been established.[124]

OTHER DUSTS AND FIBRES

- There is sufficient evidence that exposure to erionite (a fibrous zeolite similar to asbestos) causes mesothelioma.[124] Environmental and epidemiological evidence is mainly derived from high-risk populations where erionite is most prevalent (e.g., Turkey).[137,138]
- In occupations with high exposure to leather dust (e.g., boot, shoe or other leather workers), there is sufficient evidence of increased risk of sinonasal cancer.[124] The evidence has come primarily from European studies.[124]

METALS

Risk factor/exposure	Cancer	The context where high risks were reported	Magnitude of risk*	Strength of evidence[a]
Arsenic and inorganic arsenic compounds	Lung	Occupational	1.2–4.7[a]	Sufficient
		Environmental	1.1–2.2[a]	
	Skin	Environmental	1.1–2.1[a,b]	
	Bladder	Environmental	1.1–3.3[a,c]	
	Liver	Environmental	…	Limited
	Prostate	Environmental	…	
	Kidney	Environmental	…	
Nickel compounds	Sinonasal	Occupational	1.1–7.8[d]	Sufficient
	Lung	Occupational	1.2–3.8[a]	
Beryllium and beryllium compounds	Lung	Occupational	1.2–2.0[a,e]	Sufficient
Cadmium and cadmium compounds	Lung	Occupational	1.1–1.8[a]	Sufficient
	Prostate	Occupational	…	Limited
	Kidney	Occupational	…	
Chromium (VI) compounds	Lung	Occupational	1.2–4.0[a,f]	Sufficient
	Sinonasal	Occupational	…	Limited

Sources: [a]IARC, 2012 [b]Karagas et al, 2001 [c]Mink et al., 2008 [d]INCO Ontario (ICNCM, 1990) [e]Sanderson et al., 2001 [f]Cole & Rodu, 2005

* Relative risk (RR) estimate for persons exposed vs. unexposed.
... Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."

ARSENIC AND INORGANIC ARSENIC COMPOUNDS

Background

» Arsenic is a semi-metal, with both metallic and non-metallic properties. Elemental arsenic is rare in the earth's crust; it is usually found as inorganic arsenic compounds in complex minerals containing lead, iron, nickel and other metals.[124]

» Arsenic is currently used or has historically been used in several commercial applications, including pharmaceuticals, wood preservatives, agricultural chemicals and pesticides, the production of alloys, glass-making and in the mining industry.[124]

» Environmental sources of arsenic include volcanic activity, air emissions from mining and smelting operations, and the burning of fossil fuels. It can also leech into water sources and the soil from geologic deposits or rocks containing arsenic, mines and industrial sources.[124]

» Ingestion of food or water contaminated with arsenic is the primary route of exposure for the general population, while inhalation of airborne particles is the primary occupational exposure route.[124]

- There is consistent evidence that arsenic and inorganic arsenic compounds cause cancers of the lung, bladder and skin (primarily squamous cell carcinoma).[124] The evidence for these sites comes from studies examining inhalation of arsenic and its compounds in workers and of populations who ingested high concentrations in drinking water.[124]
- Workers exposed to arsenic have 1.2–4.7 times the lung cancer risk of unexposed workers.[124]

- A 1.1–2.2 times greater risk of lung cancer,[124] a 1.1–2.1 times greater risk of skin cancer[124,139] and a 1.1–3.3 increased risk of bladder cancer[124,140] is seen among individuals exposed to arsenic in drinking water at levels similar to those found in Canada;[139,141,142] higher risks are seen in studies of heavily contaminated areas.
- All associated cancer types show strong and consistent evidence of dose-response relationships with concentration, duration and cumulative exposure.[124] For lung cancer, a synergistic relationship exists between ingestion of arsenic in drinking water and cigarette smoking, with the risk from arsenic substantially elevated in smokers.[124]
- There are several proposed biologic mechanisms including oxidative DNA damage, genomic instability and epigenetic effects.[124]

NICKEL COMPOUNDS

Background

» Nickel is a hard metal that is found naturally in combination with other elements in the earth's crust and soil, and is emitted from volcanoes.[143]

» Nickel and nickel compounds are used in many processes, including the production of a variety of alloys (including steels), plating, electroforming, the production of batteries and as catalysts to increase the rate of chemical reactions.[143]

» Environmental sources of nickel include emissions from natural (e.g., volcanic activity, weathering of nickel-containing rocks or soil) and industrial sources (e.g., mining, milling, smelting).[124]

» Ingestion of food contaminated with nickel, and to a lesser extent nickel in drinking water is the primary route of exposure for the general population.[108,124] Inhalation of dust particles or fumes containing nickel and skin contact are the primary routes of occupational exposure, although ingestion is also possible.[108]

- Nickel compounds increase lung and sinonasal cancer risk in nickel refinery workers and lung cancer risk in nickel smelter workers.[124]
- Workers exposed to nickel compounds have a 1.2–3.8 times greater risk of lung cancer than unexposed workers.[124] Specific forms of nickel such as nickel chloride, nickel sulfate, water-soluble nickel compounds in general, insoluble nickel compounds, nickel oxides, nickel sulfides and mostly insoluble nickel compounds, demonstrated increased risks of lung cancer in humans.[124] The strongest evidence for a dose-response relationship is with cumulative exposure to water-soluble nickel compounds.[124]
- Workers exposed to nickel compounds have a 1–8 times higher risk of sinonasal cancer than unexposed workers,[124,144] with even higher risks seen in some studies of this rare and therefore challenging to study cancer. A dose-response relationship exists for cumulative exposure to water-soluble nickel and nickel oxide compounds.[124]
- There are many established biologic mechanisms for carcinogenesis, including DNA damage, chromosome aberrations and inhibition of DNA-repair mechanisms.[124]

BERYLLIUM AND BERYLLIUM COMPOUNDS

Background

» Beryllium is a metal occurring naturally in rocks, coal, oil, soil and volcanic dust.[124]

» Most beryllium is converted into alloys, which are used in automobiles, computers, sports equipment and dental bridges.[145] Other industries that use or produce beryllium and beryllium products include aerospace, defence, energy and electrical, fire prevention, consumer products (eg., camera shutters, bellows, computer disk drives), manufacturing and telecommunications.[146]

» Occupational exposure accounts for the majority of human exposure to beryllium, with inhalation of dust and dermal contact the main routes of exposure for this group.[108] Ingestion of food or water contaminated with beryllium is the primary route of exposure for the general population.[108,124]

- The evidence for an increased risk of lung cancer is primarily based on workers in beryllium processing plants, with the highest risk seen in workers hired before 1950 when exposures were the highest.[124]
- There is a 20% increased risk to as much as a 2 times increased risk of lung cancer among workers exposed to beryllium,[124,147] with evidence for a dose-response relationship that was strongest for the 10-year lag average-concentration exposure metric.[124]
- The established biologic mechanisms include chromosome aberrations, aneuploidy and DNA damage.[124]

CADMIUM AND CADMIUM COMPOUNDS

Background

» Pure cadmium is a soft metal found in the earth's crust.[124]

» The primary use of cadmium is in electrodes for nickel-cadmium (Ni-Cd) batteries in the form of cadmium hydroxide.[124] Cadmium compounds are also used in many other applications, including pigments, coatings and platings.[148]

» Inhalation is the primary route of exposure in occupational settings.[148] The highest potential exposures occur in occupations such as cadmium production and refining, Ni-Cd battery manufacturing, cadmium pigment manufacturing and formulation, cadmium alloy production, mechanical plating, zinc smelting, brazing with a silver-cadmium-silver alloy solder, and polyvinylchloride compounding.[124]

» The most common source of exposure to the general population is ingestion of contaminated food and inhalation of cigarette smoke.[124]

- Increased risks for lung cancer have been observed largely in studies of workers in cadmium plants and in a population-based study of residents in Belgium living near polluted areas.[124]

- Workers exposed to cadmium have a 10%–80% increased risk of lung cancer;[124] some studies demonstrated increased relative risks as high as 2.2–2.7 for the highest exposure categories.[149] The strongest evidence for dose-response relationships is with duration of employment and intensity of exposure. There is also some evidence of increasing risk with cumulative exposure.[124]
- The biologic mechanisms by which cancer risk is increased include DNA-repair inhibition and disturbance of tumour-suppressor proteins leading to genomic instability.[124]

CHROMIUM (VI) COMPOUNDS

Background

» Chromium is a metal occurring naturally in rocks, animals, plants and soil. There are three main forms of chromium: chromium (0), chromium (III) and chromium (VI).[150]

» Chromium (VI) compounds, known as hexavalent chromium, are rarely found in nature, but are manufactured to be used in a variety of processes and applications, including pigment for textile dyes, paints, inks, plastics, corrosion inhibitors, wood preservatives and metal finishing. They can therefore be found in several consumer products, such as stainless steel cookware.[150]

» Occupational exposures are the most likely source of high human exposure to chromium (VI) compounds, with inhalation of dusts, mists or fumes and skin contact with these compounds as the main routes of exposure.[150]

» Environmental exposure can occur through inhalation of contaminated outdoor and indoor air or ingestion of contaminated water.[150]

- Chromium-exposed workers have an increased risk of lung cancer, which was demonstrated in the 1980s. Evidence comes mainly from studies of workers in the production of chromate and chromate pigment production, and in chromium electroplating.[124]
- A recent meta-analysis found a 20% increase in lung cancer risk from exposure to chromium (VI) when controlling for smoking;[151] some studies have found up to a 4 times higher risk in chromium-exposed workers.[124]
- The biologic mechanisms of carcinogenicity include direct DNA damage after the reduction of chromium (VI) to chromium (III), mutation, genomic instability, aneuploidy and cell transformation.[124]

INDUSTRIAL CHEMICALS

Risk factor/exposure	Cancer	The context where high risks were reported	Magnitude of risk*	Strength of evidence[a]
Acid mists, strong inorganic	Larynx	Occupational	1.2-2.5[a]	Sufficient
	Lung	Occupational	…	Limited
Benzene	Leukemia (acute nonlymphocytic, acute myeloid)	Occupational	1.9-3.2[b]	Sufficient
	Non-Hodgkin lymphoma	Occupational	…	Limited
		Environmental	…	
	Leukemia (acute lymphocytic, chronic lymphocytic)	Occupational	…	
	Multiple myeloma	Occupational	…	
1,3-Butadiene	Hematolymphatic organs	Occupational	1.1-3.0[a,c]	Sufficient
Formaldehyde	Nasopharynx	Occupational	1.1-2.1[d,e,f]	Sufficient
	Leukemia†	Occupational	1.1-1.9[e,g]	
	Sinonasal	Occupational	…	Limited
Mineral oils, untreated or mildly treated	Skin	Occupational	1.2[a]	Sufficient

Sources: [a]IARC, 2012; [b]Khalade et al., 2010; [c]Delzell et al., 2006; [d]Bosetti et al., 2008; [e]Bachand et al., 2010; [f]Hauptmann et al., 2004; [g]Zhang et al., 2009

* Relative risk (RR) estimate for persons exposed vs. unexposed.
… Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."
† Association is particularly apparent for myeloid leukemia. Relative risk presented in the magnitude of risk column is therefore for myeloid leukemia only.

ACID MISTS, STRONG INORGANIC

Background

» Strong acid mists may be produced from the use of strong inorganic acids, including sulfuric acid.[152]

» The major industries with exposure to strong inorganic acid mists are those involved in manufacturing phosphate fertilizer, isopropanol (isopropyl alcohol), synthetic ethanol, sulfuric acid, nitric acid and lead batteries.[152]

» The primary routes of occupational exposure to strong inorganic acid mists containing sulfuric acid are inhalation, ingestion and dermal contact, although exposure depends on factors such as particle size, proximity to the source and control measures in place.[152]

- There is consistent evidence that strong inorganic acid mists cause cancer of the larynx[152] and some evidence that acid mists may cause lung cancer.[152]
- Workers exposed to acid mists are at a 1.2–2.5 times increased risk of laryngeal cancer.[152] Evidence suggests a dose-response relationship with a combined measure of duration and intensity of exposure.[153]
- The exact biologic mechanism by which strong inorganic acid mists induce cancer remains unknown; however, the high acidity from the mists may damage DNA.[152]

BENZENE

Background

» Benzene is a colourless, highly flammable liquid with a sweet odour.[154]

» Benzene is naturally found in petroleum products (e.g., crude oil and gasoline) and was formerly added to unleaded gasoline. Today, it is primarily used in the production of organic chemicals, such as styrene, phenol and chlorobenzenes.[152]

» Occupational exposure to benzene can occur in the rubber, paint (including paint applications), parts-manufacturing, crude-oil refining and chemical manufacturing industries.[152] The primary route of occupational exposure is inhalation, but exposure can also occur through dermal absorption.[152,154]

» For the general population, the primary source of exposure is inhalation of tobacco smoke or ambient air contaminated with benzene (e.g., in areas with heavy traffic or surrounding gasoline-filling stations) or ingestion of food or water that is contaminated with benzene.[152]

- Benzene causes acute myeloid leukemia (AML)/acute non-lymphocytic leukemia (ANLL).[152] This finding is based on studies of occupational exposure, as well as some evidence from studies examining population exposure. There is some evidence for a positive association with other leukemias and lymphomas.[152]
- Occupational benzene exposure is associated with a 2- to 3-fold increase in the risk of AML/ANLL.[155] Cohort studies have shown a dose-response relationship with benzene exposure and AML/ANLL in many industries and across several countries.[152]
- Genotoxicity, particularly in pluripotent haematopoietic stem cells, is thought to be the main biologic mechanism through which benzene causes cancer.[152]

1,3-BUTADIENE

Background

» 1,3-butadiene is a colourless gas at room temperature used to produce synthetic rubbers and polymers that are used in many products, such as automobiles, construction materials, appliance parts, computers and telecommunication equipment, and household articles.[152]

» Significant sources of 1,3-butadiene in the environment include industrial emissions, while minor sources include vehicle exhaust, cigarette smoke and smoke from wood fires.[156] Forest fires are a natural source of 1,3-butadiene.[156]

» The primary route of human exposure is inhalation, with the highest level of exposure occurring in occupational settings. Much lower levels of butadiene are generally detected in ambient air.[152]

- There is sufficient evidence that exposure to 1,3-butadiene causes cancer of the hematolymphatic organs.[152]
- Workers exposed to 1,3-butadiene have an approximately 1–3 times greater risk of cancer of the hematolymphatic organs,[157] with the highest risks from studies of workers

first employed before 1950. Evidence for cancer in humans comes largely from cohort studies of workers belonging to the styrene-butadiene rubber industry for leukemia , including evidence for a dose-response relationship, and the butadiene-monomer industry for hematolymphatic malignancies in general.[152]

- An ecologic study showed evidence of a dose-response relationship for environmental levels of butadiene and the risk of childhood leukemia.[158]
- There is strong evidence that the biologic mechanism through which 1,3-butadiene induces cancer involves the formation of reactive epoxides that interact with DNA and cause mutations.[152]

FORMALDEHYDE

Background

» Formaldehyde is a colourless gas at room temperature with a pungent odour, primarily used for the production of resins, which are often used in wood- and plastic-production industries. It is also used as an intermediate in the manufacturing of industrial chemicals and in aqueous solution (known as formalin) as a disinfectant and preservative.[152]

» Formaldehyde occurs naturally in the environment, primarily at low concentrations in the air.[152] Its primary source in ambient air is automobile exhaust but it can also be emitted from sources such as particle boards, carpets, paints and varnishes, and combustion processes.[152]

» Routes of occupational exposure include inhalation of formaldehyde gas and particulates[135] and absorption through the skin and eye following contact with formalin solutions or liquid resins.[108]

- There is consistent evidence that formaldehyde exposure causes cancer of the nasopharynx and now sufficient evidence that it causes leukemia, particularly myeloid leukemia.[152,159] Limited evidence suggests that formaldehyde exposure may also cause sinonasal cancer. The evidence for nasopharyngeal cancer comes from a large cohort study of industrial workers exposed to formaldehyde in the US, as well as several large case-control studies.[152] The evidence for leukemia comes from proportionate mortality studies of professional workers (e.g., embalmers, funeral parlour workers, pathologists) and from two large industrial cohort studies.[152]
- Occupational exposures to formaldehyde increase myeloid leukemia risk by 10%–90%,[160,161] with the upper end of the range for occupations known to have high exposures. The strongest evidence for a dose-response relationship has been observed for peak exposure levels.[152]
- Occupational exposures to formaldehyde increase nasopharyngeal cancer risk by 10%–30%,[160,162] although the risk increases as much as 2-fold with high occupational exposure.[163] Significant dose-response relationships have been observed for peak exposure, cumulative exposure and duration of exposure (for differentiated squamous cell and unspecified epithelial nasopharyngeal cancer).[152]
- There is strong evidence that genotoxicity is the biologic mechanism responsible for the development of nasopharyngeal cancer and that formaldehyde causes cellular replication, which promotes carcinogenicity.[152] Genotoxicity may also be the underlying biologic mechanism causing leukemia,[152] although further research is needed in this area.

MINERAL OILS, UNTREATED OR MILDLY TREATED

Background

» Mineral oils are complex mixtures of hydrocarbons prepared from crude petroleum oil; their exact composition and physical properties depend on the crude oil and refining processes used.[164]

» Mineral oils are used in many products, including lubricants (e.g., engine oils, machining fluids, transmission fluids) and non-lubricant products (e.g., agricultural spray oils, printing inks).[164]

» Occupations with opportunities for mineral oil exposure include metalworking, printing-press operating, and cotton- and jute-spinning, with inhalation and skin absorption as important routes of exposure.[152] Non-occupational exposure is largely from ingestion of contaminated food.[152]

» In the past, mineral oils were untreated or only mildly refined. Because of advances in refining processes in recent decades, however, most mineral oils in use today are highly refined.[152]

- Based on occupational exposures, untreated or mildly treated mineral oils cause skin cancer, specifically of the scrotum.[152] This conclusion was largely based on case reports and case series from the early 1900s to the 1960s, and further supported by several epidemiological studies of occupational exposures. It is thus largely from periods when mildly treated oils were still in use.
- There is an approximately 20% increased risk of skin cancer from exposure to mildly treated mineral oils,[152] with higher risks observed in older studies of scrotal cancer. An increased risk for all skin cancers is observed, although the strongest evidence is for melanoma. Studies have seen up to a 2 times higher risk for melanoma from exposure to mineral-oil based metalworking fluids.[165] Magnitudes of risk relevant to current exposures were difficult to determine due to the change in carcinogenicity of the mineral oils currently used.
- There is weak evidence for the biologic mechanism causing skin cancer.[152] Further research needs to be conducted.
- Current refining procedures used for mineral oils have reduced the levels of polycyclic aromatic hydrocarbons and other contaminants, thereby reducing the carcinogenicity of the oil. Since there are limitations in accessing direct exposure to highly-treated mineral oils, the International Agency for Research on Cancer (IARC) concluded that there is insufficient evidence for the carcinogenicity of highly-treated mineral oils.[152]

OTHER INDUSTRIAL CHEMICALS

This section highlighted the most commonly used workplace chemicals in Canada, but there are other chemicals that have been classified as carcinogenic by IARC.[152] Bis(chloromethyl)ether, chloromethyl methyl ether (technical grade), and sulfur mustard, for example, cause lung cancer and aflatoxins and vinyl chloride cause liver cancer. Other chemicals classified as group 1 carcinogens include: 2-Aminobiphenyl, benzidine, 2-Naphthylamine, ortho-toluidine, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin, aristolochic acid, dyes metabolized to benzidine, ethylene oxide, 4,4'-methylenebis (2-chloroaniline), 3,4,5,3',4'-pentachlorobiphenyl (PCB-126), 2,3,4,7,8-pentachlorodibenzofuran. More information on the evidence supporting these carcinogens including the associated cancers sites can be found in the recent IARC review of Group 1 carcinogens.[152]

COMPLEX MIXTURES

Risk factor/exposure	Cancer	The context where high risks were reported	Magnitude of risk*	Strength of evidence[a]
Diesel engine exhaust	Lung	Occupational	1.2–1.8[b-g]	Sufficient
	Bladder	Occupational	…	Limited
Polycyclic aromatic hydrocarbons	Lung	Occupational	1.1–2.3[a,h]	Sufficient
	Skin	Occupational	2.2-4.0[h]	
	Bladder	Occupational	1.4–2.4[a]	
$PM_{2.5}$	Lung	Environmental	1.15–1.37[i,j,k]	N/A

Abbreviations: $PM_{2.5}$ = Particulate matter less than 25 µm in diameter.

Sources: [a]IARC, 2012; [b]Attfield et al., 2012; [c]Silverman et al., 2012; [d]Garshick et al., 2012; [e]Laden et al., 2006; [f]Olsson et al., 2011; [g]Pintos et al., 2012; [h]Partanen & Boffetta, 1994; [i]Chen et al., 2008; [j]Turner et al., 2011; [k]Lepeule et al., 2012

* Relative risk (RR) estimate: exposed vs. unexposed (diesel engine exhaust and polycyclic aromatic hydrocarbons); per 10 µg/m^3 increase in $PM_{2.5}$.
… Magnitude of risk not shown in table if strength of evidence is "probable" or "limited."

DIESEL ENGINE EXHAUST

Background

» Diesel engine exhaust is a complex mixture of gases (e.g., carbon monoxide, nitrogen oxides, benzene, formaldehyde) and diesel particulate matter (DPM), with polycyclic aromatic hydrocarbons and nitroarenes distributed in both gas and particulate phases.[166]

» Occupations with a potential for high exposures to diesel engine exhaust include miners, truck drivers, railroad workers, firefighters, dockworkers and diesel-powered equipment mechanics.[167] For the general population, ambient air is the main exposure source, particularly in areas with heavy diesel vehicle traffic.[168]

» Inhalation is the primary route of both environmental and occupational exposure to diesel engine exhaust.[166]

- The International Agency for Research on Cancer (IARC) recently classified diesel engine exhaust as a human lung carcinogen.[166] Strong evidence comes from three cohort studies of highly exposed occupational groups—miners, truck drivers and railroad workers[169–172]—and two pooled case-control studies that include Canadian data.[173,174]
- Workers generally experience a 20%–80% increased lung cancer risk across different exposure scenarios. Underground miners, who experience some of the highest exposures, have 2- to 3-fold risks of lung cancer.[170] Although the evidence that diesel exhaust causes bladder cancer is inconclusive, a meta-analysis of studies of many exposed occupations estimates 10%–40% increases in risk.[175]
- Dose-response relationships with lung cancer appear most consistently for measures of cumulative exposure.[169,170,173,174] Some studies have demonstrated a strong interaction between diesel exhaust and smoking.[170,174,176]
- Environmental exposure to diesel exhaust also presents risks to the general population; residents of urban areas with heavy diesel pollution are exposed to levels that would cause a 50% increase in lifetime lung cancer risk.[168]

- The biologic mechanism through which diesel engine exhaust induces cancer is genotoxicity.[166] The vast majority (95%) of DPM is composed of particles less than 2.5 µm in diameter,[177] small enough to be inhaled deep into the lungs, where there are no mechanisms to remove debris. Other toxic and independently carcinogenic components of diesel exhaust may also contribute to its carcinogenicity.

POLYCYCLIC AROMATIC HYDROCARBONS

Background

» Polycyclic aromatic hydrocarbons (PAHs) are a group of more than 100 compounds containing carbon and hydrogen atoms in two or more benzene rings.[108] They are formed during incomplete combustion of organic material, such as coal, oil, wood or gas.[152,178]

» PAHs generally exist as complex mixtures, such as coal-tar pitch (the residue formed during the distillation of coal tar) and soot.[179] However, benzo[*a*]pyrene, a simple PAH, is often used as an indicator for PAH exposure.

» PAHs can be found in ambient air pollution, as well as in water, soil and sediments. Major sources of PAH exposure include motor-vehicle exhaust, industrial emissions, forest fires, tobacco smoke and fumes from cooking, furnaces, fireplaces and wood stoves.[152] PAHs are also found in some foods (e.g., charbroiled meats, vegetables and crops grown in contaminated soils).[152]

» Occupational groups highly exposed to PAHs include workers in aluminum production, roadway paving and roofing, coal gasification, coal-tar distillation, coke production and chimney sweeps.[152]

» The primary route of exposure in humans is inhalation, although skin contact in occupational settings and ingestion of PAH-containing foods for the general population are also possible routes.[152,178]

- IARC has classified individual PAHs or PAH-related exposures as carcinogenic, including benzo[a]pyrene, coal tar pitch and soot,[152] based on occupational exposures to PAHs shown to cause cancer of the lung, skin and bladder. Many other specific PAHs have been classified as probable or possible carcinogens.
- Evidence for lung cancer comes from many different PAH-related exposures. There is consistent evidence demonstrating that exposure to coal-tar pitch in roofing and paving or to soot in chimney sweeps causes lung cancer.[152] A 1.2–2.3 times increased risk of lung cancer is seen for road pavers,[152] roofers[180] and chimney sweeps.[152] A large cohort study of chimney sweeps also found evidence of a dose-response relationship with duration of employment after adjusting for smoking.[181] Other occupations with an increased risk of lung cancer include aluminum production, coal gasification and coke production.
- The strongest evidence for skin cancer from PAH exposure comes from occupational exposure to soot in chimney sweeps and coal-tar pitch in roofing and paving, which also has exposure to bitumen.[152] The risk of non-melanoma skin cancer varies across occupational groups; risk is increased 2.2 times for road pavers and highway maintenance workers and 4-fold for roofers.[180]
- The strongest evidence for bladder cancer comes from aluminum production workers, demonstrating a 1.4–2.4 times greater risk among this group[152] and a significant

dose-response relationship with cumulative exposure to benzo[*a*]pyrene.[182,183] Some evidence suggests increased risks of bladder cancer from occupational exposure to soot in chimney sweeps and to coal-tar pitch in roofing and paving, but not enough to support a causal association.[152]

- For most PAH-related exposures, there is strong evidence for genotoxicity as the main biologic mechanism causing cancer; the exception is soot and aluminum production for which the evidence for genotoxicity is weaker.[152]

PARTICULATE MATTER (< 2.5 µm)

Background

» Particulate matter (PM) consists of small solid particles or liquid droplets suspended in air.[184] PM smaller than 2.5 micrometres (µm) in diameter is known as $PM_{2.5}$ and is sometimes referred to as "fine" or "respirable" particulate matter.

» $PM_{2.5}$ consists of a complex mixture of acids (nitrates or sulfates), organic chemicals, elemental and organic carbon, and metals.[184]

» $PM_{2.5}$ is formed from all types of combustion processes, either directly or indirectly from precursor gases, such as nitrogen oxides, sulphur dioxides, volatile organic compounds and ammonia.[184]

» Major $PM_{2.5}$ emission sources in Ontario are fuel combustion from motor vehicles, residential wood burning (fireplaces and wood stoves), and industrial processes.[184] Other sources include forest fires, electric power generation and industrial processes, such as mining and smelting.[184]

» The route of exposure is inhalation; its small particle size makes $PM_{2.5}$ a greater health concern than other sub-groups of particulate matter because it is of capable of penetrating more deeply into the alveolar regions of the lungs, where gas exchange occurs, and there are no effective clearance mechanisms.

- The potential carcinogenicity of $PM_{2.5}$ has not been specifically evaluated by IARC; however, a strong body of evidence suggests that environmental exposure to $PM_{2.5}$ causes a number of adverse health effects, including lung cancer.
- A recent systematic review summarized the risk of lung cancer as increasing linearly in a dose-response fashion by 15%–21% per 10 µg/m^3 increase in ambient $PM_{2.5}$ levels, with some increase in risk observed at all exposure levels.[185] Other studies have found lung cancer risk among non-smokers of 15%–27%[186] and 37%[187] per 10 µg/m^3 increase in ambient $PM_{2.5}$.
- Those living in close proximity to major industrial sources (e.g., smelters, foundries, chemical industries) or heavy road traffic are especially at risk,[188] given their long-term exposure to high ambient levels of particulate air pollution.
- There are several potential biologic mechanisms leading to lung cancer. For instance, local inflammatory responses can cause tissue damage, and particles may enter the bloodstream and have systematic effects. Oxidative stress is another important mechanism that has cytotoxic and genotoxic effects, generating free radicals and damaging DNA.[189]

INFECTIOUS AGENTS

Risk factor/exposure	Cancers with sufficient evidence[a]	Cancers with limited evidence[a]
Epstein-Barr virus (EBV)	Nasopharynx, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin lymphoma	Stomach, lympho-epithelioma-like carcinoma
Hepatitis B virus (HBV)	Liver*	Bile duct†, non-Hodgkin lymphoma
Hepatitis C virus (HCV)	Liver*, non-Hodgkin lymphoma	Bile duct†
Human herpes virus 8 (HHV-8)‡	Kaposi sarcoma, primary effusion lymphoma	Multicentric Castleman's disease
Human immunodeficiency virus, type 1 (HIV-1)	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervix, anus, conjunctiva	Vulva, vagina, penis, skin (non-melanoma), liver*
Human papillomavirus (HPV)‡§	Cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, tonsil	Larynx
Human T-cell lymphotrophic virus, type 1 (HTLV-1)‡	Adult T-cell leukemia, lymphoma	
Helicobacter pylori	Stomach‖, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma	
Liver flukes (*C. sinensis, O. viverrini*)	Bile duct†	
Schistosoma haematobium	Bladder	
Schistosoma japonicum		Liver

Source: [a]IARC, 2012

* Association is with hepatocellular carcinoma.
† Association is with cholangiocarcinoma.
‡ Agent is a necessary but not sufficient cause of at least one of the associated cancers listed.
§ HPV types classified by IARC as Group 1 carcinogens: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.
‖ Association is with non-cardia gastric carcinoma.

EPSTEIN-BARR VIRUS

Background

» Epstein-Barr virus (EBV) is a human herpes virus, transmitted primarily through saliva. Some evidence also suggests a potential for sexual transmission.[190]

» EBV infection is common and usually does not cause serious illness. Childhood infections are generally asymptomatic or cause only mild illness, while infection during adolescence and young adulthood (most common in developed countries) can appear as infectious mononucleosis.[190]

» Following primary infection, EBV will enter and, in most cases, remain in a life-long latent state.[190]

- Epstein-Barr virus (EBV) causes nasopharyngeal carcinoma, Burkitt's lymphoma, non-Hodgkin lymphoma (immune-suppression-related), extranodal NK/T-cell lymphoma (nasal type), and Hodgkin lymphoma. Limited evidence suggests that EBV may cause gastric carcinoma and lympho-epithelioma-like carcinoma.[190]
- EBV is most strongly associated with nasopharyngeal carcinoma and various lymphomas:
  - » EBV DNA can be detected in the tissue of nearly 100% of nasopharyngeal cancers of the undifferentiated form, endemic Burkitt's lymphomas and extranodal NK/T-cell lymphomas (nasal type).[190] In western countries, EBV DNA is found in roughly 40%–50% of Hodgkin lymphomas.[191]
  - » Several observational studies have found biomarkers of EBV infection associated with nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma and nasal type extranodal NK/T-cell lymphoma.[190] Some cancers appear to have a positive dose-response relationship with EBV antibodies.[192,193]
- EBV may interact with several other factors to modify the risk of developing cancer:
  - » For Burkitt's lymphoma, particularly the endemic type, EBV seems to act as a co-factor with malaria.[192,193]
  - » The risk of Hodgkin lymphoma is increased for EBV-infected individuals with compromised immune systems or human immunodeficiency virus (HIV) infection.[194]
- EBV may induce cancer through several biologic mechanisms: EBV gene products can induce cell proliferation, inhibit apoptosis, induce genomic instability before or during tumour development, and promote tumour maintenance and cell growth.[190]

HEPATITIS B VIRUS AND HEPATITIS C VIRUS

Background

- » Hepatitis B virus (HBV) is a small hepadnavirus and hepatitis C virus (HCV) is a flavivirus. HBV and HCV are highly contagious and are transmitted through contact with infected blood via blood transfusions, injection drug use, childbirth and needle-stick injuries. Transmission through sexual contact is also common for HBV because it can be transmitted in body fluids other than blood.[190]
- » HBV or HCV infections can be symptomatic or asymptomatic and may be completely cleared by the host's immune system or may develop into a chronic infection that usually persists throughout life;[190] only 2%–5% of adults infected with HBV will become chronically infected, while most HCV infections will become persistent.[190]

- Chronic infection with hepatitis B or hepatitis C causes liver cancer (hepatocellular carcinoma) and may cause cancer of the bile duct (cholangiocarcinoma). Chronic HCV infection (and possibly chronic HBV infection) also causes non-Hodgkin lymphoma, especially of the B-cells.[190]
- Estimates of cancer risk associated with HBV and HCV vary widely across studies, likely due to differences in HBV/HCV prevalence in study populations and in duration of infection:

- Relative risk estimates for hepatocellular carcinoma associated with HBV range from 9.6 to 74 and from 1.5 to 87.4 in cohort and case-control studies, respectively.[190]
- Hepatocellular carcinoma risk in people infected with HCV is 2.5- to 88-fold greater than the risk in uninfected people in cohort studies[190] and 8.1- to 17.3-fold greater in meta-analyses.[195–197] Non-Hodgkin lymphoma risk has been estimated at 2.5- to 5.7-fold greater among people infected with HCV.[198,199]

- An increased risk of hepatocellular carcinoma may exist even in the absence of serological markers for current infection.[190]
- Co-infection with HBV and HCV is associated with a greater increase in risk of hepatocellular carcinoma than infection with either virus alone. HBV and HCV infection both appear to interact with tobacco use to influence liver cancer risk (see tobacco section on page 7).[15]
- HBV and HCV cause carcinogenesis *indirectly* through the development of chronic inflammatory liver disease (fibrosis, cirrhosis and, less often, chronic hepatitis). These conditions involve greater turnover of liver cells, which increases the risk of acquiring genetic mutations and may allow for the acquisition of selective growth advantages. HBV and HCV may also directly promote carcinogenesis through integration of the viral genome into host DNA and/or expression of viral proteins; further research is needed to clarify the cancer-causing mechanisms of these infections.[190]

HUMAN HERPES VIRUS 8 (HHV-8)

Background

- Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma herpes virus, is a gamma-2 type herpesvirus, primarily transmitted through saliva.[190]
- The risk of HHV-8 transmission is high among immunocompromised people, including individuals with end-stage renal disease, transplant recipients and individuals with HIV. Homosexual activity, the number of sexual partners and previous history of sexually transmitted infections are also associated with infection.[190]

- Human herpes virus 8 (HHV-8) causes Kaposi sarcoma and primary effusion lymphoma, a rare B-cell non-Hodgkin lymphoma. HHV-8 has also been associated with multicentric Castleman's disease.[190]
- Several observational studies, mostly in transplant recipients and people infected with HIV, have estimated the risk of Kaposi sarcoma to be at least 10-fold greater in people infected with HHV-8.[190] The excess risk of primary effusion lymphoma associated with HHV-8 infection cannot be quantified since HHV-8 is used in diagnosing this cancer.
- HHV-8 shows a positive dose-response relationship with Kaposi sarcoma risk, in people who are and who are not infected with HIV-1, with risk increasing relative to increasing titre of antibodies against HHV-8, a marker of viral load.[200,201]
- HHV-8 is a necessary, but not sufficient, cause of Kaposi sarcoma. Co-infection with HIV and, to a lesser extent, other immunocompromised states are important co-factors in the development of Kaposi sarcoma.[190]
- HHV-8 may induce carcinogenesis through several biologic mechanisms, such as promoting cell proliferation, blocking apoptosis, inducing genomic instability, and controlling cell migration and tumour progression.[190]

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)

Background

» Human immunodeficiency virus type 1 (HIV-1) is a human retrovirus that attacks the immune system. It is transmitted primarily through sexual contact, contact with infected blood (e.g., through blood transfusions or injection drug use) and mother-to-child transmission during pregnancy, childbirth or breastfeeding.[190]

» HIV infection leads to chronic, progressive illness that leaves the immune system unable to fight off other infections. This advanced stage of disease is known as acquired immunodeficiency syndrome (AIDS).[190]

- HIV-1 causes Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, and cancer of the cervix, anus and conjunctiva. HIV-1 may also cause cancer of the vulva, vagina, penis and liver (hepatocellular carcinoma), as well as skin cancers other than melanoma.[190]
- HIV infection increases the risk of developing Kaposi sarcoma by as much as several thousand times.[190] Individuals infected with HIV also have a 100–200 times greater risk of non-Hodgkin lymphoma (most often the B-cell type),[202] a roughly 30 times greater risk of anal cancer,[202] and approximately 10 times greater risk of Hodgkin lymphoma and cancer of the conjunctiva.[190,202] Cervical cancer risk is 5–10 times greater in HIV infected people than the general population.[190,202]
- For AIDS-defining cancers, including Kaposi sarcoma and non-Hodgkin lymphoma, an inverse dose-response relationship with immune competence is apparent; risk rises as immune competence declines over the duration of infection.[190,203]
- Antiretroviral therapy generally reduces the risk of many HIV-associated cancers but risk still remains high compared to the uninfected population. Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, the incidence of several AIDs-defining cancers, including Kaposi sarcoma and non-Hodgkin lymphoma, has declined.[190,204,205] Hodgkin lymphoma incidence, however, has unexpectedly increased following the introduction of HAART.[204,206]
- HIV primarily increases the risk of several cancers indirectly through immunosuppression, which allows increased replication of other oncogenic viruses such as EBV, HHV-8 and HPV.[190]

HUMAN PAPILLOMAVIRUS (HPV)

Background

» Papillomaviruses are small viruses that predominantly infect squamous epithelial cells and lead to abnormal tissue growth. There are over 120 types of human papillomavirus (HPV), transmitted mainly by skin-to-skin or skin-to-mucosa contact, most often during sexual activity.[190]

» HPV infections are most common in the anogenital tract, but can occur on the face, feet, hands, and in the mucosal area of the upper aero-digestive tract.[190]

» Most HPV infections are asymptomatic and will be cleared by the immune system within two years of infection. A small percentage of infections, however, become persistent.[190]

- Several types of human papillomavirus (HPV) are classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens in humans (HPV 16,18,31,33,35, 39,45,51,52,56,58,59). HPV 16 causes cancer of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx and tonsil, and is associated with laryngeal cancer. Cervical cancer is also caused by other high-risk HPV types (18,31,33,35,39,45,51,52,56,58,59), with limited evidence supporting a role for several additional HPV types. HPV 18 may also cause cancer of the vulva, vagina, penis, anus, oral cavity and oropharynx. HPV 33 may cause cancer of the vulva and anus.[190]
- The carcinogenicity for HPV is most established and strongest for cervical cancer, but increased risks are seen for other cancers, as well:
    - HPV DNA is found in almost all cervical cancer cases and HPV infection is considered necessary for its development.[207,208] Women infected with HPV have at least a 50-fold increased risk of cervical cancer or its immediate precursor, cervical intraepithelial neoplasia grade three (CIN3).[190] Persistent infection is particularly important for this cancer's development.[190]
    - HPV is found in 20%–50% of vulvar cancers,[190,209] 60%–70% of vaginal cancers,[190,209] roughly 45% of penile tumours,[210,211] 80%–90% of anal cancers,[190,209] 4%–74% of oral cavity tumours and 20%–70% of tumours in the oropharynx.[190] The HPV-associated risk increases for these tumours are generally less than 5- to 10-fold—far lower than for cervical cancer.[190]
- The HPV-associated cancer risk is specific for the type of oncogenic HPV infection:
    - For cervical cancer, HPV 16 and 18 are the most common HPV types present in tumour tissues, detected in over half and over 15% of cases, respectively.[208]
    - The risk of cervical cancer associated with HPV 16 appears to be an order of magnitude higher than that for all other oncogenic types, although strong risks are also associated with HPV 18 (particularly for cervical adenocarcinoma). Risks are generally lower for other high risk HPV types, although these associations are difficult to study due to a high potential for co-infection with other, and potentially more potent, HPV types.[190]
    - In addition, HPV 16 is the most common HPV type detected in tumours of the vulva,[209] vagina, [209] anus,[209] penis,[210,211] oral cavity and oropharynx,[212] and it is the only type of HPV presently causally associated with these cancers. Although other HPV types (HPV 18 and 33 [vulva and anus only]) may also cause these cancers, studies of type-specific cancer risk are limited by small numbers of cases and co-infection with other HPV types.[190]
- Infection with a high-risk type of HPV is a necessary, but not sufficient, cause of cervical cancer. Co-factors include tobacco smoking, parity, immunosuppression and co-infection with other sexually transmitted agents, such as *chlamydia trachomatis*, herpes simplex virus or HIV. Hormonal factors, diet and genetic susceptibility may also act as co-factors with HPV; more research is needed to investigate these hypotheses.[190]
- *In vitro* and *in vivo* evidence supports a direct oncogenic role for HPV, particularly for cervical cancer. HPV may promote carcinogenesis by becoming incorporated into the host genome or through the production of viral proteins, potentially resulting in disordered cell replication, inhibition of apoptosis, induction of genomic instability, and deregulation of the immune system.[190]

HUMAN T-CELL LYMPHOTROPHIC VIRUS, TYPE 1 (HTLV-1)

Background

» Human T-cell lymphotrophic virus type 1 (HTLV-1) is a retrovirus in the same class as HIV, with three possible modes of transmission: vertical mother-to-child transmission, sexual contact and parenteral transmission through injection or blood transfusion. Breastfeeding is the most common transmission mode in endemic areas (e.g., South-west Japan, parts of sub-Saharan Africa, the Caribbean and South America), while sexual contact is most common in the Western world.[190]

» Most individuals infected with HTLV-1 will remain asymptomatic; however, up to 10% of infected people are at risk of developing a serious associated disease during their lifetime.[190]

- Human T-cell lymphotrophic virus, type-1 (HTLV-1) causes adult T-cell leukemia/lymphoma (ATLL).[190]
- HTLV-1 is considered a necessary cause of ATLL and indicators of HTLV-1 infection are used in the ATLL diagnosis. HTLV-1 carriers have an estimated lifetime risk of ATLL of 2%–4%, with the latency period from infection to ATLL development estimated to be upwards of several decades.[190]
- Several factors can modify ATLL risk among HTLV-1 carriers: male HTLV-1 carriers have a higher risk than female carriers; childhood infection may pose a higher risk than infection later in life; familial clustering of ATLL in endemic areas suggests genetic influences in ATLL development.[190]
- HTLV-1 can induce ATLL in humans through the expression of viral proteins, particularly the Tax protein, which can immortalize and transform T-cells.[190]

HELICOBACTER PYLORI

Background

» *Helicobacter pylori (H. pylori)* is a small bacterium that lives in the stomach mucosa and can lead to stomach inflammation. *H. pylori* infection is thought to occur through four possible means: fecal-oral transmission through contaminated water or food, oral-oral transmission among mothers who pre-chew food given to infants, gastric-oral through exposure to infected vomit and iatrogenic through contaminated medical instruments or occupational exposure.[190]

» *H. pylori* infection may be treated by various combinations of antibiotics or other anti-acid drugs, whereas untreated infections will typically persist for life.[190]

- *Helicobacter pylori (H. pylori)* causes stomach cancer (non-cardia gastric carcinoma) and low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma, a rare form of non-Hodgkin lymphoma.[190]
- Meta-analyses have estimated a 2- to 3-fold increased risk for non-cardia gastric cancer from *H. pylori* infection;[213–215] this may, however, be an underestimate since *H. pylori* infection often disappears as the stomach becomes increasingly damaged.[190] Individuals with *H. pylori* also have an approximately 3-fold increased risk of MALT lymphoma.[216]

- Cancer risk in the presence of *H. pylori* is influenced by several other factors including *H. pylori* strain, host immune response and environmental factors.[190] Several dietary factors, for example, may interact with *H. pylori* to influence gastric cancer development; in the presence of *H. pylori*, high dietary salt may promote gastric cancer, while vegetables and fruit may inhibit the process.[190,217] Tobacco smoking may interact with *H. pylori* in the development of gastric cancer.[190,217]
- Antibiotic treatment for *H. pylori* infection can reduce the risk of MALT gastric lymphoma; 62%–100% of people with this cancer experience complete remission following eradication of the infection.[190] While *H. pylori* eradication may reduce the progression of early gastric lesions, its effect on advanced premalignant gastric lesions is unclear.[190]
- *H. pylori* infection results in chronic inflammation of the stomach mucosa that progresses to permanent damage followed by abnormal tissue development and eventually cancer.[190]

OTHER INFECTIOUS AGENTS

Background

» Liver flukes *(O. viverrini and C. sinensis)* and schistosomes *(S. harmatobium)* are flat, parasitic worms that can infect and live in the human biliary tract (particularly the intrahepatic bile ducts) and the bladder, respectively.[190]

» Human infection with liver flukes or schistosomes is often asymptomatic and is usually caused by ingesting raw or inadequately cooked fish containing liver flukes or water containing schistosomes in the infectious stage of their reproductive cycle.[190]

» Liver fluke infection is most common in East and Southeast Asia while schistosome infection is most common in Africa and Southeast Asia; both may appear in Canada due to travel or immigration.[190]

- Liver flukes *(O. viverrini* and *C. sinensis)* cause cancer of the bile duct (cholangiocarcinoma) and schistosomes *(S. harmatobium)* cause bladder cancer.[190]
- Studies mostly conducted in Thailand *(O. viverrini)* or Korea *(C. sinensis)* have reported a 1.3- to 27.1-fold greater risk of developing cancer of the bile duct (cholangiocarcinoma) in the presence of *O. viverrini* and a 2.7- to 13.6-fold greater risk in the presence of *C. sinensis*.[190]
- Case-control studies have found a 1.7- to 15-fold greater risk of urinary bladder cancer associated with *S. haematobium* infection,[190] with the most recent study reporting greater risk with first infection at younger ages (< 15 years) and a long time since diagnosis.[218]
- Liver flukes and schistosomes likely contribute to the development of cancers by inducing chronic inflammation that may activate oxidative stress pathways and lead to potentially harmful DNA alterations. Liver flukes may also directly activate cell proliferation and inhibit apoptosis.[190]

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.

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]

APPENDIX A

CRITERIA FOR ASSESSING STRENGTH OF EVIDENCE

a. Criteria used by the World Cancer Research Fund/American Institute for Cancer Research

The terms "convincing" and "probable," used to classify the strength of evidence for the relationship between a risk factor or exposure to an agent and a specific cancer type, were based on the following criteria:

Convincing

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates. All of the following are generally required:

- evidence from more than one study type
- evidence from at least two independent cohort studies
- no substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association or direction of effect
- good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias
- presence of a plausible biological gradient ("dose-response") in the association—such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly
- strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes

Probable

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer. All of the following are generally required:

- evidence from at least two independent cohort studies or at least five case-control studies
- no substantial unexplained heterogeneity between or within study types in the presence or absence of an association or direction of effect
- good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error and selection bias
- evidence for biological plausibility

Source:
World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007. Page 60.

b. Criteria used by the International Agency for Research on Cancer (IARC):
The terms "sufficient" and "limited," used to classify the strength of evidence for the relationship between a risk factor or exposure to an agent and a specific cancer type, were assigned based on the following general criteria:

Sufficient evidence of carcinogenicity in humans

The IARC Working Group uses the term "sufficient evidence" when a causal relationship has been established between exposure to the agent and human cancer at the target organ(s) or tissue(s). That is, when a positive relationship has been observed between the exposure and cancer at the target organ(s) or tissue(s) in studies in which chance, bias and confounding could be ruled out with reasonable confidence. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity in humans

The term "limited evidence" is used when a positive association is observed between exposure to the agent and cancer at the target organ(s) or tissues(s) in humans and a causal relationship is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

In addition to classifying a relationship between exposure to the agent and human cancer at a specific target organ or tissue, IARC classifies the strength of the evidence for carcinogenicity in experimental animals and also considers mechanistic and other relevant data. The body of evidence is then considered as a whole to provide an overall evaluation of the carcinogenicity of the agent itself. Agents with Group 1 or Group 2A classifications are included in this report. The criteria for these classifications are as follows:

Group 1: the agent is carcinogenic to humans

This category is used when there is *sufficient evidence of carcinogenicity* in humans (for at least one target organ or tissue). Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism.

Group 2A: the agent is probably carcinogenic to humans

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans.

Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Source:
A review of human carcinogens. Part E: Personal habits and indoor combustions / IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2009: Lyon, France). Pages 29–30.

REFERENCES

1. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100E. A review of human carcinogens. Part E: Personal habits and indoor combustions. Lyon: International Agency for Research on Cancer; 2012.
2. U.S.Department of Health and Human Services. The health consequences of smoking: A report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
3. California Environmental Protection Agency. Proposed identification of environmental tobacco smoke as a toxic air contaminant. Part B: Health effects [Internet]. [updated 2005; cited 2011 Aug 29]. Available from: http://www.arb.ca.gov/regact/ets2006/app3partb.pdf.
4. Collishaw NE, Boyd NF, Cantor KF, Hammond SK, Johnson KC, Millar J. Canadian Expert Panel on tobacco smoke and breast cancer risk. Toronto: Ontario Tobacco Research Unit, OTRU Special Report Series; 2009.
5. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer 2008;122(1):155-64.
6. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 83. Tobacco smoke and involuntary smoking. Lyon: International Agency for Research on Cancer; 2004.
7. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;300(23):2765-78.
8. Tsoi KK, Pau CY, Wu WK, Chan FK, Griffiths S, Sung JJ. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. Clin Gastroenterol Hepatol 2009;7(6):682-8.
9. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer 2009;124(10):2406-15.
10. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer 2009;125(1):171-80.
11. Bosetti C, Gallus S, Peto R, Negri E, Talamini R, Tavani A, et al. Tobacco smoking, smoking cessation, and cumulative risk of upper aerodigestive tract cancers. Am J Epidemiol 2008;167(4):468-73.
12. Bosetti C, Gallus S, Garavello W, La VC. Smoking cessation and the risk of oesophageal cancer: An overview of published studies. Oral Oncol 2006;42(10):957-64.
13. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 2009;18(2):541-50.
14. Committee on the Biological Effects of Ionizing Radiation. Health Effects of Exposure to Radon: BEIR VI. Washington DC: National Academy Press; 1999.
15. Chuang SC, Lee YC, Hashibe M, Dai M, Zheng T, Boffetta P. Interaction between cigarette smoking and hepatitis B and C virus infection on the risk of liver cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19(5):1261-8.
16. Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. Int J Epidemiol 2007;36(5):1048-59.
17. Stayner L, Bena J, Sasco AJ, Smith R, Steenland K, Kreuzer M, et al. Lung cancer risk and workplace exposure to environmental tobacco smoke. Am J Public Health 2007;97(3):545-51.
18. Lee YC, Boffetta P, Sturgis EM, Wei Q, Zhang ZF, Muscat J, et al. Involuntary smoking and head and neck cancer risk: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 2008;17(8):1974-81.
19. Pang D, McNally R, Birch JM. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. Br J Cancer 2003;88(3):373-81.
20. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. Lancet Oncol 2008;9(7):667-75.
21. Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. BMC Med 2009;7:36.
22. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 89. Smokeless tobacco and some tobacco-specific N-nitrosamines. Lyon: International Agency for Research on Cancer; 2007.
23. U.S.Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
24. World Cancer Research Fund/ American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007.
25. World Health Organization. International guide for monitoring alcohol consumption and related harm. Geneva: World Health Organization; 2000.
26. Butt P, Beirness D, Cesa F, Gliksman L, Paradis C, Stockwell T. Alcohol and health in Canada: A summary of evidence and guidelines for low-risk drinking. Ottawa,ON: Canadian Centre on Substance Abuse; 2011.
27. Bagnardi V, Blangiardo M, La VC, Corrao G. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer 2001;85(11):1700-5.
28. Corrao G, Bagnardi V, Zambon A, La VC. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med 2004;38(5):613-9.

29. Tramacere I, Negri E, Bagnardi V, Garavello W, Rota M, Scotti L, et al. A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 1: overall results and dose-risk relation. Oral Oncol 2010;46(7):497-503.

30. Islami F, Tramacere I, Rota M, Bagnardi V, Fedirko V, Scotti L, et al. Alcohol drinking and laryngeal cancer: overall and dose-risk relation--a systematic review and meta-analysis. Oral Oncol 2010;46(11):802-10.

31. Islami F, Fedirko V, Tramacere I, Bagnardi V, Jenab M, Scotti L, et al. Alcohol drinking and esophageal squamous cell carcinoma with focus on light-drinkers and never-smokers: a systematic review and meta-analysis. Int J Cancer 2011;129(10):2473-84.

32. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, Jr., et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87(11):1234-45.

33. Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med 2004;140(8):603-13.

34. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol 2011;22(9):1958-72.

35. Key J, Hodgson S, Omar RZ, Jensen TK, Thompson SG, Boobis AR, et al. Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. Cancer Causes Control 2006;17(6):759-70.

36. Druesne-Pecollo N, Tehard B, Mallet Y, Gerber M, Norat T, Hercberg S, et al. Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. Lancet Oncol 2009;10(2):173-80.

37. Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006;7(2):149-56.

38. World Cancer Research Fund/ American Institute for Cancer Research. Continuous update project. Colorectal cancer report 2010 summary. Food, nutrition, physical activity, and the prevention of cancer [Internet]. AICR; 2011 [cited 2012 Mar 8]. Available from:http://www.dietandcancerreport.org/cancer_resource_center/downloads/cu/CUP_CRC_summary_2011.pdf.

39. Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 2011;6(6):e20456.

40. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. Gastric Cancer 2007;10(2):75-83.

41. Wang XQ, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. World J Gastroenterol 2009;15(18):2204-13.

42. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology 2010;138(6):2029-43.

43. Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, et al. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. Int J Cancer 2008;122(10):2330-6.

44. Boeing H, Dietrich T, Hoffmann K, Pischon T, Ferrari P, Lahmann PH, et al. Intake of fruits and vegetables and risk of cancer of the upper aero-digestive tract: the prospective EPIC-study. Cancer Causes Control 2006;17(7):957-69.

45. Key TJ. Fruit and vegetables and cancer risk. Br J Cancer 2011;104(1):6-11.

46. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. WHO obesity technical report summary. Geneva: World Health Organization; 2000.

47. World Cancer Research Fund/ American Institute for Cancer Research. Continuous update project report summary. Food, nutrition, physical activity, and the prevention of breast cancer [Internet]. AICR; 2010 [cited 2012 Jun 19]. Available from: http://www.dietandcancerreport.org/cancer_resource_center/downloads/cu/cu_breast_cancer_report_2008_summary.pdf.

48. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M, Renehan AG, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371(9612):569-78.

49. Harriss DJ, Atkinson G, George K, Cable NT, Reilly T, Haboubi N, et al. Lifestyle factors and colorectal cancer risk (1): systematic review and meta-analysis of associations with body mass index. Colorectal Dis 2009;11(6):547-63.

50. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A, Suzuki R, et al. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. Int J Cancer 2009;124(3):698-712.

51. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 2011;103(3):250-63.

52. Bao PP, Shu XO, Gao YT, Zheng Y, Cai H, Deming SL, et al. Association of hormone-related characteristics and breast cancer risk by estrogen receptor/progesterone receptor status in the shanghai breast cancer study. Am J Epidemiol 2011;174(6):661-71.

53. Ritte R, Lukanova A, Berrino F, Dossus L, Tjonneland A, Olsen A, et al. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. Breast Cancer Res 2012;14(3):R76.

54. Mathew A, George PS, Ildaphonse G, Mathew A, George PS, Ildaphonse G. Obesity and kidney cancer risk in women: a meta-analysis (1992-2008). Asian Pac J Cancer Prev 2009;10(3):471-8.

55. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG, Crosbie EJ, et al. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19(12):3119-30.

56. Lynch BM. Sedentary behavior and cancer: a systematic review of the literature and proposed biological mechanisms. Cancer Epidemiol Biomarkers Prev 2010;19(11):2691-709.

57. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer 2010;46(14):2593-604.

58. Wolin KY, Yan Y, Colditz GA, Lee IM. Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer 2009;100(4):611-6.

59. Harriss DJ, Atkinson G, Batterham A, George K, Cable NT, Reilly T, et al. Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity. Colorectal Dis 2009;11(7):689-701.

60. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med 2008;42(8):636-47.

61. Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE. Physical activity and endometrial cancer risk, a systematic review of current evidence. Cancer Epidemiol Biomarkers Prev 2007;16(4):639-48.

62. Cust AE, Armstrong BK, Friedenreich CM, Slimani N, Bauman A. Physical activity and endometrial cancer risk: a review of the current evidence, biologic mechanisms and the quality of physical activity assessment methods. Cancer Causes Control 2007;18(3):243-58.

63. Moore SC, Gierach GL, Schatzkin A, Matthews CE. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. Br J Cancer 2010;103(7):933-8.

64. Schottenfeld D and Fraumeni JF, editors. Cancer Epidemiology and Prevention. 3rd ed. New York: Oxford University Press; 2006

65. Parkin DM. 15. Cancers attributable to reproductive factors in the UK in 2010. Br J Cancer 2011;105(Suppl 2):S73-S76.

66. Reeves GK, Pirie K, Green J, Bull D, Beral V. Reproductive factors and specific histological types of breast cancer: prospective study and meta-analysis. Br J Cancer 2009;100(3):538-44.

67. Li CI, Daling JR, Malone KE, Bernstein L, Marchbanks PA, Liff JM, et al. Relationship between established breast cancer risk factors and risk of seven different histologic types of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2006;15(5):946-54.

68. Wohlfahrt J, Mouridsen H, Andersen PK, Melbye M. Reproductive risk factors for breast cancer by receptor status, histology, laterality and location. Int J Cancer 1999;81(1):49-55.

69. Cotterchio M, Kreiger N, Theis B, Sloan M, Bahl S. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. Cancer Epidemiol Biomarkers Prev 2003;12(10):1053-60.

70. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010;127(2):442-51.

71. Karageorgi S, Hankinson SE, Kraft P, De V, I. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004. Int J Cancer 2010;126(1):208-16.

72. Tsilidis KK, Allen NE, Key TJ, Dossus L, Lukanova A, Bakken K, et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2011;105(9):1436-42.

73. Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. Int J Cancer 2006;119(5):1108-24.

74. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev 2004;13(10):1558-68.

75. Yang HP, Trabert B, Murphy MA, Sherman ME, Sampson JN, Brinton LA, et al. Ovarian cancer risk factors by histologic subtypes in the NIH-AARP Diet and Health Study. Int J Cancer 2012;131(4):938-48.

76. Danforth KN, Tworoger SS, Hecht JL, Rosner BA, Colditz GA, Hankinson SE. Breastfeeding and risk of ovarian cancer in two prospective cohorts. Cancer Causes Control 2007;18(5):517-23.

77. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350(9084):1047-59.

78. Braem MG, Onland-Moret NC, van den Brandt PA, Goldbohm RA, Peeters PH, Kruitwagen RF, et al. Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. Am J Epidemiol 2010;172(10):1181-9.

79. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 91. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. Lyon: International Agency for Research on Cancer; 2007.

80. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100A. A review of human carcinogens. Part A: Pharmaceuticals. Lyon: International Agency for Research on Cancer; 2012.

81. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 1996;347(9017):1713-27.

82. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer 2007;120(4):885-91.

83. Maheshwari S, Sarraj A, Kramer J, El-Serag HB. Oral contraception and the risk of hepatocellular carcinoma. J Hepatol 2007;47(4):506-13.

84. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371(9609):303-14.

85. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 2006;7(11):910-8.

86. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362(9382):419-27.

87. Bakken K, Fournier A, Lund E, Waaseth M, Dumeaux V, Clavel-Chapelon F, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2011;128(1):144-56.

88. Allen NE, Tsilidis KK, Key TJ, Dossus L, Kaaks R, Lund E, et al. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. Am J Epidemiol 2010;172(12):1394-403.

89. Pike MC, Pearce CL, Wu AH. Prevention of cancers of the breast, endometrium and ovary. Oncogene 2004;23(38):6379-91.

90. Wiseman RA. Breast cancer: critical data analysis concludes that estrogens are not the cause, however lifestyle changes can alter risk rapidly. J Clin Epidemiol 2004;57(8):766-72.

91. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100D. A review of human carcinogens. Part D: Radiation. Lyon: International Agency for Research on Cancer; 2012.

92. Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. Int J Cancer 1997;73(2):198-203.

93. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005;41(1):45-60.

94. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B 2001;63(1-3):8-18.

95. Caini S, Gandini S, Sera F, Raimondi S, Fargnoli MC, Boniol M, et al. Meta-analysis of risk factors for cutaneous melanoma according to anatomical site and clinico-pathological variant. Eur J Cancer 2009;45(17):3054-63.

96. Chang YM, Barrett JH, Bishop DT, Armstrong BK, Bataille V, Bergman W, et al. Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5700 cases and 7216 controls. Int J Epidemiol 2009;38(3):814-30.

97. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12(1):69-82.

98. Cust AE, Jenkins MA, Goumas C, Armstrong BK, Schmid H, Aitken JF, et al. Early-life sun exposure and risk of melanoma before age 40 years. Cancer Causes Control 2011;22(6):885-97.

99. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr 2008;(38):1-93.

100. The International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. Int J Cancer 2007;120(5):1116-22.

101. Hirst N, Gordon L, Gies P, Green AC. Estimation of avoidable skin cancers and cost-savings to government associated with regulation of the solarium industry in Australia. Health Policy 2009;89(3):303-11.

102. Lazovich D, Vogel RI, Berwick M, Weinstock MA, Anderson KE, Warshaw EM. Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. Cancer Epidemiol Biomarkers Prev 2010;19(6):1557-68.

103. Cust AE, Armstrong BK, Goumas C, Jenkins MA, Schmid H, Hopper JL, et al. Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. Int J Cancer 2011;128(10):2425-35.

104. Veierod MB, Adami HO, Lund E, Armstrong BK, Weiderpass E. Sun and solarium exposure and melanoma risk: effects of age, pigmentary characteristics, and nevi. Cancer Epidemiol Biomarkers Prev 2010;19(1):111-20.

105. Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken JF, Giles GG, et al. Artificial ultraviolet radiation and ocular melanoma in Australia. Int J Cancer 2004;112(5):896-900.

106. Schmidt-Pokrzywniak A, Jockel KH, Bornfeld N, Sauerwein W, Stang A. Positive interaction between light iris color and ultraviolet radiation in relation to the risk of uveal melanoma: a case-control study. Artificial ultraviolet radiation and ocular melanoma in Australia. Opthalmology 2009;116(2):340-8.

107. El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, et al. Special Report: Policy: A review of human carcinogens --Part D: radiation. The lancet oncology 2009;10(8)

108. National Toxicology Program. Report on Carcinogens. Research Triangle Park (NC): US Department of Health and Human Services, Public Health Service, National Toxicology Program; 2011.

109. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: Man-made Minerals Fibres and Radon, Vol 43. Lyon, France: IARC; 1988.

110. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 75. Ionizing radiation, part 1: X- and gamma-radiation, and neutrons. Lyon: International Agency for Research on Cancer; 2000.

111. Lubin JH, Boice JD, Jr., Edling C, Hornung RW, Howe GR, Kunz E, et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. J Natl Cancer Inst 1995;87(11):817-27.

112. Krewski D, Lubin JH, Zielinski JM, Alavanja M, Catalan VS, Field RW, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. Epidemiology 2005;16(2):137-45.

113. Krewski D, Lubin JH, Zielinski JM, Alavanja M, Catalan VS, Field RW, et al. A combined analysis of North American case-control studies of residential radon and lung cancer. J Toxicol Environ Health A 2006;69(7):533-97.

114. Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2005;330(7485):223.

115. Darby S, Hill D, Deo H, Auvinen A, Barros-Dios JM, Baysson H, et al. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. Scand J Work Environ Health 2006;32 Suppl 1:1-83.

116. Lubin JH, Wang ZY, Boice JD, Jr., Xu ZY, Blot WJ, De Wang L, et al. Risk of lung cancer and residential radon in China: pooled results of two studies. Int J Cancer 2004;109(1):132-7.

117. United Nations Scientific Committee on the Effects of Atomic Radiation. Effects of Ionizing Radiation. Volume 1: Report to the General Assembly, Annex A: Epidemiological Studies of Radiation and Cancer. New York: United Nations; 2006.

118. Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, et al. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res 2004;162(4):377-89

119. Land CE, Saku T, Hayashi Y, Takahara O, Matsuura H, Tokuoka S, et al. Incidence of salivary gland tumors among atomic bomb survivors, 1950-1987. Evaluation of radiation-related risk. Radiat Res 1996;146(1):28-36.

120. Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. Radiat Res 1998;149(6):625-30.

121. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. Radiat Res 2007;167(4):396-416.

122. Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, et al. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. Am J Epidemiol 2001;153(4):309-18.

123. Institute of Medicine of the National Academy of Science. Asbestos: Selected Cancers. Washington, DC: National Academies Press; 2006.

124. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100C. A review of human carcinogens. Part C: Arsenic, metals, fibres, and dusts. Lyon: International Agency for research on Cancer ; 2012.

125. Payne JI, Pichora E. Filing for workers' compensation among Ontario cases of mesothelioma. Can Respir J 2009;16(5):148-52.

126. Lenters V, Vermeulen R, Dogger S, Stayner L, Portengen L, Burdorf A, et al. A meta-analysis of asbestos and lung cancer: Is better quality exposure assessment associated with steeper slopes of the exposure–response relationships? Environ Health Perspect 2011;119(11):1547-55.

127. Anderson HA, Lilis R, Daum SM, Fischbein AS, Selikoff IJ. Household-contact asbestos neoplastic risk. Ann N Y Acad Sci 1976;271(1):311-23.

128. Ferrante D, Bertolotti M, Todesco A, et al. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. Environ Health Perspect 2007;115(10):1401-5.

129. Reid A, Heyworth J, de Klerk N, Musk AW. The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. Occup Environ Med 2008;65(11):743-9.

130. Reid A, Segal A, Heyworth JS, et al. Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. Cancer Epidemiol Biomarkers Prev 2009;18(1):140-7.

131. Camargo MC, Stayner LT, Straif K, Reina M, Al-Alem U, Demers PA, et al. Occupational Exposure to Asbestos and Ovarian Cancer: A Meta-analysis. Environ Health Perspect 2011;119(9):1211-7.

132. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, et al. Special Report: Policy: A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres. The lancet oncology 2009;10(5):453-4.

133. Yang H, Rivera Z, Jube S, Nasu M, Bertino P, Goparaju C, et al. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. Proc Natl Acad Sci USA 2010;107(28):1261-6

134. Pelucchi C, Pira E, Piolatto G, et al. Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996–2005. Ann Oncol 2006;17(7):1039-50.

135. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 62. Wood dust and formaldehyde. Lyon: International Agency for Research on Cancer; 1995.

136. Demers PA, Kogevinas M, Boffetta P, Leclerc A, Luce D, Gérin M, et al. Wood dust and sino-nasal cancer: Pooled reanalysis of twelve case-control studies. Am J Ind Med 1995;28(2):151-66.

137. Baris I, Artvinli M, Saracci R, Simonato L, Pooley F, Skidmore J, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: A four-year study in the cappadocian region of turkey. Int J Cancer 1987;39(1):10-7.

138. Baris YI, Grandjean P. Prospective Study of Mesothelioma Mortality in Turkish Villages With Exposure to Fibrous Zeolite. J Natl Cancer Inst 2006;98(6):414-7

139. Karagas MR, Stukel TA, Morris JS, Tosteson TD, Weiss JE, Spencer SK, et al. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. Am J Epidemiol 2001;153(6):559-64.

140. Mink PJ, Alexander DD, Barraj LM, Kelsh MA, Tsuji JS. Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis. Regul Toxicol Pharmacol 2008;52(3):299-310.

141. Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. Am J Epidemiol 1995;141(6):523-30.

142. Karagas MR, Tosteson TD, Morris JS, Demidenko E, Mott LA, Heaney J, et al. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. Cancer Causes Control 2004;15(5):465-72.

143. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for nickel. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service; 2005.

144. Report of the International Committee on Nickel Carcinogenesis in Man. Scandinavian journal of work, environment & health 1990;16(1 Spec No)

145. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for beryllium. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service; 2002.

146. Kreiss K, Day GA, Schuler CR. Beryllium: a modern industrial hazard. Annu Rev Public Health 2007;28:259-77.

147. Sanderson WT, Ward EM, Steenland K, Petersen MR. Lung cancer case-control study of beryllium workers. Am J Ind Med 2001;39(2):133-44.

148. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for cadmium. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service; 2012.

149. Stayner L, Smith R, Thun M, Schnorr T, Lemen R. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. Ann Epidemiol 1992;2(3):177-94.

150. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for chromium. Atlanta (GA): U.S Department of Health and Human Services, Public Health Service; 2012.

151. Cole P, Rodu B. Epidemiologic studies of chrome and cancer mortality: a series of meta-analyses. Regul Toxicol Pharmacol 2005;43(3):225-31.

152. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100F. A review of human carcinogens. Part F: Chemical agents and related occupations. Lyon: International Agency for Research on Cancer; 2012.

153. Soskolne CL, Jhangri GS, Siemiatycki J, Lakhani R, Dewar R, Burch JD, et al. Occupational exposure to sulfuric acid in southern Ontario, Canada, in association with laryngeal cancer. Scand J Work Environ Health 1992;18(4):225-32.

154. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Benzene. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service; 2007.

155. Khalade A, Jaakkola MS, Pukkala E, Jaakkola JJ. Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. Environ Health 2010;9:31. doi: 110.1186/1476-069X-9-31. PubMed PMID: 20584305; PubMed Central PMCID: PMC2903550.

156. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for 1,3-butadiene. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service; 2012.

157. Delzell E, Sathiakumar N, Graff J, Macaluso M, Maldonado G, Matthews R. An updated study of mortality among North American synthetic rubber industry workers. Res Rep Health Eff Inst 2006;(132):1-63.

158. Whitworth KW, Symanski E, Coker AL. Childhood lymphohematopoietic cancer incidence and hazardous air pollutants in southeast Texas, 1995-2004. Environ Health Perspect 2008;116(11):1576-80.

159. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk to humans: Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol, Vol 88. Lyon (France): IARC; 2006.

160. Bachand AM, Mundt KA, Mundt DJ, Montgomery RR. Epidemiological studies of formaldehyde exposure and risk of leukemia and nasopharyngeal cancer: a meta-analysis. Crit Rev Toxicol 2010;40(2):85-100.

161. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Mutat Res 2009;681(2-3):150-68.

162. Bosetti C, McLaughlin JK, Tarone RE, Pira E, La Vecchia C. Formaldehyde and cancer risk: a quantitative review of cohort studies through 2006. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2008;19(1):29-43.

163. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from solid cancers among workers in formaldehyde industries. Am J Epidemiol 2004;159(12):1117-30.

164. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 33. Polynuclear aromatic hydrocarbons, part 2, carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. Lyon: International Agency for Research on Cancer; 1984.

165. Costello S, Friesen MC, Christiani DC, Eisen EA. Metalworking fluids and malignant melanoma in autoworkers. Epidemiology 2011;22(1):90-7.

166. Benbrahim-Tallaa L, Baan RA, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. Lancet Oncol 2012;13(7):663-4.

167. Pronk A, Coble J, Stewart PA. Occupational exposure to diesel engine exhaust: a literature review. J Expo Sci Environ Epidemiol 2009;19(5):443-57.

168. Rushton L. The problem with Diesel. J Natl Cancer Inst 2012;104(11):796-7.

169. Attfield MD, Schleiff PL, Lubin JH, Blair A, Stewart PA, Vermeulen R, et al. The Diesel Exhaust in Miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst 2012;104(11):869-83.

170. Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, et al. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst 2012;104(11):855-68.

171. Garshick E, Laden F, Hart JE, Davis ME, Eisen EA, Smith TJ. Lung Cancer and Elemental Carbon Exposure in Trucking Industry Workers. Environ Health Perspect 2012;120(9):1301-6.

172. Laden F, Hart JE, Eschenroeder A, Smith TJ, Garshick E. Historical estimation of diesel exhaust exposure in a cohort study of U.S. railroad workers and lung cancer. Cancer Causes Control 2006;17(7):911-9.

173. Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Bruske I, et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. Am J Respir Crit Care Med 2011;183(7):941-8.

174. Pintos J, Parent ME, Richardson L, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer: evidence from two case-control studies in Montreal, Canada. Occup Environ Med 2012;69(11):787-92.

175. Boffetta P, Silverman DT. A meta-analysis of bladder cancer and diesel exhaust exposure. Epidemiology 2001;12(1):125-30.

176. Emmelin A, Nystrom L, Wall S. Diesel exhaust exposure and smoking: a case-referent study of lung cancer among Swedish dock workers. Epidemiology 1993;4(3):237-44.

177. Ris C. U.S. EPA health assessment for diesel engine exhaust: a review. Inhal Toxicol 2007;19 Suppl 1:229-39.

178. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for polycyclic aromatic hydrocarbons (PAHs). Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service; 1995.

179. Betts WD. Tar and pitch.New York: John Wiley & Sons; 1997.

180. Partanen T, Boffetta P. Cancer risk in asphalt workers and roofers: review and meta-analysis of epidemiologic studies. Am J Ind Med 1994;26(6):721-40.

181. Evanoff BA, Gustavsson P, Hogstedt C. Mortality and incidence of cancer in a cohort of Swedish chimney sweeps: an extended follow up study. Br J Ind Med 1993;50(5):450-9.

182. Spinelli JJ, Demers PA, Le ND, Friesen MD, Lorenzi MF, Fang R, et al. Cancer risk in aluminum reduction plant workers (Canada). Cancer Causes Control 2006;17(7):939-48.

183. Friesen MC, Demers PA, Spinelli JJ, Lorenzi MF, Le ND. Comparison of two indices of exposure to polycyclic aromatic hydrocarbons in a retrospective aluminium smelter cohort. Occup Environ Med 2007;64(4):273-8.

184. Ontario Ministry of the Environment. Air Quality in Ontario: Report for 2010 [Internet].Toronto: Queen's Printer for Ontario; 2012 [cited 2012 Aug 29]. Available from: http://www.ene.gov.on.ca/stdprodconsume/groups/lr/@ene/@resources/documents/resource/stdprod_095558.pdf.

185. Chen H, Goldberg MS, Villeneuve PJ. A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. Rev Environ Health 2008;23(4):243-97.

186. Turner MC, Krewski D, Pope CA3, Chen Y, Gapstur SM, Thun MJ. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am J Respir Crit Care Med 2011;184(12):1374-81.

187. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic Exposure to Fine Particles and Mortality: An Extended Follow-up of the Harvard Six Cities Study from 1974 to 2009. Environ Health Perspect 2012;120(7):965-70.

188. Boffetta P, Nyberg F. Contribution of environmental factors to cancer risk. Br Med Bull 2003;68:71-94.

189. Valavanidis A, Fiotakis K, Vlachogianni T. Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2008;26(4):339-62.

190. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100B. A review of human carcinogens. Part B: Biological agents. Lyon: International Agency for Research on Cancer; 2012.

191. Weiss LM. Epstein-Barr virus and Hodgkin's disease. Curr Oncol Rep 2000;2(2):199-204.

192. Carpenter LM, Newton R, Casabonne D, Ziegler J, Mbulaiteye S, Mbidde E, et al. Antibodies against malaria and Epstein-Barr virus in childhood Burkitt lymphoma: a case-control study in Uganda. Int J Cancer 2008;122(6):1319-23.

193. Mutalima N, Molyneux E, Jaffe H, Kamiza S, Borgstein E, Mkandawire N, et al. Associations between Burkitt lymphoma among children in Malawi and infection with HIV, EBV and malaria: results from a case-control study. PLoS One 2008;3(6):e2505.

194. Hsu JL, Glaser SL. Epstein-barr virus-associated malignancies: epidemiologic patterns and etiologic implications. Crit Rev Oncol Hematol 2000;34(1):27-53.

195. Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 1998;75(3):347-54.

196. Shi J, Zhu L, Liu S, Xie WF. A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. Br J Cancer 2005;92(3):607-12.

197. Cho LY, Yang JJ, Ko KP, Park B, Shin A, Lim MK, et al. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. Int J Cancer 2011;128(1):176-84.

198. Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K, Mueller NE. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. Cancer Sci 2004;95(9):745-52.

199. Dal ML, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2006;15(11):2078-85.

200. Sitas F, Carrara H, Beral V, Newton R, Reeves G, Bull D, et al. Antibodies against human herpesvirus 8 in black South African patients with cancer. N Engl J Med 1999;340(24):1863-71.

201. Newton R, Ziegler J, Bourboulia D, Casabonne D, Beral V, Mbidde E, et al. The sero-epidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in adults with cancer in Uganda. Int J Cancer 2003;103(2):226-32.

202. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370(9581):59-67.

203. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst 2007;99(12):962-72.

204. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008;123(1):187-94.

205. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst 2011;103(9):753-62.

206. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006;108(12):3786-91.

207. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189(1):12-9.

208. Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Variation by geographical region, histological type and year of publication. Int J Cancer 2011;128(4):927-35.

209. De VH, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124(7):1626-36.

210. Miralles-Guri C, Bruni L, Cubilla AL, Castellsague X, Bosch FX, de SS. Human papillomavirus prevalence and type distribution in penile carcinoma. J Clin Pathol 2009;62(10):870-8.

211. Backes DM, Kurman RJ, Pimenta JM, Smith JS. Systematic review of human papillomavirus prevalence in invasive penile cancer. Cancer Causes Control 2009;20(4):449-57.

212. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14(2):467-75.

213. Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. Gastroenterology 1998;114(6):1169-79.

214. Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001;49(3):347-53.

215. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 2003;125(6):1636-44.

216. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, et al. Helicobacter pylori infection and gastric lymphoma. N Engl J Med 1994;330(18):1267-71.

217. Wroblewski LE, Peek RM, Jr., Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev 2010;23(4):713-39.

218. Bedwani R, Renganathan E, El KF, Braga C, Abu Seif HH, Abul AT, et al. Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt. Br J Cancer 1998;77(7):1186-9.

219. Weber W, Estoppey J, Stoll H. Familial cancer diagnosis. Anticancer Res 2001;21(5):3631-5.

220. Petrucelli, N, Daly, M. B., and Feldman, G. L. BRCA1 and BRCA2 hereditary breast and ovarian cancer [Internet].In: Pagon, R. A, Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1998 [updated 2011 Jan 20; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1247/.

221. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72(5):1117-30.

222. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25(11):1329-33.

223. Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol 2005;23(2):276-92.

224. Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer 2010;46(12):2275-84.

225. Levy-Lahad E, Friedman E. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br J Cancer 2007;96(1):11-5

226. Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. Am J Hum Genet 1992;51(2):344-56.

227. Wu CC, Shete S, Amos CI, Strong LC. Joint effects of germ-line p53 mutation and sex on cancer risk in Li-Fraumeni syndrome. Cancer Res 2006;66(16):8287-92.

228. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18(2):400-7.

229. Kohlmann, W. and Gruber, S. B. Lynch syndrome [Internet].In: Pagon, R. A., Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 2004 [updated 2012 Sep 20; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1211/.

230. Kastrinos F, Syngal S. Inherited colorectal cancer syndromes. Cancer J 2011;17(6):405-15.

231. Jasperson, K. W. and Burt, R. W. APC-associated polyposis conditions [Internet].In: Pagon, R. A, Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1998 [updated 2011 Oct 27; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1345/.

232. Jenkins MA, Croitoru ME, Monga N, Cleary SP, Cotterchio M, Hopper JL, et al. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev 2006;15(2):312-4.

233. Amos, C. I., Frazier, M. L., Wei, C., and McGarrity, T. J. Peutz-Jeghers syndrome [Internet].In: Pagon, R. A, Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 2001 [updated 2011 Feb 22; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1266/ .

234. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol 2010;105(6):1258-64.

235. Stanford JL, Ostrander EA. Familial prostate cancer. Epidemiol Rev 2001;23(1):19-23.

236. Schaid DJ. The complex genetic epidemiology of prostate cancer. Hum Mol Genet 2004;13 Spec No 1:R103-R121.

237. Pakkanen S, Baffoe-Bonnie AB, Matikainen MP, Koivisto PA, Tammela TL, Deshmukh S, et al. Segregation analysis of 1,546 prostate cancer families in Finland shows recessive inheritance. Hum Genet 2007;121(2):257-67.

238. Cui J, Staples MP, Hopper JL, English DR, McCredie MR, Giles GG. Segregation analyses of 1,476 population-based Australian families affected by prostate cancer. Am J Hum Genet 2001;68(5):1207-18.

239. Carpten J, Nupponen N, Isaacs S, Sood R, Robbins C, Xu J, et al. Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat Genet 2002;30(2):181-4

240. Rokman A, Ikonen T, Seppala EH, Nupponen N, Autio V, Mononen N, et al. Germline alterations of the RNASEL gene, a candidate HPC1 gene at 1q25, in patients and families with prostate cancer. Am J Hum Genet 2002;70(5):1299-304.

241. Xu J, Zheng SL, Komiya A, Mychaleckyj JC, Isaacs SD, Hu JJ, et al. Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Nat Genet 2002;32(2):321-5.

242. Xu J, Zheng SL, Komiya A, Mychaleckyj JC, Isaacs SD, Chang B, et al. Common sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Am J Hum Genet 2003;72(1):208-12.

243. Segel GB, Lichtman MA. Familial (inherited) leukemia, lymphoma, and myeloma: an overview. Blood Cells Mol Dis 2004;32(1):246-61.

244. Gatti, R. Ataxia-Telangiectasia [Internet].In: Pagon, R. A, Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1999 [updated 2010 Mar 11; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK26468/.

245. Alter, B. P. Fanconi Anemia [Internet].In: Pagon, R. A, Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 2002 [updated 2012 Sep 6; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1401/.

246. Seif AE. Pediatric leukemia predisposition syndromes: clues to understanding leukemogenesis. Cancer Genet 2011;204(5):227-44.

247. Fong CT, Brodeur GM. Down's syndrome and leukemia: epidemiology, genetics, cytogenetics and mechanisms of leukemogenesis. Cancer Genet Cytogenet 1987;28(1):55-76.

248. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000;355(9199):165-9.

249. Rabin KR, Whitlock JA. Malignancy in children with trisomy 21. Oncologist 2009;14(2):164-73.

250. Lohmann, D. R. and Gallie, B. L. Retinoblastoma [Internet].In: Pagon, R. A, Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 2000 [updated 2010 Jun 10; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1452/.

251. D'Orazio JA. Inherited cancer syndromes in children and young adults. J Pediatr Hematol Oncol 2010;32(3):195-228.

252. Dome, J. S. and Huff, V. Wilms tumor [Internet].In: Pagon, R. A, Bird, T. D., Dolan, C. R., et al., editors. GeneReviews™ [Internet]. Seattle (WA):University of Washington, Seattle; 2003 [updated 2011 Jun 14; cited 2012 Oct 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1294/.

253. Ruteshouser EC, Huff V. Familial Wilms tumor. Am J Med Genet C Semin Med Genet 2004;129C(1):29-34.

254. Pedersen N, Duricova D, Elkjaer M, Gamborg M, Munkholm P, Jess T, et al. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am J Gastroenterol 2010;105(7):1480-7.

255. Jess T, Gamborg M, Matzen P, Munkholm P, Sorensen TI, Jess T, et al. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol 2005;100(12):2724-9.

256. Canavan C, Abrams KR, Mayberry J, Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Aliment Pharmacol Ther 2006;23(8):1097-104.

257. von Roon AC, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP, et al. The risk of cancer in patients with Crohn's disease. Dis Colon Rectum 2007;50(6):839-55.

258. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol 2012;10(6):639-45.

259. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Autoimmune disease and subsequent digestive tract cancer by histology. Ann Oncol 2012;23(4):927-33.

260. Guagnozzi D, Lucendo AJ. Colorectal cancer surveillance in patients with inflammatory bowel disease: What is new? World J Gastrointest Endosc 2012;4(4):108-16.

261. Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas--an update. J Intern Med 2008;264(6):514-27.

262. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin 2010;60(4):207-21.

263. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16(4):1103-23.

264. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4(3):369-80.

265. Wang C, Wang X, Gong G, Ben Q, Qiu W, Chen Y, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer 2012;130(7):1639-48.

266. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev 2012;28(2):109-22.

267. Yang WS, Va P, Bray F, Gao S, Gao J, Li HL, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma occurrence and prognosis: a meta-analysis of prospective cohort studies. PLoS One 2011;6(12):e27326.

268. Huxley R, Ansary-Moghaddam A, Berrington de GA, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92(11):2076-83.

269. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. Eur J Cancer 2011;47(13):1928-37.

270. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97(22):1679-87.

271. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol 2011;106(11):1911-21.

272. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol 2011;26(11):863-76.

273. Deng L, Gui Z, Zhao L, Wang J, Shen L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. Dig Dis Sci 2012;57(6):1576-85.

274. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 2006;49(12):2819-23.

275. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007;121(4):856-62.

276. Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pac J Cancer Prev 2011;12(4):1061-5.

277. Chang JT, Katzka DA. Gastroesophageal reflux disease, Barrett esophagus, and esophageal adenocarcinoma. Arch Intern Med 2004;164(14):1482-8.

278. Shaheen N, Ransohoff DF. Gastroesophageal reflux, barrett esophagus, and esophageal cancer: scientific review. JAMA 2002;287(15):1972-81.

279. Wild CP, Hardie LJ. Reflux, Barrett's oesophagus and adenocarcinoma: burning questions. Nat Rev Cancer 2003;3(9):676-84.

280. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther 2010;32(10):1222-7.

281. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340(11):825-31.

282. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011;365(15):1375-83.

283. Thomas T, Abrams KR, De Caestecker JS, Robinson RJ. Meta analysis: Cancer risk in Barrett's oesophagus. Aliment Pharmacol Ther 2007;26(11-12):1465-77.

284. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol 2008;168(3):237-49.

285. Sikkema M, de Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2010;8(3):235-44.

286. Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut 2012;61(7):970-6.

287. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst 2011;103(13):1049-57.

288. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology 2011;140(3):e18-e52.

289. Wood HM, Elder JS. Cryptorchidism and testicular cancer: separating fact from fiction. J Urol 2009;181(2):452-61.

290. Schnitt SJ. Benign breast disease and breast cancer risk: morphology and beyond. Am J Surg Pathol 2003;27(6):836-41.

291. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, et al. Benign breast disease and the risk of breast cancer. N Engl J Med 2005;353(3):229-37.

292. Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. Radiat Res 1992;131(1):98-111.

293. Finazzi G, Caruso V, Marchioli R, Capnist G, Chisesi T, Finelli C, et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. Blood 2005;105(7):2664-70.

294. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370(9581):59-67.

295. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306(17):1891-901.

296. Dantal J, Pohanka E. Malignancies in renal transplantation: an unmet medical need. Nephrol Dial Transplant 2007;22 Suppl 1:i4-10.

297. Bosetti C, Rosato V, Gallus S, Cuzick J, La VC. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 2012;23(6):1403-15.

298. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;376(9754):1741-50.

299. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369(9573):1603-13.

300. Sturmer T, Glynn RJ, Lee IM, Manson JE, Buring JE, Hennekens CH. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. Ann Intern Med 1998;128(9):713-20.

301. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294(1):47-55.

GLOSSARY

Apoptosis
Programmed cell death, in which a series of molecular steps in a cell lead to its death. This is one method the body uses to get rid of abnormal cells and may be blocked in cancer cells.

Autosomal dominant
A variant of a gene on any chromosome (except the sex chromosomes) that will express itself in the offspring, despite the presence of other variants of that gene.

Autosomal recessive
A variant of a gene on any chromosome (except the sex chromosomes) that in the presence of its dominant variant will not express itself in the offspring. It will only express itself when both copies of the gene are the same recessive variants.

Carcinogen, carcinogenic, carcinogenicity, carcinogenesis
Any substance that can cause cancer. Such substances are termed carcinogenic, or able to cause cancer; this is the property of carcinogenicity. Carcinogenesis is the process of beginning or promoting the changes that result in cancer.

Case-control study
A study that starts with the identification of people with the disease or other outcome of interest, and compares them with a suitable control group (comparison or reference group) of people without the disease.

Cohort study
A study in which subsets of a defined population are identified who are, have been, or may be exposed to the agent under investigation. The identified individuals are followed over time for the occurrence of disease or other outcomes of interest.

Dose-response
The relationship of observed outcomes (responses) in a population to varying levels of a protective or harmful agent, such as a medication or environmental contaminant. If the outcome changes when the dose of the agent changes, there is said to be a dose-response relationship between the two.

Ecologic study
A study in which the units of analysis are populations or groups of people, rather than individuals.

Epigenetic
Factors that affect gene expression without changing the DNA sequence itself.

Estrogen receptor (ER) positive/negative
Cancer cells that either require or do not require the presence of estrogen to grow. This will determine whether those cells will cease or continue growing when treated with hormones that block estrogen binding and action.

Excess relative risk
The relative risk of a disease minus 1.0. This is often expressed as the excess relative risk per unit of radiation.

Free radical
A type of unstable molecule that is made during normal cell metabolism. Free radicals can build up in cells and cause damage to other molecules, such as DNA, lipids and proteins. This damage may increase the risk of cancer and other diseases.

Genotoxic/genotoxicity
An effect that damages or otherwise interferes with the action of a gene.

Germline mutation
A gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring.

Ionizing radiation
Radiation of sufficiently high energy to cause ionization (change the electrical charge of atoms) in the medium through which it passes. It may consist of a stream of high-energy particles (e.g., electrons, protons, alpha-particles) or short–wavelength electromagnetic radiation (X-rays, gamma rays). This type of radiation can cause extensive damage to the molecular structure of a substance, either as a result of the direct transfer of energy to its atoms or molecules, or as a result of the secondary electrons released by ionization.

Interaction/effect modification
Differences in the effects of one or more factors according to the level of the remaining factor(s). For example, there is an interaction between age and sex if the effect of age on the outcome of interest is different for males and females.

Meta-analysis
A statistical synthesis of the data from comparable studies resulting in a quantitative summary of the pooled results.

Oncogene
A mutated form of a gene involved in normal cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer.

Oxidative stress
A physiologic state caused by cumulative damage done by free radicals due to an imbalance between these molecules in the body and molecules that are able to detoxify them or repair the resulting damage.

Prospective study
See cohort study.

Progesterone receptor (PR) positive/negative

Cancer cells that either require or do not require the presence of progesterone to grow, which will determine whether those cells will cease or continue growing when treated with hormones that block progesterone binding.

Randomized control trial

A study in which participants are randomly allocated into different intervention or treatment groups to compare the outcomes of different exposures.

Relative risk

The ratio of the risk of disease or death among a group of people exposed to a given risk factor/carcinogen, to the risk among an unexposed group.

Synergistic relationship

Describes an interaction between two or more factors in which the effect of one factor is enhanced by the presence of the other(s). In other words, the effect of one factor on an outcome (e.g., cancer risk) is greater in the presence of another factor than when that other is absent.

Tumour suppressor gene

A gene that encodes a protein that helps control cell growth. Mutations in these genes may lead to uncontrolled cell growth and cancer. The tumour suppressor gene is sometimes called an anti-oncogene.

For more information:

Cancer in Ontario: Overview, published 2010, is the first in a series of Cancer Care Ontario publications designed to provide information on patterns and trends for cancer and risk factors in the Province. This first report provides an overview of the burden of cancer.

Please see www.cancercare.on.ca/reports

Ontario Cancer Facts are short, monthly fact sheets intended to increase knowledge about cancer and its risk modifiers in Ontario. Data typically originate from several sources including the Ontario Cancer Registry, Cancer Care Ontario publications, and Canadian, provincial or regional health surveys. Readers may subscribe to receive Ontario Cancer Facts by e-mail.

Please see www.cancercare.on.ca/cancerfacts

The Occupational Cancer Research Centre (OCRC), established in 2009, is the first of its kind in Canada. The Centre was established to fill the gaps in our knowledge of occupation-related cancers and to translate these findings into preventive programs to control workplace carcinogenic exposures and improve the health of workers. The Centre is establishing and leading a program of integrated research that will involve collaborations between researchers, worker organizations and employers. The OCRC is jointly funded by Ontario's Workplace Safety and Insurance Board, Cancer Care Ontario, and the Canadian Cancer Society.

Please see http://occupationalcancer.ca

The Cancer Quality Council of Ontario is an advisory council to Cancer Care Ontario and the Ministry of Health and Long-Term Care established in 2002 to guide quality improvement efforts and monitor and publicly report on the performance of Ontario's Cancer System. One mechanism by which this is achieved is the **Cancer System Quality Index**, an interactive web-based tool released annually since 2005, that reports on a variety of evidence-based indicators covering every aspect of cancer control, from cancer prevention to recovery and end-of-life care, and tracks Ontario's progress against seven dimensions of quality.

Please see www.csqi.on.ca

Cancer Care Ontario
620 University Avenue
Toronto, Ontario
M5G 2L7

416 971 9800
publicaffairs@cancercare.on.ca
www.cancercare.on.ca