



CORE

Public Health Functions for BC

Evidence Review:
Chronic Disease

**Population and Public Health
BC Ministry of Healthy Living and Sport**

This paper is a review of the scientific evidence for this core program. Core program evidence reviews may draw from a number of sources, including scientific studies circulated in the academic literature, and observational or anecdotal reports recorded in community-based publications. By bringing together multiple forms of evidence, these reviews aim to provide a proven context through which public health workers can focus their local and provincial objectives. This document should be seen as a guide to understanding the scientific and community-based research, rather than as a formula for achieving success. The evidence presented for a core program will inform the health authorities in developing their priorities, but these priorities will be tailored by local context.

This Evidence Review should be read in conjunction with the accompanying Model Core Program Paper.

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EXECUTIVE SUMMARY

This review of the evidence and best practices in chronic disease prevention is part of a series of evidence reviews prepared for the Core Public Health Functions initiative in BC. As such, it is not a complete review of all chronic disease, or of all approaches to chronic disease prevention. Rather, and consistent with the definition of the chronic disease prevention program in the Core Public Health Functions Framework resource document,¹ this review focuses on chronic non-communicable diseases that are not addressed elsewhere, and on disease-specific interventions as much as possible.

The definition for chronic disease is consistent with that used in *The Framework for a Provincial Chronic Disease Prevention Initiative* (2003), namely, “chronic diseases are usually characterized by complex causality, multiple risk factors, a long latency period, a prolonged course of illness, functional impairment or disability, and in most cases, the unlikelihood of cure.”² This review focuses on chronic non-communicable diseases that are not addressed elsewhere, on disease-specific interventions as much as possible, and on conditions which present a significant burden of disease in BC. Thus the following are not included, or if included, are not extensively covered:

- Chronic communicable diseases (e.g., HIV, hepatitis C, tuberculosis) that are addressed in the Communicable Disease core program
- The common behavioural risk factors that account for roughly one-quarter of the burden of disease in BC, and were addressed earlier in the Healthy Living core program (e.g., smoking, physical inactivity, and poor eating habits)
- Conditions that are largely dealt with through the Healthy Living core program evidence review (lung cancer, many aspects of cardiovascular disease, COPD, diabetes) or through the Harm Reduction core program (e.g., alcoholic cirrhosis) are either not included or only briefly addressed
- Broad population health promotion interventions that address the determinants of health and seek to change overall living and working conditions. Such interventions can be expected to affect most if not all of the conditions addressed here

The focus of the first iteration of this report, completed in April 2006, was a review of the available evidence on the effectiveness of initiatives in primary prevention and early detection in the areas of neurological, sensory, musculoskeletal, digestive and genitourinary disorders, and breast cancer. The second iteration, completed in June 2008, added a review of diabetes, heart disease, hypertension, stroke and asthma to the earlier work. ***None of these sections have been updated in the current iteration.***

Ultimately, the evidence of effective strategies will be translated into practice through a process of implementation and performance expectations related to individual health authorities and underserved populations. Consistent with the definition of the public health function as primordial, primary, and early secondary prevention, the review does not include treatment and chronic disease management.

Not all evidence is created equal.

In recognition of this fact, a number of groups have developed methods of grading the strength of available research evidence. One such group is The Canadian Task Force on the Periodic Health Examination (CTFPHE). This group adopted a plan to use explicit analytic criteria to guide its evaluation of effectiveness research. The following table provides the criteria for assigning various grades (from I to III) to published literature.

I	Evidence from at least 1 properly randomized controlled trial (RCT).
II-1	Evidence from well-designed controlled trials without randomization.
II-2	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
II-3	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

We have used this approach in estimating the level of available evidence to support the association between specific modifiable risk factors and diseases.

Early in the process of completing this review, it became obvious that a large volume of research information was available, particularly for certain diseases. The broad range of diseases covered in this review, together with a very modest contract to complete this work, meant that the systematic reviews of other groups were utilized whenever they were available. In addition, we focussed on the most promising modifiable risk factors associated with either a significant increase or decreased risk. There were, however, situations in which the lack of an observed association (e.g., cell phone use and brain cancer) was just as important as observed significant associations.

Modifiable Risk Factors and Prevention

The following table summarizes the observed association between the various diseases and modifiable risk factors, including an estimate of the level of evidence available to support this association. This suggests areas where primary prevention should be considered.

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Disease Group	Disease	Modifiable Factor	Increase/ Decrease Risk	Level of Evidence	Note
Neurological Disorders					
	Alzheimer's				
		Integrated lifestyle	↓	II-1	
		Non-steroidal anti-inflammatory use	↓	II-2	Only with long-term use?
		Hormone replacement therapy use	???	I & II-1	See text
		Substandard education	↑	II-2	
	Parkinson's				
		Smoking	↓	II-1	
		Caffeine use	↓	II-2	
		Pesticide exposure	???	II-2	
		Occupational exposure (farming)	???	II-2	
	Multiple Sclerosis				
		Sunlight and vitamin D deficiency	↑	II-1	
		Organic solvents	↑	II-2	
	Primary Brain Cancer				
		Exposure to vinyl chloride	—	II-2	
		Exposure to radiation from cellular phones	—	II-1	Long-term (10+ years)
		Exposure to x-ray radiation	—	II-2	Not at normal doses
Sensory Disorders					
	Hearing Impairment				
		Smoking	—	II-2	In elderly
		Alcohol abuse	↑	II-2	In elderly
		Exposure to excessive noise	↑	II-2	
	Vision Impairment				
		Smoking	↑	II-1	
		Accumulated lead exposure	↑	II-2	
Musculoskeletal Disorders					
	Osteoarthritis				
		Overweight/obesity	↑	II-1	
	Rheumatoid Arthritis				
		Smoking	↑	II-1	For seropositive RA
	Lower Back Pain				
		Lumber supports	—		
		Shoe insoles	???		Insufficient research
		Physical activity/education	↓	I	
		Assistive devices	↓	II-1	
	Repetitive Strain Injuries				
		Occupation	???		Insufficient research
	Primary Bone Cancer				
		No known modifiable risk factors			
Digestive Disorders					
	Peptic Ulcers				
		Infection by <i>Helicobacter pylori</i>	↑	I	
		Non-steroidal anti-inflammatory use	↑	I	
	Inflammatory Bowel Disease				
		Appendectomy	↓	II-2	
		Smoking	↑	II-2	
		Use of oral contraceptives	↑	II-2	
		Breastfeeding	???	II-2	Limited research
	Gastric Cancer				
		"Dusty" occupations	↑	II-2	
		Moderate wine consumption	↓	II-2	
		High salt intake	↑	II-1	
		Infection by <i>Helicobacter pylori</i>	↑	II-2	
	Colorectal Cancer				
		Overweight/obesity	↑	II-2	
		Physical activity	↓	II-2	

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Disease Group	Disease	Modifiable Factor	Increase/ Decrease Risk	Level of Evidence	Note
Genitourinary Disorders					
	Renal and Bladder Stones				
		Overweight/obesity	↑	II-2	
		Appropriate diet (esp. water intake)	↓	II-2	
	Cervical Cancer				
		Infection by HPV	↑	I	
	Prostate Cancer				
		Lycopene (tomatoes)	↓	II-1	
		Selenium	↓	II-1	
		Green Tea	↓	II-2	Limited research
	Bladder Cancer				
		Smoking	↑	II-1	
		Fruit consumption	↓	II-2	
Cardiovascular Disorders					
	Coronary Artery Disease				
		Overweight/obesity	↑	II-1	
		Smoking	↑	II-1	
		Fish high in omega-3 fatty acids	↓	II-2	
		Vegetables and fruit consumption	↓	II-2	
		Physical activity	↓	II-1	
		Modest alcohol consumption	↓	II-1	
		Low-dose aspirin	↓	II-1	High-risk individuals only
	Heart Failure				
		Overweight/obesity	↑	II-1	
		Smoking	↑	II-1	
		Alcohol abuse	↑	II-1	
		DASH diet	↑	II-1	See text
		Modest alcohol consumption	↓	II-1	
		Physical activity	↓	II-1	
		Low sodium intake	↓	II-1	
	Hypertension				
		Weight reduction	↓	II-1	
		DASH diet	↓	I	See text
		Low sodium intake	↓	I	
		Physical activity	↓	II-1	
		Modest alcohol consumption	↓	II-1	
	Stroke				
		Hypertension	↑	I	
		Physical activity	↓	II-1	
		Smoking	↑	II-2	
		Overweight/obesity	↑	II-2	
		Excessive alcohol consumption	↑	II-2	
Respiratory Disorders					
	Asthma				
		Avoid house dust mites	↓	I	
		Avoid environmental tobacco smoke	↓	I	
		Avoid pet allergens	↓	I	
		Multifaceted interventions (above 30	↓	I	See text
		Breastfeeding	↓	II-2	
		Hygiene hypothesis (preventative exposure to viruses and allergens)	↓	II-3	See text

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Disease Group	Disease	Modifiable Factor	Increase/Decrease Risk	Level of Evidence	Note
Other Disorders					
	Breast Cancer				
		Overweight/obesity	↑	I	
		Physical activity	↓	II-1	
		Alcohol consumption	↑	II-1	
		Chemoprevention	↓	I	Significant side-effects
		Prophylactic surgery	↓	II-1	High-risk only
	Diabetes – Type 2				
		Overweight/obesity	↑	II-1	
		Smoking	↑	II-1	
		Depression	↑	II-2	
		Physical activity	↓	II-1	
	Diabetes – Type 1				
		Breastfeeding	↓	II-2	
		Vitamin D supplementation	↓	II-2	
		Nicotinamide	—	I	
		Pre-symptomatic insulin	—	I	

Primary Prevention

While these tables provide a useful overview, the following provides a more detailed summary of the effectiveness of primary prevention for the conditions under consideration here.

Alzheimer’s Disease

A comprehensive 2001 review of the literature on the primary prevention of Alzheimer’s disease summarized risk factors associated with AD into three categories: those that increase risk, those that decrease risk, and those for which the research is uncertain.

Increases Risk	Decreases Risk	Uncertain
<ul style="list-style-type: none"> Genetic mutations Genetic susceptibility (apolipoprotein E e4) Diabetes mellitus Positive family history Substandard education Older age Female sex Significant head injury Cerebrovascular disease 	<ul style="list-style-type: none"> Non-steroidal anti-inflammatory drug (NSAID) use Estrogen use 	<ul style="list-style-type: none"> Alcohol Cigarette smoking Toxins – aluminums, glue, fertilizers, pesticides

More recent research also indicates that an active and socially integrated lifestyle in late life might protect against dementia:

- *An integrated lifestyle:* A 2004 review concluded that “Taking into account the accumulated evidence and the biological plausibility of these hypotheses, we conclude that an active and socially integrated lifestyle in late life protects against dementia and AD.”
- *Low levels of education:* Several studies have suggested that low levels of education are a risk factor for AD. A variety of hypotheses have been suggested for the association found between low educational attainment and higher risk of AD. These range from bias in detection to the ‘cognitive reserve’ hypothesis.

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- *NSAID use:* A significant number of studies have found an association between NSAID use and a reduced risk of AD. The more systematic reviews (meta-analyses) indicate a protective effect of long-term NSAID use on the risk of developing AD.
- *Hormone replacement therapy (HRT):* A 2005 review found that “The majority of trials investigating the neuro-cognitive effects of HRT found benefits associated with estrogen therapy...”

Parkinson’s Disease

Several risk factors and protective factors for PD can be found in the literature.

Increases Risk	Decreases Risk	Uncertain
<ul style="list-style-type: none"> • History of head injury • Depression • Family history of PD • Pesticide exposure • Exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) • Well water drinking 	<ul style="list-style-type: none"> • Smoking • Caffeine use • NSAID use, specifically Ibuprofen 	<ul style="list-style-type: none"> • Vitamin E intake

- *Smoking:* There appears to be a strong inverse association between smoking and PD; smoking is associated with a decreased risk of PD. However, smoking, if explored as a protective measure against PD, should be looked at with caution. It is still unclear if smoking indeed protects against PD or if further issues exist. It is clear, however, that smoking definitively contributes to a myriad of other health problems, many of which have a much worse prognosis, and worse impacts to the individual and society, than PD.
- *Caffeine and alcohol:* Caffeine consumption was sometimes found to be protective against PD, but results are mixed. Alcohol consumption was found to have no effect on the risk of acquiring PD.

Other environmental risk factors usually associated with PD are pesticide exposure, living in a rural area, living on a farm, farming, exposure to farm animals, and well water use. Research on the associations between these risk factors and the risk of PD is largely inconclusive.

Multiple Sclerosis

A number of risk factors have been investigated with regards to MS. Although the overall research base is weak, risk factors related to MS susceptibility may include low levels of solar UV radiation, low levels of vitamin D, low levels of sex hormones in females, occupational exposure to toxins, and dental fillings or amalgams.

Primary Brain Cancer

- *Vinyl chloride*: The evidence seems to show that there is no increased risk of brain tumours with occupational exposure to vinyl chloride, although this is not the case with regards to hepatic cancer.
- *Exposure to X-ray radiation*: With the current doses of radiation in use today in the medical field, there does not seem to be an elevated risk of brain cancer. However, in the past, the required doses of radiation to produce an accurate image were much higher and were associated with some risk of meningioma.
- *Cell phones*: Based on currently available evidence, it seems reasonable to conclude that there is no risk of brain tumours associated with cell phone usage in the short- or mid-term though long-term or heavy usage has not been ruled out as a potential risk factor.

Hearing Impairment

About half of all hearing losses are preventable. A number of risk factors have been described in hearing impairment, the most important of which is excessive noise. Other main causes of hearing loss include presbycusia, which is age-related hearing loss, infections of the middle ear, and genetic factors. It is also suggested that smoking or alcohol may be risk factors for hearing loss.

One of the main targeted areas of prevention is likely to be hearing protection devices in construction and factory workers and engineers. However, in addition to making hearing protection available, education regarding the importance and use of hearing protection as well as "...development of effective and simple noise controls for the construction..." and other industries is required to reduce noise exposure.

Vision Impairment

Smoking and long-term exposure to lead appear to be related to the risk of cataract development. Smoking also increases the risk of age-related macular degeneration.

Osteoarthritis

The main focus in primary prevention of OA has been on weight reduction, improved diet, estrogen replacement, care with work-related activity, and other protections against joint injury, including exercise combating muscle weakness.

Based on the available research, obesity appears to be a risk factor for the development of OA, especially in the knee. The role of exercise in prevention remains unclear. Evidence is available on both sides of the debate concerning the impact of regular, strenuous recreational activity on lower limb joints. One review suggested that there was no evidence that physical activity directly prevents OA. Preventing injuries in the first place and careful rehabilitation following injury may also be important in preventing knee OA.

In sum, weight control has dominated the discussion of preventive efforts in OA.

Rheumatoid Arthritis

There are limited primary prevention options currently available for RA. The one exception is the contributory role of long-term smoking. Recent research suggests that “in a certain genetic context, smoking is a potential trigger for RA, and a combination of the two factors is associated with the occurrence of immune reactions long before the onset of RA.”

Given the evidence of a causal link between smoking and RA, reducing the modifiable risk factor of smoking should lead to a decreased incidence of disease, especially the subset of RA associated with specific genetic and immunologic conditions.

Lower Back Pain

The most significant predictor of lower back pain (LBP) appears to be a previous history of back pain. Although there is limited documentation of other risk factors, the most common include; heavy physical work, frequent bending, twisting, lifting, pulling and pushing, repetitive work, static postures, and vibrations. Other risk factors include psychosocial indicators such as distress, depression, beliefs, job dissatisfaction, and mental stress at work.

Lumbar back supports are found to be a common approach in industry to preventing back injury. A review of seven prevention studies and six therapeutic studies concluded that there is no strong evidence in favour of or against lumbar support effectiveness in both prevention and treatment of LBP. The results of this study suggest that lumbar supports not be recommended for primary prevention of LBP.

There is evidence that suggests physical exercise is recommended to prevent workplace absence due to back pain and to prevent the occurrence or duration of further back pain episodes. There is also evidence to suggest water gymnastics as an exercise could be recommended to reduce back pain and work loss during or following pregnancy.

A recent Cochrane review of 19 RCTs concludes that back schools in occupational settings reduce pain and improve function and return-to-work status in the short and intermediate term, but that the clinical relevance of these studies was rated as insufficient. The U.S. Preventive Services Task Force, however, has stated that there is no good evidence to recommend the use of back strengthening exercises as a prevention strategy against LBP and there is limited evidence only that back schools produce modest short-term benefits at best.

An identified area that involves prevention of LBP is education on lifting techniques. This is different from back schools in that it focuses on primary prevention, often in the workplace, as opposed to education and treatment after a back injury or LBP has been presented. The current research indicates that intensive lifting education programs are not particularly effective. Sessions a few hours in length are moderately useful when workplaces require lifting, and often teach the ‘squat lifting’ or ‘semi-squat’ method. In general, the majority of the research suggests that in instances where lifting devices can be used, such as in a hospital or nursing home, they should be implemented, as they provide a much better result in lowering the incidence of LBP. In instances where lifting devices cannot be used, a short workplace lifting seminar can be useful in teaching the proper method of lifting.

Repetitive Strain Injuries (RSI)

Repetitive strain injury (RSI) is an umbrella term that describes a group of disorders usually impacting the arms and upper body. RSIs are thought to be relatively new diagnoses and are said to be common in the workplace and community. Early identification of potential problems in the work environment is critical to preventing RSI. Areas to be considered include work overload, uncomfortable surroundings, and consideration of poor relationships between staff and supervisors. Ensuring ergonomically sound work environments and providing enough time away from work are essential components of prevention. Very little research exists, however, on the primary prevention or early detection of RSI.

Primary Bone Cancer

Ninety-five percent of those who develop bone cancer have no obvious risk factors. In light of this fact, no primary prevention measures are currently available and there are no guidelines for preventing primary bone cancer.

Peptic Ulcers

The main necessary causes of peptic ulcer disease (PUD) are *Helicobacter pylori* infection and NSAID use. The influence of other risk factors in disease development, such as smoking, depends mostly on which of the two causes is involved.

H. pylori eradication: The potential value of eradicating detected H. pylori has been intensely studied, and remains a lively area of research. Although some studies have suggested that universal screening and eradication for H. pylori may be cost-effective, most prevention research has focused on the symptomatic patients, i.e., the management of uninvestigated and functional dyspepsia.

The test-and-treat strategy has been shown to be cost-effective compared to anti-secretory therapy (as well as against early endoscopy). Thus, the test-and-treat strategy is now being recommended by many as the preferred option with younger patients with uninvestigated dyspepsia showing no alarming signs. However, the results backing up this approach remain marginal and/or debatable and other reviewers continue to advocate for the rationality of anti-secretory modes of ulcer prevention (and healing). Some researchers have suggested caution around aggressive eradication strategies as there is always the danger of creating antibiotic resistance, and possibly eliminating the value of a range of bacteria in the gastrointestinal tract. While the “jury remains out” about the advisability of and protocol for H. pylori eradication, the scale will probably continue to tip towards such a preventive measure as the other key disease linkage becomes clearer, namely, the one between infection and gastric cancer. Other preventive measures include:

- *NSAID use*: There are several preventive approaches available, of varying usefulness: Using safer NSAIDs; use of acetaminophen, which is associated with a lower side-effect profile, but it does not control the inflammation which is central to the majority of rheumatoid arthritis pain and disability (for which NSAIDs are used); and use of various gastro-protective agents, although these vary in effect and expense.
- *Smoking*: Smokers are more likely to develop ulcers; as well, smoking impedes ulcer healing and increases ulcer relapse rates. Thus, smoking cessation likely would have a

favourable impact on PUD incidence. It could also be positive in terms of PUD progression. Smoking may be a risk factor for complications such as perforation and bleeding, and one long-term study confirmed that mortality rates related to PUD were three times higher in smokers.

- *Alcohol*: While alcohol intake has not been associated with PUD per se, excessive consumption (of beer and spirits more than of wine) has been implicated in the development of complicated ulcers that manifest bleeding and perforation.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) encompasses two diseases, both of unknown etiology: Crohn's disease (CD) and ulcerative colitis (UC). It has been concluded after consideration of the epidemiological, genetic, and immunological data that UC and CD are "heterogeneous disorders of multifactorial etiology in which hereditary (genetic) and environmental (microbial, behaviour) factors interact to produce the disease."

Among the key modifiable risk factors investigated in association with IBD are smoking, oral contraceptive use, breastfeeding, diet, hormone replacement therapy, and appendectomy. The limited evidence available suggests an increased risk of CD associated with the use of oral contraceptives and the protective effect of an appendectomy associated with UC.

Gastric Cancer

Helicobacter pylori have been strongly associated with gastric cancer. The bacterium is able to invade and colonize the human stomach. There it can interact with gastric epithelial cells, leading to a number of tissue changes and disease conditions, including: inflammation, loss of mucosa (i.e., an ulcer), and development of masses from benign polyps to full cancers. *H. pylori* was first cultured in 1982, and classified as a carcinogen over 10 years ago.

It is known that only certain strains of *H. pylori* are highly pathogenic, so only a subset of the population carrying the bacteria actually experience disease; ultimately only 2% of infected people will get a malignancy. The infected pool is large, however, resulting in stomach cancer being the fourth most common cancer in the world.

The risk factors identified for gastric cancer, apart from *H. pylori*, include high salt intake. The data for smoking and alcohol consumption are less conclusive. Preventive measures include:

- At this point, anti-*H. pylori* therapies remain the best option to control disease, one that is recommended for all symptomatic infected individuals according to recent professional consensus statements. Using such an approach with the entire infected population would hardly seem to be feasible. Many uncertainties remain, including the effect of total eradication of *H. pylori* on gastric cancer incidence, and the fact that infection actually seems to be protective against certain cancers.
- Analyzing molecular markers of disease shows great promise as a treatment prompt. Detection of high risk polymorphisms and related gene expression in hosts will also allow for targeted prevention through *H. pylori* eradication. Much more research must ensue before the clinical implementation of this sort of personalized medicine.

- With the possible added risk represented by tobacco use, a clear prevention method is smoking cessation (or encouragements to not take up the habit). Controlling the intake of salted foods may also help. On the other hand, protection against gastric cancer can be added to the growing list of benefits that has been attached to moderate wine consumption.
- Finally, antioxidants in regularly consumed vegetables and fruit are thought to decrease the risk of gastric cancer by up to one third. However, the Cochrane review of antioxidant supplements in the prevention of gastric cancer cast grave doubts on their effectiveness.

Colorectal Cancer

The most important preventable risk factors associated with colorectal cancer include physical inactivity, a low consumption of fibre, and a high consumption of animal fat/red meat. More recent research indicates that both physical inactivity and obesity are risk factors for colorectal cancer.

Excess consumption of alcohol, probably in combination with a poor diet, and exposure to tobacco products early in life also appear to increase the risk of colon cancer.

Despite substantial research, the relationship between dietary factors and colon cancer remains inconclusive. Recent epidemiological evidence from long-term and randomized trials does not appear to support this association.

Renal and Bladder Stones

Urinary tract stone disease is usually caused by the super-saturation of the urine with stone-forming constituents such as calcium oxalate or phosphate. Kidney stones consist of four main chemical types. The vast majority of stones are composed of calcium oxalate (70-80%), calcium phosphate, or a combination of the two. Struvite stones are the second most common stones (15-20%) followed by uric acid stones. Cystine stones are relatively rare.

Research on the prevention of urinary stones suggests that lifestyle factors such as an appropriate diet - including a high intake of water and certain minerals such as magnesium - and a normalization of BMI are associated with a significant reduction in the risk of stone formation.

Chronic Kidney Disease

Chronic kidney disease is linked to diabetes mellitus, hypertension, ischemia, infection, obstruction, toxins, and autoimmune and infiltrative diseases. Primary prevention of chronic kidney disease is mainly about the prevention or effective management of the underlying and contributing condition.

Several trials have demonstrated the benefit of strict blood pressure control in slowing the progression of kidney disease.

Diabetes mellitus is the most common cause of chronic kidney disease. Studies have shown that the A1C level correlates with loss of renal function and that glycemic control reduces the progression of kidney disease.

Bladder Cancer

Bladder cancer is one of the most common cancers of the urinary tract and is the ninth most common cancer among men. Modifiable risk factors potentially associated with the risk of bladder cancer are physical activity, artificial sweeteners, alcohol consumption, and smoking.

The strong conclusion from several reviews of the evidence is that cigarette smoking increases the risk of bladder cancer. The role of other lifestyle factors, including an increased risk in men associated with alcohol consumption and a possible decreased risk associated with physical activity, is considerably less certain.

Cancer of the Cervix

Cervical cancer is the most prevalent and the most studied form of HPV-related cancer. Apart from persistent infection with high-risk HPV types - and the consequent connection to sexual activity - proposed risk factors for progression of lesions towards cancer have included viral load, smoking, parity, and long-term use of oral contraceptives.

One reviewer noted that “the understanding of cervical cancer as a preventable disease process hinges on the concept that it is fundamentally a sexually transmitted disease with a known causative agent: the human papillomavirus (HPV). There is essentially a one-to-one connection between cervical cancer cases and the detection of HPV DNA, suggesting that “the prevention of HPV infection would virtually eliminate cervical cancer.”

While HPV has been identified as a necessary cause of cervical cancer, the fact that a large percentage of women infected with high-risk HPV types do not progress to cancerous states demonstrates that the presence of the virus is not a sufficient cause of disease. Several potential co-agents have been noted above, including smoking and other infections. Genetic susceptibility in the host and genetic variants of the high-risk virus types have also been an area of intense interest in terms of explaining why only a subset of infected women develop cancer.

It appears that a vaccine for HPV is both highly efficacious and very well-tolerated; efficacy ranges from 90 to 100%.

Prostate Cancer

While many different risk factors have been studied, the etiology of prostate cancer remains relatively unknown. The main known risk factors are age, race, and family history. Other potential risk factors have been studied, including diet (especially the role of animal fat and vitamin supplements), tobacco consumption, exercise, occupational exposures to cadmium, zinc, and pesticides, hormone status, history of sexually transmitted disease, and vasectomy. The results of studies assessing these variables, however, remain inconclusive. The relative risk of prostate cancer is approximately two to three times higher in men with one first degree relative with prostate cancer than those who do not have a family history. How much of this additional risk is associated with environmental, dietary, or genetic factors has been difficult to assess.

A growing body of evidence suggests that some micronutrients, supplements, or dietary components may reduce the risk of prostate cancer. Of the vitamins, Vitamin E is the most

promising at this time. Selenium has been studied extensively, and in almost all studies has been found to have a protective effect against prostate cancer.

Coronary Artery Disease

Diseases of the circulatory system are the number one cause of death in North America, and, because of this, the associated risk factors have been extensively studied. The most intense behavioural focus has been on physical activity, not smoking, and a healthy diet, which have been shown as potentially effective in reducing CAD.

Beyond lifestyle factors, several more direct biological markers are associated with CAD, including cholesterol levels, hypertension, and obesity. This raises another category of primary prevention involving drugs aimed at lowering risks of coronary artery disease events through medical control of cholesterol or some other biological factor.

A very common drug used to protect against CAD is aspirin, though both mixed and adverse outcomes have been recorded. In particular, aspirin increases the risk of gastrointestinal bleeding. Although the U.S Preventive Services Task Force (USPSTF) does recommend aspirin for those considered at risk for CAD, cautions pertain to more indiscriminate usage.

Whatever the impact of risk factors, reduction targets, and the interventions aimed at them, the reality is that a large percentage of Canadians at risk of CAD are being inadequately addressed. From physical inactivity to dyslipidemia, there is a large gap between need, treatment, and adherence that must be addressed for further progress on heart disease.

Heart Failure

Heart failure can have a number of causes, including a lack of blood supply to heart muscle due to CAD, scar tissue from a heart attack, high blood pressure, diseases or infections of the heart muscle or valves, and congenital heart defects. Treatment is generally aimed at the cause of the failure, and therefore may vary from patient to patient. In extreme cases, a heart transplant becomes the appropriate intervention.

The risk factors directly implicated in HF include excessive alcohol consumption, smoking, low physical activity, low socio-economic status or education, coffee consumption, dietary sodium intake, and depression. Most of these are amenable to lifestyle/behavioural modification, and some to medical approaches. At this time, the use of either anticoagulation (e.g., warfarin) or antiplatelet agents (e.g., aspirin, clopidogrel) is not well supported in the literature.

Hypertension

Essential hypertension is responsible for approximately 95% of all cases. It has no single clear cause, but is the result of the interaction of multiple genetic and environmental variables. The genetic components of hypertension are not well understood. Secondary hypertension, on the other hand, is high blood pressure due to another condition, often of the kidneys, adrenal gland, or aorta. Perhaps the greatest risk factor for hypertension is age, although as is true for other forms of cardiovascular disease, hypertension is the result of various risk factors, and the combined effects of these build up over time.

A comparison of hypertension prevalence in Canada compared to the United States found a similar prevalence in each country (21.1% vs. 20.1%), but that only 13% of hypertensives in Canada had their blood pressure under control compared to 25% in the United States.

Many of the risk factors for high blood pressure are dietary. The association between sodium intake and incidence of hypertension, for example, is well known. Caffeine intake has also been shown to increase blood pressure, while soybeans and fish-oil have beneficial effects. Other factors that have been shown to lower blood pressure are weight reduction and physical activity. Finally, it is important to mention that risk factors for hypertension overlap significantly with those for related conditions, such as heart disease and diabetes.

Early Detection and Treatment of Hypertension as Primary Prevention

It is important to recognise that while treatment is not usually considered to be primary prevention, it is with respect to heart disease (CAD and heart failure), stroke, and renal disease; it is, for example, the single most important modifiable risk factor for stroke. Thus early detection (summarised later) and treatment here can be considered primary prevention of some of the most important causes of death in Canada and BC. The British Columbia Guidelines and Protocols Advisory Committee (GPAC) has noted that “a baseline blood pressure (BP) should be established in all adults and reassessed periodically, commensurate with age and the presence of other risk factors....Blood pressure monitoring should be rigorous in those patients who:

- Have known or newly detected elevated BP
- Have cardiovascular target organ damage (Target organ damage includes: cerebrovascular disease, coronary heart disease (CHD), left ventricular hypertrophy (LVH), chronic kidney disease (CKD), peripheral vascular disease, and hypertensive retinopathy).
- Have other risk factors
- Are receiving antihypertensive therapy”

Stroke

Stroke is the third leading cause of death in British Columbia, and it is the primary cause of acquired long-term disability in adults. Hypertension is the single most important modifiable risk factor for stroke; other risk factors for ischemic stroke are similar to those for the related conditions of hypertension and heart failure previously discussed, including obesity, smoking, physical inactivity, and alcohol consumption.

Research suggests that other risk factors for stroke may include fried fish consumption, depressive symptoms, hormone replacement therapy, elevated homocysteine levels, and high magnesium intake, though these are not as well-studied.

- **Hypertension:** Of the modifiable risk factors, hypertension carries the highest relative risk for stroke. According to one study approximately one-quarter of hemorrhagic strokes in hypertensive subjects would have been prevented if they had been receiving hypertension treatment.

- **Aspirin:** There is no evidence that aspirin reduces the risk of stroke in the general population of people at low risk, and it may actually increase risk of hemorrhagic stroke. However, the results of a large primary prevention trial support the use of aspirin for preventing a first stroke among women over age 65 who are at increased risk of cardiovascular events.

Asthma

Correlations have been found between asthma and a number of variables, including presence of pet and dust mite allergens and environmental cigarette smoke. The most promising results are found when a number of these variables can be controlled at the same time.

While support for reduction of environmental cigarette smoke is consistent, the effects of other factors are less clear. Results for dust mite and pet allergen avoidance and Omega-3 consumption are inconclusive, although multiple simultaneous interventions were more consistently positive. The hygiene hypothesis suggests that some degree of exposure to viruses and allergens may actually be beneficial. Other factors commonly studied include breastfeeding and viral infections. Exposure to chlorine has also been suggested as having a potential role.

Asthma is clearly a multi-faceted disease with numerous risk factors. The role of these risk factors has been hotly debated in the medical literature. The view of some is that “the environmental factors causally driving the temporal changes remain largely unknown. Therefore, there are few truly justified recommendations for the prevention of asthma.” Van Schayck and co-authors have wrestled with the fact that “preventive measures thus far studied with the aim of preventing (or delaying) the development of asthma have shown such disappointing results.” They suggest that “the most likely explanation is that the development of a multi-factorial disease, such as asthma, is extremely difficult, if not impossible, to prevent by eliminating only one risk factor.” To add further complexity to the issue of asthma prevention, what we sometimes think of as one disease - asthma - may in fact be a constellation of diseases.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is an umbrella term for a number of diseases which include chronic bronchitis and emphysema. Cigarette smoking is the principal underlying cause in 80% to 90% of COPD cases. The contribution of primary smoking is very clearly established, and exposure to second-hand smoke likely also plays an important, although not as well-defined, role.

About 15% of all cases of COPD are work-related. Specific settings and agents have been indicated or confirmed as linked to COPD. Coal miners, hard-rock miners, tunnel workers, concrete-manufacturing workers, and non-mining industrial workers have been shown to be at the highest occupational risk for developing COPD. Outdoor air pollution is associated with increased symptoms among those with COPD. Also, repeated childhood respiratory tract infections and childhood exposure to second-hand smoke lead to reduced levels of respiratory function, which may predispose a person to COPD. A genetic deficiency of alpha-1-antitrypsin, an anti-protease which protects the lung tissues from damage, is also associated with an increased risk of COPD.

As cigarette smoking is undoubtedly the main cause of COPD in the population, reduction or cessation of personal exposure to tobacco is of primary importance as the key preventive measure. For primary prevention to be effective, other sectors within a community must also be actively engaged along with the public health system, to address environmental air pollutants and occupational risk factors.

Breast Cancer

The concept that breast cancer may be preventable is supported by wide international variation in the incidence of breast cancer. Potential strategies to reduce the risk of breast cancer include an increase in exercise, weight loss, reduction of alcohol intake, reduction of fat intake, and chemoprevention and prophylactic surgery.

- **Physical activity:** There is evidence of a protective effect with a dose-response association for both pre- and post-menopausal breast cancer. At least a moderate level (> 4.5 MET per week) of physical activity is required.
- Obesity is associated with increased breast cancer risk, particularly in postmenopausal women.
- **Alcohol:** The consumption of alcohol (in excess of 30g per day) is also associated with an increased risk of breast cancer; one review notes that “if alcohol is consumed on a regular basis, a sufficient supply of fresh vegetables and fruit is essential”.
- **Fat intake:** The association between breast cancer and fat intake is more controversial although a low-fat diet may contribute to a reduction in breast cancer risk through helping to maintain a healthy weight.
- **Chemoprevention:** Selective Estrogen Receptor Modulators (SERMs) such as tamoxifen and raloxifene have been shown to be protective against breast cancer, reducing breast cancer risk by 48% and 66% respectively. However, there are also significant increased risks associated with the use of SERMs, including an increased relative risk of endometrial cancers and venous thromboembolic events. Thus the USPSTF recommends against the use of tamoxifen and raloxifene for the primary prevention of breast cancer in women with low or average risk for breast cancer. In women with a high risk for breast cancer (defined as a five-year risk of at least 1.6%) and a low risk for the side effects, the USPSTF recommends that clinicians discuss the possibility of chemoprevention with these women. Similar recommendations have been made by other organizations, including the Canadian Task force on Preventative Health Care.
- **Prophylactic surgery:** Prophylactic mastectomy is sometimes considered for women with a high risk of breast cancer. A recent Cochrane review concluded that “while published observational studies demonstrated that BPM was effective in reducing both the incidence, and death from, breast cancer, more rigorous prospective studies (ideally randomized trials) are needed. BPM should be considered only among those at very high risk of disease”.

Diabetes

Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM), is the most common form of diabetes, occurring in approximately 90% of patients with diabetes.

The most consistent risk factors associated with type 2 diabetes are obesity, sedentary behaviour, and smoking. The most common preventative effect reported was related to an increase in physical activity. Certain dietary changes, including replacing saturated and trans-fats with unsaturated fats, and refined grain products with those made from whole grain, were also consistently found to be beneficial. The British Columbia Guidelines and Protocols Advisory Committee (GPAC) has noted that

a large proportion of type 2 diabetes can be prevented using lifestyle modification and/or pharmacologic intervention. All individuals should be encouraged to pursue a program of lifestyle modification that includes regular physical activity (at least 150 minutes of moderate intensity aerobic exercise each week spread over 3 non-consecutive days and resistance exercise 3 times a week) and moderate weight loss (5-10% of initial body weight). Lifestyle modification is particularly important for persons considered at high risk for diabetes. Pharmacologic therapy with metformin or acarbose should also be considered for those at high risk.

Type 1 diabetes, also known as insulin-dependent diabetes mellitus (IDDM), is an autoimmune disease that occurs when the insulin-producing beta cells in the pancreas are damaged or destroyed, causing a reduction in, or the cessation of, insulin production. The etiology of type 1 diabetes is not well understood, but the disease is believed to be the result of an individual's genetic vulnerability together with a possible viral or other infectious trigger; the infection induces an autoimmune response that damages the already vulnerable insulin-producing beta cells in the pancreas.

A number of studies have looked at possible interventions for preventing type 1 diabetes. Over 125 therapies have been shown to prevent, or at least slow, the disease in animal models, but human trials have experienced only limited success to date.

Screening and Early Detection

The issue of early detection is substantially more important for some of the diseases reviewed in this report than for others.

Alzheimer's Disease

A significant amount of research effort, for example, has been expended in the area of the early detection of Alzheimer's disease (AD), particularly with respect to neuropsychologic testing, neuroimaging, and biomarkers.

Multiple longitudinal prospective studies have found that neuropsychological testing with a focus on memory and executive function can accurately predict conversion to AD. Such results have raised the question of whether or not large-scale community memory screening is feasible and practical.

Neuroimaging studies have identified hippocampal atrophy as a predictor of the decline from mild cognitive impairment to AD. The potential role of cerebrospinal fluid protein biomarkers in the early detection of AD has also been studied with some positive results.

Nevertheless the best possible approach for the early diagnosis of AD at this point in time is still a multidisciplinary approach comprising informant history, neurophysiological data, neuroimaging, and perhaps genetic testing.

Parkinson's Disease

Research in the early detection of Parkinson's disease (PD) indicates a promising potential role for functional neuroimaging. The role of biomarkers is being studied but, at this time, seems to be less useful in the early detection of PD. Overall no single method of PD detection is reliable on its own and neuroimaging must still be conducted within the scope of the classical PD clinical examination.

Multiple Sclerosis

The early diagnosis of Multiple Sclerosis (MS) is important for favourable outcomes and slowed disease progression. Several studies have shown that MRI imaging, especially of the spinal cord, can be useful in assisting with an early diagnosis of MS. Other studies discuss the success of using IgG in the cerebrospinal fluid as a reliable biomarker of MS disease. As with AD and PD, however, neither imaging nor biomarkers are currently sufficient for the early detection of MS.

Ocular Diseases

The early detection of ocular diseases is important as approximately 40% of blindness is either preventable or treatable if discovered early enough. The most important aspect of early detection in this area is regular and periodic vision examinations.

Rheumatoid Arthritis

Current research indicates that there is a “window of opportunity” in early rheumatoid arthritis (RA), within the first 3-6 months, when immune-modifying therapies have their greatest impact and potential to alter disease course. Despite the importance of early detection, there is no easy way to differentiate between RA and other forms of arthritis.

The following combination of methods for detecting RA is usually employed:

- History—symptoms lasting more than 6 weeks; morning stiffness
- Examination (from most to least accurate)—arthritis in 3 joints; arthritis of hand joints; compression pain in hand or foot joints; symmetrical arthritis; subcutaneous nodules.
- Laboratory—erythrocyte sedimentation rate and C-reactive protein do not distinguish well between RA and non-RA; measuring rheumatoid factor (RF) is a valuable tool in RA diagnosis; various antibody tests are showing promise, especially anti-cyclic citrullinated peptide (CCP); genetic typing enables discrimination between self-limiting and persistent disease in early RA, with an accuracy of 50-60%.
- Imaging—conventional X-rays; ultrasound; magnetic resonance imaging (MRI).

The use of RF has been problematic as it is not restricted to patients with RA. The use of anti-citrullinated protein/peptide antibodies (ACPA) has been recommended but even this system of early detection is flawed as ACPA has been found in other rheumatic autoimmune diseases besides RA.

Gastric Disease

Both endoscopic biopsies and non-invasive tests are used to establish whether a gastric disease process has begun, but neither of these approaches is considered cost-effective at a population level. Rather, it has been suggested that highly susceptible individuals infected with high virulence bacterial genotypes should be targeted for endoscopic monitoring to detect advanced precancerous lesions.

Colorectal Cancer

Screening for colorectal cancer is strongly recommended for men and women 50 years of age or older. An earlier onset of initial screening (e.g., age 40 rather than 50) and more frequent screening (e.g., colonoscopy every 5 years rather than every 10 years) is usually associated with screening individuals in higher risk categories. Most organizations do not emphasize one strategy over another but rather stress the importance of screening by any method for all eligible adults.

Cervical Cancer

Screening with the Pap test has had a significant impact on the morbidity and mortality associated with cervical cancer. The U.S. Preventive Services Task Force currently has the following five recommendations with respect to screening for cervical cancer:

- Strongly recommends screening for cervical cancer in women who have been sexually active and have a cervix
- Recommends against routinely screening women older than 65 for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer
- Recommends against routine Pap smear screening in women who have had a total hysterectomy for benign disease
- Concludes that the evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer
- Concludes that the evidence is insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer.

Despite the current excitement associated with vaccine development for HPV infection, routine screening will likely be required for the foreseeable future as even the best vaccines currently in development will likely only address 75% of oncogenic HPV subtypes.

Prostate Cancer

There has been considerable debate regarding the potential role of the prostate specific antigen (PSA) tests replacing the digital rectal exam for the early detection of prostate cancer. There is good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening with PSA was also found to be associated with potential harmful effects including false positives, anxiety and so on. The current research indicates that there remains no conclusive evidence that PSA screening is beneficial.

Breast Cancer

Mammography screening for breast cancer is controversial. The BC Cancer Agency encourages women from the ages of 50-69 (and otherwise healthy women aged 70-79) to have a mammogram every 24 months. The authors of the Cochrane Review in this area, however, conclude that “the currently available evidence does not show a survival benefit of mass screening for breast cancer (and the evidence is inconclusive for breast cancer mortality). Women, clinicians and policy makers should consider these findings carefully when they decide whether or not to attend or support screening programs.”

Type 2 Diabetes

According to the U.S. Preventive Services Task Force, there is good evidence that using available screening methods can detect type 2 diabetes before symptoms are evident. The benefits of screening are still in question, however, since it has not been shown that glycaemic control starting immediately after early detection is any more effective than interventions at the point of clinical diagnosis.

Heart Disease

Screening for heart diseases is an evolving issue. Many of the current methods are invasive and expensive (e.g., coronary angiogram). The ultimate goal is a completely non-invasive, relatively inexpensive method that still accurately determines the risk of heart disease. In the meantime, the recommendation is against formal screening in low-risk patients.

High Blood Pressure

Screening for high blood pressure, a key risk factor for heart disease, on the other hand, is generally recommended in all adults age 18 and over.

Stroke

Recognition and immediate response to the warning signs of stroke can significantly impact long-term prognosis. If patients with acute ischemic stroke are given intravenous thrombolytic treatment within 3 hours of the initial onset of symptoms, the patient will have improved clinical outcome at 3 months. Public awareness of stroke symptoms is imperative for early detection and treatment of stroke; only one-quarter of stroke patients receive treatment within the 3-hour critical time frame.

This summary, and the more detailed review that follows, makes it clear that in many cases the same risk factors that are addressed in the core programs in healthy living and some other core programs (e.g., injury prevention) will also contribute to prevention in a number of conditions reviewed here. In particular, not smoking, being physically active, having a healthy diet, and maintaining a healthy weight, all targets of ActNow BC and the BC Healthy Living Alliance, are important preventive factors for a number of conditions. The challenge will be to identify interventions beyond those already contemplated that will be a worthwhile addition to a core program in chronic disease prevention.

¹ www.phabc.org/pdfcore/core_functions.pdf.

² www.health.gov.bc.ca/prevent/pdf/cdp/cdpframework.pdf.

1.0 OVERVIEW/SETTING THE CONTEXT

In 2005, the British Columbia Ministry of Health released a policy framework to support the delivery of effective public health services. The *Framework for Core Functions in Public Health* identifies chronic disease prevention as one of the 21 core programs that a health authority provides in a renewed and comprehensive public health system.

The process for developing performance improvement plans for each core program involves completion of an evidence review used to inform the development of a model core program paper. These resources are then utilized by the health authority in their performance improvement planning processes.

This evidence review was developed to identify the current state of the evidence-based on the research literature and accepted standards that have proven to be effective, especially at the health authority level. In addition, the evidence review identifies best practices and benchmarks where this information is available.

1.1 An Introduction to This Paper

The current report is part of a series of evidence review papers under development since the release of *Public Health Renewal in British Columbia: An Overview of Core Functions in Public Health* in 2005. Ultimately, the evidence of effective strategies will be translated into practice through a process of implementation and performance expectations related to individual health authorities and underserved populations.

This report is not a complete review of all chronic disease, or of all approaches to chronic disease prevention. Rather, and consistent with the definition of the chronic disease prevention program in the document *A Framework for Core Functions in Public Health: Resource Document*, this review focuses on chronic non-communicable diseases that are not addressed elsewhere, and on disease-specific interventions as much as possible. Thus the following are not included, or if included, are not extensively covered:

- Chronic communicable diseases (e.g., HIV, hepatitis C, tuberculosis) that are addressed in the Communicable Disease core program.
- The common behavioural risk factors that account for roughly one-quarter of the burden of disease in BC, and were addressed earlier in the Healthy Living core program.
- Conditions that are largely dealt with through the Healthy Living core program evidence review (lung cancer, many aspects of cardiovascular disease, COPD, diabetes) or through the Harm Reduction core program (e.g., alcoholic cirrhosis) are either not included or only briefly addressed.
- Broad population health promotion interventions that address the determinants of health and seek to change overall living and working conditions. Such interventions can be expected to affect most if not all of the conditions addressed here.

The chronic conditions addressed here are those where there is a significant burden of disease in BC; neurological, sensory, musculoskeletal, digestive and genitourinary disorders, as well as diabetes, heart disease, hypertension, stroke, and asthma. The focus of the current report is a review of the available evidence on the effectiveness of initiatives in primary prevention and early detection with respect to these conditions.

1.2 The Burden of Chronic Disease in British Columbia

Chronic non-communicable diseases are of key importance as they are a major contributor to the burden of ill health and premature death, and are associated with significant economic costs (both direct health care costs and lost productivity).

The prevalence of key chronic diseases in British Columbia (percentage of total population in 2003), was:¹

- Hypertension – 14.8%
- Asthma – 7.7%
- Diabetes – 5.5%
- Osteoarthritis – 6.4%
- COPD (Chronic Obstructive Pulmonary Disease) – 1.8%
- Diabetes and Hypertension – 3.1%
- Rheumatoid Arthritis – 1.2%
- CHF (Congestive Heart Failure) – 1.8%

The burden of these diseases, expressed as disability-adjusted life years (DALYs)² in 2005, is shown in Figure 1.³ In addition to cancer, cardiovascular disease, chronic respiratory disease, and diabetes, the importance of such chronic conditions as mental disorders, neurological disorders, and dementia is readily apparent. Other major disease categories include musculoskeletal and genitourinary and digestive diseases.

Core Public Health Functions for BC: Evidence Review
Chronic Disease

Figure 1: Disability Adjusted Life Years (DALYs), Proportion of Total by Major Disease Category, BC, 2005

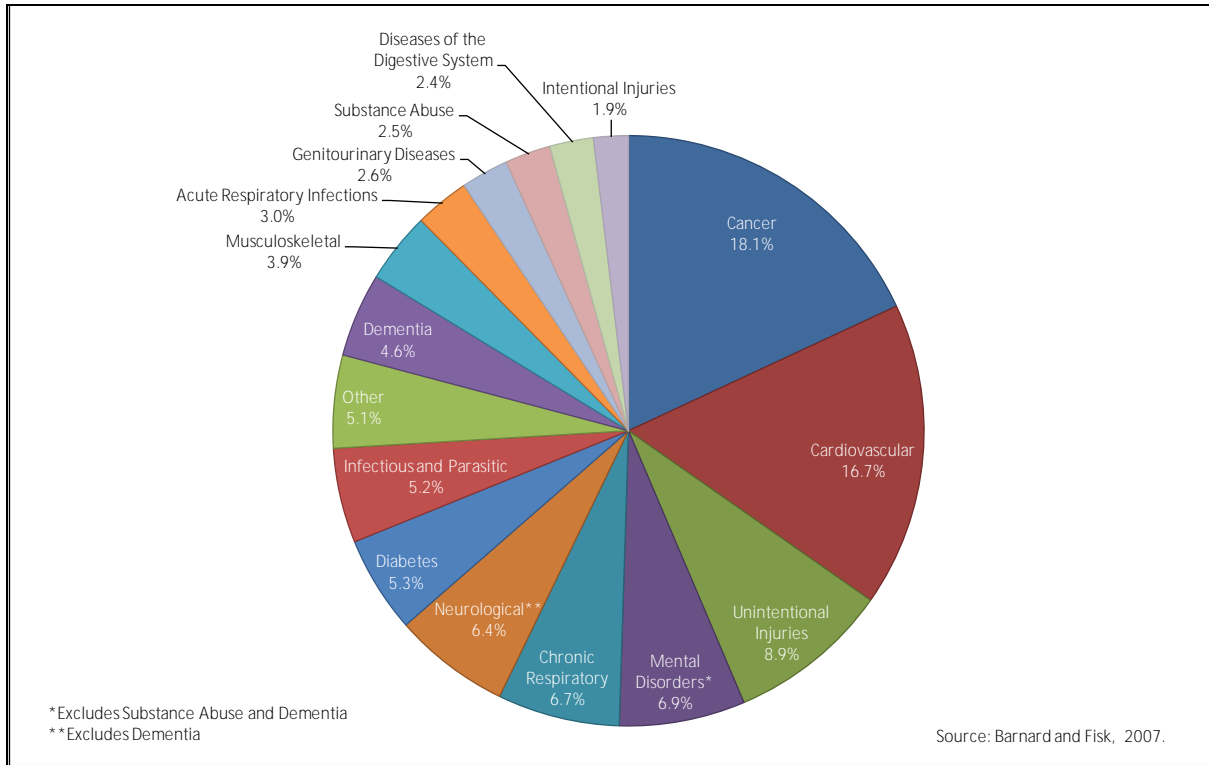


Figure 2 shows the prevalence of these conditions in 2007/2008.

Core Public Health Functions for BC: Evidence Review
Chronic Disease

Figure 2: Prevalence of Selected Chronic Conditions, BC, 2007/2008

Condition	Estimated Number of Cases (rounded to nearest hundred)			% <65 years
	<65 years	65+ years	Total	
Chronic Heart Disease				
Ischemic heart disease	36,700	95,100	131,800	27.8%
Congestive heart failure	11,900	55,700	67,600	17.6%
Angina	29,600	81,700	111,300	26.6%
Acute myocardial infarction	15,800	34,900	50,700	31.2%
Stroke	12,700	36,700	49,400	25.7%
Chronic Lung Disease				
Chronic obstructive pulmonary disease	39,400	56,700	96,100	41.0%
Cystic fibrosis	400	<10	>400	>97.0%
Asthma	384,200	7,500	391,700	98.1%
Chronic Digestive Disorders				
Peptic ulcers	54,500	35,200	89,700	60.1%
Inflammatory Bowel Disease				
Crohn's disease	18,200	4,400	22,600	80.5%
Ulcerative colitis	18,700	6,000	24,700	75.7%
Chronic Liver Disease				
Cirrhosis and chronic liver disease	20,000	6,100	26,100	76.6%
Hepatitis B and C	4,300	400	5,200	92.3%
Kidney Disease				
Chronic kidney disease	18,100	27,800	45,900	39.4%
Renal and bladder stones	47,800	20,000	67,800	70.5%
Musculoskeletal Disorders				
Rheumatoid arthritis	20,900	21,400	42,300	49.4%
Osteoarthritis	147,100	187,200	334,300	44.0%
Cancer				
Primary brain	2,400	1,200	3,600	66.7%
Primary bone	900	500	1,400	64.3%
Gastric	900	1,500	2,400	37.5%
Colorectal	9,000	19,400	28,400	31.7%
Bladder	3,400	9,900	13,300	25.6%
Renal	2,600	3,700	6,300	41.3%
Prostate	6,700	29,400	36,100	18.6%
Cervical	3,200	800	4,000	80.0%
Breast	20,300	20,500	40,800	49.8%
Pancreatic	700	1,300	2,000	35.0%
Lung	2,300	9,600	11,900	19.3%
Neurological Disorders				
Alzheimer's and other dementia	3,000	19,400	22,400	13.4%
Parkinson's disease	2,200	9,400	11,600	19.0%
Neuromuscular Disorders				
Multiple sclerosis	9,700	1,900	11,600	83.6%
Myasthenia gravis	1,700	900	2,600	65.4%
Nuscular dystrophy	3,000	1,100	4,100	73.2%
Diabetes	135,700	139,500	275,200	49.3%

Note: The numbers reported in this table are prevalent cases. An individual may have more than one condition and could thus be counted multiple times.

Source: Recent data extracted from BC Ministry of Health files.

Of particular interest is the cluster of chronic diseases which includes cardiovascular disease, some of the principal forms of cancer, chronic respiratory disease, and diabetes. This cluster has common risk factors (i.e., smoking, physical inactivity, and poor eating habits), and together, these diseases account for almost half of the burden of disease and almost a quarter of the economic burden of illness in British Columbia.⁴ Additional risk factors contributing to the burden of chronic disease include: social, economic, and cultural conditions that shape and constrain behaviours; stressful psychosocial conditions in homes, schools, workplaces and communities; environmental conditions; some infections; psychological status; biological risk factors; and genetic predisposition.⁵

Chronic diseases are not distributed evenly across the population but are linked to a number of determinants of health. As a result it is important to consider inequalities and vulnerabilities among population subgroups. Factors that contribute to these differences include inherent biological determinants such as sex, genetics, variations in physiological and biochemical functions as well as differences in social, economic, and environmental conditions that individuals and groups experience. For example, the burden of chronic disease among BC's Aboriginal people is higher than the general population; diabetes is more than 3 times as prevalent, heart disease and arthritis are higher, and life expectancy among First Nations people is 7.5 years below that of other British Columbians.⁶

1.3 The Context and Focus of the Current Report

In October of 2003, the Population Health and Wellness branch of the BC Ministry of Health Planning released *A Framework for a Provincial Chronic Disease Prevention Initiative*.⁷ This document provides an overview of the plan to address the 'massive burden of chronic disease in BC' by improving the management of the existing burden of chronic disease and preventing the development of chronic disease in the future. The report includes a comprehensive framework identifying the major factors contributing to chronic diseases, the principal mechanisms for intervention, and illustrating the complexity of this field of work.

As the Framework indicates, the factors that contribute to chronic diseases include 'upstream' social, cultural, environmental, and economic conditions, living and working conditions, and behavioural, psychological, and biological factors. Moreover, these all occur across the life course, such that early intervention – as early as during pregnancy – may have an important role to play in chronic disease prevention.

The Framework also illustrates the range of interventions: from public policy interventions to address the determinants of health, protect people, and change social norms, through the creation of supportive environments and social support, to educational interventions and clinical prevention services. There is no one 'magic bullet' to prevent chronic diseases; rather, experience with tobacco control and similar interventions has shown that it takes a multi-faceted range of interventions across whole populations and over long periods of time to bring about significant change.⁸

There are at least three broad initiatives in BC that are addressing chronic disease prevention and that provide a context that frames the focus of this report and the Chronic Disease Prevention core program:

- In response to the challenge of chronic disease prevention, BC established ActNow BC in 2005 as a means of addressing primarily the behavioural factors noted earlier that contribute to many of these chronic diseases – smoking, unhealthy eating, physical inactivity, and alcohol use in pregnancy. The province also supported the creation of the BC Healthy Living Alliance (BCHLA) that brought together a number of key NGOs working in these areas. Between them, ActNow BC and the BCHLA have developed a number of programs that address these behaviours and some of the broad determinants that underpin them.
- A Clinical Prevention Policy Review has been underway since 2007, and the draft report is recommending the adoption of a Lifetime Prevention Schedule that includes several effective and cost-effective clinical preventive services – offered primarily by family physicians and other primary care providers – that address selected chronic diseases. These include screening for breast, cervical, and colon cancer, and several cardiovascular disease preventive services; hypertension detection and management; tobacco cessation; hyperlipidemia detection and management; and ASA prophylaxis for high-risk individuals.
- The model core program paper for Healthy Living was completed in 2007 and health authorities have been developing performance improvement plans for Healthy Living. The focus of the program is on the same risk factors as are addressed by ActNow BC and the BCHLA.

It is not the intent or purpose of the Chronic Disease Prevention core program to duplicate the work of these other initiatives, and thus this evidence review has a strong (but not exclusive) focus on the ‘other’ chronic diseases and on interventions beyond behavioural change strategies, although as will become apparent, and as was expected, the ‘healthy living’ behaviours are also relevant to many other chronic diseases beyond cancer, cardiovascular disease, chronic respiratory disease, and diabetes. While the evidence with respect to clinical preventive services is presented, the extent to which this is a role for health authorities as part of their public health function is an issue that is left to the model program working group and each health authority to resolve.

2.0 METHODOLOGY

2.1 Evaluating Evidence

Not all evidence is created equal.

In recognition of this fact, a number of groups have developed methods of grading the strength of available research evidence. One such group is The Canadian Task Force on the Periodic Health Examination (CTFPHE). In 1976, this group adopted a plan to use explicit analytic criteria to guide its evaluation of effectiveness research. The following table provides the criteria for assigning various grades (from I to III) to published literature.

I	Evidence from at least 1 properly randomized controlled trial (RCT).
II-1	Evidence from well-designed controlled trials without randomization.
II-2	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
II-3	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

This information on the strength of the available evidence, together with other factors such as the generalizability of the results and implications in terms of safety, acceptability and cost, is used to provide a grading of the interventions. Interventions are given a grade from A to E (see following table).

A	Good evidence to support the recommendation that the intervention be specifically considered.
B	Fair evidence to support the recommendation that the intervention be specifically considered.
C	Poor evidence regarding inclusion or exclusion of the intervention, but recommendations may be made on other grounds.
D	Fair evidence to support the recommendation that the intervention be specifically excluded from consideration.
E	Good evidence to support the recommendation that the intervention be specifically excluded from consideration.

As a general rule, the strongest recommendations (A and E recommendations) are reserved for interventions whose value is supported or negated by high quality (grade I – randomized controlled trials) evidence. Grade II evidence is of fair quality and generally is associated with B and D recommendations.

In evaluating the available evidence for this report, we have followed the general approach of the (CTFPHE).⁹

2.2 Cost-effectiveness¹⁰

With respect to the economic benefits of prevention, the following summary is based on a draft and as yet (September 2009) unpublished report by the *Public Health Agency of Canada* (PHAC) reviewing the current research and analysis on the economics of prevention.

Consistent with other assessments of the economics of preventive health interventions, their survey of the recent evidence found that some interventions are cost-saving for the health system, and many others are cost-effective. Adopting a broader societal perspective increases the cost-effectiveness of many prevention initiatives, and increases the likelihood for overall cost-savings.

However, as Russell has pointed out more than two decades ago, one cannot make generalizations about preventive interventions as though they are all alike, nor can one take for granted the cost-effectiveness or cost-saving potential of even the most well-established and highly-regarded program.¹¹ The context-sensitive nature of public health action means that the economic benefits of the range of preventive interventions must first be assessed individually, across diverse settings and longer timeframes, before more universal conclusions can be attempted.

Moreover, the inconsistent utilization of economic evaluations across the spectrum of preventive health interventions, as well as the variable quality of the available evidence, have given rise to a number of critical knowledge gaps. Addressing these gaps should be made a research priority if economic evaluation evidence is to be consistently included as one type of decision-informing input.

Of particular concern from a Canadian perspective is the relative under-representation of economic evaluations of Canadian interventions in the total literature. Although sufficient commonalities between Canada and other key jurisdictions (i.e., the US, the UK, Australia, and New Zealand) exist to justify a cautious degree of knowledge transfer across national settings, a greater push for Canadian-specific evaluations is needed to confirm the relevance of, and/or adapt where applicable, the international data for local audiences.¹²

At the same time, the relative merits and drawbacks of systematically utilizing economic evaluations for policy-making purposes should in itself be cautiously assessed, given the limited capacity of existing analytical methodologies to capture the full scope of costs and benefits for many preventive health interventions, particularly those that target more complex “upstream” health determinants. As Goldsmith and colleagues conclude in their review of the economic evaluation of prevention literature,¹³

requiring economic evidence as a mandatory input to decision making would, in the short term, delay the implementation of preventive programs with demonstrated large population health effects that had not yet been subjected to

economic evaluation. Perhaps more importantly, in the long term such a requirement would discriminate against health promotion, health protection and healthy public policy interventions whose costs and consequences are often difficult to measure credibly because they are spread across multiple health and social domains.

Lastly, it is emphasized that while economic evaluations can offer a systematic framework for assessing the relative cost-effectiveness of different health interventions, both preventive and curative, delineating the economic impacts of these options will not obviate the need for policy-makers to make difficult choices about the allocation of finite and perpetually inadequate health sector funds.¹⁴ Where a particular intervention is known to be cost-saving, the economic argument for investment is readily apparent. Unfortunately, the instances in which this is the case are frustratingly few. More often, some interventions are relatively cost-effective in most but not all contexts, while others may be so only when delivered to a specific target population or in a particular setting. Others still may never offer favourable economic benefits, yet nevertheless warrant support on non-economic grounds. Ultimately, public investments to prevent illness and injury and improve individual and population health will be driven by societal values. Economic evaluation can inform, but cannot in itself deliver, the final determination of these priorities.

All that being said, there is some reasonable evidence on cost-effectiveness for some chronic disease prevention interventions, as summarised below from the draft PHAC report. First, some cost-saving interventions are presented—note that these are cost-saving with respect to the healthcare system (in terms of cost per QALY gained) and do not include costs incurred outside the healthcare system. Then some examples of cost-effective—but not cost-saving—interventions are presented. Note that in the health economics literature, a cost-effectiveness of up to about \$50,000 per QALY gained is usually considered to be a worthwhile investment, whether therapeutic or preventive.

- Repeated *clinical smoking-cessation counselling* is considered among the most clinically important and highest value-for-money preventive services available in medical practice and was ranked by a recent Canadian analysis as the highest priority among effective clinical preventive services based on its associated clinically preventable burden¹⁵. A US-based modelling study concluded that delivery of this intervention nationwide could save 2.5 million QALYs annually at a cost-savings of US\$500 per smoker who receives the service, largely due to the financial savings accrued from the prevention of smoking-attributable diseases.¹⁶
- The same US study (Maciosek et al., 2006), and the Canadian study based on the same model (H. Krueger and Associates Inc., 2008) also found that *ASA prophylaxis* for those at moderate to high risk of cardiovascular disease was cost saving, as was alcohol screening and brief counselling.
- The Department of Human Services in Victoria, Australia, reviewed the cost-effectiveness of 13 *obesity interventions for children and adolescents*, and identified six as “extremely good” value-for-money (i.e., cost-saving). These included school-based programs to reduce television viewing and soda consumption, family-based programs targeting obese children, and partial bans on advertisements of unhealthy foods during

children's television programming. This last intervention was determined to have a 100% chance of being cost-saving, by as much as AU\$300 million.¹⁷

Overall, however, cost-saving interventions constitute only a small minority of the total, indicating that preventive health interventions are generally not cost-saving for the payer. Examples of cost-effective preventive interventions include:

- **Tobacco Control:** The restriction of tobacco sales and prohibition of smoking in designated areas are two of the most well-established regulatory public health initiatives in Canada, and have helped to establish the country's reputation as a global leader in tobacco control. Overall, the cost-effectiveness of these types of preventive health interventions has also been encouraging.

For example, in their review of the cost-effectiveness of various youth-focused smoking prevention measures, Rasch and Greiner described a simulation study that modelled the cost-effectiveness of enhanced enforcement of the prohibition of tobacco sales among underage US adolescents. Even the most pessimistic scenario, involving the highest estimates of additional enforcement and related costs and the lowest reasonable expectations of impact on teenage smoking rates, produced a cost-effectiveness ratio of US\$3,100 per life-year saved. Mid-range assumptions resulted in cost-effectiveness ratios ranging from US\$260 to \$1,100 per life year saved.¹⁸

Smoke-free workplaces are another common tobacco control intervention. In a systematic review of 26 studies in Canada, the US, Australia, and Germany, Fichtenberg and Glantz found that complete workplace smoking bans resulted in a 3.8% reduction in prevalence of smoking and an absolute reduction of 3.1 cigarettes smoked per day per continuing smoker. On a per employee basis (smokers and non-smokers combined), these findings translated to a 29% relative reduction in total employee cigarette use, an effect roughly equivalent to a 73% increase in cigarette pricing.¹⁹

Other research suggests that even small reductions in smoking attributable to workplace smoking bans are economically efficient. For instance, smoke-free workplaces appear to be cost-effective relative even to free nicotine replacement therapy (NRT) programs, which themselves are known to be very cost-effective. According to one US study, a free state-wide NRT program was estimated to generate a cost-effectiveness ratio of \$4,440/QALY, nearly 9 times higher than the \$506/QALY ratio associated with the implementation of a state-wide smoke-free workplace policy.²⁰

- **Colorectal Cancer Screening:** CRC screening with faecal occult blood test (FOBT) has been shown to be both effective in reducing mortality in large randomised trials and cost-effective based on economic analyses that compare intervention cost against commonly used benchmark standards (e.g., \$50,000/QALY). In one Canadian study, the potential impact of population-based screening with FOBT followed by colonoscopy on CRC mortality was estimated through micro-simulation modelling.²¹ Biennial screening of 67% of individuals aged 50 to 74 in the year 2000 resulted in a 15% rise in demand for colonoscopy in the first year, a 17% reduction in 10-year CRC mortality, and an average 15-day increase in life expectancy. The estimated cost of screening was \$112 million per

year or \$11,907 per life-year gained. Similarly, another modelling study utilizing a hypothetical birth cohort of 40,000 adults 50 and older in British Columbia found CRC screening to have a cost-effectiveness ratio of \$11,100 per QALY gained.²²

The cost-effectiveness of screening to prevent CRC is further supported by international data. For example, CRC screening with FOBt was estimated by a recent UK study to cost £2,600-£6,000 (approximately CA\$4,500-\$10,500) per QALY gained.²³

- **Diabetes Prevention:** Clinical trials have shown that diabetes can be prevented through clinically-based lifestyle modification programs, with some studies reporting a reduced cumulative incidence of as much as 58% compared to placebo.²⁴ Moreover, these health gains appear to be achievable at costs generally considered acceptable to society. One review study found that, compared to placebo, a lifestyle intervention involving a healthy diet and moderate physical activity generated a cost per QALY gained of US\$1,100 (2000 dollars) when only direct intervention costs were considered. When a societal perspective was adopted, which included costs of participant time, exercise classes, exercise equipment, food and food preparation items, and transportation, the cost per QALY increased to \$8,800. These cost-effectiveness ratios were found to be substantially lower than those of a popular pharmaceutical intervention (vs. placebo).²⁵

2.3 Search Strategy

In searching for evidence of primary prevention, early detection, and secondary prevention, the general approach was to enter the disease of interest together with the terms “primary prevention”, “early detection” and “secondary prevention” in a Medline search using Pub Med.²⁶ Early research focused on determining the availability of review articles published in the last three years. For Alzheimer’s disease, for example, this approach yielded a number of broad review articles published in 2005^{27,28} as well as more specific review articles on such topics as the potentially protective role of an active and socially integrated lifestyle²⁹, the role of dietary factors in AD³⁰ and the role of neuroimaging^{31,32} and biomarkers³³ in early detection.^{34,35}

When review articles were available, the research focused on the references cited in the review articles, supplemented with an additional search using the ‘related articles’ function in Pub Med, particularly with a view to accessing the most recent published articles. When recent review articles were not available, individual research articles were accessed through the initial search and then supplemented with the “related articles” function in Pub Med.

When large amounts of clinical research evidence are available, we also used systematic reviews produced by other clinical evidence groups. In particular, the following sources were accessed:

- British Medical Journal Publishing Group
- Cochrane Database of Systematic Reviews
- U.S. Preventive Services Task Force

Additional information about these information sources is provided in Appendix 1.

3.0 NEUROLOGICAL DISORDERS

The neurological disorders covered in this evidence review exclude stroke, infectious diseases such as meningitis and encephalitis and mental disorders. These have been or will be covered in other evidence reviews.

3.1 Alzheimer's Disease

3.1.1 The Disease

Alzheimer's Disease (AD) is a chronic degenerative neurological illness.³⁶ As a progressive degenerative disease, AD attacks the brain and, through brain cell death, gradually causes a decline in function affecting all aspects of a person's life.

The definitive diagnosis of AD is difficult as there is usually a preclinical period of 20-30 years. A diagnosis usually begins with the exclusion of other causes of dementia while a definitive diagnosis must wait for a biopsy of brain tissue after death.³⁷ Diagnosis usually includes medical and family histories, a mental exam, a physical exam, blood work and diagnostic imaging, all of which help to form a reasonable decision regarding the AD diagnosis.^{38,39}

Behaviourally, AD manifests itself through cognitive deterioration, beginning with small issues such as the regular loss of objects and forgetting pieces of information, to more severe issues such as the loss of memory, the ability to speak and the display of inappropriate behaviour.

The Alzheimer's Society of Canada⁴⁰ notes that the following symptoms are associated with the disease.

- Mental abilities
 - A person's ability to understand, think, remember and communicate will be affected.
 - The ability to make decisions will be reduced.
 - Simple tasks that have been performed for years will become more difficult or be forgotten.
 - Confusion and memory loss, initially for recent events and eventually for long-term events, will occur.
 - The ability to find the right words and follow a conversation will be affected.
- Emotions and moods
 - A person may appear uninterested and stop hobbies or other activities previously enjoyed.
 - She may quickly lose interest in an activity.
 - The ability to control mood and emotion may be lost.

- Some individuals have less expression and are more withdrawn.
- Behaviour – Changes in the brain will bring about changes in the way the person reacts to her environment. These actions may seem out of character for the person. Some common reactions include:
 - repeating the same action or words
 - hiding possessions
 - physical outbursts
 - restlessness
 - inappropriate sexual behaviour
- Physical abilities – The disease can affect a person's physical co-ordination. As the disease progresses, there will be a gradual physical decline. These changes will impact on the person's ability to independently perform day-to-day tasks, such as eating, bathing and getting dressed.

At present, it is not possible to restore lost function caused by brain cell death, although treatments and strategies are available to assist in coping with the disease for both affected individuals and their caregivers, such as limited medications which can be used to treat symptoms of the disease.^{41,42}

3.1.2 Epidemiology

AD is the most common form of dementia and a common disorder in developed nations. The Alzheimer's Society of British Columbia reports that approximately 279,000 Canadians had AD in 2005, with almost 41,000 living in the province of BC. (see Figure 3).⁴³

Figure 3: Estimated Prevalence of Alzheimer's Disease in Canada, 2005

Province	Male	Female	Total
British Columbia	11,730	29,150	40,880
Ontario	28,150	76,090	104,240
Quebec	15,730	49,660	65,390
Alberta	6,250	16,300	22,550
Saskatchewan	3,350	9,000	12,350
Manitoba	3,310	8,860	12,170
Nova Scotia	2,270	6,870	9,140
New Brunswick	1,870	5,240	7,110
Newfoundland	1,140	2,870	4,010
Prince Edward Island	300	890	1,190
Total	74,100	204,930	279,030

The incidence of AD increases with age, as indicated in Figure 4.⁴⁴

Figure 4: Incidence of Alzheimer’s Disease in Canada, by Age and Gender

Age Group	Female	Male
65-69	1.4	–
70-74	2.9	3.7
75-79	4.8	7.8
80-84	19.0	13.5
85+	49.0	44.2
All Ages (65+)	7.4	5.9

Note: Rate per 1,000 person years.

In addition to age, a further major risk factor is a family history of dementia. Two subtypes of AD exist, Sporadic Alzheimer’s Disease and Familial Autosomal Dominant Alzheimer Disease. Sporadic AD seemingly strikes randomly, and has no known pattern of origin. Familial Autosomal Dominant (FAD) AD is inherited and follows a traditional and common inheritance pattern. The Alzheimer Society of Canada reports that Sporadic AD is the more common form of AD and accounts for 90-95% of AD cases.⁴⁵

Other primary risk factors include genetic markers such as *APOE* ε4, trisomy 21, mutations in presenilin 1 and 2, female gender after age 80 years of age and cardiovascular risk factors such as hypertension, diabetes, obesity, and hypercholesterolemia.⁴⁶

Economic burden of AD is also an important issue. Using data from the Canadian Study of Health and Aging, Hux et al. found that the societal costs of care increased from \$9,451 per year for individuals with mild AD to \$36,794 for individuals with severe AD (see Figure 5).⁴⁷

Figure 5: Mean Annual Cost of Alzheimer’s Disease, per Patient by Disease Severity

Component of Care	Disease Severity			
	Mild	Mild to Moderate	Moderate	Severe
Medications, Physician Fees	\$226	\$230	\$260	\$310
Community Services	\$1,973	\$2,315	\$1,227	\$568
Unpaid Net Supervision Time	\$1,597	\$1,603	\$2,525	\$1,452
Unpaid Direct Care Time	\$5,655	\$7,047	\$5,379	\$3,506
Nursing Home Stay	\$0	\$4,859	\$16,332	\$30,958
Total	\$9,451	\$16,054	\$25,723	\$36,794

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3.1.3 Evaluating Available Evidence

Primary Prevention

A comprehensive 2001 review of the literature on the primary prevention of Alzheimer’s disease summarized risk factors associated with AD into three categories, those that increase risk, those that decrease risk, and those for which the research is uncertain.⁴⁸

Increases Risk	Decreases Risk	Uncertain
<ul style="list-style-type: none"> • Genetic mutations • Genetic susceptibility (apolipoprotein E e4) • Diabetes mellitus • Positive family history • Substandard education • Older age • Female sex • Significant head injury • Cerebrovascular disease 	<ul style="list-style-type: none"> • Non-steroidal anti-inflammatory drug (NSAID) use • Estrogen use 	<ul style="list-style-type: none"> • Alcohol • Cigarette smoking • Toxins – aluminums, glue, fertilizers, pesticides

More recent research also indicates that an active and socially integrated lifestyle in late life might protect against dementia.⁴⁹

In the following review of the literature (Table 1), we will focus on the most current research in the area of an integrated lifestyle, education, NSAID use, and hormone replacement therapy.

Table 1: Research on the Association Between an Integrated Lifestyle and Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Fratiglioni et al (2004) ⁵⁰	Review (115 references)		The effect of social network, physical leisure and non-physical activity on cognition and dementia	For all three lifestyle components (social, mental and physical) a beneficial effect on cognition and a protective effect against dementia are suggested	“Taking into account the accumulated evidence and the biological plausibility of these hypotheses, we conclude that an active and socially integrated lifestyle in late life protects against dementia and AD.”
Gustafson et al (2003) ⁵¹	Longitudinal prospective study (18 year follow-up)	392	BMI and the risk of dementia	“For every 1.0 increase in BMI at age 70 years, AD risk increased by 36%. These associations were not found in men”	
Rovio et al (2005) ⁵²	Longitudinal prospective study (mean follow-up of 21 years)	1,449 of which 117 had dementia and 64 had AD	Leisure-time physical activity in mid-life and subsequent risk of dementia and AD	Leisure-time physical activity at least twice per week was associated with a reduced risk of dementia (OR of 0.48; CI of 0.25 – 0.91) and AD (OR of 0.38; CI of 0.17 – 0.85)	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Kivipelto et al (2005) ⁵³	Longitudinal prospective study (mean follow-up of 21 years)	1,449 of which 117 had dementia and 64 had AD	Obesity (BMI > 30) at mid-life and subsequent risk of dementia and AD	Obesity at mid-life was associated with an increased risk of dementia and AD (OR of 2.1; CI of 1.0 – 4.6) after adjusting for socio-demographic variables, blood pressure, cholesterol levels and smoking.	
Podewils et al (2005) ⁵⁴	Longitudinal prospective study (mean 5.4 year follow-up)	3,375	Physical energy expenditure and number of physical activities over a two week period	Relative risk of dementia, highest vs. lowest quartile of energy expenditure of 0.85 (CI of 0.61 – 1.19), ≥ 4 activities vs. 0 or 1, 0.51 (CI of 0.33 – 0.79)	“Our results also suggest that participation in a number of different activities may be as or more important than frequency, intensity, and duration of physical activity with respect to dementia risk”
Luchsinger and Mayeux (2004) ⁵⁵	Review (129 references)		The relationship between dietary factors and AD	“Some studies suggest that high intake of vitamins C, E, B6, and B12, and folate, unsaturated fatty acids, and fish are related to low risk of AD, but reports are inconsistent. Modest to moderate alcohol intake, particularly wine, may be related to a low risk of AD”	“Available data do not permit definitive conclusions regarding diet and AD or specific recommendations on diet modification for the prevention of AD”

In their review of the available literature, Fratiglioni et al⁵⁶ note that “it is a common belief that maintenance of an active life helps old people to preserve their physical and mental health.” The conclusion at the end of their review does indeed suggest that this is the case. “Taking into account the accumulated evidence and the biological plausibility of these hypotheses, we conclude that an active and socially integrated lifestyle in late life protects against dementia and AD.”

The hypotheses they refer to are the cognitive-reserve hypothesis, the vascular hypothesis and the stress hypothesis. In essence, environmentally enriched conditions have the potential to prevent or reduce cognitive deficits. Furthermore, social, mental and physical stimulation has a positive effect on cardiovascular disease and stroke. Vascular disorders and vascular risk factors are involved in the pathogenesis and progression of AD. Finally, having active individuals with more social contacts leads to more positive emotional states such as self-esteem and lower stress levels. Stress is associated with increased risk of AD.

Several studies have also suggested that low levels of education are a risk factor for AD. This research is summarized in Table 2.

Table 2: Research on the Association Between Level of Education and Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Cobb et al (1995) ⁵⁷	Longitudinal prospective study (17 year follow-up)	3,330 including 258 cases of incident dementia including 149 with AD	Level of education, grade school or less vs. at least a high school diploma	The relative risk for those with a lower education was as follows: <i>Dementia</i> – RR 1.31 (95% CI 0.90 – 1.90) <i>AD</i> – RR 1.04 (95% CI 0.90 – 1.90) <i>Non-AD dementia</i> – RR 1.75 (95% CI 1.03 – 2.98)	
Letenneur et al (1999) ⁵⁸	Longitudinal prospective study (5 year follow-up)	2,881	Sex and educational attainment	“The risks of dementia and Alzheimer’s disease were associated with a lower educational attainment (Hazard ratio 1.8, p<0.001). The increased risk of Alzheimer’s disease in women was not changed after adjustment for education”	
Geerlings et al (1999) ⁵⁹	Longitudinal prospective study (average 3.2 year follow-up)	3,378, 77 with AD	Low (primary education or lower) vs. high (partial secondary to completed university) education	Low level of education was associated with incident AD – OR adjusted for age and sex of 2.09 (95% CI: 1.29-3.38)	
Launer et al (1999) ⁶⁰	Pooled analysis of four population-based prospective studies	528 incident dementia patients with 28,768 person-years of follow-up	Risk of AD associated with a family history of dementia, female gender, low levels of education, smoking and head trauma	Female gender, current smoking and low levels of education increased the risk of AD significantly. The association of low levels of education (< 8 years) was confined to women. RR of 4.55 (95% CI 1.64-12.57). RR for men of 1.0.	
Qiu et al (2001) ⁶¹	Longitudinal prospective study (average 3.2 year follow-up)	1,296, 147 with dementia and 109 with AD	Low (< 8 years) vs. high (≥ 8 years) level of education	Subjects with a low level of education had a relative risk of 2.6 (95%CI of 1.5 – 4.4) for AD and 1.7 (95%CI of 1.1 – 2.6) for dementia	“These findings can be accounted for by the ‘cognitive reserve’ hypothesis. Alternatively, the observed association between educational level and incidence of AD or dementia may partly reflect detection bias, by which subjects with a low level of education tend to be clinically diagnosed at an earlier point in time”
Karp et al (2004) ⁶²	Longitudinal prospective study (3 year follow-up)	931, 101 with dementia and 76 with AD	Is the association between low education level and increased risk of AD explained by occupation-based socio-economic status (SES)?	“The association between low education and increased AD risk was not mediated by adult SES or socio-economic mobility”	“This suggests that early life factors may be relevant”

A variety of hypotheses have been suggested for the association found between low educational attainment and higher risk of AD. These range from bias in detection to the ‘cognitive reserve’ hypothesis.

A significant number of studies have found an association between NSAID use and a reduced risk of AD. The results of three reviews are summarized in Table 3.

Table 3: Research on the Association Between NSAID Use and Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Launer (2003) ⁶³	Review (59 references)		The effect of NSAIDs on the risk of AD	“To date, randomised, double-blind, clinical trials in patients with AD have been negative.”	“At present, no recommendations can be made concerning the when, what, who, and for how long, a person should take an NSAID to reduce his or her risk for AD.”
Etminan et al (2003) ⁶⁴	Systematic review and meta-analysis	9 studies (6 cohort studies, total of 13,211 participants, and 3 case-control, 1,443 participants)	Analysis of use of all NSAIDs in adults aged > 55 years on AD development risk	“The pooled relative risk of Alzheimer’s disease among users of NSAIDs was 0.72 (95 % CI of 0.56 – 0.94). The risk was 0.95 (0.70 – 1.29) among short term users (< 1 month) and 0.83 (0.65 to 1.06) and 0.27 (0.13 to 0.58) among intermediate term (mostly > 24 months) and long term (mostly > 24 months) users, respectively. The pooled relative risk in the eight studies of aspirin users was 0.87 (0.70 to 1.07).”	“NSAIDs offer some protection against the development of Alzheimer’s disease. The appropriate dosage and duration of drug use and the ratios of risk to benefit are still unclear.” Decreased risk is only observed in long-term users of NSAIDs (> 2 years).
Szekely et al (2004) ⁶⁵	Systematic review and meta-analysis	11 studies (3 case-control, 4 cross-sectional, and 4 prospective)	Exposure to non aspirin NSAIDs and risk of AD	For the 3 case-control and 4 cross-sectional studies, the combined risk estimate for developments of Alzheimer’s disease was 0.51 (95% CI = 0.40-0.66). In the prospective studies, the estimate was 0.74 (95% CI = 0.62-0.89) for the 4 studies reporting lifetime NSAID exposure and it was 0.42 (95% CI = 0.26-0.66) for the 3 studies reporting a duration of use of 2 or more years.”	“Based on analysis of prospective and non-prospective studies, NSAID exposure was associated with decreased risk of Alzheimer’s disease.”

The more systematic reviews (meta-analysis) indicate a protective effect of long-term NSAID use on the risk of developing AD.

As with NSAID use, there is a significant body of research suggesting a protective role of hormone replacement therapy (HRT). This research is summarized in Table 4.

Table 4: Research on the Association Between Use of HRT and Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Tang et al (1996) ⁶⁶	Longitudinal	1,124 elderly females	Measure oestrogen hormone use and the onset of AD	Relative risk of AD was significantly reduced (9/156 [5.8%] oestrogen users vs. 158/968 [16.3%] non users; 0.40 [95% CI 0.22-0.85], p<0.01), even after adjustment for differences in education, ethnic origin, and apolipoprotein-E genotype.	“Oestrogen use in postmenopausal women may delay the onset and decrease the risk of Alzheimer’s disease.”
Kawas et al (1997) ⁶⁷	Prospective	472 post- or peri-menopausal females	Oestrogen replacement use and AD risk	“After adjusting for education, the relative risk for AD in ERT users as compared with nonusers was 0.46 (95% CI, 0.209-0.997)”	“Our finding offers additional support for a protective influence of estrogen in AD.”
Zandi et al (2002) ⁶⁸	Prospective	3,246 (1,357 male and 1,889 female)	Diagnosis of incident AD	“Adjusted HRs were 0.41 (95% CI, 0.17-0.86) for HRT users compared with nonusers and 0.77 (95% CI, 0.31-1.67) compared with men.”	“Prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use unless such use has exceeded 10 years.”
Shumaker et al (2003) ⁶⁹	Randomized, double-blind, placebo-controlled clinical trial	4,532 (2,229 receiving oestrogen, 2,303 receiving a placebo)	Incidence of probable dementia, mild cognitive impairment	“The hazard ratio (HR) for probable dementia was 2.05 (95% confidence interval [CI], 1.21-3.48; 45 vs 22 per 10 000 person-years; <i>P</i> = .01).” “Treatment effects on mild cognitive impairment did not differ between groups (HR, 1.07; 95% CI, 0.74-1.55; 63 vs 59 cases per 10 000 person-years; <i>P</i> = .72).”	“Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In addition, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women.”
Gleason et al (2005) ⁷⁰	Review Article	27 studies	Cognitive benefits of oestrogen therapy for cognitively healthy postmenopausal women	19 studies found the use of HRT to be beneficial, 7 found no benefit and 1 found HRT to be harmful	“The majority of trials investigating the neurocognitive effects of HRT found benefits associated with estrogen therapy... Only the Women’s Health Initiative Memory Study (WHMIS) trial suggested a possible harmful effect”

The summary by Gleason et al. of this literature is particularly relevant. “The majority of trials investigating the neurocognitive effects of HRT found benefits associated with estrogen therapy... Only the Women’s Health Initiative Memory Study (WHMIS) trial suggested a possible harmful effect.” Indeed, the Women’s Initiative study has recently been criticised as having several design flaws that contributed to the observed results.⁷¹

Early Detection

Early diagnosis and interventions of incipient AD may allow many patients to live out the rest of their lives without complete debilitation...If measures to prevent or even delay disease progression are developed, then early intervention will be key to living a full life after the onset of cognitive symptoms with only slight cognitive impairment.⁷²

From the modest but important breakthroughs in the treatment of Alzheimer’s disease (AD), diagnostic focus has increasingly shifted to the accurate detection of the earliest phase of the disease.⁷³

Currently, a definitive diagnosis of AD is only possible with a histopathologic examination of brain tissue after death. In addition, there are no neuro-imaging or laboratory tests available that allow for the reliable diagnosis of pre-symptomatic AD.

There is, however, a considerable amount of research in the areas of neuropsychologic testing, neuro-imaging and biomarkers with respect to the possibility of finding a reliable predictive method for the early detection of AD.

Neuropsychologic Testing

The concept of mild cognitive impairment (MCI) has emerged as a transitional state between normal cognition and Alzheimer’s disease. Patients with MCI display declining memory which can be assessed by virtue of neuropsychologic testing. The purpose of research in this area is to identify functional tests that are more reliable and predictive than others in identifying an early diagnosis of AD (see Table 5).

Table 5: Research on Neuropsychologic Testing for Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Dartigues et al (1997) ⁷⁴	Prospective longitudinal (3 year follow-up)	2,276	Mini Mental State Examination, Benton Visual Retention Test, Isaacs Set Test	“After adjustment for age and educational level, the three test scores remained strongly related to the risk of dementia or AD”	
Howeison et al (1997) ⁷⁵	Prospective longitudinal (mean 2.8 year follow-up)	139	Ten neuropsychological measures	“Individuals who subsequently developed dementia showed evidence of verbal memory impairment ... 2.8 years before clinical evidence of dementia”	
Rubin et al (1998) ⁷⁶	Prospective longitudinal (up to 15.5 year follow-up)	82	Clinical Dementia Rating (CDR), 1.5 hour psychometric battery (episodic and semantic memory, visuospatial ability, language, executive function, and attention)	59% of patients with a CDR of >0 over 12 years had symptoms consistent with AD or incipient AD	“This pattern of an abrupt decline in global psychometric performance concurrent with clinically detectable cognitive change suggests a possible strategy to detect dementia in its early stages”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Fox et al (1998) ⁷⁷	Prospective longitudinal (6 year follow-up)	63	Clinical interview, neurological examination, neuropsychological assessment, MRI examination	Subjects who eventually developed AD had significantly lower initial scores on the recognition memory test for words, performance IQ and composite cognitive score.	“These findings imply that...disease cognitive decline predates symptoms by several years and that verbal memory deficits predate more widespread deterioration”
Chen et al (2001) ⁷⁸	Prospective longitudinal (10 year follow-up)	551	CERAD 10-item Word List, Story Recall, Trail-Making Tests A and B, Category Fluency, Initial Letter Fluency, the Boston Naming Test, CERAD Praxis, Clock Drawing, and the time/place orientation subtest of the MMSE	Subjects who eventually developed AD performed significantly poorer 3.5 to 1.5 years prior to clinical disease onset than those who did not on the following tests: Trail-Making Test B, CERAD Praxis, Trail Making Test A, Word List (third immediate learning trial), and Word List (delayed recall)	“Memory and executive dysfunction showed the greatest decline over time in individuals who would manifest AD 1.5 years later”
Saxton et al (2004) ⁷⁹	Prospective longitudinal (median follow-up of 7.4 years)	693	6 measures from the WMS-R (information, verbal, visual and general memory, delayed memory and attention/ concentration) and 3 from the WAIS-R (digit symbol, vocabulary, block design). Additional measures included Trails A&B, Fluency for Fruit, Fluency P&S, and the Boston Naming Test	Impaired performance at baseline was significantly associated with AD onset for four tests (WMS-R General and Delayed Recall, Fluency for Fruit, and Trail Making Part B).	“Cognitive changes can be detected well before onset of Alzheimer disease”
Tierney et al (2005) ⁸⁰	Prospective longitudinal (5 and 10 year follow-up)	Follow-up 5 year - 551 10 year - 263	12 measures including Rey Auditory-Verbal Learning Test (short delayed recall score), Buschke Cued Recall Test (total delayed recall score, object naming), WAIS-R subtests (similarities, comprehension, block design, digit symbol), phonemic fluency, animal fluency, WMS subtests (information, digit span forward), Benton Visual Retention tests (number of designs correctly identified)	In the 10 year follow-up only the short delayed verbal recall tests was predictive of subsequent AD. In the 5 year follow-up, 3 tests (short delayed verbal recall, animal fluency, information) were predictive.	“In a large epidemiologic sample of nondemented participants, neuropsychological tests accurately predicted conversion to Alzheimer disease after 5 and 10 years”

As noted in the previous table, multiple longitudinal prospective studies have found that neuropsychological testing with a focus on memory and executive function can accurately predict conversion to AD. Such results have raised the question of whether or not large-scale community memory screening is feasible and practical.⁸¹

Neuroimaging

“To accurately predict the development of Alzheimer’s disease (AD) at its prodementia stage would be a major breakthrough from both therapeutic and research standpoints.”⁸²

Major brain changes during the course of AD include brain atrophy, abnormal deposition of β -amyloid protein, hyperphosphorylated tau protein leading to neurofibrillary tangles (NFTs), neuronal death in specific brain regions, and inflammation.⁸³ As such, there has been steady development in the use of computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) in the assessment of AD.

Table 6: Research on Structural Neuroimaging for the Early Detection of Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Dickerson et al (2001) ⁸⁴	Comparison of 3 groups 1) healthy elderly controls (NC) 2) patients with cognitive complaints (ND), and 3) patients with diagnosed mild AD	NC (34) ND (28) AD (16)	MRI derived hippocampal formation (HF) and entorhinal cortex (EC) volume	ND and AD differed from NC in EC volume but not from each other. All groups differed in HF volume, with the AD group indicating the greatest atrophy.	“The in vivo anatomical results presented here are in agreement with post mortem pathological studies and underscore the early involvement of the entorhinal cortex in AD”
Visser et al (2002) ⁸⁵	Prospective longitudinal study (average follow-up of 1.9 years)	31	MRI derived volume of the hippocampus, parahippocampal gyrus and qualitative rating of medial temporal lobe atrophy (MTA)	Measures of medial temporal atrophy predicted outcome at follow-up with the best predictor being the volume of the hippocampus	In patients with minor cognitive impairment, measures of medial temporal atrophy improved the predicted outcome accuracy of age and delayed recall performance for outcome of AD
deToledo-Morrell et al (2004) ⁸⁶	Prospective longitudinal study (follow-up of 36 months)	27	MRI derived hippocampal formation (HF) and entorhinal cortex (EC) volume	Right hemisphere EC volume predicted conversion to AD with a concordance rate of 93.5%	
Jack et al (2004) ⁸⁷	Prospective longitudinal comparison of 3 groups 1) normal elderly subjects 2) mild cognitive impairment (MCI), and 3) patients with diagnosed AD (follow-up of 5 years)	Cognitively normal (55), MCI (41), AD (64)	MRI derived hippocampus, entorhinal cortex, whole brain and ventricle volume	“All four atrophy rates were greater among normal subjects who MCI or AD than those who remained stable, greater among MCI subjects who converted to AD than among those who remained stable, and greater among fast than slow AD progressors.”	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Korf et al (2004) ⁸⁸	Prospective longitudinal study (mean follow-up of 34 months)	75 patients with MCI	Visual assessment of medial temporal lobe atrophy (MTA) using a 5 point rating scale, MTA assessed by MRI	MTA assessed using a standardized visual rating scale was significantly associated with dementia at follow-up.	“Visual assessment of MTA on brain MRI ... is a powerful and independent predictor of conversion to dementia in relatively young MCI patients”

Table 7: Research on Functional Neuroimaging for the Early Detection of Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Arnaiz et al (2001) ⁸⁹	Prospective longitudinal study (follow-up at 36.5 months)	20 patients with MCI	Reduced fluorodeoxyglucose (FDG) metabolism as measured by Positron Emission Tomography (PET), neuropsychological test assessment	Two variables that most effectively predicted future development of AD were reduced glucose metabolism from the left temporoparietal area and performance on the block design. The correct classification rate was higher if both variables were used (90% vs. 75% and 65% respectively).	
Chetelat et al (2003) ⁹⁰	Prospective longitudinal study (follow-up at 18 months)	17 patients with MCI	Reduced FDG uptake in the right temporoparietal cortex as measured by PET	Individuals who progressed to AD had lower FDG uptake than those who did not	
Cabranes et al (2004) ⁹¹	Prospective longitudinal study (follow-up at 3 years)	42 patients with MCI	Neuropsychological test assessment, cerebral blood flow measured by Tc-ECD-SPECT	“The left frontal relative blood flow, the CAMCOG and orientation scoring were the best data to predict the risk of progression to AD”	
Dickerson et al (2004) ⁹²	Prospective longitudinal study (follow-up at 2.5 years)	32 patients with MCI	Memory-associated activation of medial temporal lobe (MTL) region by functional MRI (fMRI)	Greater extent of activation in the hippocampal formation and parahippocampal gyrus (PHG) was correlated with better memory performance. On the other hand, patients with greater clinical impairment recruited a larger extent of the right PHG during encoding	“We hypothesize that increased activation in MTL regions reflects a compensatory response in accumulating AD pathology and may serve as a marker of impending clinical decline”

Biomarkers

Research in the area of biomarkers has concentrated on determining whether a predictive or diagnostic biomarker can be found in the cerebrospinal fluid (CSF) of patients with MCI which would be indicative of a conversion from MCI to AD. The focus of the research to date has been on the correlation between decreases in concentration of β -amyloid protein in CSF and increases in CSF levels of tau and AD.

Table 8: Research on Biomarkers for the Early Detection of Alzheimer’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Andreasen et al (1998) ⁹³	Case control	75 demented patients, 18 healthy controls and 18 neurological controls	Concentrations of total tau in CSF, clinical measures and apoE polymorphism	CSF-tau was markedly increased in both patients with AD and vascular dementia compared to controls	CSF tau has a high sensitivity (95%) for the diagnosis of AD, but a low specificity (86% of patients with vascular dementia also had high concentrations)
Clark et al (2003) ⁹⁴	Prospective study with 2-8 years of follow-up	106 patients with dementia and 73 normal controls	Correlation of CSF tau and β -amyloid with final diagnosis	Elevated CSF tau levels are associated with AD pathology. However, 16% of patients with diagnosed AD did not achieve cut-off levels	
Blennow (2004) ⁹⁵	Review of 64 research articles				“It is concluded that CSF biomarkers may have clinical utility in the differentiation between AD and several important differential diagnosis, including normal aging, depression, alcohol dementia, and Parkinson’s disease”

A major review of the utilization of neuroimaging and biomarkers in assisting with the early diagnosis of AD concluded that “both neuropathology and neuroimaging studies converge on observations that hippocampal formation pathology is an early feature of AD. Over the past 15 years, numerous studies have identified hippocampal atrophy as a predictor of the decline from MCI to AD”.⁹⁶ A similar review on cerebrospinal fluid protein biomarkers concluded that “CSF biomarkers may have clinical utility in the differentiation between AD and several important differential diagnosis, including normal aging, depression, alcohol dementia, and Parkinson’s disease”.⁹⁷ Despite these relatively positive results, there is the recognition that research results are clouded by differences in methodology and the populations studied,⁹⁸ as well as by relatively loose diagnostic criteria.⁹⁹

The best possible approach for the early diagnosis of AD is a multidisciplinary approach. Nestor et al note that “present evidence suggest there is no single marker of MRI atrophy or even PET metabolic change is likely to achieve perfect discriminant value for individual subjects at this prodromal stage on a single scan”.¹⁰⁰ In their review of the research on the diagnosis and prediction of progression of preclinical AD, Chong and Sahadevan conclude that “the best components of a multidisciplinary approach (comprising informant history, neurophysiological data, neuroimaging, and perhaps genetic testing) [are required] for identifying MCI subgroups who have a high risk of dementia”.¹⁰¹

3.2 Parkinson’s Disease

3.2.1 The Disease

Parkinson’s disease (PD) is a neurodegenerative disorder that affects an area of the brain known as the substantia nigra, which contains cells responsible for producing dopamine.¹⁰² Dopamine is a neurotransmitter necessary for the brain to execute muscle coordination and movement. When the cells that produce dopamine are damaged, a number of obvious signs and symptoms of its deficiency are observed.^{103,104} These signs and symptoms include resting tremors, rigidity of limbs and body, bradykinesia (general slowness of movement), and difficulty walking or handling objects.^{105,106,107} While movement disorders are the most obvious changes associated with PD, the lack of dopamine also affects many other body systems. These changes include gastrointestinal motility or bowel function, dermatological aberrations, psychiatric changes such as depression, dementia, sleep disturbances and hallucinations and sexual dysfunction.¹⁰⁸ PD is a progressively debilitating neurodegenerative disorder with no known cure.

3.2.2 Epidemiology

The worldwide incidence and prevalence of PD are estimated at 10-20 per 100,000 per year and 200-300 per 100,000 population, respectively.¹⁰⁹ PD can affect people of all ages, but the incidence rate increases significantly with age. The prevalence rates per 100,000 range from approximately 5 for those under age 40 to 300-700 for individuals in their 60s and >700 for those in their 70s.¹¹⁰ The mean age of onset is in the early to mid-sixties, though the symptoms for young and juvenile-onset PD occur between 21-40 years of age and before the age of 20, respectively.¹¹¹ Only about 30% of people with Parkinson’s are under 50.¹¹²

PD is also a costly disease. Huse and coauthors compared the annual direct medical cost of an individual with PD to matched controls in the United States.¹¹³ Their results, as shown in Figure 6, indicate that individuals with PD utilize twice the resources (\$23,101 vs. \$11,247) as matched controls.

Figure 6: Cost of Direct Medical Care of Parkinson’s Disease, Compared to Matched Controls

Cost Category	PD Cases	Controls
Inpatient acute care	\$3,036	\$1,274
Inpatient non-acute care	\$8,119	\$2,474
Emergency room visits	\$29	\$13
All outpatient services	\$8,557	\$5,768
Prescription drugs	\$3,366	\$1,720
Total Cost	\$23,101	\$11,247

These direct costs, however, are just a relatively small part of the overall burden of PD. In Canada, the overall costs of PD have been estimated at \$558.1 million per year, with \$87.8 (15.7%) million of these as direct costs and \$470.3 (84.3%) as indirect costs.^{114,115} Indirect costs are based on estimates of the economic burden associated with long-term disability and premature mortality.

3.2.3 Evaluating Available Evidence

Primary Prevention

Several risk factors and protective factors for PD can be found in the literature. Among them is a compound known as MPTP, a non-idiopathic PD inducing compound often produced accidentally during the manufacture of the illicit drug MPPP, and also found in certain herbicides.¹¹⁶

Increases Risk	Decreases Risk	Uncertain
<ul style="list-style-type: none"> • History of head injury • Depression • Family history of PD • Pesticide exposure • Exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) • Well water drinking 	<ul style="list-style-type: none"> • Smoking • Caffeine use • NSAID use, specifically Ibuprofen 	<ul style="list-style-type: none"> • Vitamin E intake

A relatively large number of studies exist which discuss the inverse relationship between smoking and PD. Many of these studies find that smoking is associated with a decreased risk of PD. Coffee and alcohol are also discussed as potential PD risk reduction substances.

Table 9: Research on the Association Between Smoking, Coffee, Alcohol Consumption and Parkinson’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Checkoway et al (2002) ¹¹⁷	Case-control	557 (cases n=210, controls n=347)	In-person questionnaires measuring smoking and PD	Ever smoked odds ratio of 0.5 (95% CI of 0.4-0.8), Ex-smoker odds ratio of 0.6 (95% CI of 0.4-0.9), Current smoker odds ratio of 0.3 (95% CI of 0.1-0.7).	“Ever having smoked cigarettes was associated with a reduced risk of PD. A stronger relation was found among current smokers.” “No associations were detected for coffee consumption or total caffeine intake or for alcohol consumption. However reduced risks were observed for consumption of 2 cups/day or more of tea and two or more cola drinks/day”
Hernan et al (2002) ¹¹⁸	Meta-analysis	Based on 44 case-control and 4 cohort studies for smoking and 8 case-control and 5 cohort studies for coffee	Smoking and coffee drinking status	Relative risk was 0.59 (95% CI of 0.54-0.63) for ever smokers, 0.8 (95% CI of 0.69-0.93) for past smokers, and 0.39 (95% CI of 0.32-0.47) for current smokers. Compared with non-coffee drinkers, relative risk of Parkinson’s disease was 0.69 (95% CI of 0.59-0.80) for coffee drinkers.	“This meta-analysis shows that there is strong epidemiological evidence that smokers and coffee drinkers have a lower risk of Parkinson’s Disease.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Tan et al (2003) ¹¹⁹	Case-control	700 (cases n=200, control n=500)	Comparison of PD and non-PD affected individuals and measuring coffee, tea, alcohol, smoking and heavy metal exposure.	Significant factors associated with PD: Coffee (odds ratio 0.79, 95% CI of 0.66-0.93) Tea (odds ratio 0.72, 95% CI of 0.56-0.94) Cigarettes smoked (odds ratio 0.38, 95% CI of 0.20-0.72) Heavy metal and toxin exposure (odds ratio 11.84, 95% CI of 1.08-130.37) Heart disease (odds ratio 5.52, 95% CI of 1.38-22.12)	“We demonstrated a dose-dependent protective effect of PD in coffee and tea drinkers and smokers in an ethnic Chinese population.”
Allam et al (2004) ¹²⁰	Systematic review	7 prospective studies	Comparison of ever and never smokers with ever smokers subdivided into past and current smokers.	Ever vs. never smoker, RR of 0.53 (95% CI of 0.42-0.66). Ever vs. never smoker in males, RR of 0.53 (95% CI of 0.42-0.68). Current vs. never smoker RR of 0.37 (95% CI of 0.24-0.58). Former vs. never smoker, RR of 0.63 (95% CI of 0.41-0.96).	“Although our pooled estimates show that smoking is inversely associated with the risk of PD, the four prospective studies that were based on follow-up of mortality of smokers had many limitations.”
Allam et al (2004) ¹²¹	Review of 26 studies	21 case-control, 4 cohort and 1 cross-sectional	Current, former and never smokers	Current smoking vs. never smokers, RR of 0.37 (95% CI of 0.33-0.41). Former smokers vs. never smokers, RR of 0.84 (95% CI of 0.76-0.92).	“Current and former smoke do not, therefore, exert the same protective effect against PD so that it is unnecessary to postulate a biological mechanism through which smoking protects against PD. The results show that the reverse direction of causation is a more probable explanation.”
Hernan et al (2004) ¹²²	Case-control study nested within a prospectively followed population	11,142 (1,019 cases and 10,123 matched controls)	Alcoholism and the risk of Parkinson’s disease	“Overall we did not find a lower incidence of PD among alcoholics compared with nonalcoholics (odds ratio: 1.09; 95% CI of 0.67-1.78).”	
Ascherio et al. (2004) ¹²³	Prospective	1,249 (909 males and 340 females)	Coffee consumption and the modifying effects of oestrogen	“Coffee consumption was inversely associated with Parkinson’s disease mortality in men...but not in women.... In women, this association was dependant on postmenopausal estrogen use; the relative risk for women drinking 4 or more cups (600 ml) of coffee per day compared with non-drinkers was 0.47 (95% CI of 0.27-0.80, p=0.006) among never users and 1.31 (95% CI of 0.75-2.30, p=0.34) among users.”	“These results suggest that caffeine reduces the risk of Parkinson’s disease but that this hypothetical beneficial effect may be prevented by the use of estrogen replacement therapy.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Galanaud et al (2005) ¹²⁴	Case-control	923 (247 cases and 676 controls)	Smoking and pesticide exposure	“We found an inverse relationship between ever cigarette smoking and PD (odds ratio = 0.6; 95% confidence interval of 0.4-0.9).” “An inverse association was also present among subjects professionally exposed to pesticides. (odds ratio = 0.5; 95% CI of 0.3-0.8)”	“We confirm the inverse association between cigarette smoking and PD in a population characterized by a high prevalence of professional pesticide exposure”
Wirdefeldt et al (2005) ¹²⁵	Nested case-control study within a cohort	In the unrelated control subject comparison: 2856 (476 PD cases and 2,380 control subjects). In the co-twin control comparison: 415 same sex pairs.	Smoking, alcohol, coffee, area of living and education (less than or greater than 6 years)	External control subjects comparison: Smoker vs. never smoker (Males OR 0.50, 95% CI of 0.33-0.77; Females OR 0.67, 95% CI of 0.37-1.21), higher education level (Males OR 1.19, 95% CI of 0.83-1.71; Females OR 1.63, 95% CI of 1.12-2.37) These significant differences were not observed with the co-twin controls	

In these studies, alcohol consumption was found to have no effect on the risk of acquiring PD.¹²⁶ Caffeine consumption was sometimes found to be protective against PD, but results are mixed. There appears to be, however, a strong inverse association between smoking and PD. This correlation has been debated and alternate hypotheses have been postulated. Among these alternative hypotheses is the one that patients with movement disorders preferentially give up smoking due to the increasing difficulty of continuing the habit, thus affecting the validity of results from case-control studies.¹²⁷

Smoking, if explored as a protective measure against PD, should be looked at with caution. It is still unclear if smoking indeed protects against PD or if further issues exist. It is clear, however, that smoking definitively contributes to a myriad of other health problems, many of which have a much worse prognosis, and worse impacts to the individual and society, than PD.

Other environmental risk factors usually associated with PD are pesticide exposure, living in a rural area, living on a farm, farming, exposure to farm animals, and well water use.¹²⁸ The results of studies examining these risk factors are summarized on the following table. The chemical MPTP is also included as it is present in some pesticides.

Table 10: Research on the Association Between Environmental Risk Factors and Parkinson's Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Priyadarshi et al (2001) ¹²⁹	Meta-analysis	16 studies for living in a rural area, 18 for well water drinking, 11 for farming and 14 for pesticide exposure.	Rural living, farming, pesticide exposure, and well water drinking	“The combined OR for rural residence was 1.56 [95% confidence interval (95% CI) 1.18-2.07] for all the studies, and 2.17 (95% CI 1.54-3.06) for studies performed in United States. The combined OR for well water use was 1.26 (95% CI 0.97-1.64) for all the studies, and 1.44(95% CI 0.92-2.24) for studies done in United States. The combined OR for farming, exposure to farm animals, or living on a farm was 1.42 (95% CI 1.05-1.91) for all studies, and 1.72(95% CI 1.20-2.46) for studies done in United States. The combined OR for pesticides exposure was 1.85 (95% CI 1.31-2.60) for all studies, and 2.16 (95% CI 1.95-2.39) for studies done in United States.”	“Our findings suggest that living in a rural area, drinking well water, farming, and exposure to pesticides may be a risk factor for developing PD.”
Gorell et al (2004) ¹³⁰	Population based case-control	608 (144 PD cases and 464 frequency matched controls)	Exposure to manganese or to copper, individually; exposure to either lead and copper, copper and iron, or lead and iron; a positive family history of PD; exposure to insecticides or herbicides; exposure to farming; and smoking.	“Logistic regression resulted in a final model that included >20 years joint occupational exposure to lead and copper (p=0.009; population attributable risk [PAR]=3.9%), occupational exposure to insecticides (p=0.002; PAR=8.1%), a positive family history of PD in first- and second-degree relatives (p=0.001; PAR=12.4%), and smoking <=30 pack-years or not smoking (p=0.005; PAR=41.4%). All four variables combined had a PAR=54.1%.”	“Our final model of PD risk suggests that occupational, environmental lifestyle and, likely, genetic factors, individually and collectively, play a significant role in the etiology of the disease.”
Firestone et al (2005) ¹³¹	Population based case-control	688 (250 incident PD cases and 388 controls)	Self reported occupational pesticide exposures, Well water consumption	Odds ratios for occupational exposures (pesticide worker, crop farmer, animal and crop farmer, dairy farmer) were not significant. Elevated ORs from exposure to herbicides (OR, 1.41; 95% CI, 0.51-3.88) and paraquat (OR, 1.67; 95% CI, 0.22-12.76). No evidence of risk from home-based pesticide exposures. Significantly increased ORs from lifelong well water consumption (OR, 1.81; 95% CI, 1.02-3.21).	“The findings for occupational pesticide exposures are consistent with a growing body of information linking pesticide exposures with PD. However, the lack of significant associations, absence of associations with home-based exposures, and weak associations with rural exposures suggest that pesticides did not play a substantial etiologic role in this population.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Li et al (2005) ¹³²	Review of 147 references		Exposure to pesticides in both epidemiological and animal studies	“These epidemiologic studies were limited by a lack of detailed and validated pesticide exposure assessment. In animal studies, no pesticide has yet demonstrated the selective set of clinical and pathologic signs that characterize human PD, particularly at levels relevant to human populations.”	“We conclude that the animal and epidemiologic data reviewed do not provide sufficient evidence to support a causal association between pesticide exposure and PD.”
Brown et al (2006) ¹³³	Review of 121 references		Exposure to pesticides and incidence of PD.	“From the epidemiologic literature, there does appear to be a relatively consistent relationship between pesticide exposure and PD. This relationship appears strongest for exposure to herbicides and insecticides, and after long durations of exposure.”	“At present, the weight of evidence is sufficient to conclude that a generic association between pesticide exposure and PD exists but is insufficient for concluding that this is a causal relationship or that such a relationship exists for any particular pesticide compound or combined pesticide and other exogenous toxicant exposure.”

Research on the association between the risks of PD and pesticide exposure, living in a rural area, living on a farm, farming, exposure to farm animals, and well water use is largely inconclusive.

Early Detection

Early detection in Parkinson’s disease is difficult given the site of pathology; however, some research exists on various options and methods for diagnosing PD. Functional neuroimaging research focuses on PET and SPECT scanning using various radiotracers.¹³⁴ Biomarkers are another area of research focusing on those biochemical compounds found in the body that are specifically associated with PD pathology.

Table 11: Research on Early Detection of Parkinson’s Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Piccini & Whone (2004) ¹³⁵	Review of 114 references		Functional neuroimaging and PD diagnosis	“Although the diagnosis of IPD and other parkinsonian syndromes is essentially a clinical assessment, the role of functional neuroimaging such as PET and SPECT is becoming increasingly important both from the perspective of an early and accurate diagnosis, and as an in vivo method to answer questions about the basic pathophysiology of these diseases.”	
Michell et al (2004) ¹³⁶	Review of 149 References		Biomarkers in PD diagnosis	“We currently have no definitive diagnostic test [for PD].” “Overall, it is clear that no biomarker will be able to do it all in Parkinson’s disease... Given the heterogeneity of the disease it is likely that a biomarker will only prove useful in certain situations, whilst the strength of the clinical examination is its breadth and ability to detect non-dopaminergic symptoms.”	

Research in PD early detection shows that functional neuroimaging is a promising technique. Specifically three-dimensional PET scanning is considered most effective followed by other forms of PET scanning.¹³⁷ SPECT scanning is more readily available than PET. However, the ability to differentiate between atypical forms is decreased. Biomarkers seem to be less useful in early detection of PD and are found to be somewhat less reliable in general.¹³⁸ Overall no single method of PD detection is reliable on its own and neuroimaging must still be conducted within the scope of classical PD clinical examination.^{139,140}

3.3 Multiple Sclerosis

3.3.1 The Disease

Multiple Sclerosis (MS) is a neurodegenerative disorder which attacks the myelin sheath of neurons in the central nervous system.¹⁴¹ This effectively means that neurons are damaged and cannot conduct electrical impulses properly leading to, in general, movement, balance and coordination issues. A widely held hypothesis is that MS is an autoimmune disorder and that MS is activated by the body's own immune response triggered by an environmental factor.¹⁴² MS tends to progress slowly.¹⁴³

The symptoms of MS can vary from case to case; the MS Society of Canada lists the following as possible symptoms of MS:¹⁴⁴

- vision disturbances such as double or blurred vision
- extreme fatigue
- loss of balance
- problems with coordination
- stiffness of muscles
- speech problems
- bladder and bowel problems
- short-term memory problems
- partial or complete paralysis

It is generally accepted that there are four different clinical courses of MS which can manifest themselves in both a mild or severe form:^{145,146}

- ***Relapsing-Remitting*** – The most common type of MS characterized by attacks or relapses of symptoms followed by partial or complete remissions.
- ***Primary-Progressive*** – A relatively rare form of MS characterized by a slow and steady worsening of symptoms over time with no distinct attacks or remissions.
- ***Secondary-Progressive*** – Characterized by a steady worsening of symptoms after an initial period of relapsing-remitting type symptoms.

- **Progressive-Relapsing** – Characterized by a steady worsening of symptoms over time, with clear relapses and remissions.

3.3.2 Epidemiology

Less is known about MS epidemiology than AD or PD. MS is known to be quite rare in tropical regions and much more common in temperate areas and this has caused some to postulate that MS has a link to climate or sun exposure, although these studies have been criticized as promising but insufficient in terms of the evidence presented.^{147,148,149} In any case, it seems geography plays a bigger role in MS epidemiology than for some other chronic diseases.

The Multiple Sclerosis Society of Canada states that approximately 50,000 people in Canada are affected by MS, and that there are approximately 1,000 new cases per year.¹⁵⁰ This is supported by recent research indicating that prevalence of MS in Canada is about 100 per 100,000 population and which suggests that BC has one of the highest rates of MS in the world.^{151,152} Although MS is a very costly disease, its overall economic burden in Canada is somewhat diminished due to its lower prevalence compared to PD and AD.¹⁵³ Studies have shown, however, that costs associated with MS, especially indirect costs such as loss of ability to work, are substantial and require management especially in high prevalence regions such as Canada.¹⁵⁴ It is estimated by one study that approximately \$500 million was spent on MS in 1994 in Canada.^{155,156}

3.3.3 Evaluating Available Evidence

Primary Prevention

Several risk factors for MS have been identified and discussed in the literature. These include oral contraceptives/sex hormones, solar UV radiation, dietary fat/fatty acids, infection, occupational exposures and toxins, stress and dental fillings. Some of these risk factors are likely to be correlated with MS, whereas others are not as likely.

Table 12: Research on Risk Factors Associated with Multiple Sclerosis

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Coo & Aronson (2004) ¹⁵⁷	Review of 103 references		Solar UVR, sex hormones and dietary fat/fatty acids	Plausibility of Solar UVR and sex hormones as risk factors for MS are ‘good’ and plausibility of dietary fats/fatty acids are fair. The epidemiologic evidence was found to be insufficient in all areas.	“...priority for research should be given to potential risk factors that meet the criteria of plausibility in terms of the postulated biologic mechanisms and conformity to the features of MS...”
Marrie (2004) ¹⁵⁸	Review of 149 references		Infection, occupational exposures and toxins, physical environment (sunlight), stress	“Any given environmental agent may be only one of many factors capable of causing MS in a genetically susceptible individual”	“Enough biological and epidemiological data have accumulated that it is now reasonable to postulate causal pathways...and to systematically test these pathways.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Alonso et al (2005) ¹⁵⁹	Case-control	1,107 (106 female incident cases of MS, and 1,001 matched controls)	Oral contraceptives and incidence of first symptoms of MS	“Incidence of MS was 40% lower in oral contraceptive users compared with non-users...” (odds ratio: 0.6; 95% CI of 0.4-1.0). “The risk of MS increased in the 6 months after pregnancy (odds ratio: 2.9; 95% CI of 1.2-6.6), but it was not otherwise related to parity.”	“The hormonal changes that occur during oral contraceptive use and pregnancy may be associated with a short-term reduction in the risk of MS, and the postpartum period may be associated with a short-term increase in the risk of MS.”
VanAmerongen et al (2004) ¹⁶⁰	Review of 162 references		Vitamin D deficiency	“This review provides some epidemiological and ecological evidence for the preventive role that vitamin D nutrition may play in decreasing susceptibility to MS.”	
Chaudhuri (2005) ¹⁶¹	Review of 73 references		Vitamin D deficiency	“In areas of high MS prevalence, dietary supplementation of Vitamin D in early life may reduce the incidence of MS.”	
Holick (2004) ¹⁶²	Review of 129 references		Sunlight and vitamin D deficiency and MS	“There is compelling evidence that [the risk of developing multiple sclerosis] is attributable to a decrease in UVB light exposure.”	
Ponsonby et al (2005) ¹⁶³	Review of 96 references		Multiple sclerosis, type 1 diabetes, rheumatoid arthritis	There is some evidence that vitamin D and/or sun exposure is correlated with MS.	“There remains a lack of human experimental studies on the effect of UVR and/or vitamin D on the onset or progression of these three diseases.”
Riise et al (2002) ¹⁶⁴	Meta-analysis of 13 studies (9 case-control, 2 prevalence comparison, 1 ecologic, and 1 proportional mortality)	Three cohort studies of 11,542 painters, 36,899 construction workers and 9,314 food-processing workers from the 1970 census in Norway	Organic solvents	“A total of nine painters, 12 construction workers and six food workers had received a disability pension because of MS. The relative risk for painters compared with workers not exposed to organic solvents was 2.0 (95% confidence interval = 0.9-4.5) for MS.”	“These results are compatible with the hypothesis of organic solvents being a possible risk factor for MS.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
McGrother et al (1999) ¹⁶⁵	Case-control	“Thirty-nine females with multiple sclerosis (of recent onset) were matched with 62 controls for age, sex and general practitioner”	“DMFT index and blood and urine mercury and lead levels”	“The odds of being a MS case increased multiplicatively by 1.09 (95% CI 1.00, 1.18) for every additional unit of DMFT index of dental caries. This represents an odds ratio of 1.213 or a 21% increase in risk of MS in relation to dental caries in this population. There was no difference between cases and controls in the number of amalgam fillings or in body mercury or lead levels. There was a significant correlation between body mercury levels and the number of teeth filled with amalgam (controls: $r = +0.43$, $P = 0.006$, cases: $r = +0.60$, $P = 0.001$).”	“There was evidence of excess dental caries among MS cases compared with the controls. This finding supports the strong geographical correlation between the two diseases.”
Prochazkova et al (2004) ¹⁶⁶		305 patients (35 of which were diagnosed with an autoimmune disease)	“Health impact of amalgam replacement in mercury-allergic patients with autoimmunity.”	“Results of lymphocyte reactivity measured with MELISA indicate that in vitro reactivity after the replacement of dental amalgam decreased significantly to inorganic mercury, silver, organic mercury and lead. Out of 35 patients, 25 patients (71%) showed improvement of health. The remaining patients exhibited either unchanged health (6 patients, 17%) or worsening of symptoms (4 patients, 11%). The highest rate of improvement was observed in patients with multiple sclerosis, the lowest rate was noted in patients with eczema.”	“Mercury-containing amalgam may be an important risk factor for patients with autoimmune diseases.”

A number of risk factors have been investigated with regards to MS. Although the overall research base is weak, risk factors related to MS susceptibility may include low levels of solar UV radiation, low levels of vitamin D, low levels of sex hormones in females, occupational exposure to toxins, and dental fillings or amalgams.

Early Detection

Early detection of MS is important to slow the progression of the disease and improve outcomes. Following is a review of research on the use of MRI and the detection of IgG in cerebrospinal fluid for the early detection of MS.

Table 13: Research on Early Detection of Multiple Sclerosis

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Lycklama et al (2003) ¹⁶⁷	Review		Spinal cord MRI in MS	“First, asymptomatic spinal-cord lesions are very rare in disorders other than MS. For example, in a patient with equivocal brain findings such as an elderly patient with vascular-ischaemic lesions, a normal spinal-cord examination can help rule out MS. Second, presence of asymptomatic spinal lesions may help confirm a diagnosis of MS when few or no brain lesions are present.”	“In the diagnostic setting, spinal-cord imaging is valuable.”
Miller (2004) ¹⁶⁸	Review		MRI as an indicator in the diagnosis of MS	“The evolution of thought concerning early treatment in MS is based on an increased understanding of the pathology of the disease. Axonal loss occurs early in the disease process, and both white matter and gray matter are affected. Studies that have analyzed early treatment in patients highly likely to have MS (clinically isolated events with evidence of lesions on MRI) report significant benefits in delaying further changes on MRI and further attacks. Patients who begin treatment later do not reap the same benefits as those who begin treatment earlier during the disease course.”	“Patients with clinically isolated events should be referred promptly to a neurologist for assessment, including MRI scans. An early recognition of the inflammatory process enables patients to begin treatment with an immunomodulatory agent even before the technical diagnosis of definite MS so that the degenerative progression of MS can be retarded.”
Pohl et al (2004) ¹⁶⁹	Prospective	136 patients with MS onset before age 16	Characteristics of CSF (cerebrospinal fluid) in children with MS	“In the initial diagnostic lumbar puncture, CSF-pleocytosis was observed in 66%, blood-CSF barrier dysfunction in 13%, and oligoclonal IgG in 92% of the early-onset MS (EOMS) patients. CSF oligoclonal IgG supports the early diagnosis of MS in childhood with a sensitivity similar to adult-onset MS.”	“CSF analysis to rule out acute inflammatory and neurometabolic diseases and to find evidence and neurometabolic diseases and to find evidence for a chronic CNS immune reaction is an important tool in supporting the diagnosis of MS.”
Villar et al (2005) ¹⁷⁰	Prospective observational study	385 patients with various neurologic disorders	The OCGB detection test for MS diagnosis	“Intrathecal IgG synthesis was found in 127 patients with MS (96.2%), 18 (35.3%) with central nervous system infections, and 1 with motor neuron disease.” “Considering all patients, the sensitivity for the diagnosis of MS was 96.2%, and the specificity was 92.5%.”	“The accuracy of this OCGB method reinforces the value of cerebrospinal fluid studies in the early differential diagnosis of MS.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Tremlett et al (2006) ¹⁷¹	Retrospective review of prospectively collected data in British Columbia	“2,837 patients, followed prospectively for 22,723 patient years.”	Sustained progression to expanded disability status scale (EDSS) 6	“The study included 2,837 patients, followed prospectively for 22,723 patient years. The median time to EDSS 6 was 27.9 years, 15 years after onset; only 21% reached EDSS 6, and by age 50, 28% required a cane. Men progressed 38% more quickly than women from onset ($p < 0.0005$), yet both required canes at similar ages: 58.8 years for men and 60.1 for women ($p = 0.082$). A younger onset age predicted a slower progression, but those older at onset were consistently older when reaching EDSS 6. A primary progressive course predicted a more rapid progression from both onset ($p < 0.0005$) and birth (hazard ratio = 2.7 [95% CI: 2.2 to 3.3]). No onset symptom consistently predicted progression.”	“Disability progression in multiple sclerosis (MS) accrued more slowly than found in earlier longitudinal studies. The authors also challenged two fundamental concepts in MS, demonstrating that neither male sex nor older onset age was associated with worse disease outcome.”
Traboulsee and Li (2006) ¹⁷²	Review		MRI in diagnosis of MS	“The sensitivity of diagnosing MS within the first year after a single attack is 94%, with a specificity of 83%. The MRI evidence required to support the diagnosis varies, depending on the strength of the clinical findings.”	“MRI evidence plays a supportive role in what is ultimately a clinical diagnosis of MS, in the appropriate clinical situation, and always at the exclusion of alternative diagnoses.”

Early diagnosis of MS is found to be important for favourable outcomes and slowed disease progression.¹⁷³ Several studies have shown that MRI imaging, especially of the spinal cord, can be useful in assisting with an early diagnosis of MS. Other studies reviewed discuss the success of using IgG in the cerebrospinal fluid as a reliable biomarker of MS disease. More recent findings by Traboulsee and Li suggest MRI is not reliable enough to rule out clinical diagnosis, but confirm the usefulness of such a technique.¹⁷⁴

3.4 Primary Brain Cancer

3.4.1 The Disease

The origin of primary brain cancer is in the brain, as opposed to the more common secondary brain cancer which is manifested by a metastatic growth from another area of the body.¹⁷⁵ Primary brain tumours rarely spread to other parts of the body as the blood-brain barrier keeps this from happening. However, tumours may spread to other parts of the CNS via the cerebrospinal fluid.

Brain cancers are classified according to how fast they grow, such as benign and malignant, and are named according to the type of cell from which they were derived.¹⁷⁶ In this respect there are close to 100 different types of brain tumours and the effects on the individual can vary depending on the type, and especially the location, of the tumour.¹⁷⁷ Although it is complicated to apply standard symptoms to brain cancer, the BC Cancer Agency¹⁷⁸ lists the following as standard signs and symptoms of brain cancer:

- Headache
 - May be due to pressure inside the brain from tumour mass itself or swelling
 - Can be caused by distortion of the outer membrane or blood vessels of the brain by the tumour
 - May be associated with vomiting, double vision, decreased visual acuity, drowsiness
 - Pain may be worsened by coughing or straining
- Seizures
 - Partial or full seizures may be due to either tumour, brain swelling or to scar formation
- Neurological Dysfunction
 - May affect speech, memory, vision
 - Localized weakness or sensory loss due to invasion or compression of adjacent brain tissue
 - The resultant neurologic loss dependant on the location of the tumour

3.4.2 Epidemiology

Brain cancers, in general, comprise about 5-9% of all cancers.¹⁷⁹ Compared to secondary brain cancer, primary brain cancer has a low incidence. In the US, an estimated 22% of all brain cancers are primary brain cancers.¹⁸⁰ According to the BC Cancer agency, “primary brain tumours account for 3% of all neoplasms.” Approximately 80% of brain tumours initiate in adults between 50 and 60 years of age.¹⁸¹

3.4.3 Evaluating Available Evidence

Primary Prevention

Although, research on prevention of primary brain cancer has included a number of various possible risk factors, it appears to be focussed in 3 main areas: exposure to vinyl chloride, exposure to radiation from cellular phones, and exposure to x-ray radiation. Vinyl chloride exposure is known to be a carcinogen associated with certain types of cancer, specifically hepatic cancer, but risk associated with brain cancer is less clear. Risk of brain cancer due to exposure to radiation from cell phones and x-rays is often debated.

Table 14: Research on the Association between Primary Brain Cancer and Vinyl Chloride and X-rays

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Bosetti et al (2003) ¹⁸²	Review of 2 studies	2 Studies (including over 22,000 workers)	Exposure to vinyl chloride and risk of cancer	“The SMRs for soft tissue sarcoma, brain, lymphoid and haematopoietic system cancers were not materially different from unity.”	This study “did not indicate an association between brain cancer and VC exposure.”
Lewis et al (2003) ¹⁸³	Meta-analysis	8 studies	Exposure to vinyl chloride and risk of brain and liver cancer	“Louisville experienced significantly elevated liver (standardized mortality analyses [SMR] = 400) and brain cancer (SMR = 229) mortality. Liver cancer mortality remained significantly elevated (SMR = 344) in the remaining cohort; however, brain cancer mortality was markedly reduced (SMR = 112) when Louisville was removed.”	“In contrast with liver cancer, a preliminary review of work assignments did not suggest that the brain cancer excess was related to VC exposure.”
Boffetta et al. (2003) ¹⁸⁴	Meta-analysis	8 studies (Two multicentre cohort studies and 6 smaller studies)	Exposure to vinyl chloride and risk of cancer mortality	“The meta-SMR for brain cancer, based on 5 studies, was 1.26 (95% CI 0.98-1.62).”	“Increased mortality from lung and brain cancers and from lymphatic and hematopoietic neoplasms cannot be excluded; mortality from other neoplasms does not appear to be increased.”
Longstreth et al (2004) ¹⁸⁵	Population-based case-control study	200 patients	Dental X-rays and risk of meningioma (a certain type of brain tumour)	“...only the full-mouth series (specifically, > or = 6 over a lifetime) was associated with a significantly increased risk of meningioma (odds ratio, 2.06; 95% confidence limits, 1.03-4.17). However, evidence for a dose-response relation was lacking (P for trend = 0.33).”	“Dental X-rays involving full-mouth series performed 15-40 years ago, when radiation exposure from full-mouth series was much greater than it is now, were associated with an increased risk of meningioma. The authors did not observe an increased risk with bitewings, lateral cephalometric, and panoramic radiographs.”
Phillips et al (2005) ¹⁸⁶	Population-based case-control study	600 (200 cases and 400 controls)	Ionizing radiation in occupational and medical settings and risk of meningioma	“No significant associations were observed for diagnostic studies or occupational settings, but associations were observed for radiation therapy to head or neck (odds ratio 3.7, 95% CI 1.5 to 9.5), especially for neoplastic conditions. Only four patients (2%) had meningiomas that followed high-dose cranial radiation.”	The evidence does not show a link between intracranial meningioma and ionizing radiation in medical or occupational settings.

Table 15: Research on Primary Brain Cancer and Mobile Phones

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Hansson Mild et al (2003) ¹⁸⁷	Review of 25 references		Mobile phones and risk of brain tumours	The current state of the literature is unknown and although studies have emerged that show evidence either way, a consistent picture cannot be produced from the literature.	More research is required in this area.
Lonn et al (2004) ¹⁸⁸	Population-based case-control	752 (148 cases and 604 controls)	Mobile phones and risk of brain tumours	“The overall odds ratio for acoustic neuroma associated with regular mobile phone use was 1.0 (95% confidence interval = 0.6-1.5). Ten years after the start of mobile phone use the estimates relative risk increased to 1.9 (0.9-4.1); when restricting to tumors on the same side of the head as the phone was normally used, the relative risk was 3.9 (1.6-9.5).”	“Our findings do not indicate an increased risk of acoustic neuroma related to short-term mobile phone use after a short latency period. However, our data suggest an increased risk of acoustic neuroma associated with mobile phone use of at least 10 years' duration.”
Ahlbom et al (2004) ¹⁸⁹	Review of 98 references		Mobile phones and risk of brain tumours	“Results of these studies to date give no consistent or convincing evidence of a causal relation between RF exposure and any adverse health effect. On the other hand, the studies have too many deficiencies to rule out an association.”	
Lonn et al (2005) ¹⁹⁰	Population-based case-control	1,318 (371 glioma cases, 273 meningioma cases, and 674 controls)	Mobile phones and risk of brain tumours	“For regular mobile phone use, the odds ratio was 0.8 (95% confidence interval: 0.6, 1.0) for glioma and 0.7 (95% confidence interval: 0.5, 0.9) for meningioma. Similar results were found for more than 10 years' duration of mobile phone use. No risk increase was found for ipsilateral phone use for tumors located in the temporal and parietal lobes. Furthermore, the odds ratio did not increase, regardless of tumor histology, type of phone, and amount of use.”	“This study includes a large number of long-term mobile phone users, and the authors conclude that the data do not support the hypothesis that mobile phone use is related to an increased risk of glioma or meningioma.”
Christensen et al (2005) ¹⁹¹	Population-based case-control	1,249 (252 glioma cases, 175 meningioma cases and 822 population-based controls)	Mobile phones and risk of brain tumours	“Use of cellular telephone was associated with a low risk for high-grade glioma (OR, 0.58; 95% CI, 0.37 to 0.90). The risk estimates were closer to unity for low-grade glioma (1.08; 0.58 to 2.00) and meningioma (1.00; 0.54 to 1.28).”	“The results do not support an association between use of cellular telephones and risk for glioma or meningioma.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Hardell et al (2005) ¹⁹²	Case-control	1009 (317 cases and 692 controls)	Mobile phones and risk of brain tumours	“The use of analog cellular phones yielded odds ratio (OR) of 2.6 and a 95% confidence interval (CI) of 1.5-4.3, increasing to OR=3.5 and 95% CI=2.0-6.4 with a >10-year latency period. Regarding digital cellular telephones, the corresponding results were OR=1.9, 95% CI=1.3-2.7 and OR=3.6, 95% CI=1.7-7.5, respectively. Cordless telephones yielded OR=2.1, 95% CI=1.4-3.0, and with a >10-year latency period, OR=2.9, 95% CI=1.6-5.2.”	“In summary our study showed an increased risk for malignant brain tumours associated with the use of analog and digital cellular telephones and cordless phones. The risk was highest for the most malignant brain tumours, high-grade astrocytoma.”
Schoemaker et al (2005) ¹⁹³	Six population-based case-control studies	4,231 (678 cases and 3553 controls)	Mobile phones and risk of acoustic neuroma	“The risk of acoustic neuroma in relation to regular mobile phone use in the pooled data set was not raised (odds ratio (OR) = 0.9, 95% confidence interval (CI): 0.7-1.1). There was no association of risk with duration of use, lifetime cumulative hours of use or number of calls, for phone use overall or for analogue or digital phones separately. Risk of a tumour on the same side of the head as reported phone use was raised for use for 10 years or longer (OR = 1.8, 95% CI: 1.1-3.1).”	“The study suggests that there is no substantial risk of acoustic neuroma in the first decade after starting mobile phone use. However, an increase in risk after longer term use or after a longer lag period could not be ruled out.”
Hepworth et al (2006) ¹⁹⁴	Population-based case-control	2,682 (966 cases and 1716 controls)	Mobile phones and risk of glioma	“The overall odds ratio for regular phone use was 0.94 (95% confidence interval 0.78 to 1.13). There was no relation for risk of glioma and time since first use, lifetime years of use, and cumulative number of calls and hours of use. A significant excess risk for reported phone use ipsilateral to the tumour (1.24, 1.02 to 1.52) was paralleled by a significant reduction in risk (0.75, 0.61 to 0.93) for contralateral use.”	“Use of a mobile phone, either in the short or medium term, is not associated with an increased risk of glioma. This is consistent with most but not all published studies.”
Schuz et al (2006) ¹⁹⁵	Population-based case-control	2,241 (366 glioma cases, 381 meningioma cases, 1,494 controls)	Mobile phones and risk of brain tumours	“Overall use of a cellular phone was not associated with brain tumor risk; the respective odds ratios were 0.98 (95% confidence interval (CI): 0.74, 1.29) for glioma and 0.84 (95% CI: 0.62, 1.13) for meningioma. Among persons who had used cellular phones for 10 or more years, increased risk was found for glioma (odds ratio = 2.20, 95% CI: 0.94, 5.11) but not for meningioma (odds ratio = 1.09, 95% CI: 0.35, 3.37).”	“In conclusion, no overall increased risk of glioma or meningioma was observed among these cellular phone users; however, for long-term cellular phone users, results need to be confirmed before firm conclusions can be drawn.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Hardell et al (2006) ¹⁹⁶	Pooled analysis of two case-control studies	3,416 (1,254 cases and 2,162 controls)	Mobile phones and risk of brain tumours	“For acoustic neuroma, the use of analogue cellular phones gave an odds ratio (OR) of 2.9 and a 95% confidence interval (CI) of 2.0-4.3; for digital cellular phones, OR=1.5; 95% CI=1.1-2.1; and for cordless telephones, OR=1.5, 95% CI=1.04-2.0. The highest OR was found for analogue phones with a latency period of >15 years; OR=3.8, 95% CI=1.4-10. Regarding meningioma, the results were as follows: for analogue phones, OR=1.3, 95% CI=0.99-1.7; for digital phones, OR=1.1, 95% CI=0.9-1.3; and for cordless phones, OR=1.1, 95% CI=0.9-1.4.”	Results are mixed for cell phones as a risk factor for brain tumours.

Based on three review articles on the association between brain cancer and vinyl chloride, the evidence seems to show that there is no increased risk of brain tumours with occupational exposure to vinyl chloride, although this is not the case with regards to hepatic cancer. Exposure to X-ray radiation was reviewed in two studies and it was found that with the current doses of radiation in use today in the medical field, there does not seem to be an elevated risk of brain cancer. However, as reported by Longstreth et al, in the past required doses of radiation to produce an accurate image were much higher and were associated with some risk of meningioma.¹⁹⁷

Exposure to radiation from cell phones and risk of brain cancer was reviewed in 10 relevant and very recent research articles. Of the 10 articles, 2 were review articles and reported that research was insufficient and therefore drew no conclusions. The remaining eight articles were all various types of case-control studies. Of these studies, six found that there was no associated risk of brain cancer with cell phone radiation exposure (although two of these reported that long term exposure results were inconclusive). The remaining two studies, authored by the same individuals, found positive correlations between exposure to cell phone radiation and risk of developing brain tumours. Based on currently available evidence, it seems reasonable to conclude that there is no risk of brain tumours associated with cell phone usage in the short- or mid-term though long-term or heavy usage has not been ruled out as a potential risk factor.

Early Detection

The BC Cancer Agency reports that there are “no useful prevention or screening measures in healthy people” for brain cancer.¹⁹⁸ Research in the area of early detection of brain tumours is limited. Diagnosis can include medical and neurological exams, as well as medical imaging, but no methods of early detection have yet been documented.¹⁹⁹

4.0 SENSORY DISORDERS

The sensory disorders covered in this evidence review exclude vision and hearing. These have been or will be covered in other evidence reviews.

4.1 Hearing Impairment

4.1.1 The Disease

Hearing impairment is a common condition and can occur at all ages, however incidence increases with age. Causes of hearing impairment or loss are genetic defects, illness, infection, or injury.²⁰⁰ Injury includes those caused by sound, and is substantially preventable in many cases, whereas hearing losses caused otherwise are not as easily preventable.

There are two main types of hearing loss, conductive hearing loss, which occurs when a defect is present in the outer or middle ear preventing sound from reaching the cochlea or inner ear, and sensorineural hearing loss, which occurs when a defect is present in the inner ear or neurons transmitting sound to the brain.²⁰¹ Sensorineural is the type associated with long term exposure to loud noise, and as such is the most preventable.

4.1.2 Epidemiology

Hearing impairment is extremely common in the United States and Canada with approximately 10% of the total population affected.^{202,203} That translates into approximately three million people in Canada.

4.1.3 Evaluating Available Evidence

Primary Prevention

About half of all hearing losses are preventable.²⁰⁴ This is likely due to the fact that exposure to excessive noise over prolonged periods is the most common and best known risk factor.²⁰⁵ Other main causes of hearing loss include presbycusia, which is age related hearing loss, infections of the middle ear and genetic factors. It is also suggested that smoking or alcohol may be risk factors for hearing loss.

Table 16: Research on Risk Factors Associated with Hearing Impairment

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Fransen et al (2003) ²⁰⁶	Review of 46 references		Age-related hearing impairment in elderly individuals	Tobacco smoking associated with hearing loss is a controversial issue and could not be substantially demonstrated; whereas “an association between clear alcohol abuse and hearing loss could be demonstrated”, however, moderate alcohol intake was shown not to be a risk factor for hearing loss. Many studies have been dedicated to noise exposure and age-related hearing loss, but other environmental factors are less known. The genetics of age-related hearing loss are not well known.	More research should be done on other risk factors and genetics of age-related hearing loss.
Neitzel & Seixas (2005) ²⁰⁷	Longitudinal (5 year follow-up)	267	Hearing loss on construction workers and effectiveness of hearing protection	“Use of hearing protection devices reduced overexposure situations among operating engineers by more than two-thirds, followed by sheet metal workers, with a reduction of more than half. Overexposure situations among electricians and iron-workers, however, were reduced by less than 7% by use of hearing protection devices.”	“On average, the construction workers examined in this study reported using hearing protection less than one-quarter of the time that their measured exposure levels exceeded 85 dBA.” “Clearly, additional efforts, including expanded availability of hearing protection and training on how, when, and where hearing protectors are to be worn, are needed.”
Lynch & Kil (2005) ²⁰⁸	Review of 79 references		Drugs for prevention of noise-induced hearing loss	Pharmaceuticals may be able to prevent and treat hearing loss due to excessive noise. This type of prevention would best be applied in military or commercial settings and would be applied preventatively in conjunction with other procedures.	Pharmaceuticals that can prevent and treat hearing loss are promising and have entered clinical development.
O’Neill et al (2005) ²⁰⁹	BMJ Clinical Evidence Review		Tympanostomy in young children and decreases in infections and infection related hearing loss	“...tympanostomy tube insertion reduced the mean number of episodes of acute otitis media during the first 6 month period after treatment compared with myringotomy alone or no surgery, but not during the subsequent 18 month.” “It found more tympanosclerosis in ears that received ventilation tubes compared with those that received myringotomy alone or no surgery.”	Some benefits were seen; however, drawbacks to tympanostomy were also seen, calling into question the overall benefit of this procedure for prevention.
O’Neill et al (2005) ²¹⁰	BMJ Clinical Evidence Review		Long term antibiotic prophylaxis for prevention of infections	Some studies show that antibiotic prophylaxis versus placebo prevented recurrence of acute otitis media. However, most studies indicate that the lower rate of infection is not significant.	Insufficient evidence exists on how long, which antibiotic and how many previous episodes of infection are required to justify antibiotic prophylaxis.

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
O'Neill et al (2005) ²¹¹	BMJ Clinical Evidence Review		Use of xylitol chewing gum or syrup	One study showed that “xylitol syrup or chewing gum reduced the proportion of children with at least one episode of acute otitis media compared with control.” “It found that more children taking xylitol withdrew because of abdominal pain or other unspecified reasons compared with control.”	The effect of xylitol could not be accurately determined due to subjects withdrawing from the study due to various reasons.

A number of risk factors have been described in hearing impairment, the most important of which is excessive noise. Research on age related hearing impairment is limited, although some evidence exists to show that excessive alcohol intake could be related to hearing loss in the aged population.²¹² Pharmaceuticals for prevention of occupational hearing loss are suggested, primarily aimed at the military and aviation fields, however clinical trials have yet to confirm the success of these methods.²¹³ Suggested preventative methods for ear infections in children are use of tympanostomy, antibiotic prophylaxis, and xylitol chewing gum; however, the benefits of each of these methods are not well described and the current evidence does not support their clinical application. One of the main targeted areas of prevention is likely to be hearing protection devices in construction and factory workers and engineers. However, in addition to making hearing protection available, education regarding the importance and use of hearing protection as well as “...development of effective and simple noise controls for the construction...” and other industries is required to reduce noise exposure.²¹⁴

4.2 Vision Impairment

4.2.1 The Disease

Although vision impairment can be interpreted to include minor vision disturbances requiring corrective lenses, it is generally accepted as including the following: partially sighted, low vision, legally blind, and totally blind.²¹⁵ Conditions associated with the progression to various stages of visual impairment include cataracts, glaucoma, macular degeneration, retinal detachment and retinitis pigmentosa.²¹⁶ This review will attempt to define vision impairment at this level, as these disorders would lead to the most severe activity limitation. The definition of low vision is based on vision of 20/60 or less after correction.²¹⁷ The definition of partially sighted is not standard and often seems to describe conditions between common correctable vision problems and low vision. The focus in this section will be on low vision, blindness and associated conditions.

4.2.2 Epidemiology

The Canadian National Institute for the Blind (CNIB) reports that approximately 635,000 Canadians have identified themselves as having blindness or low vision based on a Statistics Canada 1991 census.²¹⁸ An epidemiological review published in 2004 concluded that approximately 1 in 28 Americans had blindness or low vision.²¹⁹ Although this number appears higher than the Canadian figure, it is suspected by the CNIB that a number of Canadians do not report their low vision status, resulting in under reporting in Canada.

4.2.3 Evaluating Available Evidence

Primary Prevention

Although some evidence exists for risk factors on the prevention of certain ocular diseases, many are not well researched. Research often focuses on a specific disease as opposed to visual impairment in general. However, primary prevention measures do exist for some of the risk factors. These are summarized in Table 17.

Table 17: Research on Risk Factors Associated with Vision Impairment

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Klein et al (2003) ²²⁰	Population-based longitudinal epidemiologic study	4,926	Income, education, occupation, smoking, alcohol, caffeine and multivitamin use and incidence of cataracts	“After adjustment for age and sex, income (or education) was inversely and smoking was directly related to the 10-year cumulative incidence of nuclear cataract.”	“Incident nuclear cataract was associated with income and smoking 10 years earlier.”
Thornton et al (2005) ²²¹	Systematic review of 17 studies		Age-related macular degeneration (AMD) and smoking	“A total of 13 studies found a statistically significant association between smoking and AMD with increased risk of AMD of two- to three-fold in current-smokers compared with never-smokers. Five studies found no association between smoking and AMD. There was also evidence of dose-response, a temporal relationship and reversibility of effect.”	“The literature review confirmed a strong association between current smoking and AMD, which fulfilled established causality criteria.”
Schaumberg et al (2004) ²²²	Longitudinal study	2280 males	Age-related cataracts and exposure to lead	“The age-adjusted OR (95% CI) for cataract for men in the highest vs lowest quintile of tibia lead level was 2.68 (1.31-5.50). Further adjustment for pack-years of cigarette smoking, diabetes, blood lead levels, and intake of vitamin C, vitamin E, and carotenoids resulted in an OR of 3.19 (95% CI, 1.48-6.90). For patella lead level, there was an increased risk of cataract in the highest vs lowest quintile (OR, 1.88; 95% CI, 0.88-4.02), but the trend was not significant (P = .16). Blood lead levels, more indicative of short-term exposure levels, were not significantly associated with cataract (OR, 0.89; 95% CI, 0.46-1.72; P = .73).”	“These epidemiological data suggest that accumulated lead exposure, such as that commonly experienced by adults in the United States, may be an important unrecognized risk factor for cataract. This research suggests that reduction of lead exposure could help decrease the global burden of cataract.”
Bartlett & Eperjesi (2004) ²²³	Review of 119 references		Nutritional supplements and vision impairments	Nutritional supplements highlighted for possible inclusion were vitamins A, B, C and E, carotenoids beta-carotene, lutein, and zeaxanthin, minerals selenium and zinc, and the herb, Ginkgo biloba.	Based on their review of the available evidence, the authors recommend the following formulation: 40 mg vitamin C and E, and 12 mg lutein/zeaxanthin

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Based on the above evidence, smoking and long-term exposure to lead appear to be related to the risk of cataract development.^{224,225} Smoking also increases the risk of age-related macular degeneration.²²⁶

Early Detection

Early detection of ocular diseases is important, as approximately 40% of blindness is either preventable or treatable if discovered early enough.²²⁷ Rowe et al. suggest that regular and periodic vision examinations are important in this respect, indicating that a potential area for basic vision education and evaluation is the primary care setting. In this sense “primary care clinicians can play a vital role in preserving vision in their patients by managing systemic diseases that impact eye health and by ensuring that patients undergo periodic evaluations by eye care professionals and receive needed eye care.”²²⁸

5.0 MUSCULOSKELETAL DISORDERS

The musculoskeletal disorders covered in this evidence review exclude injury prevention. Injury prevention has been or will be covered in another evidence review.

5.1 Arthritides

5.1.1 The Disease

Arthritis is a non-specific umbrella term which simply refers to a condition or symptom where one or more joints of the body are inflamed.²²⁹ Depending on the classification system, the identified arthritides²³⁰ comprise some 130 to 150 types. Of these, the most important in terms of prevalence and burden are osteoarthritis and rheumatoid arthritis.²³¹

Osteoarthritis is the most common form of arthritis.²³² According to the World Health Organization, it ranks fourth in health impact among women and eighth among men.²³³ The impact of osteoarthritis and other arthritides will continue to expand in the aging populations of industrialized countries.

Osteoarthritis

Osteoarthritis (OA) is a chronic condition affecting movable joints. The disease is characterized by focal destruction of articular cartilage, bone growth, and, frequently, a synovial reaction. It is the most prevalent form of arthritis, especially in the elderly, and the greatest single cause of functional impairment due to a musculoskeletal disorder.²³⁴ In the entire inventory of disabling medical conditions, OA is only rivalled by cardiovascular disease.²³⁵ OA can represent a significant burden for individual patients, resulting in high cumulative economic costs to society.^{236,237} Age is the clearest and strongest risk factor for OA. British Columbia and other developed jurisdictions in the world face a growing burden due to OA as the elderly cohort increases in the population.^{238,239}

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the classic inflammatory arthritis. There is a strong link between the inflammation and immunity, with both mechanisms being influenced significantly by an individual's genetic make-up. Disorders such as RA, which result in the immune system destroying normal body tissue, are known as *autoimmune diseases*. Individually rare (with the one exception being rheumatoid arthritis itself), cumulatively these disorders affect some 5% of Western populations.²⁴⁰

The sometimes rapid progression, degree of severity, and consequent disability associated with RA, as well as the expense of newer treatments, cause the disease to be a disproportionate economic burden in every developed nation in the world.

5.1.2 Epidemiology

Osteoarthritis

Determining definitive prevalence and incidence rates of osteoarthritis poses methodological problems. First, it is important to distinguish between symptomatic OA and radiographic disease. Symptomatic OA means just what it says, disease that presents with actual symptoms of pain and disability. When the condition only shows up on x-rays or other forms of imaging, it is called radiographic OA.

The majority of adults over 55 years of age show radiographic evidence of osteoarthritis; however, not all people with radiographic OA develop symptomatic OA.²⁴¹

Symptomatic OA is the most important from a clinical perspective. The landmark *Arthritis in Canada* study reported the estimated prevalence of symptomatic OA cumulatively over all joints as 10% of Canadian adults, or about 3 million people.²⁴² This is consistent with the estimate of 12% in the US population aged 25 to 75 years.²⁴³ Another comparison using the cumulative approach is the figure of 8.5% for symptomatic OA in the Swedish population aged 50-70 years.²⁴⁴ These figures can also be compared with rates for *all* chronic arthritis. In Canada, the data for 1994 showed an arthritis rate of 14.2% for adults over 20; for 2001 it was 16.4% for adults over 15.^{245,246}

One attempt to evaluate the prevalence of *severe* OA cases is the estimate for disability attributed to arthritis in the Canadian population aged 15 and over, namely 2.3% (or 595,000 people) in 1991 and an estimated 3.3% (or over 1 million people) in 2031.²⁴⁷ A thumbnail sketch would indicate that serious cases of OA are about one quarter of symptomatic cases, which in turn are roughly one quarter of radiographic rates.²⁴⁸ The serious cases would further exhibit a range of severity and expected progression.

Modifiable Risk Factors

Many factors predisposing to OA have been investigated, in addition to non-modifiable ones such as age, gender and genetic make-up.

Risk factors are sometimes specific to joint sites, e.g.,

- Knee misalignment (congenital or acquired) has a strong association with disease progression in knee OA.²⁴⁹
- Hip dysplasia predisposes to hip OA.
- Acute trauma (such as sports injuries) or repetitive microtrauma to a joint promotes OA development in that joint.²⁵⁰

Other risk factors apply to all *load-bearing* joints, e.g., obesity and occupational practices such as bending / lifting.^{251,252,253}

There is a class of risks associated with generalized osteoarthritis (GOA), including, again, obesity, as well as high bone density, low antioxidant intake, reduced estrogen at menopause, and especially genetic factors.^{254,255}

Rheumatoid Arthritis

The prevalence for RA in the Canadian population was identified in the recent *Arthritis in Canada* report,²⁵⁶ where the authors quoted the “official” figure of 1% of the population aged 15 and over (as published by the Arthritis Society).²⁵⁷ This is consistent with results from the US as well as many European settings.²⁵⁸ The rate in developed countries is usually pegged conservatively at 0.5-1.0%. With some exceptions, international data confirm a prevalence rate for RA near or just below 1% in adult populations, with 2 to 3 times more women than men developing the disease. The remarkable fact that emerges from comparisons with other geographical areas is not the variability in occurrence but the similarity. Although Asian and African populations show on average a lower prevalence, all regions of the world are consistently between 2 and 10 per 1000 adults for RA prevalence.²⁵⁹ A final point potentially relevant to the BC context is the higher rates of arthritis in First Nations communities, though data specific to RA are limited.²⁶⁰ One study showed a prevalence rate for RA of up to 4% in specific First Nations in northwestern Ontario.²⁶¹

A final international perspective involves trends in incidence. Evidence from the US and other jurisdictions suggests that there has been a statistically significant decline in RA occurrence during the last century.^{262,263} These findings, though requiring further investigation, support “the theory that the occurrence of RA is determined, at least in part, by an environmental agent, whose greatest effect might be early in life and whose occurrence or infectivity has declined.”²⁶⁴

An abnormally sustained response to infection is the most likely trigger for RA. Environmental factors that are non-infectious also may come in to play. For example, diet has been investigated extensively, though it is a notoriously difficult area of research. Studies have shown that omega-3 fatty acids can improve outcomes with RA.²⁶⁵ The other main focus has been on vitamins, trace elements and minerals in a diet, though little conclusive information has been reported. Much more definitive has been the linkage between cigarette smoking, elevated RF levels and poorer disease prognosis, especially for men.^{266,267,268,269} Conversely, there has been little evidence associating RA and occupational risk;²⁷⁰ the only exceptions to this rule involve exposure to mineral oils and silica.^{271,272}

In sum, there is only a limited foundation for primary prevention strategies for RA (see below).²⁷³

Another posited factor involves the impact of sex hormones (perhaps explaining the female excess of RA, noted earlier); admittedly, some research remains ambiguous.²⁷⁴ Hormonal influences show up in a variety of ways, including:^{275,276,277,278,279}

- reduced incidence (or at least postponed onset) with oral contraceptives
- reduced onset and remission (or at least improved prognosis) during pregnancy
- increased risk or relapse postpartum and at menopause.

5.1.3 Evaluating Available Evidence

Primary Prevention: Osteoarthritis

As noted under the epidemiology section above, an integrated approach to identifying the risk of OA onset includes factors that increase general susceptibility to the disorder, as well as biomechanical characteristics that modify risk at specific joint sites.²⁸⁰ Of most interest to health care are those factors that are deemed modifiable.

The main focus in primary prevention of OA has been on weight reduction, improved diet, estrogen replacement, care with work-related activity, and other protections against joint injury, including exercise combating muscle weakness.²⁸¹

The role of exercise in prevention remains unclear. Evidence is available on both sides of the debate concerning the impact of regular, strenuous recreational activity on lower limb joints.^{282,283,284} One review suggested that there was no evidence that physical activity directly prevents OA.²⁸⁵

In sum, weight control has dominated the discussion of preventive efforts in OA. Relevant evidence summaries will be presented in Table 18.

Table 18: Relationship between Obesity and Osteoarthritis

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Coggan et al. (2001) ²⁸⁶	Population-based case control study	525 cases, 525 controls	Odds ratio of knee OA with increasing BMI	BMI OR 95% CI <20 0.1 (0.0-0.5) 24-25 Ref. 25-29 2.5 (1.8-3.6) ≥30 6.8 (4.4-10.5) ≥36 13.6 (5.1-36.2)	If all overweight or obese people brought their weight to recommended levels, about a quarter of surgical knee OA cases could be avoided.
Nevitt et al. (2002) ²⁸⁷	Review article	38 references			“That obesity is strongly associated with an increased risk of OA has been widely studied and confirmed for knee OA.”
Lievensen et al. (2002) ²⁸⁸	Review article	12 studies (1 cohort, 4 case-control, 7 cross-sectional)		Moderate evidence for a positive association between hip OA and obesity, with an odds ratio of about 2	Association is stronger for clinical OA compared with that defined by radiological criteria
Powell et al. (2005) ²⁸⁹	Review article	26 references		One twin study showed a dose response: 9-13% increased risk for OA onset with every kg. increase in weight	“Given that obesity is modifiable by conservative treatment such as weight loss, its potential importance in reducing the incidence of OA cannot be underestimated.”

Based on the available research, obesity appears to be a risk factor for the development of OA, especially in the knee.²⁹⁰ Body weight probably works through both mechanical as well as metabolic pathways, explaining why non-weight-bearing joints in the hand are also affected by obesity. Ongoing research will “help us understand these associations and allow us to evaluate new biomarkers for symptomatic incident and progression of established knee OA as well as the

relationship of obesity and generalized OA.²⁹¹ Another important focus of attention is the synergistic effect of joint injury combined with obesity.²⁹² Thus, there may be preventive value in targeted advice to overweight individuals dealing with a knee injury. Preventing injuries in the first place and careful rehabilitation following injury may also be important in preventing knee OA.²⁹³

Primary Prevention: Rheumatoid Arthritis

If more successful strategies for preventing tobacco use could be developed, the burden of RA in the population could be significantly reduced.²⁹⁴

As noted above, there are limited primary prevention options currently available for RA. The one exception is the contributory role of long term smoking.²⁹⁵ Recent research suggests that “in a certain genetic context, smoking is a potential trigger for RA, and a combination of the two factors is associated with the occurrence of immune reactions long before the onset of RA.”²⁹⁶

These immune reactions may take place up to ten years prior to the onset of clinical disease. Individuals with a specific genetic susceptibility are four times more likely to get RA than those without the genetic susceptibility. If individuals with the genetic susceptibility also smoke, the relative risk increases by a factor between 4 and 34. See more data supporting the association between smoking and RA in Table 19.

Table 19: Relationship between Smoking and Rheumatoid Arthritis

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Albano et al. (2001) ²⁹⁷	Review article	6 studies on the risk of developing RA and 4 studies on RA severity	Odds ratio or relative risk of RA with various intensities and lengths of smoking history	The RR of developing RA in the largest study (7,967 cases with RA) was 1.39 (95% CI of 1.27 to 1.52) for ≥ 25 cigs. / day.	“Tobacco smoking may encourage further production of RF and other inflammatory elements as well as directly cause endothelial damage and dysfunction.”
Criswell et al. (2002) ²⁹⁸	Prospective cohort study (11 year follow-up)	31,336 women (158 cases) ages 55 – 69	Age adjusted relative risk of RA with various lengths of smoking history compared to never smokers	RR of 2.0 (95% CI of 1.3 to 2.9) for current smokers. RR of 0.9 (95% CI of 0.5 to 2.6) for women who had quit at least 10 years	“The results suggest that abstinence from smoking may reduce the risk of RA among postmenopausal women.”
Stolt et al. (2003) ²⁹⁹	Population-based case control	679 cases; 847 controls	The association between smoking and developing seropositive /seronegative RA	Current smokers, ex-smokers, and ever-smokers of both sexes had an increased risk for seropositive but not seronegative RA	“The increased risk was only apparent among subjects who had smoked ≥20 years, was evident at an intensity of smoking of 6-9 cigarettes / day, and remained for up to 10-19 years after smoking cessation.”
Krishnan et al. (2003) ³⁰⁰	Case control	1,095 cases; 1,530 controls	The association between smoking, gender and developing RA.	Smoking is a risk factor for RA in men (OR of 2.0; 95% CI of 1.2 to 3.2) but not in women	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Padyukov et al. (2004) ³⁰¹	Population-based case control	858 cases; 1,048 controls	Gene-environment interaction between smoking and seropositive RA.	“Smokers carrying double shared epitope genes displayed a relative risk of RF-seropositive RA of 15.7 (95% CI 7.2-34.2).”	
Klareskog et al. (2006) ³⁰²	Case control	913 cases; 1126 controls	Interaction between smoking, major susceptibility genes included in the shared epitope (SE) of HLA-DR and the presence of antibodies to proteins modified by citrullination.	“The combination of smoking and the presence of double copies of HLA-DR SE genes increased the risk of RA 21-fold” for anticitrulline-positive RA.	

Given the evidence of a causal link between smoking and RA, reducing the modifiable risk factor of smoking should lead to a decreased incidence of disease, especially the subset of RA associated with specific genetic and immunologic conditions.

Early Detection: Osteoarthritis

“The efficacy of therapeutic interventions is complicated by the time required to observe radiographic signs.”³⁰³

As with many human diseases, one of the “holy grails” in rheumatology research is early detection and, better, preclinical prediction of disease development.

Once OA symptoms are present, usually the clinician is no longer dealing with early disease. Plain radiography, the reference technique for assessing the severity of joint destruction, does not necessarily offer an improvement in terms of early detection. While it provides direct information on bones, it only contributes indirect information on a soft tissue such as cartilage; as well, it is often necessary to wait 1 to 3 years to obtain reliable data on disease progression.³⁰⁴

Other forms of imaging are being investigated and may yet prove to be beneficial in early detection of OA. These include computed tomography (CT) scans, thermography, and arthrography (where a radiopaque substance is injected). Sonography is also being refined as a tool to detect cartilage changes.

Magnetic resonance imaging (MRI) provides direct information on the alteration of different joint tissues. In particular, it has been increasingly used to identify subtle cartilage damage and to monitor disease progression.³⁰⁵ This imaging method is still being optimized for OA, but it has already been deemed the best non-invasive approach for assessment of articular cartilage.³⁰⁶ However, MRI has demonstrated limitations, including how much information can be provided about cartilage physiology.³⁰⁷ While progress is being made on the facility of MRI for early detection of arthritis (through approaches such as MR T2 mapping), the sheer expenses of such methods currently prohibits their employment in general disease screening. It seems that imaging will continue to be mostly useful in assessment of disease progression, identifying focal articular cartilage defects (to guide novel therapies), and monitoring therapeutic effects.

Conventional laboratory tests, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are used in the diagnosis of OA, most importantly to differentiate it from inflammatory arthritis such as RA. The same may be said for white blood cell counts in synovial fluid (SF). While the diagnosis of certain kinds of OA (e.g., septic, crystal-based) may be facilitated through SF assay,^{308,309} this approach has traditionally not been known for early detection per se but rather for the confirmation of established joint disease that is not OA. However, recent investigation of highly sensitive CRP has raised the possibility of it detecting the low-grade inflammation associated with OA.³¹⁰

In light of the current limitations attached to both imaging techniques and conventional tests, biomarkers have received growing attention in an effort to improve diagnosis, to assess disease activity and severity, and to evaluate the effects of therapy.³¹¹ The relevant biomarkers in the case of arthritis are molecules found in synovial fluid, blood and urine that are the by-products of cartilage or bone degeneration. Collagen synthesis markers are also of interest. Many such biomarkers are undergoing intense investigation. The researchers face challenges: “One criticism of the use of metabolic products of connective tissue as markers of OA is the ubiquitous nature of these molecules and their lack of specificity for joint disease.”³¹²

Finally, there is a step beyond the relatively non-invasive approach of SF aspiration and assay, that is, the collection of tissue through so-called blind needle biopsy or via arthroscopic guidance. This of course represents an invasive procedure that would not normally be warranted in preclinical stages of the disease. Most biopsy studies have been performed in RA patients.³¹³

Early Detection: Rheumatoid Arthritis

*It is believed that rheumatoid arthritis (RA) is the most common, potentially treatable cause of disability in the Western world.*³¹⁴

*Delaying treatment by as little as 8 or 9 months sets the stage for damage that cannot be reversed.*³¹⁵

Conventional treatment with disease modifying drugs and biological agents aim to reduce or prevent the morbidity, work loss and premature mortality associated with RA. Strategies involving a combination of disease modifying therapies, with or without prednisone, and initiation of treatment very early in the disease process are effective. These approaches have been studied in prospective controlled trials which demonstrate improved outcomes in terms of damage and disability compared with traditional regimens using a single DMARD.

Current research indicates that there is a “window of opportunity” in early RA, within the first 3-6 months, when immune modifying therapies have their greatest impact and potential to alter disease course.^{316,317, 318,319,320,321}

Based on research into very early RA, new models have been developed to identify patients with a high likelihood of disease progression, and to speed up the access to appropriate medical treatment and education. Early access programs and early RA programs target individuals with less than 1 year of symptoms and optimize treatment beginning at the earliest possible stage; some data show that starting before 3 months of disease duration may be significantly better.

In a 2005 review article, Visser offered the following inventory of methods for detecting early RA or predicting its development:³²²

- **History:** symptoms lasting more than 6 weeks; morning stiffness
- **Examination** (from most to least accurate): arthritis in 3 joints; arthritis of hand joints; compression pain in hand or foot joints; symmetrical arthritis; subcutaneous nodules.
- **Laboratory:** erythrocyte sedimentation rate and C-reactive protein do not distinguish well between RA and non-RA; measuring rheumatoid factor (RF) is a valuable tool in RA diagnosis; various antibody tests are showing promise, especially anti-cyclic citrullinated peptide (CCP); genetic typing enables discrimination between self-limiting and persistent disease in early RA, with an accuracy of 50-60%.
- **Imaging:** conventional X-rays; ultrasound; magnetic resonance imaging (MRI).

Because of the effectiveness of early aggressive, it is vital to differentiate between RA and other forms of arthritis as early as possible after the development of symptoms. Even better is the prediction of persistent and erosive disease at an early stage.

The use of RF has been problematic as

it is becoming more and more clear that the presence of RF is not restricted to patients with RA, but that it can also be detected in subsets of patients suffering from other diseases and even in a percentage of healthy (especially elderly) individuals.³²³

The use of anti-citrullinated protein/peptide antibodies (ACPA) has been recommended as the “only antibody system that combines good sensitivity with superior specificity for RA.”³²⁴ Recent reports, however, have suggested that even this system of early detection is flawed as ACPA has been found in other rheumatic autoimmune diseases besides RA.³²⁵

This is a lively area of research, with some newer diagnostic tests becoming more established and new frontiers being explored (e.g., parameters of the neuroendocrine system, synovial biopsies).^{326,327,328}

5.2 Lower Back Pain

5.2.1 The Disease

Low back pain (LBP) is a disabling condition that affects most people at some stage in their life. It can be acute or chronic, and accounts for more sick leave time taken from work than any other single condition.

5.2.2 Epidemiology

LBP alone has been described as an “epidemic,” especially in the developed world. Back pain is said to be “highly prevalent” in the United States. 15- 20% of individuals tend to report back pain during a 1-year period.³²⁹ A majority of people will experience an episode of LBP during their life, with lifetime prevalence estimates ranging up to 80% or even higher.^{330,331} LBP is second only to the common cold as a reason to visit a general practitioner.³³²

The estimated costs of back pain help to underscore the tremendous socio-economic burden of this condition, with approximately 90% of costs due to work absenteeism and disablement.^{333,334,335}

The economic cost of back disorders has been estimated at approximately \$100 billion per year in North America as a result of treatment and lost time from work.³³⁶ What is also known is that a small subgroup of patients with chronic back pain is responsible for most of the costs. Some reports state that only 10-25% of back pain patients account for 75% of the costs.^{337,338}

Back pain is the most common cause of disability in the US for those under age 45.³³⁹ About two-thirds of US adults experience back pain at some time in their lives. One Canadian comparison comes from Alberta, where over 25% of work loss claims were associated with LBP.³⁴⁰

5.2.3 Evaluating Available Evidence

Primary Prevention

Lumbar back supports are found to be a common approach in industry to preventing back injury. The aim of using such back supports is to prevent the initial onset of LBP (primary prevention) as well as the recurrent LBP episodes (secondary prevention).³⁴¹ A review of seven prevention studies and six therapeutic studies concluded that there is no strong evidence in favour of or against lumbar support effectiveness in both prevention and treatment of LBP. The authors found limited evidence that certain types of lumbar supports may be more effective in reducing LBP than others although most reviewed studies did not provide details regarding the type of supports that were used. The results of this study suggest that lumbar supports not be recommended for primary prevention of LBP.

Another area of interest involves the use of shoe insoles for the prevention of back pain. Sahar et al. have developed a protocol with plans to review several studies which consider the effectiveness of different kinds of shoe insoles and their impact on back pain.³⁴² They have determined that the popularity of shoe insoles to deal with the high incidence of back pain requires a systematic review of this practice.

Burton et al. suggests that the most promising approaches to LBP prevention appear to involve physical activity and education.³⁴³ After consideration of two systematic reviews she found evidence that suggests physical exercise is recommended to prevent workplace absence due to back pain and will prevent the occurrence or duration of further back pain episodes. There was also evidence to suggest water gymnastics as an exercise could be recommended to reduce back pain and work loss during or following pregnancy.

A recent Cochrane review of 19 RCTs concludes that back schools in occupational settings reduce pain and improve function and return-to-work status in the short and intermediate term, but that the clinical relevance of these studies was rated as insufficient.³⁴⁴ The U.S. Preventive Services Task Force however, has stated that there is no good evidence to recommend the use of back strengthening exercises as a prevention strategy against LBP and there is limited evidence only that back schools produce modest short-term benefits at best.³⁴⁵

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An identified area that involves prevention of low back pain is education on lifting techniques education.³⁴⁶ This is different from back schools in that it focuses on primary prevention, often in the workplace, as opposed to education and treatment after a back injury or low back pain has been presented.

Table 20: Research on Lifting Techniques and Low Back Pain

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Daltroy et al (1997) ³⁴⁷	Randomized controlled trial	4,000 U.S. Postal Workers	Rates of back injury and training and education interventions	“Physical therapists trained 2534 postal workers and 134 supervisors. Over 5.5 years of follow-up, 360 workers reported low back injuries, for a rate of 21.2 injuries per 1000 worker-years of risk. The median time off from work per injury was 14 days (range, 0 to 1717); the median cost was \$204 (range, zero to \$190,380). After their return to work, 75 workers were injured again. Our comparison of the intervention and control groups found that the education program did not reduce the rate of low back injury, the median cost per injury, the time off from work per injury, the rate of related musculoskeletal injuries, or the rate of repeated injury after return to work; only the subjects’ knowledge of safe behaviour was increased by the training.”	“A large-scale, randomized, controlled trial of an educational program to prevent work-associated low back injury found no long-term benefits associated with training.”
Yassi et al (2001) ³⁴⁸	Randomized controlled trial	346 Nurses and unit assistants	Lifting devices and incidence of lifting injuries	“Frequency of manual patient handling tasks was significantly decreased on the “no strenuous lifting” arm. Self-perceived work fatigue, back and shoulder pain, safety, and frequency and intensity of physical discomfort associated with patient handling tasks were improved on both intervention arms, but staff on the mechanical equipment arm showed greater improvements. Musculoskeletal injury rates were not significantly altered.”	“The “no strenuous lifting” program, which combined training with assured availability of mechanical and other assistive patient handling equipment, most effectively improved comfort with patient handling, decreased staff fatigue, and decreased physical demands.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Li et al (2004) ³⁴⁹	Pre-post intervention study	61 pre-intervention and 36 post intervention	Usage of mechanical lifts and training	“Statistically significant improvements in musculoskeletal comfort (p<0.05) were reported for all body parts, including shoulders, lower back, and knees. Injury rates decreased post-intervention, with a relative risk (RR) of 0.37 (95% confidence interval (CI) 0.16 to 0.88); decreased injury rates persisted after adjustment for temporal trends in injury rates on non-intervention units of the study hospital (TT = 0.35, 95% CI 0.10 to 1.16). Annual workers’ compensation costs averaged \$484 per FTE pre-intervention and \$151 per FTE post-intervention.”	“Reductions were observed in injury rates, lost workday injury rates, workers’ compensation costs, and musculoskeletal symptoms after deployment of mechanical patient lifts.”
Collins et al (2004) ³⁵⁰	Pre-post intervention trial	1,728 nursing staff in 6 nursing homes	Mechanical lifts and repositioning aids usage, a zero lift policy, and employee training and low back pain claims	“Adjusted rate ratios were 0.39 (95% confidence interval (CI) 0.29 to 0.55) for workers’ compensation claims, 0.54 (95% CI 0.40 to 0.73) for Occupational Safety and Health Administration (OSHA) 200 logs, and 0.65 (95% CI 0.50 to 0.86) for first reports of employee injury. The initial investment of \$158 556 for lifting equipment and worker training was recovered in less than three years based on post-intervention savings of \$55 000 annually in workers’ compensation costs. The rate of post-intervention assaults on caregivers during resident transfers was down 72%, 50%, and 30% based on workers’ compensation, OSHA, and first reports of injury data, respectively.”	“The “best practices” prevention program significantly reduced injuries for full time and part time nurses in all age groups, all lengths of experience in all study sites.”
Hartvigsen et al (2005) ³⁵¹	Intervention/Control study	309 nurses returned the questionnaire at the beginning and 255 at follow-up	Intensive education in lifting techniques and incidence of low back pain	“At follow up, no significant differences were found between the two groups for any of the LBP variables, and both groups thought that education in patient transfer techniques had been helpful. Within group changes in LBP status was not related to the intervention or to satisfaction with participation in the project.”	“Intensive weekly education in body mechanics, patient transfer techniques, and use of low-tech ergonomic equipment was not superior to a one time only three hour instructional meeting for home care nurses and nurses’ aids.”

The current research indicates that intensive lifting education programs are not particularly effective.³⁵² Sessions a few hours in length are moderately useful when workplaces require lifting, and often teach the “squat lifting” or “semisquat” method.^{353,354} In general, the majority of the research suggests that in instances where lifting devices can be used, such as in a hospital or nursing home, they should be implemented as they provide a much better result in lowering the incidence of low back pain.^{355,356,357} In instances where lifting devices cannot be used, a short workplace lifting seminar can be useful in teaching the proper method of lifting.

The “risk” of LBP is significant when considering the concept of prevention. This subject appears to be poorly understood with little documentation. At this time, the most significant predictor of LBP appears to be a previous history of back pain. Although there is limited documentation of other risk factors, the most common include; heavy physical work, frequent bending, twisting, lifting, pulling and pushing, repetitive work, static postures and vibrations. Other risk factors include psychosocial indicators such as distress, depression, beliefs, job dissatisfaction and mental stress at work.³⁵⁸

Effective interventions aimed at preventing LBP will help to reduce a tremendous economic burden. Clearly, further evidence based research in this area is required to demonstrate significant effectiveness of the interventions that are intended to prevent low back pain.

5.3 Repetitive Strain Injuries (RSI)

5.3.1 The Disease

Repetitive strain injury (RSI) is an umbrella term that describes a group of disorders usually impacting the arms and upper body. RSIs are thought to be a relatively new diagnoses and are said to be common in the workplace and community.^{359,360} These disorders are caused by repetitive movements affecting the body’s soft tissue structures such as muscles, tendons and nerves.^{361,362} They often include tendon-related disorders (e.g., rotator cuff tendonitis) or peripheral nerve entrapment disorders (e.g., carpal tunnel syndrome).³⁶³ RSIs tend to develop over time unlike other disorders that may occur at a single point in time. The symptoms of RSI can often last for years and include pain, numbness and tingling. The impact of RSI may include work disability, functional limitations and disordered sleep.³⁶⁴

The controversial name of this disorder has created challenges for research in this area. It “transgresses the basic principles of taxonomy through the use of terms which assume or imply findings and causality that have not been established.”³⁶⁵ Other names for this disorder that have been used include “non-specific work-related upper limb disorder,” “occupational overuse syndrome,” “repetitive strain disorder,” and “cumulative trauma disorder.”³⁶⁶ More recently a standardized system of classification has been developed that may be helpful in the development of epidemiological research.³⁶⁷

5.3.2 Epidemiology

Among work-related RSIs, occupation type seems to be the most significant risk factor. A recent report states that women in non-managerial positions had elevated rates of reporting an RSI. Men working in “sales or service; trades, transport or equipment operating; farming, forestry, fishing or mining; and processing, manufacturing or utilities had high odds of reporting an RSI.”³⁶⁸ Stress also appears to increase the risk of RSIs. “- a fast work pace, role ambiguity, worry, monotonous tasks and stress have been associated with RSIs.”³⁶⁹ There is also evidence that psychological and social factors or mood disorders such as depression seem to play an important role in RSI. It is unclear, however, whether the mood disorder results from the RSI or are a predisposing factor.³⁷⁰ Daily smokers have a higher risk of RSI than non daily smokers. Furthermore, RSI is positively associated with a higher body mass index (BMI) in women.³⁷¹ Generally, work related positions that involve repetitive movements of the wrist or arm, involve

monotonous work and where employees feel a lack of autonomy, tend to place individuals at higher risk for RSI. Interestingly, individuals who might fit these categories also tend to meet the criteria for chronic widespread pain.³⁷²

The challenges previously mentioned around naming and classifying upper limb disorders impacts the ability to clearly review and research these disorders. The name RSI assumes findings and a causality that have not been clearly established. It seems however that RSI as currently defined, is increasing among Canadians, as indicated in Figure 7.³⁷³

Figure 7: Prevalence of Repetitive Strain Injury, Household Population Aged 20 or Older, Canada

	Both Sexes %	Male %	Female %
1996/97	8.0	8.2	7.9
1998/99	9.4	9.6	9.3
2000/01	10.1	9.9	10.3

Evaluating Available Evidence

Early identification of potential problems in the work environment is critical to preventing RSI. Areas to be considered include work overload, uncomfortable surroundings as well as consideration of poor relationships between staff and supervisors.³⁷⁴ Ensuring ergonomically sound work environments and providing enough time away from work are essential components of prevention.³⁷⁵ Very little research exists, however, on the primary prevention or early detection of RSI.³⁷⁶

5.4 Primary Bone Cancer

5.4.1 The Disease

Cancer occurs when cells in the body divide without control or order. In the relatively rare bone cancer, these cancer cells grow in the bone tissue. This cancer may start in bone tissue (primary bone cancer) or it may travel to the bone from elsewhere (secondary or metastatic cancer). Types of bone cancer include:³⁷⁷

- **Osteosarcoma:** a cancerous tumour of the bone, usually of the arms, legs, or pelvis; osteosarcoma is the most common primary cancer.
- **Chondrosarcoma:** cancer of the cartilage; chondrosarcoma is the second most common primary cancer.
- **Ewing's Sarcoma:** tumours that usually develop in the cavity of the leg and arm bones.
- **Fibrosarcoma and Malignant Fibrous Histiocytoma:** cancers that develop in soft tissues (e.g., tendons, ligaments, fat, muscle) and move to the bones of the legs, arms, and jaw.
- **Giant Cell Tumour:** a primary bone tumour that is malignant (cancerous) only about 10% of the time; most common in the arm or leg bones.
- **Chordoma:** primary bone tumour that usually occurs in the skull or spine.

5.4.2 Epidemiology

The BC Cancer Agency reports that bone cancers account for just 0.5% of all malignant neoplasms in humans.³⁷⁸ Children and young people are more likely than adults to have bone cancer. Although the cause of bone cancer is unknown, genetics appears to play a major role in most cases.^{379,380} There is a suggestion that a higher and sustained increased prevalence in young males may coincide with the adolescent growth spurt.

Risks for bone cancer include age (children and young people have a greater incidence); heredity (familial predisposition) and Paget's disease (a non cancerous disease characterized by abnormal bone development). Ninety-five percent of those who develop bone cancer, however, have no obvious risk factors.³⁸¹ In light of these facts, no primary prevention measures are currently available and there are no guidelines for preventing primary bone cancer.^{382,383}

6.0 DIGESTIVE DISORDERS

The digestive disorders covered in this evidence review exclude acute infectious enteric conditions. Acute infectious enteric conditions have been or will be covered in another evidence review.

6.1 Peptic Ulcers

6.1.1 The Disease

Peptic ulcers are localized tissue destruction of the gastric or intestinal mucosa with damage at least to the depth of the muscle layer known as the muscularis mucosa; below this level are found vessels of sufficient size to cause clinically detectable bleeding.

The basic science of this disease has only recently been understood. For nearly 100 years, physicians thought that ulcers were caused by stress, spicy food, and alcohol. Treatment involved bed rest and a bland diet. The label “peptic” referred to the next mistaken idea, namely, that the peptic activity of digestion is the primary driver of disease development. This led to treating ulcers with antacids. In fact, causation in peptic ulcer disease (PUD) is a more complex story. The etiological investigation took a big leap forward with the discovery of *Helicobacter pylori* and its disease connection in 1982, an achievement which garnered the Nobel Prize in medicine and physiology for two scientists in 2005.³⁸⁴

Ulcers occur in the stomach, the duodenum and other specific sites in the gastro-intestinal tract; based on the two main locations, they are sometimes referred to as gastroduodenal ulcers.

6.1.2 Epidemiology

The most common direct causes of ulcers are:

- infection by *H. pylori*, and
- use of nonsteroidal anti-inflammatory drugs (NSAIDs) to control the pain caused by arthritis and other conditions.

These two etiologies lead to the overwhelming preponderance of PUD cases. For instance, in duodenal ulcer patients not taking NSAIDs, the disease will be due to *H. pylori* infection 95% of the time.³⁸⁵ A recent study in southern Europe suggested that only 1.6% of duodenal ulcers and 4.1% of gastric ulcers were not associated with *H. pylori* or NSAIDs.³⁸⁶ The presence of one or other agency, however, does not always generate disease (thus making them necessary but not sufficient causes). Duodenal ulcers are most commonly related to infection, whereas gastric ulcers are more often derived through NSAID use. Both causes, however, can create ulcers at both sites.

H. pylori exists in up to 50% of the global population, making it the most common chronic bacterial infection in humans. In developing countries, the dominant means of transmission is consumption of sewage-contaminated water or food. Oral-to-oral transmission is also possible (e.g., by kissing), as well as via contaminated secretions (such as vomit). Generally, the bacterium is harder to contract in developed countries, but there, as in other parts of the world,

transmission typically occurs in early childhood, and within a family context.^{387,388} Although *H. pylori* initially induces acute gastritis, this immunological response is generally not sufficient to clear infection from the host. Thus, without treatment, *H. pylori* is a chronic infection that persists for life.³⁸⁹

As for NSAIDs (including aspirin), they tend to work in a particular way, i.e., blocking the prostaglandins which dilate blood vessels and cause inflammation and pain.³⁹⁰ The properties which make NSAIDs effective in the treatment of painful and/or arthritic conditions also create a variety of adverse gastrointestinal effects, from mild dyspepsia to perforated ulcers.³⁹¹ Interestingly, patients with rheumatoid arthritis have twice the rate of serious complications from NSAID use compared to those with osteoarthritis.³⁹² Mortality in the US due to gastrointestinal toxicity from NSAID use is about 2 deaths per 1000 patients per year—a significant phenomenon.³⁹³

While *H. pylori* or NSAIDs are involved in the vast majority of PUD, there are other known, though uncommon causes. These include multiple endocrine neoplasia, duodenal Crohn's disease, radiation and stress or anxiety.³⁹⁴

The prevalence of both *H. pylori* infection and PUD are falling in developed countries. For example, the annual age-standardized period prevalence of peptic ulceration in England and Wales decreased from 3.3/1000 in 1994 to 1.5/1000 in 1998 for men, and from 1.8/1000 to 0.9/1000 for women.³⁹⁵

As the impact of *H. pylori* has decreased, so the importance of NSAIDs as a cause of PUD has increased. Low-dose aspirin is now the fastest growing cause of ulcer complications such as bleeding.³⁹⁶

Whatever the changing incidence and prevalence, the disease still represents a tremendous burden. For example, in 2001, 2.7% of Australians self-reported having duodenal ulceration.³⁹⁷ In the US, 10% of adults have physician-diagnosed ulcer disease at some point, with one third of these individuals reporting having an ulcer in the past year.³⁹⁸ In Canada, approximately 400,000 people have peptic ulcers, and 35,000 new cases are diagnosed each year.³⁹⁹

6.1.3 Evaluating Available Evidence

Primary Prevention

As noted above, the main necessary causes of PUD are *H. pylori* infection and NSAID use. The influence of other risk factors in disease development, such as smoking, depends mostly on which of the two causes is involved.^{400,401}

Given its strong etiological association, the potential value of eradicating detected *H. pylori* has been intensely studied, and remains a lively area of research. Since the discovery of an association between *H. pylori* and ulcers, there have been over 3,000 randomized controlled trials that examined the effect of eradication therapy.⁴⁰²

A preventive role for eradicating *H. pylori* arises in a number of contexts:

- when there is history of ulcers, to prevent recurrence
- when there is a history of complicated ulcers, to prevent new bleeding, perforation, etc.
- population screening and prophylactic treatment
- when NSAIDs are prescribed, especially in a patient with a history of ulcers
- when there is dyspepsia or some other sign suggesting early PUD

The latter two contexts will be dealt with later. As for preventing recurrence, an exhaustive systematic review demonstrated that *H. pylori* eradication was superior to no treatment in preventing recurrence of PUD but not significantly better than standard ulcer healing (anti-secretory) therapy.⁴⁰³ However, another review showed that *H. pylori* eradication was superior to anti-secretory therapy in preventing recurrence of complicated ulcers, or re-bleeding.⁴⁰⁴

We see once again that smoking is implicated in increased disease, though the story is complex. With PUD, smoking mostly functions in conjunction with infection, as there is little evidence of independent influence after *H. pylori* eradication. One Danish study showed the odds ratio of an effect modification demonstrated between *H. pylori* and smoking was 70.9.⁴⁰⁵ While their results basically supported the notion that smoking only causes PUD if infection is present, smoking was also seen to be an independent risk factor after controlling for *H. pylori*. This contradicts earlier reports concluding that smoking is not an independent risk factor.⁴⁰⁶ However, even with the potential impact remaining uncertain, patients should be advised to cease smoking regardless of their infection status.

It is unclear whether smoking increases the risk of NSAID-related ulcers. This means that, though smoking increases PUD at both gastric and duodenal sites, its strongest association is with duodenal ulcers, where *H. pylori* etiology predominates.

In sum, smokers are more likely to develop ulcers; as well, smoking impedes ulcer healing and increases ulcer relapse rates. Thus, not smoking or cessation likely would have a favourable impact on PUD incidence. It could also be positive in terms of PUD progression. Smoking may be a risk factor for complications such as perforation and bleeding, and one long-term study confirmed that mortality rates related to PUD were three times higher in smokers.⁴⁰⁷

While alcohol intake has not been associated with PUD per se, excessive consumption (of beer and spirits more than of wine) has been implicated in the development of *complicated* ulcers that manifest bleeding and perforation.⁴⁰⁸

When NSAIDs are being used, especially in high dose, long-term or with other agents such as glucocorticoids, then taking steps to prevent PUD should be considered. This is especially important when patients are older or have a history of complicated ulcers. There are several preventive approaches available, of varying usefulness:⁴⁰⁹

- Using safer NSAIDs, such as COX-2 inhibitors (though these have recently become notorious due to elevated cardiovascular disease risk). It is also important to note that any protective benefit of COX-2 therapy is eliminated if low-dose aspirin is also being taken.⁴¹⁰
- Acetaminophen is associated with a lower side-effect profile, and is suitable for mild symptoms and patients with spontaneously remitting disease, but it does not control the inflammation which is central to the majority of rheumatoid arthritis pain and disability.
- Various gastroprotective agents⁴¹¹ may be prescribed to make NSAID use safer, but these vary in effect and expense.⁴¹²

Whether *H. pylori* infection increases the risk of ulcer formation in patients using NSAIDs remains a controversial topic, as does the application of *H. pylori* testing and eradication as a prophylactic measure. The evidence is tilting towards the value of this approach, at least in chronic users of NSAIDs who are at a high risk of developing PUD.⁴¹³ One week of eradication therapy in such patients prevents recurrent ulcer bleeding.

Early Detection

H. pylori infection can be detected either with invasive techniques such as endoscopy and biopsy or non-invasive approaches involving serologic assays, urea breath test or stool antigen analysis. The latter two are able to detect “active” infection, whereas the serologic tests only show that the markers of exposure to *H. pylori* are present. In most cases, the experience of dyspepsia would prompt the application of a detection test in the first place. The following table and discussion outline the state-of-the-art in reference to initial management of dyspepsia that may have a preventive benefit in terms of avoiding the full development of ulcers.

Although some studies have suggested that universal screening and eradication for *H. pylori* may be cost-effective,^{414,415,416} most prevention research has focused on the symptomatic patients, i.e., the management of uninvestigated and functional⁴¹⁷ dyspepsia. With the presentation of upper abdominal pain, the choice is between direct investigation (usually via endoscopy) and so-called empiric therapy.⁴¹⁸

If treatment-without-direct-investigation is the preferred option (a position that is in fact supported by the evidence), then the issue becomes: which treatment? The two main empiric approaches are anti-secretory drugs and test-and-treat for *H. pylori*. These methods offer comparable improvements in dyspepsia, with testing for and then eradication of *H. pylori* perhaps having a slight edge (especially since concerns about side effects have recently been allayed).⁴¹⁹ The test-and-treat strategy has been shown to be cost-effective compared against anti-secretory therapy (as well as against early endoscopy).^{420,421} Thus, the test-and-treat strategy is now being recommended by many as the preferred option with younger patients with

uninvestigated dyspepsia showing no alarming signs. This was the position put forward as recently as February 23, 2006, in the *New England Journal of Medicine*,⁴²² as well as in the January 28, 2006, issue of the *British Medical Journal*.⁴²³ However, the results backing up this approach remain marginal and / or debatable. Therefore other reviewers continue to advocate for the rationality of anti-secretory modes of ulcer prevention (and healing).^{424,425} Another option being investigated is combination therapy, *H. pylori* eradication plus an anti-secretory drug.

Of course, regardless of cost-effectiveness arguments, early eradication of *H. pylori* has one distinct advantage over basic endoscopy in terms of our present topic, namely, the likely cure of any ulcers that are present or developing. As such, it combines a detection and prevention role. As described earlier, the same argument can be made with regard to a history of PUD: eradicating *H. pylori* reduces the rate of recurrence.

Despite these advantages, some researchers have suggested caution around aggressive eradication strategies. There is always the danger of creating antibiotic resistance, and possibly eliminating the value of a range of bacteria in the gastrointestinal tract. There may also be other, unforeseen side effects. One recent study demonstrated that *H. pylori* eradication was associated with incidence of obesity, serum total cholesterol and triglycerides.⁴²⁶ In short, it may not be true that the “only good *Helicobacter pylori* is a dead *Helicobacter pylori*.”⁴²⁷

While the “jury remains out” about the advisability of and protocol for *H. pylori* eradication, the scale will probably continue to tip towards such a preventive measure as the other key disease linkage becomes clearer, namely, the one between infection and gastric cancer.^{428,429}

6.2 Inflammatory Bowel Disease

6.2.1 The Disease

Inflammatory bowel disease (IBD) encompasses two diseases both of unknown etiology; i.e., Crohn’s disease (CD) and ulcerative colitis (UC).^{430,431} Although these two diseases resemble each other, they do differ enough to be regarded as independent entities.⁴³² Both diseases cause inflammation in the intestines. The most common symptoms of IBD include diarrhoea (often with bleeding), abdominal pain, malabsorption and weight loss. The many other symptoms may include “fever, anorexia (poor appetite), anemia (low blood counts), skin rashes, especially erythema nodosum (tender red bumps or nodules on the front of the lower legs) and pyoderma gangrenosum (painful skin ulcers), oral aphthous ulcers, and hepatitis (inflammation of the liver).”⁴³³ Patients may also have fistulas, abscesses or fissures around the rectum.

6.2.2 Epidemiology

The incidence of IBD is influenced by geography, ethnicity, age and gender.

There appears to be a geographical distribution with a North-South and West-East slope in incidence. “The occurrence of IBD is high in North America and Northern and Western Europe, is less so in South Africa, Australia, and South and Middle Europe, and is rare in Asia and Africa.”⁴³⁴

Research on different populations and ethnic relations reveal interesting data which may reflect genetic, inherited, environmental and behavioural factors.⁴³⁵

Age is also a factor in this disease. Disease onset occurs more frequently in the second or third decade of life but evidence suggests that events early in life may have long term effects on both health and disease.⁴³⁶

Regarding distribution by gender, UC is slightly more common in men while CD is slightly more common in women.⁴³⁷

Research in Manitoba indicates incidence/prevalence rates of 14.6 and 198.5 / 100,000 for CD and 14.3 and 169.7 / 100,000 for UC.⁴³⁸ In that province, a higher incidence of IBD was associated with higher average family income, a lower proportion of immigrant and Aboriginal populations, and a smaller average family size.⁴³⁹

It has been concluded after consideration of the epidemiological, genetic and immunological data that UC and CD are “heterogeneous disorders of multifactorial etiology in which hereditary (genetic) and environmental (microbial, behaviour) factors interact to produce the disease.”⁴⁴⁰

6.2.3 Evaluating Available Evidence

Among the key modifiable risk factors investigated in association with IBD are smoking, oral contraceptive use, breastfeeding, diet, hormone replacement therapy and appendectomy. The limited research is summarized in Table 21.

Table 21: Research on Risk Factors Associated with Inflammatory Bowel Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Corrao, et al (1998) ⁴⁴¹	Case control	819 cases of IBD and 819 matched controls	The odds ratio and attributable risk of IBD in relation to smoking, oral contraceptive (OC) use and breastfeeding	Increased risk of CD associated with currently smoking (OR 3.0), OC use (OR 3.4) and lack of breastfeeding (OR 1.9). Increased risk of UC associated with formerly smoking (OR 1.7) and lack of breastfeeding (OR 1.5).	“Taken together, the considered factors were responsible for a proportion of IBD ranging from 26% (CD females) to 36% (CD males).”
Baron et al (2005) ⁴⁴²	Population based case control study	564 (282 cases and 282 controls)	To examine environmental risk factors for IBD in a paediatric population prior to developing IBD	Crohn’s Disease- factors associated with an increased risk include family history of IBD (OR 4.3), breast feeding (OR 2.1), bacilli Calmette-Guerin vaccination (OR 3.6), history of eczema (OR 2.1) while regular drinking of tap water was protective (OR 0.56). Ulcerative colitis – increased risk for family history of IBD (OR 4.3), disease during pregnancy (OR 8.9), bedroom sharing (OR 7.1) while appendectomy was protective (OR 0.06).	

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Rodriguez et al (2005) ⁴⁴³	Case control	444 incident cases of IBD and 10,000 matched controls	Assessment of risk factors in 20-84 year olds including smoking, use of oral contraceptives (OC), hormone replacement therapy (HRT) and appendectomy	Increased risk of CD associated with use of OC (OR 3.15), HRT (OR 2.60) and smoking (OR 1.76) while appendectomy was associated with a reduced risk of UC (OR 0.37).	
Sakamoto et al (2005) ⁴⁴⁴	Multi-centre case control study	239 IBD cases aged 15 – 34 and 219 matched controls	To evaluate the role of dietary factors in the aetiology of IBD	Higher consumption of sweets was associated with an increased risk for UC and CD. Higher intakes of fats, oils, fish and shellfish were also associated with increased risk of CD.	

The results of these studies are mixed at best, including different directionality associated with both breastfeeding and smoking. The areas in which two studies agreed both on the risk factor and directionality includes the increased risk of Crohn’s Disease associated with the use of oral contraceptives and the protective effect of an appendectomy associated with ulcerative colitis.

6.3 Gastric Cancer

6.3.1 The Disease

About 90% of gastric cancers are adenocarcinomas; the remainder mostly comprise non-Hodgkin’s lymphomas and leiomyosarcomas. Adenocarcinomas in the stomach come in two categories: the well-differentiated, so-called intestinal type, with cohesive cells forming gland-like structures that often ulcerate, and the diffuse type that involves thickening of the stomach wall but not a discrete mass. The former is more common in males and older age groups.⁴⁴⁵

One of the challenges encountered with gastric cancer is the fact that it is often “clinically silent” at the start, so people frequently present with advanced stages of disease. Once cancer cells have invaded the muscular layer of the stomach wall, 5-year survival rates drop to about 20%.⁴⁴⁶

H. pylori have been strongly associated with gastric cancer. The bacterium is able to invade and colonize the human stomach. There it can interact with gastric epithelial cells, leading to a number of tissue changes and disease conditions, including: inflammation, loss of mucosa (i.e., an ulcer), and development of masses from benign polyps to full cancers.⁴⁴⁷ *H. pylori* was first cultured in 1982, and classified as a carcinogen over 10 years ago.

Two primary pathways are thought to be involved with gastric carcinogenesis: proliferation of epithelial cells in the gut and oxidative stress of stomach mucosa.⁴⁴⁸ The precise molecular mechanisms at work in these processes are still being worked out, including the defensive strategies that protect the bacterium in the unstable, often hostile microenvironment of the stomach.⁴⁴⁹

6.3.2 Epidemiology

It is known that only certain strains of *H. pylori* are highly pathogenic, so only a subset of the population carrying the bacteria actually experience disease. A larger proportion develops some sort of pre-neoplasias, but ultimately only 2% of infected people will get a malignancy. The infected pool is large, however, resulting in stomach cancer being the fourth most common cancer in the world.

There is a wide variation in incidence in the world; for example, the gastric cancer rate in Japan is more than 12 times higher than that seen among US Caucasians. Korea, China and some countries in Latin America also show very high rates. Differences in exposure to *H. pylori* and a range of lesser environmental factors are thought to account for much of the variation in incidence over time and between countries.⁴⁵⁰

The incidence of gastric cancer rises progressively with age; cases in patients under 30 years of age are rare.⁴⁵¹

6.3.3 Evaluating Available Evidence

Although treatments for gastric cancer do exist, there is great optimism about the possibility of environmental prevention because of the following factors:⁴⁵²

- The precancerous process usually takes years
- The “track record” of declining incidence in recent decades
- The main etiologic factors (related to infection and diet) are potentially controllable
- The second and later generations arising from immigrants moving from higher-risk countries such as Japan tend to reflect the lower disease incidence of the host country
- Research into the genetic make-up of the bacteria and the host has identified polymorphisms that confer high risk, leading to the possibility of population screening and prophylactic treatment in people of high susceptibility to cancer development

Primary Prevention

The risk factors identified for gastric cancer, apart from *H. pylori*, include high salt intake. The data for smoking and alcohol consumption are less conclusive.⁴⁵³ The association between occupations and gastric cancer is still under investigation. Selected evidence for risk factors and prevention is offered in Table 22.

Table 22: Research on Risk Factors Associated with Gastric Cancer

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Raj et al (2003) ⁴⁵⁴	Review	128 references		“There is considerable evidence that occupations in coal and tin mining, metal processing, particularly steel and iron, and rubber manufacturing industries lead to an increased risk of gastric cancer.”	Dust is thought to be a contributor but the causative agents are not clear.
Barstad et al. (2004) ⁴⁵⁵	Prospective study	28,463 men and women followed for a total of 389,051 person years	Intake of wine, beer and spirits and the risk of gastric cancer	1-6 glasses of wine per week: RR 0.76 (95% CI of 0.50-1.16) >13 glasses of wine per week: RR 0.16 (95% CI of 0.02-1.18)	“There was no association between beer and spirits drinking and gastric cancer....the present study suggest that a daily intake of wine may prevent development of gastric cancer.”
Tsugane et al. (2005) ⁴⁵⁶	Review	37 references	Intake of salt and the risk of gastric cancer	“While salted food may increase the rate of Helicobacter pylori infection, it can also act synergistically to promote the development of gastric cancer.”	“Based on substantial evidence...dietary modification involving less salt and salted food intake is a practical strategy with which to prevent gastric cancer.”
Zhang and Farthing (2005) ⁴⁵⁷	Review	62 references	Vitamin C, H. pylori and gastric cancer	H. pylori infection reduces the effectiveness of vitamin C. Vitamin C may be protective against gastric cancer but H. pylori reduces this effectiveness.	“Many questions however, remain unanswered regarding the role of vitamin C in H. pylori associated gastric carcinogenesis.”
Malfertheiner et al. (2005) ⁴⁵⁸	Review article	181 references		H. pylori eradication can be effective in preventing gastric cancer development, including the progression to preneoplastic conditions	Despite supportive indications, there is as yet “no conclusive evidence that H. pylori eradication prevents gastric cancer.”

Given the ubiquity of the bacterium and its ease of transmission, it seems unlikely that *exposure* prevention will ever be the cornerstone of a public health strategy, at least not in the developed world. The basic sanitary measures required in developing countries are not really an issue in North America.⁴⁵⁹

At this point, anti-*H. pylori* therapies remain the best option to control disease, one that is recommended for all *symptomatic* infected individuals according to recent professional consensus statements.⁴⁶⁰ Using such an approach with the entire infected population would hardly seem to be feasible.⁴⁶¹ Many uncertainties remain, including the effect of total eradication of *H. pylori* on gastric cancer incidence, and the fact that infection actually seems to be protective against certain cancers.^{462,463} One Canadian review has called for a major demonstration project to help answer some of the scientific and pragmatic questions.⁴⁶⁴

Analyzing molecular markers of disease shows great promise as a treatment prompt.⁴⁶⁵ Detection of high risk polymorphisms and related gene expression in hosts will also allow for targeted prevention through *H. pylori* eradication.⁴⁶⁶ Much more research must ensue before the clinical implementation of this sort of personalized medicine.

As for comparing *H. pylori* eradication methods, the Cochrane review is still at the protocol stage.⁴⁶⁷ The reality is that there has been little recent advance in therapies for *H. pylori*, though many long term intervention trials (with gastric cancer as the end-point) are now underway in the US and Europe.⁴⁶⁸ Many compounds can kill the bacterium *in vitro*, but reproducing such effects in live bodies is more elusive.

Animal models are helping in the development of vaccines; there has been some success, but no clear strategy has emerged.^{469,470} One cost-effectiveness analysis suggested that resource allocation for vaccine development and implementation only makes sense in the context of developed countries.⁴⁷¹

With the possible added risk represented by tobacco use, a clear prevention method is smoking cessation (or encouragements to not take up the habit).⁴⁷² Controlling the intake of salted foods may also help. On the other hand, protection against gastric cancer can be added to the growing list of benefits that has been attached to moderate wine consumption.

Finally, antioxidants in regularly consumed vegetables and fruit are thought to decrease the risk of gastric cancer by up to a third.^{473,474} However, the Cochrane review of antioxidant supplements in the prevention of gastric cancer cast grave doubts on their effectiveness.⁴⁷⁵ Among the flavonoid classes, one case-control study showed that only flavanone (found in fruit) was inversely associated with gastric cancer risk.⁴⁷⁶ In sum, regularly eating whole vegetables and fruit may be more beneficial than trying to abstract the protective dietary component.

Early Detection

Both endoscopic biopsies and non-invasive tests are used to establish whether a gastric disease process has begun, but neither of these approaches are considered cost-effective at a population level.⁴⁷⁷ However, the potential benefits of surveillance may propel this approach onto the high priority list in the next few years.⁴⁷⁸ Correa has suggested that highly susceptible individuals infected with high virulence bacterial genotypes should be targeted for endoscopic monitoring to detect advanced precancerous lesions.⁴⁷⁹

The value of early detection relates to the therapies available to reverse disease. As was seen in primary prevention, the strongest evidence has been accumulated around anti- *H. pylori* therapy, but after the onset of cancer, it seems unlikely that eradicating this organism would reverse the disease.

6.4 Colorectal Cancer

6.4.1 The Disease

Colorectal cancer is any cancer which develops in the colon, rectum or appendix. The colon and rectum are responsible for the final steps of the digestive process, and as such, these areas contain the waste products of digestion. Most colorectal cancers start as polyps, otherwise known as adenomas, which can be defined as an abnormal growth at the site of a mucous membrane. These polyps are an effective avenue for prevention as a pre-cancerous polyp can be present for some time before colorectal cancer becomes active.⁴⁸⁰ Colorectal cancers have a high mortality, but are considered substantially preventable if detected early.⁴⁸¹

6.4.2 Epidemiology

According to The Canadian Cancer Society, an estimated 19,600 Canadians will be diagnosed with colorectal cancer in 2005 and 8,400 will die from it. One in 14 men develop colorectal cancer and one in 28 die from it, while one in 16 women develop colorectal cancer during their lifetime and one in 31 will die from the disease.⁴⁸²

6.4.3 Evaluating Available Evidence

Primary Prevention

The most important preventable risk factors associated with colorectal cancer include physical inactivity, a low consumption of fibre and a high consumption of animal fat/red meat.

Hardman's review of the available evidence in 2001 indicated that a 40-50% reduction in colon cancer among the most active individuals when compared to the least active individuals.⁴⁸³ Slattery has estimated that approximately 12-14% of colorectal cancer can be attributed to the "lack of frequent involvement in vigorous physical activity."⁴⁸⁴ Furthermore, she notes that somewhere between 3.5 and 4 hours of vigorous activity per week may be required to optimize protection. More recent research indicates that both physical inactivity and obesity are risk factors for colorectal cancer.^{485,486}

There also appears to be a relationship between colon cancer and the consumption of certain food groups. In particular, the consumption of red and processed meats is hypothesized to increase the risk of colon cancer while the consumption of dietary fibres (especially wheat bran and cellulose) and certain vegetable (e.g., Brussels sprouts, cabbage, broccoli) appears to reduce the risk of colon cancer. Excess consumption of alcohol, probably in combination with a poor diet, and exposure to tobacco products early in life also appear to increase the risk of colon cancer.^{487,488}

Despite substantial research, the relationship between dietary factors and colon cancer remains inconclusive.⁴⁸⁹ Recent epidemiological evidence from long-term and randomized trials do not appear to support this association.⁴⁹⁰ Hill has suggested that the relationship is more complex than initially suggested due to the variety of colon cancer subtypes and the possible differential effect of certain dietary components on these subtypes.⁴⁹¹

Early Detection

Several tests exist to screen for colorectal cancer, the three most common being the faecal occult blood test (FOBT), sigmoidoscopy and colonoscopy. FOBT detects blood in the stool and is useful as a screening tool because colorectal cancer have the propensity to bleed. A major criticism of the FOBT, however, is its poor sensitivity in detection pre-malignant and early stage lesions.⁴⁹² Flexible sigmoidoscopy examines part of the descending colon, the sigmoid colon and rectum where approximately two-thirds of colorectal cancers arise. This procedure is superior to FOBT as it can detect even small polyps that are occult blood negative but does not visualize/screen the entire colon.⁴⁹³ Colonoscopy allows for visualization of the entire colon and has the best sensitivity of these three screening methods. Disadvantages include cost, increased risk of perforations and bleeding, difficult preparations for the patient and the need for sedation.⁴⁹⁴

Newer, relatively expensive procedures that are not currently recommended for population screening include fecal DNA testing and virtual colonoscopy.^{495,496} Virtual colonoscopy involves the use of thin-section, helical computed tomography to create high resolution two and three-dimensional images of colon.

The U.S Preventative Services Task Force “strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer.”⁴⁹⁷ While this is the current sentiment of most organizations, there are varying recommendations on screening protocols and the age at which screening should begin and end. An earlier onset of initial screening (e.g., age 40 rather than 50) and more frequent screening (e.g., colonoscopy every 5 years rather than every 10 years) is usually associated with screening individuals in higher risk categories.⁴⁹⁸ With respect to discontinuing screening in the elderly, Walter and colleagues note that “decisions to either continue or discontinue screening in the elderly should be based on health status, the benefits and harms of the test, and preferences of the patient, rather than solely on the age of the patient.”⁴⁹⁹ Most organizations do not emphasize one strategy over another but rather stress the importance of screening by any method for all eligible adults.⁵⁰⁰

7.0 GENITOURINARY DISORDERS

The focus in this section of the review will be on renal and bladder stones, chronic kidney disease, and the more common genitourinary cancers. Cancer of the genitourinary system can include a large number of cancers specific to this part of the body. The BC Cancer Agency reports that diagnoses in 2003 of ovarian, uterine, testicular, and other genital cancers as well as kidney and other urinary cancers contributed a total of 1,339 cases.⁵⁰¹ It is beyond the scope of this report to examine all of these cancers. For the purpose of this report, only cancer of the cervix, prostate, and bladder will be considered.

7.1 Renal and Bladder Stones

7.1.1 The Disease

The term urolithiasis generally includes renal, ureteral and bladder stones. Nephrolithiasis means that the stone formed in the kidney. Because ureteral calculi almost always originate in the kidney, the term nephrolithiasis or renal stone is often used.

Urinary tract stone disease is usually caused by the supersaturation of the urine with stone-forming constituents such as calcium oxalate or phosphate. Normal urine contains inhibitors that prevent crystals from forming, growing or aggregating.

Small crystals pass freely. Larger crystal aggregates may be unable to pass and form the nucleus for later stone growth. Small stones may pass relatively easily, but this is usually accompanied by severe pain (renal colic).

Kidney stones consist of four main chemical types. The vast majority of stones are composed of calcium oxalate (70-80%), calcium phosphate or a combination of the two. Struvite stones are the second most common stones (15-20%) followed by uric acid stones. Cystine stones are relatively rare.

After a first stone, 40% of patients will have a recurrence by 5 years, 60% by 10 years, and over 90% by 25 years.

7.1.2 Epidemiology

Renal and bladder stones are relatively common with rates between 1 and 20% of the population. The prevalence of renal and bladder stones varies by region: 1-5% in Asia, 5-9% in Europe, 12% in Canada, 13% in the USA, and 20% in Saudi Arabia. A slightly higher rate of renal stone disease is seen in males compared to females and in Caucasians compared to African Americans. There also appears to be an association between increased BMI and stone formation, particularly in women.⁵⁰²

7.1.3 Evaluating Available Evidence

Primary Prevention

Research on the prevention of renal and bladder stones has focussed on diet, especially the consumption of adequate amounts of water, body weight, and to a lesser extent, physical activity. Selected studies are summarized in Table 23.

Table 23: Research on Risk Factors Associated with Renal and Bladder Stones

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Siener et al (2004) ⁵⁰³	Cohort	527 calcium oxalate stone formers (363 males and 164 females)	Overweight and obesity on the risk of calcium oxalate stone formation	“...The risk of stone formation increased significantly with increasing BMI among both men and women with urolithiasis (p = 0.015).”	“The risk of calcium oxalate stone formation, median number of stone episodes, and frequency of diet-related diseases were highest in overweight and obese men.”
Curhan et al (2004) ⁵⁰⁴	Prospective (8 year follow-up)	96,245 females	Dietary factors and incident kidney stones	The following risks were found for kidney stone formation: a higher dietary calcium intake, RR 0.73 (95% CI of 0.59-0.90); phytate intake, RR 0.63 (95% CI of 0.51-0.78); fluid, RR 0.68 (95% CI of 0.56-0.83); and sucrose, RR 1.31 (95% CI of 1.07-1.60).	
Taylor et al (2004) ⁵⁰⁵	Prospective cohort study (14 year follow-up)	45,619 males	Dietary factors and kidney stones	Relative risks were as follows: Calcium: RR 0.69 (95% CI of 0.56-0.87) but only in men aged <60 yrs Vitamin C: RR 1.41 (95% CI of 1.11-1.80) Magnesium: RR 0.71 (95% CI of 0.56-0.89) Potassium: RR 0.54 (95% CI of 0.42-0.68) Fluid: RR 0.71 (95% CI of 0.59-0.85).	“In conclusion, the association between calcium intake and kidney stone formation varies with age. Magnesium intake decreases and total vitamin C intake seems to increase the risk of symptomatic nephrolithiasis.”
Qiang & Ke (2005) ⁵⁰⁶	Cochrane Review	“No trials of increased water intake ...met the inclusion criteria” of an RCT or quasi RCT, reviewed 1 trial of 199 patients	Water intake and recurrence of urinary calculi	“One trial with 199 patients provided results of increased water intake for the recurrence of urinary calculi. The recurrence rate was lower in the increased water intake group than that of the no intervention group (12% versus 27%, P = 0.008, RR = 0.45, 95% CI 0.24 to 0.84).”	“The evidence from only one trial indicates that increased water intake reduces the risk of recurrence of urinary calculi and prolongs the average interval for recurrences.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Straub & Hautmann (2005) ⁵⁰⁷	Review	53 references	Dietary habits and kidney stone prevention	“Modern lifestyle, dietary habits and obesity emerge to be the promoters of idiopathic stone disease. Cross-sectional studies showed significant correlations between these factors and kidney stones with direct implications on our preventive concepts: normalization of body mass index, adequate physical activity, balanced nutrition and sufficient circadian fluid intake.”	“Up to 85% of all stone patients could anticipate lower risk of stone recurrence with elementary reorientation of their lifestyle and dietary habits. Normalizing the major risk factors is easy and cheap. About 15% of patients forming stones require additional specific pharmacological prevention.”

Research on the prevention of urinary stones suggests that lifestyle factors such as an appropriate diet including a high intake of water, certain minerals such as magnesium and a normalization of BMI is associated with a significant reduction in the risk of stone formation.

Early Detection

Research on early detection of urinary stones is thin. Although using urinary biomarkers for predictive detection may or may not be possible, the literature does not discuss this topic. It also seems the case that early detection in the area of urinary stones would merely give more notice to the patient to adjust dietary patterns. In order to alleviate the burden of urinary stone treatment on the healthcare system, it then seems that the best course of action is to promote proper diet and healthy eating along with proper levels of water intake and continue to treat the remaining 15% that develop stones despite changes to diet.

7.2 Chronic Kidney Disease

7.2.1 The Disease

Chronic kidney disease is a progressive condition that results in significant morbidity and mortality. The National Kidney Foundation defines chronic kidney disease as kidney damage or a glomerular filtration rate (GFR) of less than 60 mL per minute per 1.73 m² (body surface area) for three months or more.⁵⁰⁸ Chronic kidney disease is linked to diabetes mellitus, hypertension, ischemia, infection, obstruction, toxins, and autoimmune and infiltrative diseases. Although it is important to identify the cause(s) of the chronic kidney disease so that specific therapy can be instituted, the disease often progresses despite appropriate treatment. As kidney function deteriorates, patients develop complications related to fluid overload, electrolyte and acid-based imbalances, and the build-up of nitrogenous waste. To survive, some patients eventually need hemodialysis or kidney transplantation.⁵⁰⁹

7.2.2 Epidemiology

The incidence and prevalence of the disease has doubled in the past decade, most likely because improved treatments for hypertension, diabetes mellitus, and coronary disease have increased longevity in affected patients and, therefore, their likelihood of developing chronic kidney disease.⁵¹⁰ Estimated medical and other economic costs of chronic kidney disease are expected to approach \$28 billion annually in the US by 2010, with an additional \$90 billion in annual costs related to associated increases in cardiovascular disease, infections, and hospitalizations.⁵¹¹

Data from the Canadian Organ Replacement Register⁵¹² indicates that: an estimated 2 million Canadians have kidney disease, or are at risk of the disease; in 2005, there were 32,375 Canadians on renal replacement therapy and this number is expected to double over the next 10 years; and over half of new patients in 2005 were 65 years or older. Among the 32,375 patients on renal replacement therapy on December 31, 2005: 12,654 or 39% had a functioning transplant, and 19,721 or 61% were on dialysis.

Causes of chronic kidney disease and related conditions:

- **Hypertension** is a frequent cause of chronic kidney disease. Systemic hypertension causes direct damage to small blood vessels in the nephron. The kidneys lose their ability to autoregulate glomerular filtration flow and pressure. Several trials have demonstrated the benefit of strict blood pressure control in slowing the progression of kidney disease.^{513,514}
- **Diabetes mellitus** is the most common cause of chronic kidney disease. Hyperglycemia is an independent risk factor for nephropathy. The pathophysiology of diabetic nephropathy is complex and most likely involves both hemodynamic and glucose-dependent factors. Studies have shown that the A1C level correlates with loss of renal function and that glycemic control reduces the progression of kidney disease.⁵¹⁵
- **Dyslipidemia** is a primary risk factor for cardiovascular disease and a common complication of progressive kidney disease. Most patients with chronic kidney disease have an abnormal lipid panel that increases their risk for atherogenesis. Dyslipidemia contributes to cardiovascular mortality, which is 10 to 20 times higher in dialysis patients than in the normal population even after adjustments are made for age, sex, and diabetes mellitus.⁵¹⁶
- **Anemia** occurs primarily because of lower production of erythropoietin by the decreased mass of functioning renal tubular cells. It results in fatigue, reduces exercise capacity, decreases cognition, and impairs immunity. Thus it decreases quality of life. In addition, it increases workload on the heart and the related risk of death from heart failure or ischemic heart disease.⁵¹⁷ Study results⁵¹⁸ have shown that correction of anemia can limit the progression of chronic kidney disease and possibly decrease mortality.
- **Smoking** is a strong risk factor for cardiovascular mortality in patients at risk for chronic kidney disease. It is strongly associated with the progress of nephropathy.⁵¹⁹ The results of one small study showed that smoking cessation reduced the progression of kidney disease by 30% in patients with type 1 diabetes.⁵²⁰

7.2.3 Evaluating Available Evidence

Primary Prevention

Studies on primary prevention for chronic renal disease are not detailed in this section, as they are addressed elsewhere. Prevention of cardiovascular disease, a key risk factor for chronic kidney disease, is addressed in this paper under Cardiovascular Disorders. In addition, diabetes is addressed in the section entitled Other Disorders. The prevention of other major causal factors including poor nutrition and smoking have been addressed in the evidence review for the core program on healthy living which includes tobacco cessation, healthy nutrition, and physical exercise.

Early Detection

Early recognition and intervention are essential to slowing disease progress, maintaining quality of life, and improving outcomes. Family physicians have the opportunity to screen at-risk patients, identify affected patients, and ameliorate the impact of chronic kidney disease by initiating early therapy and monitoring disease progression. Aggressive blood pressure control, with a goal of 130/80 mm Hg or less, is recommended in patients with chronic kidney disease. Hyperglycemia should be treated: the goal is an A1C concentration below 7%. For patients with dyslipidemia, statin therapy is appropriate to reduce the risk of cardiovascular disease. Anemia should be treated as well as hyperparathyroid disease. Counselling on adequate nutrition should be provided, and smoking cessation must be encouraged at each office visit.⁵²¹

7.3 Cancer of the Cervix

7.3.1 The Disease

Cervical cancer is the most prevalent and the most studied form of HPV-related cancer; as such, it has been paradigmatic in research on HPV-mediated tumorigenesis.⁵²² The cancers of the cervix mainly include carcinomas, especially squamous cell carcinoma (80 to 90% of cases) and adenocarcinomas.^{523,524,525}

7.3.2 Epidemiology

Proactive cytology screening and management has contributed to a significant decline in overall cervical cancer incidence and mortality in the last 50 years, however the downward trend seems to have flattened recently.^{526,527} In fact, the mortality rate in the US has remained virtually unchanged since the mid-1980s. Reasons for the “plateauing” include increasing numbers of high-risk women who are not regularly screened and sexual activity at a younger age.⁵²⁸ Another anomaly noted in US statistics is the recent increases in incidence of cervical adenocarcinomas among younger women.^{529,530} The trends beyond North America also require surveillance; for instance, increasing cervical cancer incidence is being reported in some European settings.^{531,532}

The estimated number of new cases of cervical cancer in Canada for 2005 is 1,350, while some 400 women are expected to die of the disease. The incidence rate in BC, at about 7 per 100,000 women, represents about 150 new cases for 2005.⁵³³ This reflects a decline in incidence compared with data from the 1990s.⁵³⁴

In Canada, incidence is particularly high within aboriginal populations; among the Inuit, cervical cancer accounts for 15% of female cancers, and the age-standardized rate among First Nations in Saskatchewan is 6 times higher than the national average.⁵³⁵

Apart from persistent infection with high-risk HPV types - and the consequent connection to sexual activity - proposed risk factors for progression of lesions towards cancer have included viral load, smoking, parity,⁵³⁶ and long-term use of oral contraceptives.^{537,538,539,540,541,542,543,544} For example, women who smoke do not seem to clear an HPV infection as quickly as non-smokers.⁵⁴⁵

7.3.3 Evaluating Available Evidence

Primary Prevention

Nutritional factors such as beta-carotene, folate, and vitamins A and C appear to play a protective role.^{546,547,548,549} Diet ultimately may influence between-country differences in cervical cancer rates, which could suggest a possible public health prevention strategy for regions with nutritional deficiency.^{550,551}

Co-infections may play a role in cervical carcinogenesis.^{552,553,554,555} This is especially true with the immunocompromised conditions related to HIV. Infection with HIV has been shown to be a strong risk factor for precancerous lesions and at least *in-situ* cervical cancer.⁵⁵⁶ The evidence for a connection between HIV and *invasive* cervical cancer rates has been more equivocal.⁵⁵⁷ Fortunately, the standard prevention programs are still effective for HIV-positive women, offering the possibility of reduced incidence of invasive cervical cancer.⁵⁵⁸

One reviewer noted that “the understanding of cervical cancer as a preventable disease process hinges on the concept that it is fundamentally a sexually transmitted disease with a known causative agent: the human papillomavirus (HPV).”⁵⁵⁹

There is essentially a one-to-one connection between cervical cancer cases and the detection of HPV DNA, suggesting that “the prevention of HPV infection would virtually eliminate cervical cancer.”⁵⁶⁰ As Walboomers et al. concluded in 1999, “the presence of HPV in virtually all cervical cancers implies the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer.”⁵⁶¹ In short, HPV has been proposed as the first-ever necessary cause of a human cancer identified by researchers.^{562,563} Put differently, there is a strong consensus implicating the persistence of “high risk” or oncogenic HPV types as the main risk factor for the development of cervical cancer.⁵⁶⁴

While HPV has been identified as a necessary cause of cervical cancer, the fact that a large percentage of women infected with high-risk HPV types do not progress to cancerous states demonstrates that the presence of the virus is usually not a *sufficient* cause of disease. Several potential co-agents have been noted above, including smoking and other infections. Genetic susceptibility in the host and genetic variants of the high-risk virus types have also been an area of intense interest in terms of explaining why only a subset of infected women develop cancer.^{565,566}

Vaccination can either be prophylactic (preventing contact with a virus from developing into an active infection) or therapeutic (clearing an existing infection). There has been a great deal of excitement and energy around creating and testing a vaccine targeting HPV. This has been a special focus in the context of developing countries, for two reasons: the bulk of the annual 200,000 deaths related to cervical cancer occur there (making it the most prevalent cause of female cancer mortality), and less than 5% of these women currently participate in the other major public health strategy, namely, screening.⁵⁶⁷ As the potential launch date for an HPV vaccine nears, however, there are also questions regarding the applicability of such a vaccine in nations with comprehensive cervical screening programs.

There have been several studies exploring either preventive or therapeutic HPV vaccines in humans. These studies have considered monovalent, bivalent, and quadrivalent vaccines and are outlined in Table 24.

Table 24: Research on the Efficacy of Vaccines for HPV Infection

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Koutsky et al. (2002) ⁵⁶⁸	Double-blind, placebo-controlled, randomized trial.	2,392 women 16-23 years of age	To determine whether an HPV 16 vaccine would prevent HPV 16 infection in women.	The vaccine not only prevented the development of disease, but also seems to prevent “its causative agent from residing in the genital tract where it can infect new sexual partners.”	The main caveat emerging from this study was evidence that vaccination against one type of HPV will not protect against infection by different types. Another limitation is that the vaccine does not appear to reverse infection or cervical cancer once it is present.
Harper et al. (2004) ⁵⁶⁹	Double-blind, multi-centre, placebo-controlled, randomized trial.	1,113 women 15-25 years of age	To assess the efficacy of a bivalent vaccine against incident and persistent infections with HPV 16 and HPV 18.	In women who followed the full vaccination protocol, vaccine efficacy was 91.6% against incident infection and almost 100% against persistent infection with HPV 16/18.	The vaccine was highly efficacious. This was true even among the partially adherent subset.
Villa et al. (2005) ⁵⁷⁰	Double-blind, placebo-controlled, randomized trial.	1,158 women 16-23 years of age	To assess the efficacy of a quadrivalent vaccine targeting the HPV types associated with 70% of cervical cancers and 90% of genital warts.	The vaccine reduced the combined incidence of persistent infection from HPV 16/18/6/11—as well as related genital disease such as cervical pre-cancers and genital warts—by 90%.	

Based on these three studies, it appears that a vaccine for HPV is both highly efficacious and very well-tolerated. Efficacy ranges from 90 to 100%. The lower efficacy seems to be seen when vaccination protocols are not completely followed or when vaccines target multiple HPV types in a less select group of women (e.g., including those with a previous HPV infection).

Early Detection

Cancer screening is designed to detect the presence of precancerous cells or lesions and then prompt preventive measures. By identifying the precursor lesions associated with HPV infection, screening programs based on cytology⁵⁷¹ have reduced the incidence of invasive cervical cancer. The most common screening test that goes beyond a regular gynaecologic examination is the Pap smear, the name being a shortened form of its originator, G.N. Papanicolaou.⁵⁷² He published results concerning the correlation between abnormalities in scraped cells and cervical cancer in a cornerstone paper in 1941. The aim, and the eventual result, of a simple screening test was to save “millions of women who would otherwise have discovered their cancer of the cervix uteri at a non-curable stage.”⁵⁷³ Precursor lesions usually appear a considerable length of time before a carcinoma; thus early detection and prompt management can lead to effective prevention of the disease. Table 25 outlines two systematic reviews of a large number of studies which suggest that screening is a key component in cervical cancer prevention.

Table 25: Research on Early Detection of Cervical Cancer

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Hartmann et al. (2002) ⁵⁷⁴	Systematic evidence review	109 references	To examine evidence about risks/benefits of screening among older women and those who have had hysterectomies.	Findings consistently showed a reduced risk of cervical cancer or abnormality with increasing age. Vaginal lesions are rare after a hysterectomy. Validated literature about new diagnostic tools is limited. HPV testing was found to be competitive with conventional cytology.	“The yield of screening among older women who have been previously screened decreases with age; if recommendations are not modified, older women are disproportionately likely to have evaluations for false-positive findings.”
U.S. Preventive Services Task Force (USPSTF) (2003) ⁵⁷⁵	Systematic evidence review	32 references	Summary of the current USPSTF recommendations on screening for cervical cancer.	Five recommendations: “strongly recommends screening for cervical cancer in women who have been sexually active and have a cervix” “recommends against routinely screening women older than 65 for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer” “recommends against routine Pap smear screening in women who have had a total hysterectomy for benign disease” “concludes that the evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer” “concludes that the evidence is insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer”.	

7.4 Prostate Cancer

7.4.1 The Disease

The prostate is an exocrine gland of the male reproductive system that secretes and stores fluid contributing to the semen. A healthy human prostate is slightly larger than a walnut and surrounds the urethra just below the urinary bladder. It is located in front of the rectum and can be felt during a rectal exam. Prostate cancer is now the most commonly diagnosed cancer in men. The risk of developing prostate cancer after age 50 for men born in Canada, is estimated at one in seven.⁵⁷⁶ With a history of the disease in the man’s family, this risk increases by 2 to 4 times. Not only is the risk of getting prostate cancer high, but its successful treatment may leave

the man both impotent and incontinent. It is also suggested that among types of cancer mortality, prostate cancer is second only to lung cancer.⁵⁷⁷ Prevention of this debilitating disease is a worthwhile and significant goal.

7.4.2 Epidemiology

Prostate cancer has been an epidemiological enigma.⁵⁷⁸ While many different risk factors have been studied, the etiology of prostate cancer remains relatively unknown. The main known risk factors are age, race and family history. Other potential risk factors have been studied, including diet (especially the role of animal fat and vitamin supplements), tobacco consumption, exercise, occupational exposures to cadmium, zinc and pesticides, hormone status, history of sexually transmitted disease and vasectomy.⁵⁷⁹ The results of studies assessing these variables, however, remain inconclusive.

Perhaps the most compelling evidence for race as a risk factor comes from an international comparison of age-standardized incidence rates, as shown in Figure 8.

Figure 8: International Comparison of Age-Standardized Incidence Rates for Prostate Cancer

USA – Black Population	137.0
USA – White Population	100.8
Canada	64.7
Japan	6.8
China	2.3

Source: Table 15, Canadian Cancer Statistics, 1998

Note:

- 1) Rates are standardized to the World Standard Population and cannot be compared to other figures standardized to the 1991 Canadian population.
- 2) Based on data from 1998-1992.

The variation in international incidence rates is significant. There may be, however, several possible reasons for this variance.⁵⁸⁰ The first is that the identified differences are in fact true differences. The second is potential differences in the completeness of reporting the disease to registries in the various countries. The third is potential differences in the prevailing clinical interest in reporting the disease. And the fourth is changes in practices of screening for the disease. Each of these reasons may account for a portion of the international variation in the incidence of prostate cancer but the overall magnitude is such that race as a risk factor is highly likely.

The American Cancer Society suggests that as many as 234,460 American men will be diagnosed with prostate cancer in 2006. One in six men will be diagnosed with this disease in his lifetime and 1 in thirty-four men will die from this disease.⁵⁸¹ Prostate cancer is also the most common cancer among Canadian men. In 2005, the Canadian Cancer Society predicted that 20,500 Canadian men would be diagnosed with the disease and 4,300 Canadian men would die of it. They state that every week, 394 new prostate cancer diagnoses will be made and 83 Canadian men will die of it.⁵⁸²

7.4.3 Evaluating Available Evidence

Primary Prevention

A growing body of evidence suggests that some micronutrients, supplements or dietary components may reduce the risk of prostate cancer. Of the vitamins, vitamin E is the most promising at this time. It has antioxidant activity and some scientists feel that this may explain its possible anticancer effect, the exact mechanism of which is unknown.

The minerals zinc and selenium have been suggested to protect against prostate disease. While the prostate has some of the highest levels of zinc in the body, the effect of zinc has really not been sufficiently studied to allow an evaluation of this substance. Selenium on the other hand, has been studied extensively and in almost all studies, has been found to have a protective effect against prostate cancer.⁵⁸³ Selenium is available in a number of formulations including brewer’s yeast tablets.

Isoflavenoids are a class of substances found in plants that have a weak female-hormone (estrogen) activity and these substances may reduce prostate cancer risk by decreasing the male hormone stimulation of the prostate. Phytoestrogens are found in soy products leading to a suggestion by some scientists that the soy-rich diet of Asian men may partially explain their low rates of prostate cancer. Green tea is similarly thought to have chemopreventive properties.⁵⁸⁴ Carotenoids are a class of vitamin A-like substances that may cause abnormal cells to revert back to a more normal form. They are generally found in green leafy and yellow vegetables. One specific carotenoid, lycopene, found in cooked tomato products and best absorbed with some fat in the meal, has been suggested to be associated with a reduced prostate cancer risk.⁵⁸⁵

A family history of prostate cancer may point to a common exposure to environmental factors or to an inherited susceptibility. Studies in this area tend to be biased due to the increased awareness of the disease in the family and the heightened probability of screening for the disease. Nevertheless, a number of studies have found a significant increase in the risk of prostate cancer if there is a family history of the cancer. The relative risk of prostate cancer is approximately two to three times higher in men with one first degree relative with prostate cancer than those who do not have a family history. How much of this additional risk is associated with environmental, dietary, or genetic factors has been difficult to assess.⁵⁸⁶

Table 26: Research on Prevention of Prostate Cancer

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Giovannucci (2005) ⁵⁸⁷	Meta-analysis	11 case-controlled studies and 10 cohort studies	Summarize the results of recent studies on lycopene and prostate cancer.	The meta-analysis indicates a 25-30% reduction in the risk of prostate cancer associated with a high intake of cooked tomato products.	
Sonn et al. (2005) ⁵⁸⁸	Systematic review	93 references	To review the current literature on the relationship between dietary components and prostate cancer (PC).	Confirmed the results of Giovannucci above re-cooked tomato products. Selenium is associated with a reduced risk of PC. Green tea may be associated with a reduced risk of PC.	

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Early Detection

Prostate cancer is a disease requiring effective detection as well as prevention measures. There continues to be a lack of consensus, however, among national organizations and professionals regarding the benefit of prostate cancer screening. Controversy around lack of accuracy with numerous “false positives” and the resulting increased anxiety fuels this debate. The American Cancer Agency continues to recommend an annual digital rectal exam (DRE) and a prostate-specific antigen (PSA) test be offered to men over 50 years of age. Men at high risk (family history or of African descent) should be offered this screening at age 45 years.^{589,590} No Canadian Cancer Agency, however, recommends PSA for routine screening.

Table 27 describes the results of three reviews which consider the available evidence regarding the use of PSA screening for the early detection of prostate cancer.

Table 27: Research on Early Detection of Prostate Cancer

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Harris & Lohr (2002) ⁵⁹¹	Systematic evidence review	164 references	To assist the U.S. Preventive Services Task Force in reviewing evidence on screening and treatment for prostate cancer	Prostate-specific antigen (PSA) and digital rectal examination (DRE) are able to detect prostate cancer at an earlier stage than could be detected clinically. The heterogeneity of prostate cancer, however, presents a problem. It appears that most cancers detected by screening are clinically unimportant. There was no conclusive evidence that screening reduces prostate cancer mortality.	Research can help by developing new screening methods that will reduce harm and cost.
U.S. Preventative Services Task Force (USPSTF) (2002) ⁵⁹²	Summary Recommendation		Statement of the current USPSTF recommendations on screening for prostate cancer and the supporting scientific evidence.	“The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes.” Screening was also found to be associated with potential harms including false positives, anxiety etc.	“Evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.”
Postma & Schroder (2005) ⁵⁹³	Systematic evidence review	72 references	To review PSA screening studies in light of ongoing debates over the last decade. Ten criteria developed to justify population-based screening provide the backbone of this review.	Despite over ten years of U.S. recommendations for annual PSA testing, there remains no conclusive evidence that PSA screening is beneficial.	“At the moment, there is no scientific basis for population-based prostate cancer screening outside of randomized clinical trials that are designed to assess its effectiveness and identify men who might benefit from screening.”

7.5 Bladder Cancer

7.5.1 The Disease

Bladder cancer is one of the most common cancers of the urinary tract and is the ninth most common cancer among men.

The most common symptom of bladder cancer is blood in the urine, although blood in the urine may also be associated with bladder infection or renal stones. The blood often appears suddenly with no apparent cause, and there is unlikely to be any pain associated with it. Sometimes blood clots can form and cause pain or obstruction to the flow of urine.

7.5.2 Epidemiology

In British Columbia, there were 471 new bladder cancer cases in 2003. Of these, 352 (75%) were in men. The vast majority of new bladder cancer cases occur between the ages of 60-79 (268 or 57%).⁵⁹⁴

7.5.3 Evaluating Available Evidence

Primary Prevention

Modifiable risk factors potentially associated with the risk of bladder cancer are physical activity, artificial sweeteners, alcohol consumption and smoking.

Table 28: Research on Risk Factors Associated with Bladder Cancer

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Zeegers et al. (2000) ⁵⁹⁵	Meta-analysis	8 cohort and 35 case control studies	To summarize and quantify the impact of different smoking characteristics on urinary tract cancer risk	Smoking status and amount and duration were associated with an increased risk of urinary tract cancer. The summary odds ratio for smokers and former smokers, compared to non smokers, was 3.33 (95% CI of 2.63-4.21) and 1.98 (95% CI of 1.72-2.29).	“In Europe, approximately half of urinary tract cancers cases among males and one-third of cases among females might be attributable to cigarette smoking.”
Sommer et al. (2003) ⁵⁹⁶	Review	91 references	To review literature on the association of lifestyle issues and genitourinary tumours.	“Smoking appears to be the most relevant lifestyle factor significantly increasing both incidence and mortality from bladder cancer.” Physical activity may be associated with a decreased risk while the results regarding alcohol consumption are mixed. “So far no single study has convincingly demonstrated a statistically significant risk of bladder cancer due to the consumption of artificial sweeteners.”	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Zeegers et al. (2004) ⁵⁹⁷	Systematic review	102 references	The association between smoking, beverage consumption, diet and bladder cancer was reviewed	A clear positive association with cigarette smoking and bladder cancer. Other forms of smoking were not clear. A small but non-significant association between alcohol consumption and bladder cancer in men. Total fluid intake is not associated with bladder cancer. A small decrease in risk is associated with increased fruit consumption and no association with vegetable intake. There are mixed associations with vitamin intake and bladder cancer.	The most important risk factor for developing bladder cancer was determined to be cigarette smoking.

The strong conclusion from these evidence reviews is that cigarette smoking increases the risk of bladder cancer. The role of other lifestyle factors, including an increased risk in men associated with alcohol consumption and a possible decreased risk associated with physical activity, is considerably less certain.

8.0 CARDIOVASCULAR DISORDERS

Heart diseases are often grouped into 5 categories: congenital heart defects, coronary artery disease (CAD), heart failure, valvular heart disease, and electrophysiological problems. The focus in this report will be on coronary artery disease and heart failure.

8.1 Coronary Artery Disease

8.1.1 The Disease

The most common type of cardiovascular disease (CVD) is coronary artery disease (CAD), also known as coronary heart disease. The basic pathophysiology involves atherosclerotic plaques accumulating in and narrowing the coronary arteries (a process known as stenosis), and eventually causing reduced or even interrupted blood flow. When heart tissue is no longer supported by the level of blood flow (a condition known as ischemia), a myocardial infarction (heart attack) commonly occurs. The term for the symptoms (especially angina, or chest pain) associated with such events is acute coronary syndrome.

The most serious acute events result from plaque rupture and consequent thrombus formation, leading to abrupt occlusion of the arterial lumen, reduced blood (and oxygen) flow to the heart muscle, tissue death, and disturbed cardiac function. This is the classic heart attack.⁵⁹⁸ In summary, then, CAD may lead to angina pectoris,⁵⁹⁹ silent ischemia,⁶⁰⁰ severe cardiac insufficiency, myocardial infarction (MI), and sudden cardiac death.⁶⁰¹

8.1.2 Epidemiology

CVD remains the leading cause of death in Canada and other industrial countries. Over a third of the deaths in Canada may be attributed to CVD.⁶⁰² Among these, deaths due to CAD dominate, especially due to heart attacks. Figure 9 indicates CVD-related mortality in Canada in 1999.⁶⁰³

Figure 9: Cardiovascular Disease Mortality, Canada, 1999

Cause	Deaths	%
Myocardial Infarction	20,926	26.5
Other CAD	21,693	27.5
Heart Failure	4,491	5.7
Cerebrovascular Disease (Stroke)	15,409	19.5
Aortic Aneurysm	2,164	2.7
Other CVD	14,259	18.1

Source: Adapted from Public Health Agency of Canada

While it is well-known that behavioural/lifestyle considerations (especially related to dietary components such as cholesterol) play a large role in risk analysis related to CAD, heredity is actually thought to contribute about half of the total risk for atherosclerosis. This fact explains the importance of considering patient ethnicity and different genotypes when considering risk.⁶⁰⁴ The incidence of CAD is not consistent across the ethnically diverse populations of Canada. Studies among Aboriginal peoples and South Asians reveal higher incidence, whereas Chinese Canadians demonstrate a lower rate of CVD.^{605,606,607} There is a strong link between diabetes and CVD—indeed, a large component of CAD prevention may be characterized as avoiding heart

problems secondary to diabetes.⁶⁰⁸ Recent increases in CAD among some Canadian Aboriginal peoples have been traced to genetic susceptibility related to diabetes.⁶⁰⁹

Age is an even more crucial non-modifiable risk factor. As the population gets older, it is expected that the prevalence of CAD will increase, with a concomitant growth in the financial impact on the health care system.^{610,611} It is estimated that already over 10% of all healthcare spending in Canada is related to CVD.⁶¹²

One of the most enduring myths is that heart disease is an affliction of men. The tendency is for only a minority of women in a country like Canada to realize that CVD is the leading cause of death for women as well.⁶¹³ Compared to men, the onset of CVD in women is somewhat later, by approximately 10 years, and women are less likely than men to seek care or be investigated and treated with a wide a range of interventions.⁶¹⁴

The evidence on gender differences in the burden of CVD for women in Canada reveals some important differences. Factors such as diet, obesity, smoking status, psychological factors and health literacy have been shown to have a different effect on women's heart health, when compared to men. In particular, women with a family history of CVD are at greater risk compared to men; women experience more dramatic changes in lipid profiles with age and experience greater health risks from smoking. Risk factors for women are further shaped by social, economic, and historical processes which enhance or hinder opportunities for women's cardiovascular health. For example, gender-biased research and the historical framing of heart disease as a man's disease has contributed to the lack of general awareness regarding women's heart disease. Some evidence also indicates that women tend to value other's health above their own, what has been referred to as an "otherness orientation". Moreover, different sub-populations of women experience different risk, for example, non-white ethnic minority, low-income, and rural-dwelling women are among those who have greater risk and encounter more barriers to preventive health.⁶¹⁵

8.1.3 Evaluating Available Evidence

Primary Prevention

As noted above, diseases of the circulatory system are the number one cause of death in North America, and, because of this, the associated risk factors have been extensively studied. The most intense behavioural focus has been on physical activity, not smoking, and a healthy diet—one including unsaturated fats, whole grains, fruit, vegetables, nuts and fish. These approaches represent relatively inexpensive, potentially non-medical controls, more or less accessible by every individual. Furthermore, activity, smoking cessation, and healthy diets have been shown as potentially effective in reducing CAD.

For example, Åkesson et al. studied a combination of lifestyle factors in women, including diet, exercise, smoking, and alcohol consumption, and identified an ideal combination that reduced the chance of heart attack by 92% compared to the least healthy stratum. As noted in the table below, the authors suggested that as many as 77% of the heart attacks that occurred in the study population could have been avoided with adherence to suggested lifestyle standards.

Not surprisingly, the Cochrane Collaboration has been active in this area of health care, with many completed reviews and several in the protocol pipeline. For instance, an older review by Hooper et al. confirmed that “cutting down or reducing the fat we eat may reduce our risk of heart disease.”⁶¹⁶ However, as detailed in the table below, the results of the review were, at best, modest. Similarly, other Cochrane reviews were less positive than, for example, Hu and Willett (see the table) about the effectiveness of certain diets, including the consumption of whole grains, omega-3 fatty acids, and low glycaemic index foods.^{617,618,619} Finally, two Cochrane reviews have suggested that offering dietary advice can help lower biological risk factors for CAD in the short term, with physicians being less effective than nurses or dieticians, but (remarkably) all professional input being trumped by self-help resources.^{620,621}

Beyond lifestyle factors, several more direct biological markers are associated with CAD, including cholesterol levels, hypertension, and obesity. This raises another category of primary prevention involving drugs aimed at lowering risks of coronary artery disease events through medical control of cholesterol or some other biological factor. Pravastatin is one drug that has been found to lower cholesterol, and therefore also reduce risk of heart disease (see the table below). The Cochrane review of statins preventing CVD is still at the protocol stage.⁶²² The same is true for many other therapies aimed at lowering the risk of heart disease. The Cochrane reviews that have been completed have either not generated a favourable conclusion (e.g., for hormone replacement therapy or the investigational drug triflusal) or, in the case of several secondary preventive measures, have suggested that more extensive studies are required.^{623,624,625} Similar to the result for self-help approaches noted above, one Cochrane review supported personal or family counselling/education over pharmacology alone for achieving risk factor reduction.⁶²⁶

A very common drug used to protect against CAD is aspirin, though both mixed and adverse outcomes have been recorded. In particular, aspirin increases the risk of gastrointestinal bleeding.⁶²⁷ Although the USPSTF does recommend aspirin for those considered at risk for CAD, cautions pertain to more indiscriminate usage. In a Swiss study, for example, Rodondi et al. contend that more targeted use of aspirin could still reduce the expected CAD deaths by almost 10%, while avoiding 700 cases of gastrointestinal bleedings and hemorrhagic strokes over a ten-year period among those at low risk of coronary events.⁶²⁸

Also of note are studies on the efficacy of aspirin in women compared to men. The Women’s Health Study, a randomized controlled trial of low dose aspirin in women, demonstrated a significant reduction in the risk of stroke but not for MI.⁶²⁹ These findings were confirmed in two recent meta-analyses of randomized controlled trials of aspirin for the primary prevention of cardiovascular events. The studies demonstrated that aspirin reduces the risk of MI in men, but not women, and reduces the risk of stroke for women but not men.^{630,631} In addition, studies have found that women reported more contra-indications to aspirin than men (20.5% versus 12.5%).⁶³²

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Table 29: Research on Risk Factors Associated with Coronary Artery Disease

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Hooper et al. (2000) ⁶³³ Cochrane	Review	27 studies	CVD mortality and events with reduced or modified intake of dietary fat	Significant protection from cardiovascular events (rate ratio 0.84, 95% CI 0.72-0.99). The result became non-significant on sensitivity analysis. Trials for more than 2 years showed significantly reduced events in high risk groups.	
Hu & Willett (2002) ⁶³⁴	Review	147 studies and reviews	Optimal diet for prevention of CAD	This study found 3 effective strategies: substitute unsaturated fats for saturated and trans-fats, increase consumption of omega-3 fatty acids, and consume a diet high in fruit, vegetables, nuts and whole (rather than refined) grains.	“Such diets, together with regular physical activity, avoidance of smoking, and maintaining a healthy weight, may prevent the majority of cardiovascular disease in Western populations.”
USPSTF (2002) ⁶³⁵	Review	17 studies	Aspirin in primary prevention of cardiovascular events	“Men older than 40 years, postmenopausal women, and younger people with risk factors for coronary heart disease (e.g., hypertension, diabetes, or smoking) are at increased risk for heart disease and may wish to consider aspirin therapy.”	
Hung et al. (2004) ⁶³⁶	Cohort study	71,910 women & 37,725 men	Fruit & vegetable intake and CVD risk	The relative risk of cardiovascular disease for people eating five servings of fruit and vegetables a day was 0.88 (95% CI, 0.81-0.95).	
Ridker et al. (2005) ⁶³⁷	Randomized, double-blind, placebo-controlled trial	39,876 healthy women	Low-dose aspirin in CVD primary prevention	“... aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes, leading to a nonsignificant finding with respect to the primary end point.”	
Mozaffarian & Rimm (2006) ⁶³⁸	Clinical review	207 studies	Fish intake and CAD	“Modest consumption of fish (e.g., 1-2 servings/wk) ... reduces risk of coronary death by 36% (95% CI, 20%-50%) and total mortality by 17% (95% CI, 0%-32%).”	“For major health outcomes among adults, based on both the strength of the evidence and the potential magnitudes of effect, the benefits of fish intake exceed the potential risks.”
Åkesson et al. (2007) ⁶³⁹	Factor analysis in a prospective cohort	24,444 post-menopausal women	Diet, physical activity, alcohol consumption, smoking, waist-hip ratio and MI	A combination of low-risk diet, 40 minutes of daily walking or biking, moderate alcohol consumption, not smoking and a waist-hip ratio below the 75 th percentile reduced risk of MI by 92% (95% CI 72-98%).	“This combination of healthy behaviours, present in 5% [of the women], may prevent 77% of MI’s in the study population.”
Wister et al. (2007) ⁶⁴⁰	Randomized controlled trial	315 primary prevention subjects	Low-intensity lifestyle intervention versus usual care and CAD risk factors	Cholesterol, blood pressure, and other indicators were significantly improved.	“We found evidence for the efficacy of an intervention addressing multiple risk factors for primary prevention at 1 year using Framingham risk score report cards and telephone counselling.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Domanski (2007) ⁶⁴¹	Review	3 trials	Effect of cholesterol-lowering pravastatin on coronary events	“After an average follow-up of 4.9 years, there was a statistically significant difference in the rate of the primary end point, nonfatal myocardial infarction or death from coronary heart disease, between the pravastatin group and the placebo group (5.5% vs 7.9%, P<0.001).”	
Stanek et al. (2007) ⁶⁴²	Retrospective cohort analysis	30,348 patients	Relationship of different lipid categories with CVD events	“Therapeutic strategies should focus on assessment and management of multiple lipid abnormalities.”	
Bouchard et al. (2007) ⁶⁴³	Cohort study	20,543 patients	Adherence to statins and nonfatal CAD events	“The incidence of nonfatal CAD events decreases when >90% of the prescribed medications is used over at least one year.”	

Whatever the impact of risk factors, reduction targets, and the interventions aimed at them, the reality is that a large percentage of Canadians at risk of CAD are being inadequately addressed. From physical inactivity to dyslipidemia, there is a large gap between need, treatment, and adherence that must be addressed for further progress on heart disease.^{644,645,646} As suggested by the last two studies in the table, management of lipids is a particularly vital and challenging goal. However, the recent Canadian RCT conducted by Wister et al. (see above) also suggests that low-intensity approaches across a broad population hold great promise.

Finally, in terms of investigational risk factors, research has also been conducted on the connection between cardiovascular diseases and depression. Depressive disorders may be considered a risk factor for coronary incidents, but it is unknown whether antidepressant treatment can improve cardiovascular outcomes.⁶⁴⁷

The British Columbia Guidelines and Protocols Advisory Committee (GPAC) has noted that key risk factors for coronary artery disease include smoking, lack of physical activity, unhealthy eating habits, and excess body weight.⁶⁴⁸ “Excess body weight and lack of physical activity contribute to diabetes, increased blood pressure, and dyslipidemia, which in turn significantly increase the risk of heart disease and stroke.” Physicians are encouraged to advise complete cessation of smoking and exposure to second-hand smoke, moderate intensity dynamic activity (such as walking 3 km in 30 minutes once per day or walking 1.5 km in 15 minutes two times per day, jogging, cycling, or swimming), maintenance of a healthy body weight, or, if overweight, loss of weight, and to recommend a diet that emphasizes fruits, vegetables, low-fat dairy products, fibre, whole grains, and protein sources that are low in trans-fat, saturated fat, and cholesterol while reducing sodium intake and increasing consumption (at least 2 servings per week) of fish that are high in omega-3 fatty acids.

Early Detection

The first symptom of CAD is often a heart attack, leading to the obvious drive to develop screening techniques to provide warnings before such serious acute events occur. Initial screening methods involve putting stress on the heart muscle in a controlled setting, either through exercise or chemical stimulation. If non-invasive examinations are inconclusive, the standard test is a coronary angiogram, which involves the insertion of a catheter via an artery in order to inject radiographic contrast material into heart vessels. The X-ray images then taken are

intended to show the extent of arterial blockages.⁶⁴⁹ The development of new angiographic techniques is ongoing, including multi-slice computerized tomography.⁶⁵⁰ The ultimate goal is a completely non-invasive method that still accurately determines the risk of heart disease.

Current standard methods of screening for CAD demonstrate certain downsides. False-positive tests can lead to over-treatment, including invasive procedures with sometimes high associated risks. As many as 35% of coronary angiograms are negative, which means that, for instance, over 350,000 people are tested unnecessarily in the U.S. each year.⁶⁴⁹ For this reason, the USPSTF, while recognizing that tests can sometimes detect heart disease before symptoms appear, recommends against various forms of screening in people deemed at low risk for CAD. Such cautions apply to exercise treadmill tests, electrocardiography, and electron-beam computerized tomography.⁶⁵¹

Studies have found that women were about 40% less likely to be referred for diagnostic testing for coronary heart disease than men.⁶⁵² The American College of Cardiology / Heart Association issued guidelines in 2005 for non-invasive evaluation of women with atypical or typical chest pain symptoms.⁶⁵³ While current evidence does not support the use of imaging in low-risk asymptomatic women, evidence is emerging for the use of imaging in asymptomatic women with an intermediate risk score (Framingham Risk Score).⁶⁵⁴ Some authorities have found that the Framingham risk assessment tool may underestimate or overestimate cardiovascular risk in women. Pletcher and Baron suggest that risk estimation can be improved by using serum CRP levels, coronary artery calcium scanning, or other novel risk factors for women at intermediate risk for CVD.⁶⁵⁵

8.2 Heart Failure

8.2.1 The Disease

Heart failure (HF), also known as congestive heart failure (CHF), occurs when the heart is unable to pump blood sufficiently around the body. This often results in blood backing up or pooling in tissues (such as the lungs)—hence the qualifier “congestive.” Diagnosis of heart failure is primarily based on visible symptoms, and there is no universally accepted definition. A failing heart causes many problems within the body, and the measurements that should be used to define the condition are not always agreed upon.⁶⁵⁶

As well as a multitude of symptoms, heart failure can have a number of causes, including a lack of blood supply to heart muscle due to CAD, scar tissue from a heart attack, high blood pressure, diseases or infections of the heart muscle or valves, and congenital heart defects.⁶⁵⁷ Treatment is generally aimed at the cause of the failure, and therefore may vary from patient to patient. In extreme cases, a heart transplant becomes the appropriate intervention.

8.2.2 Epidemiology

Heart failure is a disease that becomes more common with age. The average age for an HF event is deemed to be between 71 and 75 years. As detailed in Figure 10, more than 83% of HF patients in British Columbia in 2003/04 were 65 or older.⁶⁵⁸

Figure 10: Number of People with Diagnosed Congestive Heart Failure

By Health Authority		By Age Group	
1 – Interior	16,793	00-04	175
2 – Fraser	23,516	05-09	212
3 – Vancouver Coastal	17,135	10-14	137
4 – Vancouver Island	13,706	15-19	67
5 – Northern	4,504	20-24	120
Unknown	233	25-29	162
Total	75,887	30-34	243
		35-39	391
		40-44	686
		45-49	1,080
		50-54	1,895
		55-59	3,085
		60-64	4,366
		65-69	6,130
		70-74	9,151
		75-79	12,440
		80-84	14,483
		85+	21,064
		Total	75,887

HF is also connected to a number of other factors, including gender. Men are considered at greater risk than women.

A number of diseases are associated with HF, especially hypertension, myocardial infarction, diabetes mellitus, valve disease, overweight/obesity, and other conditions that tax the heart and circulatory system.⁶⁵⁹ Because of the nature of the underlying factors, heart failure is one of the few cardiovascular diseases demonstrating growing incidence in Western society. It is the end stage of many other heart diseases, so improvements in survival on other fronts, such as CAD, ironically may lead to an increase in HF occurrence.⁶⁶⁰ Meanwhile, the generally aging population continues to drive the absolute number of HF patients, along with all types of chronic diseases.⁶⁶¹

Heart failure also has a known genetic component. Certain genotypes have been shown to increase risk of heart failure by as much as tenfold. Evidence for differences in risk between ethnic groups, however, is inconclusive, though some populations have been shown to be more likely to develop certain risk factors for heart failure.⁶⁶²

8.2.3 Evaluating Available Evidence

Primary Prevention

Since heart failure often occurs as a result of, or together with, diseases such as diabetes, hypertension, and CAD, research on primary prevention efforts for heart failure are closely tied to work on those conditions. The risk factors directly implicated in HF include excessive alcohol consumption, smoking, low physical activity, low socio-economic status or education, coffee consumption, dietary sodium intake and depression.⁶⁶² Most of these are amenable to lifestyle/behavioural modification, and some to medical approaches.

Table 30: Research on Risk Factors Associated with Heart Failure

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Abramson et al. (2001) ⁶⁶³	Prospective cohort study	2,235 patients	The effects of moderate alcohol consumption on HF risk in elderly people	In the population studied, “increasing levels of moderate alcohol consumption are associated with a decreasing risk of heart failure.”	“Heavy alcohol consumption can have toxic effects on the heart that result in heart failure.”
He et al. (2001) ⁶⁶⁴	Prospective cohort study	13,643 men and women with no HF history	Risk factors for HF and HF onset	Factors found to be related to heart failure include: <High school (RR 1.22, 95% CI 1.04-1.42) Low physical activity (1.23, 1.09-1.38) Cigarette smoking (1.59, 1.39-1.83) Overweight (1.30, 1.12-1.52) Hypertension (1.40, 1.24-1.59) Diabetes (1.85, 1.51-2.28) Valvular heart disease (1.46, 1.17-1.82) Coronary heart disease (8.11, 6.95-9.46)	
Wilhelmsen et al. (2001) ⁶⁶⁵	Cohort study	7,495 men	Risk factors and prevalence, etiology and prognosis of heart failure	Risk factors identified: tobacco smoking, high coffee consumption, alcohol abuse and high BMI, but not high cholesterol or psychological stress. Of those who developed HF during the study, 5.8% had valvular heart disease, 58.8% CAD with or without hypertension, 20.3% had only hypertension, and 4.5% diabetes. Of the remaining 12.1%, 96% were smokers and 64% registered for alcohol abuse.	
He et al. (2002) ⁶⁶⁶	Prospective cohort study	5,233 non-overweight and 5,129 overweight men and women	Dietary sodium intake and incidence of HF	After adjusting for other known factors, sodium intake was found to increase the risk of heart disease by 43% (95% CI, 7 to 91%.	“A reduction in sodium intake may play an important role in the prevention of CHF in overweight individuals and populations.”
Rutledge et al. (2006) ⁶⁶⁷	Meta-analysis	36 studies	The relationship between HF and depression	“Clinically significant depression was present in 21.5% of HF patients.” “Combined results suggested higher rates of death and secondary events (RR = 2.1, 95% CI 1.7-2.6), trends toward increased health care use, and higher rates of hospitalization and emergency room visits among depressed patients.”	

A small number of Cochrane Collaboration reviews related to HF have been published, mostly related to secondary prevention. At this time, the use of either anticoagulation (e.g., warfarin) or antiplatelet (e.g., aspirin, clopidogrel) agents are not well supported in the literature.^{668,669}

Early Detection

Many of the techniques used in screening for heart failure are the same as those used for CAD. Some more specific symptoms, such as edema or heart arrhythmias, are also noticeable during routine check-ups. Since heart failure is often a secondary disease, a review of medical history often plays an important role in diagnosis.⁶⁷⁰ According to the American College of Cardiology/American Heart Association 2005 Guidelines, the past or current areas about which patients should be questioned include the following:⁶⁷¹

- Hypertension; obesity; diabetes; dyslipidemia
- Valvular heart disease; coronary or peripheral vascular disease

- Smoking; alcohol consumption
- Exposure to sexually transmitted infection
- Myopathy; rheumatic fever; thyroid disorder
- Sleep-disordered breathing
- Exposure to cardiotoxic agents; mediastinal irradiation

Identifying high-risk groups according to these criteria lessens the need for HF screening among the general population. Among high-risk patients, however, screening and monitoring are vital if serious health complications are to be avoided.

The British Columbia Guidelines and Protocols Advisory Committee (GPAC) has noted that

routine screening for asymptomatic left ventricular dysfunction is currently not recommended. For selected patients at high risk for heart failure due to multiple risk factors, the decision to screen (such as by echocardiography) should be individualized.⁶⁷²

8.3 Hypertension

8.3.1 The Disease

Hypertension is a medical condition defined by chronically high blood pressure. It is closely linked with obesity and is a risk factor for many cardiovascular diseases. Because of this it is often considered the top contributing factor of mortality in developed countries.⁶⁷³

There are two main categories of hypertension, termed essential and secondary. Essential hypertension is responsible for approximately 95% of all cases. It has no single clear cause, but is the result of the interaction of multiple genetic and environmental variables. The genetic components of hypertension are not well understood.⁶⁷⁴ Secondary hypertension, on the other hand, is high blood pressure due to another condition, often of the kidneys, adrenal gland, or aorta.

Chronic high blood pressure has many adverse effects on the body, but often few immediate symptoms, even while the condition worsens. In its most severe state, however, hypertension can damage not only the heart and circulatory system, but also potentially the kidney, brain, retina and optical nerve.⁶⁷⁵ The fragile blood vessels in these areas put them at risk. Perhaps of even greater impact, though, is the effect high blood pressure has in promoting other conditions. It is estimated that hypertension is responsible for more than a third of the myocardial infarctions and strokes and half of the episodes of heart failure among Americans, not to mention a quarter of all of the premature deaths in the country.⁶⁷⁶

8.3.2 Epidemiology

An estimated 30% of all adults have a blood pressure in excess of 140/90 mm Hg, the level necessary to be considered hypertension.⁶⁷⁷ Among North Americans, hypertension is especially common among people of African descent. Overall, hypertension affects an estimated one billion people worldwide.⁶⁷⁸ In British Columbia, more than 610,000 people have diagnosed hypertension. Perhaps the largest risk factor for hypertension is age, as indicated in Figure 11.⁶⁷⁹

Figure 11: Number of People with Diagnosed Hypertension, BC, 2003/2004

By Health Authority		By Age Group	
1 – Interior	108,582	00-04	178
2 – Fraser	202,251	05-09	285
3 – Vancouver Coastal	142,064	10-14	471
4 – Vancouver Island	120,619	15-19	831
5 – Northern	35,389	20-24	1,907
Unknown	1,774	25-29	4,067
Total	610,679	30-34	8,001
		35-39	13,509
		40-44	23,793
		45-49	37,058
		50-54	54,245
		55-59	67,431
		60-64	69,097
		65-69	71,537
		70-74	76,215
		75-79	71,121
		80-84	59,284
		85+	51,649
		Total	610,679

As is true for other forms of CVD, hypertension is the result of various risk factors, and the combined effects of these build up over time. But whereas death from most forms of cardiovascular disease has decreased in the last few decades, “the age-adjusted death rate attributable to hypertension as a primary or contributing cause of death actually rose by 36.4% over the past decade (data from 1991 to 2001), with the actual number of deaths increasing even more, by an alarming 53%.”⁶⁸⁰ In the United States, an estimated 30% of individuals with hypertension do not know that they have it. Of those with diagnosed hypertension, approximately 59% are on medication, but only 34% have adequately controlled blood pressure.⁶⁸¹

A comparison of hypertension prevalence in Canada compared to the United States found a similar prevalence in each country (21.1% vs. 20.1%), but that only 13% of hypertensives in Canada had their blood pressure under control compared to 25% in the United States.⁶⁸²

8.3.3 Evaluating Available Evidence

Primary Prevention

Many of the risk factors for high blood pressure are dietary. The association between sodium intake and incidence of hypertension, for example, is well known. On the other hand, nutrients such as calcium and potassium have been shown in some trials to lower risk, although the available evidence for calcium in particular is less than conclusive at this point. Caffeine intake has also been shown to increase blood pressure, while soybeans and fish-oil have beneficial effects.

Other factors that have been shown to lower blood pressure are weight reduction and physical activity. Of course, these variables are interconnected, but independent effects were also seen for both weight reduction and physical activity.

Finally, it is important to mention that risk factors for hypertension overlap significantly with those for related conditions, such as heart disease and diabetes.

Israili and co-authors suggest the following blood pressure reductions associated with lifestyle modifications (Figure 12).⁶⁸³

Figure 12: Reduction in Blood Pressure by Lifestyle Modification

	Systolic BP	Diastolic BP
Weight reduction	3-10 mm Hg	2-3 mm Hg
Adoption of DASH ⁶⁸⁴ diet	8-14 mm Hg	3-5 mm Hg
Dietary sodium reduction	2-8 mm Hg	1-4 mm Hg
Physical activity	4-13 mm Hg	2-3 mm H
Moderation of alcohol consumption	2-4 mm Hg	1 mm Hg

Table 31: Research on Risk Factors Associated with Hypertension

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Whelton et al. (1997) ⁶⁸⁵	Meta-analysis	33 trials with 2,609 participants	The effect of oral potassium intake on blood pressure	“Our results support the premise that low potassium intake may play an important role in the genesis of high blood pressure. Increased potassium intake should be considered as a recommendation for prevention and treatment of hypertension, especially in those who are unable to reduce their intake of sodium.”	
Mulrow et al. (2000) ⁶⁸⁶	Cochrane review	18 trials	Whether weight-reducing diets can affect hypertension	“The data suggested that weight loss in the range of 4% to 8% of body weight was associated with a decrease in blood pressure in the range of 3 mm Hg systolic and diastolic.”	“Weight-reducing diets may decrease dosage requirements of persons taking antihypertensive medications.”
Geleijnse et al. (2002) ⁶⁸⁷	Review	36 trials	Intake of fish oil and hypertension	“High intake of fish oil may lower [blood pressure], especially in older and hypertensive subjects. The antihypertensive effect of lower doses of fish oil (<0.5 g/day) however, remains to be established.”	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Whelton et al. (2002) ⁶⁸⁸	Review	54 trials with 2,419 participants	The effect of aerobic exercise on blood pressure	“Aerobic exercise reduces blood pressure in both hypertensive and normotensive persons. An increase in aerobic physical activity should be considered an important component of lifestyle modification for prevention and treatment of high blood pressure.”	
Hooper et al. (2004) ⁶⁸⁹	Cochrane review	11 studies including 3,514 patients	Reduction of dietary salt as a prevention of cardiovascular disease	Systolic and diastolic blood pressures were reduced by 1.1 mm Hg (95% CI 1.8 to 0.4) and 0.6 mm Hg (95% CI 1.5 to -0.3) respectively in the subjects given low sodium advice. “This reduction was not enough to expect an important health benefit.”	“Evidence from a large and small trial showed that a low sodium diet helps in maintenance of lower blood pressure following withdrawal of antihypertensives.”
Noordzij et al. (2005) ⁶⁹⁰	Meta-analysis	16 studies including 1,010 subjects	Blood pressure response to caffeine and coffee intake	“Regular caffeine intake increases BP. When ingested through coffee, however, the blood pressure effect of caffeine is small.”	
He et al. (2005) ⁶⁹¹	Randomized, double-blind, controlled trial	302 participants	Effect of soybean protein on hypertension	After a 12 week intervention, systolic and diastolic blood pressures were lowered by 4.31 mm Hg (95% CI, 2.11-6.51) and 2.76 mm Hg (1.35-4.16), respectively.	“These findings suggest that increased intake of soybean protein may play an important role in preventing and treating hypertension.”
Dickinson et al. (2006) ⁶⁹²	Cochrane review	13 trials with 485 participants	The effect of dietary calcium supplementation on blood pressure	“In view of the poor quality of included trials and the heterogeneity between trials, the evidence in favour of causal association between calcium supplementation and blood pressure reduction is weak and is probably due to bias.”	“Larger, longer duration and better quality double-blind placebo controlled trials are needed to assess the effect of calcium supplementation on blood pressure and cardiovascular outcomes.”
He & MacGregor, 2007 ⁶⁹³	Cochrane review	31 trials	Effect of longer-term modest salt reduction on blood pressure	“Our meta-analysis demonstrates that a modest reduction in salt intake for a duration of 4 or more weeks has a significant and, from a population viewpoint, important effect on blood pressure on both individuals with normal and elevated blood pressure....Furthermore, our meta-analysis demonstrates a correlation between the magnitude of salt reduction and the magnitude of blood pressure reduction.”	

Early Detection and Treatment of Hypertension as Primary Prevention

It is important to recognise that while treatment is not usually considered to be primary prevention, it *is* with respect to heart disease (CAD and heart failure), stroke, and renal disease. Thus treatment here can be considered primary prevention of some of the most important causes of death in Canada and BC.

As noted earlier, as many as 30% of individuals with hypertension are not aware of this condition. This number is surprisingly high, especially considering the fact that blood pressure testing is generally recommended as part of a routine medical check-up.

Diagnosis does have some complications. One factor affecting screening for hypertension is known as the “white coat effect”⁶⁹⁴, the tendency for some patients’ blood pressure to rise due to nervousness when in a medical setting, giving a false positive result. Other patients have been shown to give a false negative result on official tests. Because of this, repeated testing, perhaps in a more comfortable setting, is often recommended prior to an official diagnosis of hypertension.

Recommendations by the Canadian Task Force on the Periodic Health Examination (CTFPHE) date back to 1994 when they noted that “there is fair evidence to measure BP in young and middle-aged adults (B Recommendation). Case-finding should be considered in all persons aged 21 to 64 years.”⁶⁹⁵ A further review with a focus on screening in the elderly noted that “while earlier recommendations have emphasized the importance of screening for hypertension in young and middle life, there is now good evidence to extend these recommendations to those aged over 65 years.” Furthermore, “given the high prevalence of hypertension in older people, the risks of death and morbid events resulting from untreated hypertension, and the proven effectiveness of pharmacological treatment, screening for this condition can be confidently recommended in those aged 65 to 84 years.”⁶⁹⁶

A more recent review by the USPSTF recommends “screening for high blood pressure in adults aged 18 years and older. This is a grade A recommendation.”⁶⁹⁷

The British Columbia Guidelines and Protocols Advisory Committee (GPAC) has noted that “a baseline blood pressure (BP) should be established in all adults and reassessed periodically, commensurate with age and the presence of other risk factors....Blood pressure monitoring should be rigorous in those patients who:

- Have known or newly detected elevated BP
- Have cardiovascular target organ damage (*Target organ damage includes: cerebrovascular disease, coronary heart disease (CHD), left ventricular hypertrophy (LVH), chronic kidney disease (CKD), peripheral vascular disease and hypertensive retinopathy.*)
- Have other risk factors
- Are receiving antihypertensive therapy”⁶⁹⁸

8.4 Stroke

8.4.1 The Disease

Stroke is the result of either a disruption in blood supply to the brain (ischemic stroke) or bleeding into the brain due to a ruptured blood vessel (hemorrhagic stroke). Permanent brain damage is often a consequence, and death occurs in 15% of stroke cases. Stroke is a leading cause of morbidity and mortality in North America, and the fourth leading cause of death in Canada.^{699,700}

Approximately 80% of strokes are ischemic. They are caused by a blood clot in an artery in the brain, which either travelled there from another part of the body, or formed around fatty deposits (atherosclerosis) in blood vessels in the brain. Most risk factors for ischemic stroke are associated with atherosclerosis.^{701,702}

The less common type of stroke is hemorrhagic; the two major causes of hemorrhagic strokes are hypertension and aneurysm. Hypertension causes blood vessels to weaken, which are then more likely to leak. An aneurysm is a weakened area in an artery, usually present from birth. It may bleed or burst, resulting in a hemorrhagic stroke. Hypertension may contribute to weakening an aneurysm, further increasing the risk of stroke.⁷⁰³

A transient ischemic attack (TIA) is a short-term reduction in the flow of blood to the brain, and is often termed a “mini-stroke”. Most only last less than 10 minutes, but they can last as long as 24 hours. Most TIAs do not cause permanent brain damage, and the symptoms may only last a short time, but it is still very important to seek medical attention. Once a person has experienced a TIA, they are at increased risk of having another TIA or a stroke.

8.4.2 Epidemiology

Stroke is the second most common cause of mortality worldwide; it caused an estimated 5.7 million deaths in 2005.^{704,705} There are between 40,000 and 50,000 strokes each year in Canada, and about 300,000 Canadians are living with the effects of stroke.⁷⁰⁶ Refer to the table below for regional data in British Columbia. Approximately 18% of strokes in Canada occur in BC. The prevalence of stroke is highest in the elderly; risk of stroke doubles every ten years after the age of 55. Stroke occurs more often in men than in women, and some U.S. studies have shown that stroke incidence is higher in African American than Caucasian men and women.⁷⁰⁷

Figure 13: Prevalence/Incidence of Stroke in BC, by Health Authority, 2005/06

Health Authority	Prevalence	Incidence
1 – Interior	10,487	1,592
2 – Fraser	17,055	2,667
3 – Vancouver Coastal	13,115	1,883
4 – Vancouver island	10,411	1,499
5 – Northern	2,643	360
Unknown	184	14
Total	53,895	8,015

Note: To be considered a case, an individual must have one hospitalization or two medical claims coded with the specified ICD-10 codes (161, 163, 164) within 365 days.

The number of global deaths due to stroke is projected to rise to 6.5 million in 2015 and to 7.8 million in 2030, if there is no intervention.⁷⁰⁸ This rising burden is partly attributable to the aging population, but is also due to poor management of stroke patients in developing countries – where over two-thirds of worldwide stroke deaths occur.⁷⁰⁹

8.4.3 Evaluating Available Evidence

Primary Prevention

Stroke is the third leading cause of death in British Columbia, and it is the primary cause of acquired long-term disability in adults. It is the most costly neurological disease, estimated at \$327 million annually in this province, and stroke incidence is expected to rise with the aging population.⁷¹⁰ Primary prevention, as a result, is a key focus of research and national and provincial stroke strategies.

Hypertension is the single most important modifiable risk factor for stroke. In 2001, 54% of strokes worldwide were attributable to hypertension and lesser degrees of high blood pressure.⁷¹¹ Other risk factors for ischemic stroke are similar to those for the related conditions of hypertension and heart failure previously discussed, including obesity, smoking, physical inactivity, and alcohol consumption.

Figure 14: Selected Modifiable Risk Factors for Ischemic Stroke, Canada and BC, 2005

Risk Factor	Prevalence (% of Population)	
	Canada	British Columbia
Hypertension ^a	15.0%	13.2%
Smoking ^b	19.6%	15.7%
Physical Inactivity ^c	47.8%	41.0%
Obesity ^d	15.8%	13.5%
Alcohol Consumption ^e	17.2%	16.7%

^aPopulation aged 12+; refers to hypertension as diagnosed by a health professional.

^bPopulation aged 12+ who are current smokers (including both daily smokers and occasional daily smokers).

^cPopulation aged 12+, based on estimated total daily energy expenditure values.

^dPopulation aged 18+, excluding pregnant women; obesity as defined by a body mass index (BMI) of 30 or more, based on self-reported height and weight.

^ePopulation aged 12+ consuming 5 or more drinks on one occasion 12 or more times a year.

Research suggests that other risk factors for stroke may include fried fish consumption, depressive symptoms, hormone replacement therapy, elevated homocysteine levels, and high magnesium intake, though these are not as well-studied.

Of the modifiable risk factors, hypertension carries the highest relative risk for stroke.⁷¹² Among hypertensive patients who suffer a hemorrhagic stroke, as many as half are either unaware of their hypertension, non-compliant with the medication, or have not been regularly monitoring their blood pressure.⁷¹³ According to a study by Woo et al., approximately one-quarter of hemorrhagic strokes in hypertensive subjects would have been prevented if they had been receiving hypertension treatment.⁷¹⁴

In British Columbia, less than 50% of those with hypertension are aware of their condition. A hypertension campaign is one of the priority actions identified by the BC & Yukon Heart and Stroke Foundation, and increasing the awareness of British Columbians who are unaware of their hypertensive condition is one of the proposed targets.⁷¹⁵

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Aspirin has long been used for secondary prevention of cardiovascular disease, but its use in primary prevention of stroke remains controversial. There is no evidence that aspirin reduces the risk of stroke in the general population of people at low risk, and it may actually increase risk of hemorrhagic stroke.^{716,717} However, in a large primary-prevention trial, asymptomatic women were given aspirin therapy and followed for ten years, and a 19 percent reduction in the risk of stroke was observed.⁷¹⁸ This study supports the use of aspirin for preventing a first stroke among women over age 65 who are at increased risk of cardiovascular events.

Table 32: Research on Risk Factors Associated with Stroke

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Salaycik et al. (2007) ⁷¹⁹	Prospective	4,120 participants	Whether depressive symptoms are associated with increased risk of stroke/TIA	“Our study provides evidence supporting an association between depressive symptoms and an increased risk of stroke/TIA in individuals below the age of 65 years.”	
Kurth et al. (2003) ⁷²⁰	Prospective cohort	22,022 participants	The impact of smoking on intracerebral hemorrhage (ICH) in men	Current smokers of <20 cigarettes per day had a relative risk of 1.65 for total hemorrhagic stroke; current smokers of ≥ 20 cigarettes per day had a relative risk of 2.36 for total hemorrhagic stroke	“This prospective study suggests an increased risk of total hemorrhagic stroke, ICH, and SAH [subarachnoid hemorrhage] in current cigarette smokers with a graded increase in risk that depended on how many cigarettes were smoked.”
Kurth et al. (2003) ⁷²¹	Prospective cohort	39,783 participants	The impact of smoking on ICH in women	Current smokers of <15 cigarettes per day had a relative risk of 1.93 for total hemorrhagic stroke; current smokers of ≥15 cigarettes per day had a relative risk of 3.29 for total hemorrhagic stroke	“This prospective study indicates an increased risk of total hemorrhagic stroke, ICH, and SAH in women who are current cigarette smokers. The risk increases with the amount of cigarettes smoked.”
Wiberg et al. (2006) ⁷²²	Prospective	2,313 participants	The impact of lipometabolic and glucometabolic disturbances on stroke incidence in middle-aged men	“Indices of an unhealthy dietary fat intake and a high serum lipoprotein(a) level predicted fatal and nonfatal stroke/TIA independently of established risk factors in a community-based sample of middle-aged men followed for 32 years.”	
Howard et al. (2006) ⁷²³	Randomized controlled trial	48,835 participants	The effect of a dietary intervention on risk of cardiovascular disease (CVD) in post-menopausal women	“Over a mean of 8.1 years, a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD [coronary heart disease], stroke, or CVD in postmenopausal women and achieved only modest effects on CVD risk factors, suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk.”	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Fung et al. (2008) ⁷²⁴	Prospective cohort	88,517 participants	The effect of the Dietary Approaches to Stop Hypertension (DASH) diet on risk of coronary heart disease and stroke in women	“Adherence to the DASH-style diet is associated with a lower risk of CHD and stroke among middle-aged women during 24 years of follow-up.”	
Weikert et al. (2007) ⁷²⁵	Population-based cohort	25,538 participants	Single and joint effects of risk factors on the incidence of stroke and TIA	“Our data indicate that classical risk factors [hypertension, diabetes mellitus, high alcohol consumption, hyperlipidemia, and smoking] may explain almost 60% of ischemic stroke but only one in four TIA cases.”	
Mozaffarian et al. (2005) ⁷²⁶	Population-based longitudinal cohort	4,775 participants	Association between fish consumption and stroke risk in adults 65 years and older	Consumption of fish 1-4 times per week resulted in a 27% lower risk of ischemic stroke, compared to an intake of less than once per month. Consumption of fried fish/fish sandwiches more than once per week resulted in a 44% higher risk of ischemic stroke relative to consumption of less than once per month. Fish consumption was not associated with hemorrhagic stroke.	“Among elderly individuals, consumption of tuna or other broiled or baked fish is associated with lower risk of ischemic stroke, while intake of fried fish or fish sandwiches is associated with higher risk. These results suggest that fish consumption may influence stroke risk late in life.”
Larsson et al. (2008) ⁷²⁷	Population-based cohort	26,556 participants	Effect of high intake of magnesium, calcium and potassium and a low intake of sodium on stroke risk in male smokers	“A high magnesium intake was associated with a statistically significant lower risk of cerebral infarction but not with intracerebral or subarachnoid haemorrhages.” “Calcium, potassium, and sodium intake was not significantly associated with risk of any subtype of stroke.”	“These findings in male smokers suggest that a high magnesium intake may play a role in the primary prevention of cerebral infarction.”
Giles et al. (1998) ⁷²⁸	Survey	4,534 participants	Whether elevated homocysteine levels is a risk factor for stroke in both whites and blacks	“In this nationally representative sample of US adults, [homocysteine] concentration was independently associated with an increased likelihood of nonfatal stroke. This association was present in both black and white adults.”	
Grodstein et al. (2008) ⁷²⁹	Prospective analyses		Association of stroke risk with hormone therapy in younger women, recently menopausal women, and older women	“Hormone therapy is associated with an increased risk of stroke, and this increased risk does not appear to be related to the timing of the initiation of HT.”	

Early Detection

*Late arrival to the hospital after the onset of acute stroke symptoms is a plague of unheralded proportions that is not easily treated or cured.*⁷³⁰

Recognition and immediate response to the warning signs of stroke can significantly impact long-term prognosis. If patients with acute ischemic stroke are given intravenous thrombolytic treatment within 3 hours of the initial onset of symptoms, the patient will have improved clinical outcome at 3 months.⁷³¹ The symptoms of stroke include: weakness, difficulty speaking, vision problems, headache, and dizziness. Public awareness of these symptoms is imperative for early detection and treatment of stroke; despite various public education campaigns, only 20-25% of stroke patients actually receive treatment within the critical time frame of 3 hours from the onset of symptoms.⁷³²

A transient ischemic attack (TIA) may be considered a warning sign for increased risk of stroke. A TIA is a temporary reduction in blood flow to the brain, lasting less than 24 hours, in which no permanent brain damage occurs. Symptoms of TIA are similar to those for stroke, as is the importance of early detection and treatment. The risk of stroke within the first week after TIA ranges from 10-30%. Patients can undergo preventative treatments after experiencing TIA, which may reduce the short-term risk of stroke by as much as 80%.⁷³³ However, approximately half of those who experience TIA do not report it to their healthcare provider.⁷³⁴

In British Columbia, a mere 30% of the population know the major risk factors for stroke, and only 35% can identify at least three warning signs of a stroke. A multimedia public awareness campaign was recommended by the Heart and Stroke Foundation of BC & Yukon, with the target of increasing the stroke awareness of British Columbians (in both categories given above) to 75% of the population.⁷³⁵

9.0 RESPIRATORY DISORDERS

9.1 Asthma

9.1.1 The Disease

Asthma is an allergic disease, and the most common chronic disease in children.⁷³⁶ It is widely considered to have multiple causes, including genetic and environmental components. It is also closely related to a number of other disorders, including eczema and food allergies. These conditions generally appear in early childhood and are becoming increasingly prevalent, although this increase may have reached a plateau more recently in some countries.⁷³⁷

The main symptom of asthma is a shortness of breath caused by bronchospasms, sudden constriction of airway muscles, and an inflammation of airways equivalent to an allergic reaction. Over time, repeated inflammation can damage the airways irreparably, reducing elasticity and muscle effectiveness. In patients prone to allergy, asthma attacks also appear to cause a reaction in the skin or intestine. There is evidence that sleep and cognition may also be affected.⁷³⁸

Up until recently, treatment for asthma was focussed on allowing the sufferer to breathe by using muscle relaxants or other methods to relieve bronchospasm. Some newer treatments relieve the underlying inflammation instead. The hope is that these techniques will reduce the lasting damage of repeated asthmatic episodes.⁷³⁸

9.1.2 Epidemiology

An estimated 5% of adults and 10% of children and teens in Canada have active asthma when active asthma is defined as physician-diagnosed asthma and being on medication during the last 12 months or symptoms or attacks in the past 12 months.⁷³⁹ Ever-diagnosed (by a physician) rates are higher than the 5% in adults or 10% in children. In children, the age of onset is often before the age of six. Hessel and colleagues found that 20% of children with asthma were diagnosed by age one, 57% by age four, and 67% by age five.⁷⁴⁰

In British Columbia, 317,000 individuals have been diagnosed with asthma, an overall prevalence of 7.6% of the population (see Figure 15).⁷⁴¹ As expected, the highest prevalence (18.3%) is among children aged 5-9.

Figure 15: People with Diagnosed Asthma, BC, 2003/2004

By Health Authority	Cases	Population	Prevalence
1 – Interior	48,921	689,344	7.1%
2 – Fraser	118,039	1,428,372	8.3%
3 – Vancouver Coastal	70,950	1,038,117	6.8%
4 – Vancouver Island	53,087	707,990	7.5%
5 – Northern	23,778	291,547	8.2%
Unknown	1,925		
Total	316,700	4,155,370	7.6%

By Age Group	Cases	Population	Prevalence
00-04	–		
05-09	43,604	237,816	18.3%
10-14	45,440	262,624	17.3%
15-19	38,072	281,091	13.5%
20-24	25,610	286,239	8.9%
25-29	22,538	268,015	8.4%
30-34	24,358	299,024	8.1%
35-39	27,196	320,605	8.5%
40-44	31,216	354,382	8.8%
45-49	30,573	338,314	9.0%
50-54	28,093	300,897	9.3%
55-59	–		
60-64	–		
65-69	–		
70-74	–		
75-79	–		
80-84	–		
85+	–		
Total	316,700	4,155,370	7.6%

Asthma is much more common in developed than in developing countries. Some possible explanations for this include differences in diet, prevalence of cigarette smoke, air quality, and level of physical activity between populations from different countries, although none of these entirely explain the almost thirty-fold differences between nations.⁷⁴² Variation in case-finding may also play an important role.

Asthma prevalence appears to differ along socio-economic and ethnic lines, with higher rates, for example, in African-American populations in the United States than in Caucasian populations.⁷⁴³

Finally, there is a genetic component associated with asthma—as many as 118 individual genes have been found to be associated with the disease.⁷⁴⁴

9.1.3 Evaluating Available Evidence

Primary Prevention

Asthma’s large and growing prevalence makes it an important target for primary prevention. Research in this area is extensive and varied. Many possible connections have been studied, and correlations have been found between asthma and a number of variables, including presence of pet and dust mite allergens and environmental cigarette smoke. The most promising results are found when a number of these variables can be controlled at the same time.

Table 33: Research on Risk Factors Associated with Asthma – Environmental Allergens and Smoke

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Becker et al. (2004) ⁷⁴⁵	Randomized, controlled study	545 infants with immediate family history of asthma	Whether a multifaceted intervention program (avoidance of house dust mite, pet allergen, and environmental tobacco smoke) in the first year of life affects future asthma.	“Significantly fewer children had asthma in the intervention group compared with in the control group (16.3% vs. 23.0%) with 60% less asthma at 2 years.” “Exposure to maternal environmental tobacco smoke during pregnancy or the first year was a risk factor for asthma.” “A positive skin test response, particularly to food, at 12 months predicted asthma at 2 years.”	“This multifaceted intervention program during a window of opportunity in the first year of life was effective in preventing asthma in high-risk children at 2 years of age. Future studies with this cohort at school age are important.”
Lau et al. (2004) ⁷⁴⁶	Cohort study	750 German children followed to age 10	Cat allergen exposure	“Sensitization to cat allergen (IgE) is a risk factor for childhood asthma.”	
Peat et al. (2004) ⁷⁴⁷	Randomized controlled trial	526 children with family history of asthma	Effects of dietary supplementation from 6 months with omega-3 fatty acids and house dust mite allergen avoidance.	In atopic children, the fatty acids reduced prevalence of cough by 10% (95% CI, 10.11-14.3). Active allergen avoidance led to a reduction in sensitization. No significant differences in wheeze were found with either intervention.	
Arshad (2005) ⁷⁴⁸	Review	130 references	Review of potential environmental risk factors that could predict the onset of asthma and allergy.	Exclusive breastfeeding and avoidance of exposure to tobacco smoke is recommended. A combined food and house dust mite allergen avoidance regimen offers some protection against atopic dermatitis in infancy and asthma in later childhood.	“Further randomized controlled trails are also needed with long-term follow up to evaluate combined approaches that might provide maximum benefit.”
Becker (2005) ⁷⁴⁹	Review	86 references	Reviews effectiveness of environmental control measures for prevention of allergy and asthma.	A strong relationship found between exposure to house dust mites, allergen sensitization, and asthma. Exposure to pets and animals in a farming environment early in life may be protective against development of asthma.	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Chan-Yeung et al. (2005) ⁷⁵⁰	Randomized, controlled study	380 of 545 children	Follow-up of Becker et al. (2004)	“The prevalence of pediatric allergist-diagnosed asthma was significantly lower in the intervention group than in the control group (14.9% vs. 23%; adjusted risk ratio, 0.44; 95% CI, 0.25-0.79).”	“The multifaceted intervention program was effective in reducing the prevalence of asthma in high-risk children at 7 years of age.”
Schönberger et al. (2005) ⁷⁵¹	Randomized controlled trial	443 high risk children	Clinical effectiveness of a multi-faceted educational prevention (reduced dust mite, pet allergen and tobacco smoke exposure)	During the first 2 years, asthma-like symptoms were significantly reduced only among females in the intervention group. At 2 years, the entire intervention group had fewer symptoms.	“Follow-up is necessary to confirm whether the intervention can actually prevent the development of asthma.”
Marks et al. (2006) ⁷⁵²	Randomized controlled trial	516 children with family history of asthma	House mite avoidance and dietary fatty acid modification	Neither factor was found to prevent the onset of asthma, eczema or atopy in high-risk children.	

While support for reduction of environmental cigarette smoke is consistent, the effects of other factors are less clear. Results for dust mite and pet allergen avoidance and Omega-3 consumption are inconclusive, although multiple simultaneous interventions were more consistently positive. The hygiene hypothesis, first put forth by David Strachan in 1989,⁷⁵³ suggests that some degree of exposure to viruses and allergens may actually be beneficial.

Other factors commonly studied include breastfeeding and viral infections. Exposure to chlorine has also been suggested as having a potential role.

Table 34: Research on Other Risk Factors Associated with Asthma

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Kull et al. (2004) ⁷⁵⁴	Cohort study	4,089 children	Breast-feeding’s preventative effect on asthma	“Breast-feeding reduces the risk of asthma during the first 4 years of life.”	
Oddy et al. (2004) ⁷⁵⁵	Prospective cohort study	2,195 children in Perth, Australia were followed up to 6 years.	To investigate the relationship between breastfeeding, asthma and atopy, and child BMI.	Less exclusive breastfeeding was associated with increased asthma and atopy. High BMI was found to be a risk factor for asthma.	“To date, only a multifaceted intervention program has been successful as a primary prevention strategy for the development of asthma in young children.”
Friedman et al. (2005) ⁷⁵⁶	Review	20 studies concerning asthma	The role of breast-feeding in the development of allergies and asthma	Breastfeeding was found to play a role in preventing or delaying asthma development (OR 0.70; 95% CI, 0.60-0.81)	
Lee et al. (2007) ⁷⁵⁷	Randomized controlled trial	455 children at “high risk” for asthma development	“The contribution of respiratory viral infections to the onset of asthma.”	“In high risk children... exposures to [parainfluenza virus and respiratory syncytial virus] during the first year of life are associated with the initial onset of possible asthma.”	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Kusel et al. (2007) ⁷⁵⁸	Community-based cohort study	198 children at high risk of atopy, followed from birth to 5 years.	The nature of potential interactions between severe lower respiratory infections and atopic sensitization as independent risk factors for asthma.	This study suggests that viral infections can interact with atopy in infancy to promote later asthma. Both events occurring in a narrow developmental window are associated with maximal risk.	“Protection of high-risk children against the effects of severe respiratory infections during infancy may represent an effective strategy for primary asthma prevention.”
Nickmilder & Bernard (2007) ⁷⁵⁹	Ecological study	189, 150 children aged 13-14 years in 69 European centres 94,549 children aged 6-7 in 33 centres.	To evaluate whether the rise in childhood asthma could in part result from the increasing exposure of children to toxic chlorination products in the air of indoor swimming pools.	Across Europe, the prevalence of asthma among children aged 13-14 years increased by 2.73% (95% CI 1.94 to 3.52) with an increase of one chlorinated pool per 100,000 inhabitants. An increase of 1.47% (95% CI .21 to 2.74) was found in children aged 6-7 years.	“The prevalences of childhood asthma and the number of indoor chlorinated swimming pools in Europe are linked through associations that are geographically consistent and independent of climate, altitude, and the socio-economic status of the country.”

Asthma is clearly a multi-faceted disease with numerous risk factors. The role of these risk factors has been hotly debated in the medical literature. The view of some is that “the environmental factors causally driving the temporal changes remain largely unknown. Therefore, there are few truly justified recommendations for the prevention of asthma.”⁷⁶⁰ Van Schayck and co-authors have wrestled with the fact that “preventive measures thus far studied with the aim of preventing (or delaying) the development of asthma have shown such disappointing results.” They suggest that “the most likely explanation is that the development of a multi-factorial disease, such as asthma, is extremely difficult, if not impossible, to prevent by eliminating only one risk factor.”⁷⁶¹ To add further complexity to the issue of asthma prevention, what we sometimes think of as one disease - asthma - may in fact be a constellation of diseases.

Early Detection

Asthma is often detected in a patient early in life. It is relatively easy to detect for a number of reasons. Those with an immediate family member with the disease are considered to be at high risk to develop it themselves. This familiarity with the disease generally leads to early detection. Even for those unfamiliar with asthma the symptoms, persistent wheeze and shortness of breath, for example, are conspicuous. Both the Canadian Task Force on the Periodic Health Examination (CTFPHE) and the USPSTF are silent with respect to screening / early detection for asthma. The British Columbia Guidelines and Protocols Advisory Committee guidelines on asthma simply state that “when asthma is suspected from symptoms and clinical presentation, and other disorders have been considered and ruled out, confirm the diagnosis by objective measures of variable airflow obstruction and assess severity.”⁷⁶²

9.2 Chronic Obstructive Pulmonary Disease (COPD)

9.2.1 The Disease

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. It causes shortness of breath and cough and sputum production. COPD is an umbrella term for a number of diseases which include chronic bronchitis and emphysema. Chronic bronchitis is defined as the presence of cough and sputum production for at least 3 months in each of two consecutive years.

Emphysema, or destruction of the gas-exchanging surface of the lung (alveoli), is often used to describe one of several structural abnormalities present in patients with COPD.⁷⁶³

9.2.2 Epidemiology

COPD is a major cause of morbidity and mortality throughout the world. It is ranked twelfth as a worldwide burden of disease and is projected to rank fifth by the 2020 as a cause of lost quantity and quality of life.⁷⁶⁴ While symptoms of the disease do not often appear in people younger than age 55 years, changes to the lung begin many years earlier. In Canada, the rates for COPD for women and men in 2005, by age group, are shown in Figure 16.⁷⁶⁵

Figure 16: Proportion of Women and Men with Physician-Diagnosed COPD, Canada, 2005

Age (Years)	Women	Men
35-44	2.5%	1.6%
45-54	4.0%	2.7%
55-64	6.0%	4.1%
65-74	7.2%	6.7%
75+	7.5%	11.8%

Source: Public Health Agency of Canada.

9.2.3 Modifiable Risk Factors

Several modifiable risk factors are known to contribute to COPD. The Public Health Agency of Canada notes that in 80% to 90% of COPD cases, cigarette smoking is the principal underlying cause. The contribution of primary smoking is very clearly established, and exposure to second-hand smoke likely also plays an important, although less well-defined, role.⁷⁶⁶

Information from the research literature indicates that about 15% of all cases of COPD are work-related. Specific settings and agents have been indicated or confirmed as linked to COPD. Coal miners, hard-rock miners, tunnel workers, concrete-manufacturing workers, and non-mining industrial workers have been shown to be at the highest occupational risk for developing COPD.⁷⁶⁷

Outdoor air pollution is associated with increased symptoms among those with COPD. Also, repeated childhood respiratory tract infections and childhood exposure to second-hand smoke lead to reduced levels of respiratory function, which may predispose a person to COPD. A genetic deficiency of alpha-1-antitrypsin, an anti-protease which protects the lung tissues from damage, is also associated with an increased risk of COPD.⁷⁶⁸ Genetic factors are still being explored but there appears to be a preponderance of women who are affected by early-onset and non-smoking related COPD, which requires further study.⁷⁶⁹

9.2.4 Evaluating Available Evidence

Primary Prevention

As cigarette smoking is undoubtedly the main cause of COPD in the population, reduction or cessation of personal exposure to tobacco is of primary importance as the key preventive measure. For primary prevention to be effective, other sectors within a community must also be actively engaged along with the public health system, to address environmental air pollutants and occupational risk factors.⁷⁷⁰

As other core public health programs address tobacco cessation and healthy community environments, the related primary prevention studies in this area are not addressed in this review.

10.0 OTHER DISORDERS

10.1 Breast Cancer

10.1.1 Epidemiology

Breast cancer is a common disease affecting approximately one in eight women in North America.⁷⁷¹ In British Columbia, 2,471 women were diagnosed with breast cancer in 2003. This number of new cases surpasses by a substantial margin the second highest incident cancer in women; lung cancer, with 1,138 new cases in 2003. While breast cancer primarily affects women, 23 men in British Columbia were also diagnosed with breast cancer in 2003.⁷⁷²

The risk of breast cancer increases with an individual's age, increasing (in British Columbia) from 2.5 cases per 100,000 population for women aged 20-39 to 166.1 and 325.6 for women aged 40-59 and 60-79, respectively.⁷⁷³

Approximately 5-10% of breast cancers are the result of a hereditary genetic predisposition. An estimated 80-90% of these are caused by mutations in the BRCA1 and BRCA2 genes. Other important genetic predispositions include Cowden syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome and ataxia-telangiectasia.⁷⁷⁴ Women with these genetic predispositions are usually considered to be in the 'high risk' category. Estimates of the lifetime risk for women with the BRCA1 and BRCA2 genes range from 56 to 85%, compared with 11-12% for the general populations of women.^{775,776}

10.1.2 Evaluating Available Evidence

Primary Prevention

The concept that breast cancer may be preventable is supported by wide international variation in the incidence of breast cancer.⁷⁷⁷ Potential strategies to reduce the risk of breast cancer include an increase in exercise, weight loss, reduction in alcohol intake, reduction in fat intake, chemoprevention, and prophylactic surgery.⁷⁷⁸

Thune and Furberg reviewed the available literature on the association between breast cancer and physical activity and found a protective effect with a dose-response association for both pre- and post-menopausal breast cancer.⁷⁷⁹ At least a moderate level (> 4.5 MET per week) of physical activity was required.

Obesity is associated with increased breast cancer risk, particularly in postmenopausal women. In women who have never used hormone replacement therapy, women weighing more than 82.2 kg have a relative risk of breast cancer of 2.85 (95% CI of 1.81 to 4.40) compared to women weighing less than 58.7 kg.⁷⁸⁰

The consumption of alcohol (in excess of 30g per day) is also associated with an increased risk of breast cancer.⁷⁸¹ There may, however, be a protective effect/interaction associated with alcohol consumption, breast cancer and vegetable consumption. Women who consume alcohol and have a diet poor in folate and carotenoid-rich vegetables and salad greens are at particular

risk of breast cancer. The review by Hanf and Gonder concludes that “if alcohol is consumed on a regular basis, a sufficient supply of fresh vegetables and fruit is essential”.⁷⁸²

The association between breast cancer and fat intake is more controversial although a low-fat diet may contribute to a reduction in breast cancer risk through helping maintain a healthy weight.^{783,784}

Selective Estrogen Receptor Modulators (SERMs) such as tamoxifen and raloxifene have been shown to be protective against breast cancer, reducing breast cancer risk by 48% and 66% respectively.⁷⁸⁵ However, there are also significant increased risks associated with the use of SERMs, including an increased relative risk of endometrial cancers (RR of 2.4; 95% CI of 1.5 to 4.0) and venous thromboembolic events (RR of 1.9; 95% CI of 1.4 to 2.6).^{786,787}

Largely because of this increased risk, the USPSTF recommends against the use of tamoxifen and raloxifene for the primary prevention of breast cancer in women with low or average risk for breast cancer. In women with a high risk for breast cancer (defined as a five-year risk of at least 1.6%) and a low risk for the side effects, the USPSTF recommends that clinicians discuss the possibility of chemoprevention with these women.^{788,789} Similar recommendations have been made by other organizations, including the Canadian Task force on Preventative Health Care.^{790,791}

A prophylactic mastectomy is sometimes considered for women with a high risk of breast cancer. The Cochrane Review of this procedure found that all relevant studies reported reduction in the incidence of breast cancer and disease-specific mortality after bilateral prophylactic mastectomy (BPM). The studies also reported high satisfaction with the decision to have the procedure but more variable satisfaction with the cosmetic results. In addition, worry over breast cancer was significantly reduced. Based on these findings, the reviewers concluded that

while published observational studies demonstrated that BPM was effective in reducing both the incidence, and death from, breast cancer, more rigorous prospective studies (ideally randomized trials) are needed. BPM should be considered only among those at very high risk of disease.⁷⁹²

Early Detection

Screening mammography is the use of a mammogram (an X-ray of the breasts) to identify unsuspected breast cancer in asymptomatic women. Mammography screening for breast cancer is controversial.

The BC Cancer Agency encourages women from the ages of 50-69 (and otherwise healthy women aged 70-79) to have a mammogram every 24 months.⁷⁹³

The Cochrane Review in this area found that the evidence indicated a relative risk of overall mortality after 13 years of breast cancer screening of 1.01 (95% CI of 0.99 to 1.03). Furthermore, the best trials failed to show a significant reduction in breast cancer mortality with a relative risk of 0.97 (95% CI of 0.82 to 1.14). Only when all studies were included did the relative risk become significantly reduced with mammography screening (RR of 0.80; 95% CI of 0.71 to 0.89). The authors conclude that “the currently available evidence is inconclusive for breast

cancer mortality). Women, clinicians and policy makers should consider these findings carefully when they decide whether or not to attend or support screening programs”.⁷⁹⁴

10.2 Diabetes

Diabetes mellitus is a chronic disorder of metabolism. It occurs when the body can no longer absorb glucose due to the lack of insulin production or the inability to use the insulin that is produced. Insulin, a hormone produced in the pancreas, is required for glucose to be absorbed from the blood stream into cells, where the glucose is metabolized to produce energy. Without insulin, or without the ability of the body to use insulin appropriately, glucose remains in the blood stream, starving cells of energy; as well, the excess glucose in the blood stream, over time, may result in damage to a variety of body organs and systems. For instance, if there is not enough insulin for the body’s cells to use the available glucose, the body begins to use fat instead, resulting in ketoacidosis; this condition, if left untreated, eventually leads to unconsciousness and death.

There are four main types of diabetes: type 1, type 2, gestational diabetes, and diabetes secondary to other conditions. The focus in this report will be on type 1 and 2 diabetes.

10.3 Type 2 Diabetes

10.3.1 The Disease

Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM), is the most common form of diabetes, occurring in approximately 90% of patients with diabetes. Type 2 diabetes results when the pancreas produces sufficient insulin, but the body cannot use the insulin effectively. This condition, known as insulin resistance, causes the pancreas to secrete additional insulin to maintain normal blood sugar levels. In approximately one-third of people with insulin resistance, either the body’s cells do not respond to the higher levels of insulin or, over time, insulin production decreases, resulting in the high blood glucose levels characteristic of type 2 diabetes. Obesity and physical inactivity aggravate insulin resistance, contributing to the severity of disease.

10.3.2 Epidemiology

While the incidence of type 1 diabetes is highest in children, type 2 diabetes tends to begin manifesting in adults at mid-life.⁷⁹⁵ It should be noted, however, that the prevalence of type 2 diabetes in children is increasing in concert with the emerging epidemic of childhood obesity.⁷⁹⁶ Incidence rates rise in older populations. In Ontario, for example, the incidence of diabetes in 1999 was 0.41 per 100 for women 35-49 years of age, but 0.95 per 100 for women 50-64 years of age and 1.28 per 100 for women 65-74 years of age.⁷⁹⁷ The rates for men were slightly higher, at 0.51, 1.28 and 1.65, respectively.

Twin and family studies have also identified a strong genetic component to type 2 diabetes, with a risk among siblings of an individual with diabetes that is at least three times higher than a general population of individuals with European ancestry.^{798,799} The strongest genetic link known at this time involves variants of the calpain-10 gene, though a number of other genes have been implicated.⁸⁰⁰

The prevalence of type 2 diabetes is increasing, both in adults and, perhaps of more concern, in children and adolescents. The most likely contributing factor is increasing rates of overweight and obesity.

In British Columbia, there were an estimated 228,013 individuals with diagnosed diabetes in 2003/04, as indicated in Figure 17.⁸⁰¹

Figure 17: Number of People with Diagnosed Diabetes, BC, 2003/2004

By Health Authority		By Age Group	
1 – Interior	38,596	00-04	181
2 – Fraser	78,903	05-09	543
3 – Vancouver Coastal	54,329	10-14	940
4 – Vancouver Island	40,525	15-19	1,317
5 – Northern	14,838	20-24	1,796
Unknown	822	25-29	2,592
Total	228,013	30-34	4,464
		35-39	6,940
		40-44	10,576
		45-49	15,261
		50-54	21,257
		55-59	26,545
		60-64	26,918
		65-69	27,196
		70-74	27,729
		75-79	23,729
		80-84	17,366
		85+	12,663
		Total	228,013

While the diagnosis of diabetes is relatively straightforward, 2 to 3% of the population appears to have undiagnosed type 2 diabetes.^{802,803,804}

10.3.3 Evaluating Available Evidence

Primary Prevention

The most consistent risk factors associated with type 2 diabetes are obesity, sedentary behaviour, and smoking. The consumption of unsaturated fats and whole grains rather than saturated/trans-fats and refined grains, as well as moderate alcohol intake, may be beneficial in protecting against type 2 diabetes. Depression may also be an independent risk factor associated with type 2 diabetes, though this relationship is not yet clear. A potential explanation is the fact that depression is also closely associated with stress and obesity.

The most common preventative effect reported was related to an increase in physical activity. Certain dietary changes, including replacing saturated and trans-fats with unsaturated fats, and refined grain products with those made from whole grain, were also consistently found to be beneficial.

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Table 35: Research on Risk Factors Associated with Type 2 Diabetes

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Musselman et al. (2003) ⁸⁰⁵	Review	141 references	The relationship between depression and diabetes	“Even after controlling for potential confounding factors such as age, race, gender, socio-economic status, education, use of health services, other psychiatric disorders, and body weight, depression remains a significant risk factor for development of diabetes.”	“Rather than merely a secondary emotional response to diabetic complications, depression may be an independent risk factor in initiating type 2 diabetes.”
Golden et al. (2004) ⁸⁰⁶	Cohort study	11,615 initially non-diabetic adults aged 48-67, followed for 6 years	Whether depressive symptoms predict type 2 diabetes	“After adjusting for age, race, sex, and education, [depressive individuals] had a 63% increased risk of developing diabetes.” After further adjusting for lifestyle, the increase shrunk to 28%; and, after adjusting for metabolic factors, to 38%.	
Steyn et al. (2004) ⁸⁰⁷	Review	248 references	Lifestyle factors affecting type 2 diabetes	Convincing evidence for decreased risk was found for voluntary weight loss in obese people and physical activity. Evidence for non-starch polysaccharide consumption was probable. Consumption of n-3 fatty acids and low glycaemic index foods, as well as breastfeeding, was listed as possible. Insufficient evidence was found for vitamin E, chromium, magnesium or alcohol consumption. Conversely, obesity and maternal diabetes were found to increase risk.	
Schulze & Hu (2005) ⁸⁰⁸	Review	152 references	Lifestyle factors affecting type 2 diabetes	Obesity is the strongest diabetes risk factor; physical activity reduces risk by helping to maintain a healthy body weight and improving insulin sensitivity. Consumption of unsaturated fats and whole grains rather than saturated/trans-fats and refined grains is beneficial. Smoking avoidance and moderate alcohol consumption reduce risk.	“Excessive body weight, even at average levels for the U.S. population, increases the risk of diabetes.” “Overall, a healthy diet, together with regular physical activity, maintenance of a healthy body weight, moderate alcohol consumption, and avoidance of sedentary behaviours and smoking, could nearly eliminate type 2 diabetes.”
Jeon et al (2007) ⁸⁰⁹	Systematic review and meta-analysis	10 cohort studies involving 301,221 participants	Physical activity of moderate intensity and risk of type 2 diabetes	“...relative risk of type 2 diabetes was 0.69 (95% CI, 0.58-0.83) for regular participation in physical activity of moderate intensity compared with being sedentary.”	
Willi et al (2007) ⁸¹⁰	Systematic review and meta-analysis	25 cohort studies; 1.2 million participants	Active smoking and risk of type 2 diabetes	The relative risk of type 2 diabetes for individuals who smoke was found to be 1.44 (95% CI, 1.31-1.58). Heavy smokers had a greater risk than lighter smokers, and active smokers greater than former, consistent with a dose-response phenomenon.	

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Auchincloss et al. (2008) ⁸¹¹	Population-based residential survey	2,026 adults aged 45-84 from 3 sites	The influence of the built environment (i.e., neighbourhood resources) on health	“Greater neighbourhood physical activity resources consistently were associated with lower insulin resistance. Adjusted for age, sex, family history of diabetes, race/ethnicity, income and education, insulin resistance was reduced by 17% (95% CI, 31% to 1%).”	“Diabetes prevention efforts may need to consider features of residential environment.”

The British Columbia Guidelines and Protocols Advisory Committee (GPAC) has noted that

a large proportion of type 2 diabetes can be prevented using lifestyle modification and/or pharmacologic intervention. All individuals should be encouraged to pursue a program of lifestyle modification that includes regular physical activity (at least 150 minutes of moderate intensity aerobic exercise each week spread over 3 non-consecutive days and resistance exercise 3 times a week) and moderate weight loss (5-10% of initial body weight). Lifestyle modification is particularly important for persons considered at high risk for diabetes. Pharmacologic therapy with metformin or acarbose should also be considered for those at high risk.⁸¹²

Early Detection

As noted earlier, 2-3% of the population may have undiagnosed diabetes, despite well-documented, easily accessible lists of symptoms and established screening methods.

Diabetes and milder forms of impaired glucose tolerance can be detected by an Oral Glucose Tolerance Test. A standard OGTT involves two blood tests, one taken in the morning after an overnight fast of at least 8 hours, the second two hours after intake of 75g of glucose. Fasting plasma glucose (FPG) over 7.0 mmol/L (or 2-hour post-load plasma glucose above 11.1 mmol/L) indicates diabetes. Levels under 6.1 and 7.8, respectively, are considered normal, and results in between signify impaired fasting glucose or impaired glucose tolerance.⁸¹³

According to the USPSTF, there is good evidence that using these screening methods can detect type 2 diabetes before symptoms are evident. The benefits of screening are still in question, however, since it has not been shown that glycemic control starting immediately after early detection is any more effective than interventions at the point of clinical diagnosis.⁸¹⁴

Nonetheless, the 2003 Canadian Diabetes Association Clinical Practice Guidelines recommend that “all individuals should be evaluated annually for type 2 diabetes risk on the basis of demographic and clinical criteria.”⁸¹⁵ Furthermore, screening for diabetes should be performed every 3 years in individuals > 40 years of age.

More frequent and/or earlier testing should be considered in people with additional risk factors, including:

- First-degree relative with diabetes
- Member of high-risk population (e.g., people of Aboriginal, Hispanic, Asian, South Asian, or African descent)
- History of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Presence of complications associated with diabetes
- Vascular disease
- History of gestational diabetes mellitus (GDM)
- History of delivery of a macrosomic infant
- Hypertension
- Dyslipidemia
- Overweight
- Abdominal obesity
- Polycystic ovary syndrome
- Acanthosis nigricans
- Schizophrenia

It should be noted, however, that these recommendations are based on a Grade D, or clinical consensus, level of evidence, rather than support from experimental studies.

10.4 Type 1 Diabetes

10.4.1 The Disease

Type 1 diabetes, also known as insulin-dependent diabetes mellitus (IDDM), is an autoimmune disease that occurs when the insulin-producing beta cells in the pancreas are damaged or destroyed, causing a reduction in, or the cessation of, insulin production. The etiology of type 1 diabetes is not well understood, but the disease is believed to be the result of an individual's genetic vulnerability together with a possible viral or other infectious trigger; the infection induces an autoimmune response that damages the already vulnerable insulin-producing beta cells in the pancreas.

10.4.2 Epidemiology

The incidence of type 1 diabetes in Canada is highest in children 10-14 years of age.^{816,817} In Ontario, for example, the incidence rate for female children in the calendar year 2000 ranged from 19.9 per 100,000 among 0-4 year-old females to 33.5 in 10-14 year-old females.⁸¹⁸ Similar results are seen in male children, with the incidence rates ranging from 25.0 per 100,000 among 0-4 year-old males to 35.9 in 10-14 year-old males. Type 1 diabetes is considerably less common than type 2 diabetes, accounting for less than 10% of diabetes cases.

10.4.3 Evaluating Available Evidence

Primary Prevention

A number of studies have looked at possible interventions for preventing type 1 diabetes. Over 125 therapies have been shown to prevent, or at least slow, the disease in animal models, but human trials have experienced only limited success to date.⁸¹⁹

For example, animal studies have indicated that high doses of nicotinamide can prevent diabetes by protecting β -cells from inflammatory insults and improving residual β -cell function. However, two randomized controlled trials in children (the DENIS and ENDIT trials; see following table) found nicotinamide to be ineffective in preventing type 1 diabetes. Similarly, animal models have shown that parenteral insulin therapy can prevent type 1 diabetes. As with nicotinamide, the results of a randomized controlled trial in children (DPT-Type 1) found this approach to be lacking.

A further promising area of study is the link between type 1 diabetes and breastfeeding. However, as is so often the case, there is conflicting evidence. The current TRIGR study is based on the finding that the avoidance of cow's milk proteins in early infancy reduces the incidence of type 1 diabetes in high-risk individuals. However, mothers with type 1 diabetes themselves are often unable to breastfeed for an adequate length of time due to health complications. In these cases, it is suggested that hydrolyzed weaning formulas, in which the proteins in question are broken down by an outside chemical reaction, should be provided.⁸²⁰

In addition, there is increasing evidence that vitamin D intake during childhood may be preventive against the development of type 1 diabetes, though some discrepancies exist among study results.^{821,822} It is unclear, for example, if maternal vitamin intake during pregnancy can be effective, or if dietary supplementation should only be initiated directly, after the child is born. At the same time, some conclusions are emerging. For instance, vitamin D from natural food sources appears to reduce risk more than intake by supplementation.^{823,824}

Finally, the potential for a vaccine is being explored. As suggested by one author, however, "environmental agents that promote autoimmune β -cell destruction are likely to be ubiquitous and therefore a single intervention, for example vaccination against a specific virus, is unlikely to be the ultimate solution".⁸²⁵

Table 36: Research on Type 1 Diabetes

Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Lampeter et al. (1998) ⁸²⁶ DENIS	Randomized, placebo-controlled trial	2,415 3-12 year-old siblings of patients with IDDM	The clinical effect of nicotinamide on type 1 diabetes	“We conclude that in this subgroup of diabetes-prone individuals at very high risk and with an assumed rapid disease progression, nicotinamide treatment did not cause a major decrease or delay of diabetes development.”	“The data do not exclude the possibility of a less strong, but potentially meaningful, risk reduction in this cohort, or a major clinical effect of nicotinamide in individuals with less risk of progressions to IDDM than studied here.”
Hyppönen et al. (2001) ⁸²⁷	Birth-cohort study	10,366 children in Finland, followed from birth for up to 31 years	Vitamin D supplementation or deficiency in infancy and risk of developing type 1 diabetes	Children regularly receiving the recommended dose of vitamin D had a relative risk of 0.22 (95% CI, 0.05-0.89), compared to those with a deficiency.	“Ensuring adequate vitamin D supplementation for infants could help to reverse the increasing trend in the incidence of type 1 diabetes.”
Kimpimäki et al. (2001) ⁸²⁸	Case-control study	355 Finnish infants with high genetic risk for type 1 diabetes	The relationship between early infant nutrition and β -cell autoimmunity	Infants breastfed at least 4 months had a relative risk of 0.24 (95% CI, 0.06-0.94) of developing the auto-antibodies that can lead to type 1 diabetes, compared to those breastfed less than 2 months.	
Skyler et al. (2002) ⁸²⁹ DPT-Type1	Randomized, controlled, non-blinded trial	2,103 1 st & 2 nd degree relatives of diabetic patients who tested positive for islet-cell antibodies	The effect of pre-symptomatic insulin in patients considered at risk for developing type 1 diabetes	“In persons at high risk for diabetes, insulin at the dosage used in this study does not delay or prevent type 1 diabetes.”	
Fronczak et al. (2003) ⁸³⁰	Cohort study	233 mothers + offspring at risk of type 1 diabetes	Maternal intake of vitamin D and type 1 diabetes	After adjustment, maternal vitamin D intake from food reduced risk of islet autoimmunity in offspring (adjusted HR 0.37, 95% CI 0.17 – 0.78). Vitamin D from supplements or fatty acids during pregnancy was not associated with type 1 diabetes.	
Stene et al. (2003) ⁸³¹	Cohort study	545 children with type 1 diabetes and 668 control subjects	Effect of cod liver oil + other sources of vitamin D on type 1 diabetes	Cod liver oil was found to reduce risk of type 1 diabetes (odds ratio 0.74, 95% CI 0.56 – 0.99), but other supplements were not. No maternal intake of vitamin D from any source during pregnancy was found to affect risk.	
Ziegler et al. (2003) ⁸³²	Prospective natural history cohort study	1,610 German newborns of parents with IDDM	Early infant feeding and type 1 diabetes risk	“Reduced total or exclusive breastfeeding duration did not significantly increase the risk of developing islet autoantibodies.”	
Gale et al. (2004) ⁸³³ ENDIT	Randomized, double-blind, placebo-controlled trial	552 relatives of diabetic patients with high levels of islet cell antibodies	The effect of nicotinamide on development of type 1 diabetes	“There was no difference in the development of diabetes between the treatment groups. Of 159 participants who developed diabetes in the course of the trial, 82 were taking nicotinamide and 77 were on placebo.”	“Large scale controlled trials of interventions designed to prevent the onset of type 1 diabetes are feasible, but nicotinamide was ineffective at the dose we used.”

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Study	Study Type	Sample Size	Outcome Measures	Results	Comments
Virtanen et al. (2006) ⁸³⁴	Prospective cohort study	3565 Finnish infants genetically susceptible to IDDM	Age of introduction of new foods and advanced β -cell autoimmunity	Overall or exclusive duration of breastfeeding was not associated with the risk of developing β -cell autoimmunity.	"...early age at introduction of fruits and berries and roots associates independently with beta cell autoimmunity, contradicting earlier findings from smaller cohort studies."
Holmberg et al. (2007) ⁸³⁵	Population-based follow-up study	7,443 families in south-east Sweden	Breast-feeding's protective effect against development of type 1 diabetes	"The positive association between a short duration of both total and exclusive breast-feeding, as well as an early introduction of formula, and positivity for β -cell autoantibodies in children from the general population suggests that breast-feeding modifies the risk of β -cell autoimmunity, even years after finishing breast-feeding."	
Krischer et al. (2007) ⁸³⁶ TRIGR	Double-blind, prospective, placebo-controlled trial	2,160 children, from 15 countries, considered at risk	Comparing extensively hydrolyzed infant formula & conventional cow's milk	Recruitment for this trial was finished at the end of 2006. Results are pending.	

Early Detection

Type 1 diabetes is often characterized by rapid onset at a young age, making early detection difficult. Standard forms of screening can be more effective, however, when it comes to detecting cases where onset comes more gradually or later in life. As with type 2 diabetes, a diagnosis of type 1 often requires a positive blood test. A low or undetectable level of insulin, often combined with high blood sugar, is a sign of the disease.⁸³⁷

Another method of detection, potentially capable of identifying patients before insulin levels drop, relies on testing for certain genes known to be associated with diabetes, with more than 20 genes identified to date.⁸³⁸ Certain genes, however, dominate at specific ages and in different populations.

As noted by Dahlquist,

screening for genetic markers for diseases with such complex aetiology encounters pitfalls due to the low predictive value of each single marker in the general population...Type 1 diabetes stills needs more precise risk markers in addition to a very safe prevention strategy before neonatal screening programmes may be instituted."

This explains the caution of the 2003 Canadian Diabetes Association guidelines, which note that,

while randomized trials testing prevention strategies have been completed recently or are now underway, safe and effective preventive therapies have not been identified...[so] any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.⁸³⁹

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APPENDIX 1: ACCESSED SOURCES OF SYSTEMATIC REVIEWS

The *British Medical Journal* Publishing Group produces clinical evidence reviews based on the following approach:

For each question, the literature is searched using the Cochrane Library, Medline, Embase and, occasionally, other electronic databases, looking first for good systematic reviews of RCTs; then for good RCTs published since the search date of the review. Where we find no good recent systematic reviews, we search for individual RCTs back to 1966. The date of the search is recorded in the methods section for each topic. Of the studies that are identified in the search, we select and summarise only a small proportion. The selection is done by critically appraising the abstracts of the studies identified in the search, a task performed independently by information scientists using validated criteria similar to those of Sackett et al¹ and Jadad.^{2,3} Where the search identifies more than one or two good reviews or trials, we select those we judge to be the most robust or relevant. Where we identify few or no good reviews or trials, we include other studies but highlight their limitations. Contributors, chosen for their clinical expertise in the field and their skills in epidemiology, are asked to review our selection of studies and to justify any additions or exclusions they wish to make.⁴

Another source of rigorous systematic reviews is the Cochrane Collaboration. The Cochrane Collaboration is an international non-profit and independent organisation, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. Review articles are available in the *Cochrane Database of Systematic Reviews*. The approach of the Cochrane Collaboration is as follows:

Cochrane reviews investigate the effects of interventions for prevention, treatment and rehabilitation in a healthcare setting. They are designed to facilitate the choices that doctors, patients, policy makers, and others face in health care. Most Cochrane reviews are based on randomised controlled trials, but other types of evidence may also be taken into account, if appropriate. Cochrane reviews have the following general features:

- A structured format helps the reader to find his/her way around the review easily.
- A detailed methods section allows the reader to assess whether the review was done in such a way as to justify its conclusions.
- The quality of clinical studies to be incorporated into a review is carefully considered, using predefined criteria.
- A thorough and systematic search strategy, which includes searches for unpublished and non-English records, aims to provide as complete a picture as possible to try to answer the question considered.

- If the data collected in a review are of sufficient quality and similar enough, they are summarised statistically in a meta-analysis, which generally provides a better overall estimate of a clinical effect than the results from individual studies...
- Reviews aim to be relatively easy to understand for non-experts (although a certain amount of technical detail is always necessary). To achieve this, Review Groups like to work with "consumers", for example patients, who also contribute by pointing out issues that are important for people receiving certain interventions...
- Multinational editorial teams try to ensure that a review is applicable in different parts of the world.
- Reviews are updateable. Results from newly completed or identified clinical trials can be incorporated into the review after publication.⁵

The Agency for Healthcare Research and Quality (AHRQ) of the United States Department of Health & Human Services also has a clinical prevention section with reports and recommendations regarding prevention and early detection of chronic and acute diseases provided by the USPSTF. The USPSTF is responsible for investigating and making recommendations about preventative services and determining which should be implemented into routine primary care. The following is a description of the methods employed by the USPSTF:

The U.S. Preventive Services Task Force (USPSTF/Task Force) represents one of several efforts to take a more evidence-based approach to the development of clinical practice guidelines. As methods have matured for assembling and reviewing evidence and for translating evidence into guidelines, so too have the methods of the USPSTF. This paper summarizes the current methods of the third USPSTF, supported by the Agency for Healthcare Research and Quality (AHRQ) and two of the AHRQ Evidence-based Practice Centers (EPCs).

The Task Force limits the topics it reviews to those conditions that cause a large burden of suffering to society and that also have available a potentially effective preventive service. It focuses its reviews on the questions and evidence most critical to making a recommendation. It uses analytic frameworks to specify the linkages and key questions connecting the preventive service with health outcomes. These linkages, together with explicit inclusion criteria, guide the literature searches for admissible evidence.

Once assembled, admissible evidence is reviewed at three strata: (1) the individual study, (2) the body of evidence concerning a single linkage in the analytic framework, and (3) the body of evidence concerning the entire preventive service. For each stratum, the Task Force uses explicit criteria as general guidelines to assign one of three grades of evidence: good, fair, or poor. Good or fair quality evidence for the entire preventive service must include studies of sufficient design and quality to provide an unbroken chain of evidence-supported linkages, generalizable to the general primary care population, that connect the preventive service with health outcomes. Poor evidence contains a formidable

break in the evidence chain such that the connection between the preventive service and health outcomes is uncertain.

For services supported by overall good or fair evidence, the Task Force uses outcomes tables to help categorize the magnitude of benefits, harms, and net benefit from implementation of the preventive service into one of four categories: substantial, moderate, small, or zero/negative.

The Task Force uses its assessment of the evidence and magnitude of net benefit to make a recommendation, coded as a letter: from A (strongly recommended) to D (recommend against). It gives an I recommendation in situations in which the evidence is insufficient to determine net benefit.

The third Task Force and the EPCs will continue to examine a variety of methodologic issues and document work group progress in future communications.⁶

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