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Guest Editorial on Public Health Aspects of Breast Cancer Gene Testing in Canada

Simon B Sutcliffe

The technology of medicine has outrun its sociology.
Henry E Sigerist (1891–1957)

In this issue of *Chronic Diseases in Canada*, Mark Elwood provides a comprehensive overview of the state of knowledge related to the risks, interventions, selection criteria for testing and potential models to address the need and demand for breast cancer gene testing. The information has broad applicability to the specific—BRCA1 and BRCA2 testing for breast cancer—and to the general—public health issues associated with the determination of hereditary predisposition to cancer and perhaps, more broadly, to determination of genetic predisposition for sporadic cancer.

What might we have hoped for in a cancer gene test? I would say a reliable, reproducible assay that, if positive, tells whether you will get the disease, ... if negative, that you will not get the disease; that is specific to one type of cancer; that provides for application of curative or preventive measures through early identification of pre-disease; and that is embraced by a confident public as a beneficial health care measure.

This is what we have now according to Elwood's distillation of the facts of the BRCA1/2 situation.

- The mutations are in tumour suppressor gene(s) that give a predisposition to breast cancer, ovarian cancer and other epithelial neoplasms.
- The risk of cancer in gene mutation carriers may be substantially lower in more recent, population-based studies than in older, selected, multicase family studies.
- The frequency of mutation detection in cancer patients or families with a strong history of cancer is lower in more recent, population-based studies.
- False positives occur due to identification of mutations of no known significance.
- False negatives occur (specific mutation missed, another known gene responsible, unknown gene responsible, multiple low penetrance genes, familial and shared environmental factors, sporadic case in high-risk family)—a negative test is only informative when the relevant mutation is both known and screened for.
- Evidence-based screening is variably available and accessible.
- The value of interventions based upon detection of breast cancer susceptibility mutation is at a low level of evidence.
- Of those women who pursue counselling based upon family history, many have a grossly overinflated perception of risk, heightened anxiety and a lack of understanding of the benefits, limitations and risks of genetic testing.
- The exaggerated perception of risk may not be modified by thorough and detailed counselling.
- Publicity regarding genetic factors conferring high risk of developing cancer may influence participation in prevention and early detection programs favourably or adversely, depending upon a perception of risk that may or may not be justified.
- It will be necessary to establish a population-based monitoring system to achieve optimal determination of the highest probability of providing service to those most likely to benefit (i.e. gene mutation carriers), largely through the ability to obtain accurate, standardized family histories and to provide a coherent, auditable counselling service that triages the most appropriate individuals to genetic testing, while appropriately allaying the anxiety of those tested and those declined for testing.

Given that autosomal dominant genes inducing cancer syndromes appear to be rare and that the hereditary cancer syndromes more commonly involve tumour

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suppressor or DNA mismatch repair syndromes as a basis for predisposition to mutations and cancer risk, it seems likely that Elwood's conclusions will apply in similar measure to familial cancers other than breast cancer. Furthermore, as such mutations are likely to characterize the genetic progression of acquired carcinogenesis, similar technical, clinical and socio-behavioural issues may prevail.

What then might we expect as awareness of genetic testing and genetic predisposition to cancer achieves a higher profile, and as more genes associated with cancer predisposition are defined?

- *Scientific issues* (the "test" performance parameters): What are the relevant mutations, for what disease(s) do they predict, what are the false positive and negative test rates, what is the positive predictive value? Also, of substantial importance, what test methods are employed, what are the laboratory standards, what is the reproducibility of the test and how does this compare within and between laboratories, within and between provinces or countries?
- *Clinical issues:* Who should see well people who have a genetic predisposition for cancer—clinical geneticists … genetic counsellors … family doctors … oncologists? Who is training health care professionals to function as molecular biologists/ therapists of the well, "at risk" population? When, and how, will the rote elicitation of a family history become a detailed lineage map for inherited predisposition studies? Who will triage genetic testing and/or counselling services according to the level of risk (and how will they do it)? How will we address the issue of availability and evaluation of interventions (e.g. screening versus chemoprevention versus prophylactic surgery) that can modify the development and outcome of cancer based upon genetic predetermination of risk?
- *Socio-economic issues:* Currently the majority of our health care funds are directed to alleviating the burden of illness of those people with disease. Determination of risk of disease through genetic testing poses the dilemma of increasing the allocation of funds to the "well" to prevent illness. While determination of the burden of familial predisposition to cancer might be finite and encompassable, the issue of determination of risk predisposition for sporadic cancer in the "well," on a serial basis, has enormous potential implications. Use, and abuse, of genetic testing within a socialized medicine context would threaten laboratory, counselling and clinical resources. Within a "finite envelope," how do we pay for the well to stay well, in addition to the ill deriving the benefits of curative and palliative medicine? What impact would this have on health care premiums/contributions … for the well, for the ill, equalized across all citizens, customized to the individual health care situation?
- *Health care practice*: Our health care paradigm moves increasingly toward the integration of chronic and episodic care (community and tertiary), the total management of illness and the aggregation of risk across populations. Our management/information systems will need to track and link risks in health to disease development, treatment and prognosis. How will we deal with "genetic privacy," highly individualized and intensive counselling and confidentiality with registration linkage of documentable events in the process of carcinogenesis, and "managed care" practice that seeks consensus regarding "best practice" across populations throughout recognized phases of the trajectory of wellness and illness?
- *Ethical and legal issues*: What is genetic privacy? Who has access to information and under what circumstances? Does it differ for family versus non-family members? What are the ethics of testing when there may be no effective intervention, and what is the nature of informed consent and counselling in such circumstances? If genetic predisposition is to be "registered" as a part of the continuum of wellness, potentially leading to illness, how is confidentiality maintained and who is entitled to know—the employer, the insurer, … ?
- *Personal and socio-behavioural issues:* How do we convey information that is accurate, helpful, allays anxiety and induces a responsible attitude toward health care practice and use of health care resources? How do we ensure that the appropriate studies are performed, with public support and confidence, to provide the scientific, clinical and sociological information to place a genetic test in a true and accurate perspective? Given that behaviours "in health" lie very much within the public domain, how do we establish the confidence and support to vest genetic testing for cancer, be it hereditary or sporadic, within the public health care system?

In the following articles, Elwood presents a personal interpretation of the evolving science relating to the clinical and sociological impacts of detection of breast cancer susceptibility gene mutation. His views may convey a pessimism reflecting the early nature of the science, or the "worst case" scenario that hereditary breast cancer may pose. One thing is clear—furthering the science has provided no easy solutions. Indeed, it has posed more questions than it has answered, and the issues raised must be approached in the context of sound, ethical research and public health.

> *Health cannot be forced upon the people. It cannot be dispensed to the people. They must want it and be prepared to do their share and to cooperate fully in whatever health program a country develops.*
>
> *Can J Public Health* 1944;35:260

Public Health Aspects of Breast Cancer Gene Testing in Canada Part 1: Risks and Interventions

J Mark Elwood

Abstract

The risks (penetrance) of breast and ovarian cancer in carriers of the BRCA1 or BRCA2 genes are high, but it is likely that estimates based on selected large multicase families are inflated by selection bias. Estimates based on a population survey of Ashkenazi Jews are lower, but other population-based estimates are still not available. The proportion of breast or ovarian cancers related to the genes is similarly lower in population-based samples than in referred selected families, and, even for subjects with cancer onset at young ages or with a family history, it is quite small. Other genes with lower prevalence are also important, and there is evidence of some gene–environmental interactions. The management of female BRCA gene carriers includes intensive surveillance, prophylactic surgery and the use of tamoxifen. Apart from screening justified by randomized trials in the general community, such as mammography, recommendations for surveillance and prophylactic surgery are based only on expert opinion, and there has been little consideration of risk-benefit or cost-benefit comparisons. Tamoxifen reduced breast cancer incidence in one trial of high-risk women, but not in two other smaller trials, and the effect on mortality has not been determined. The limitations of genetic testing, and particularly of intervention strategies, deserve close scrutiny.

Key words: *BRCA1; BRCA2; breast neoplasms; Canada; genes; genetic screening; mass screening; ovarian neoplasms; predictive value; risk*

Introduction and Methods

This is the first of three papers that will address some key issues in regard to genetic testing for cancer susceptibility in Canada, from an epidemiologic and public health perspective.[1,2] They will concentrate on the genes for breast and ovarian cancers, BRCA1 and BRCA2, as these illustrate most of the issues that will apply to similar new developments. Part 1 reviews background information on genetic risks and on interventions for test-positive subjects.

This work is based on an initial literature review, primarily using MEDLINE, discussions with many authorities in Canada in August–October 1997 and an update of the literature review to November 1998. Key words searched were *breast neoplasms, ovarian neoplasms, BRCA1, BRCA2, genetic screening, mass screening, genetic counselling, predictive value, attitude to health, decision making, risk, genes* and *Canada.*

Genes Conferring High Risks of Breast Cancer

Cancer develops as a result of accumulated damage to one or more genes, producing either somatic mutations within the cells that will form the cancer or germ line mutations that confer susceptibility by raising the probability of transformation to cancer cells and of progression. Two genetic loci conferring an increased risk of breast cancer have been identified and cloned, and several other genes relate to breast cancer risk. The work has been facilitated by the International Breast Cancer Linkage Consortium (IBCLC), which has collated data on over 200 high-risk families worldwide.

In 1990, the breast susceptibility gene BRCA1 was located on chromosome 17q in 23 families, with an average of six breast cancer cases per family; linkage was confined to those families with a mean age of onset of breast cancer of less than 46 years.[3] This gene was found in almost all families showing both breast cancer

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and ovarian cancer,[4,5] but only in about half of the families showing breast cancer alone.

The BRCA1 locus was cloned in 1994.[6] Several hundred different mutations have been described so far. Most are frameshift, nonsense, splice or regulatory mutations that give a truncated protein product, so tests for these common types of mutations may detect around 80% of all gene mutations.[7] The tests are most reliable where a specific mutation has been identified in a cancer case in the family, so that other family members are tested for that mutation. The most common mutations so far described are the 185delAG and 5382insC mutations. BRCA1 is likely to be a tumour suppressor gene;[8,9] thus gene therapy, introducing the active wild type gene, could in principle restore tumour suppressor function.[10]

The second breast cancer susceptibility gene, BRCA2 on chromosome 13q, was identified in families with apparent dominant inheritance showing no linkage to BRCA1, and it was isolated in 1995.[11] So far, all identified mutations involve premature termination of protein synthesis.[9] BRCA2 appears to be linked to an increase in male breast cancer, but not to a large excess of ovarian cancer. Studies of high-risk families suggest that BRCA2 is involved in 12% of families with four or five cases of breast cancer and in 61% with six or more cases.[12] A specific mutation of BRCA2, 6174delT, is common in Ashkenazi Jews, occurring in about 1% of that population. Its penetrance may be less than that of BRCA1 185delAG, but together these two mutations may account for 25% of early onset breast cancer in Ashkenazi women.[9]

BRCA1 and BRCA2: Risk of Cancers in Carriers

Until recently, the most widely quoted estimates of cancer risks were based on the selected high-risk families involved in the IBCLC studies (Table 1). Ford et al.[13] analyzed data from 33 families, each with at least four cases of breast or ovarian cancer diagnosed before age 60, and estimated risks from the occurrence of second cancers in subjects with breast cancer. The cumulative risk of breast cancer (the penetrance) in carriers by age 50 was estimated at 73%, and by age 70 at 87%, and the corresponding risks of ovarian cancer were 29% and 44%. There were also increases in risk of colon and prostate cancers in carriers. Substantially different estimates were derived from the same data by an independent method, by maximizing the LOD score over a range of possible penetrance functions;[14] this produced lower estimated risks at young ages. A better fit to the data was given by assuming two different alleles (Table 1). The variability in these estimates, their quite wide confidence limits and, most importantly, the fact that these families are highly selected, all limit the general application of these estimates.

TABLE 1

Risks of breast or ovarian cancer in BRCA1 or BRCA2 mutation carriers, by age

Study	Population	Risks (%) in carriers by age shown (95% confidence interval)[a]					
		Breast cancer			Ovarian cancer		
		Age 50	Age 60	Age 70	Age 50	Age 60	Age 70
Derived from large high-risk families							
Ford et al.[13]	IBCLC multicase families; 33 families: BRCA1[b]	73 (49 87)		87 (72 95)	29 (16 40)		44 (28 56)
Easton et al.[14]	IBCLC multicase families; 33 families: BRCA1[b]	51	54 (27 71)	85	23	30 (8 47)	63
	(Allele in 71%)		62			11	
	(Allele in 29%)		39			42	
Easton et al.[15]	2 BRCA2 families	60 (26 79)		80 (29 98)			
	Male breast cancer			6 (1 26)			
Derived from a population-based sample							
Struewing et al.[16]	Ashkenazi Jews, Washington DC; recruited by media: BRCA1 or BRCA2	33 (23 44)		56 (40 73)	7 (2 14)		16 (6 28)

[a] Confidence interval given only where given in original.

[b] The two IBCLC studies use different methods: see text.

IBCLC = International Breast Cancer Linkage Consortium

Other results from these studies are that the risk of a second, contralateral breast cancer in carriers who have one breast cancer is high (48% by age 50, 64% by age 74) and their risk of ovarian cancer is also greatly increased (29% by age 50, 44% by age 70).[13] The risk may vary with the precise mutation: for ovarian cancer, mutations in the 3' portion of the BRCA1 gene confer a lower risk than do other mutations.[7] The BRCA1 gene does not appear to be associated with male breast cancer. As ovarian cancer is not easily diagnosed early and has a very poor survival rate, BRCA1 carriers may have a greater loss of life expectancy from ovarian cancer rather than from breast cancer.

For BRCA2, Easton et al.[15] assessed risks in two large families, using a maximum LOD score method, estimating breast cancer risks of 60% by age 50 and 80% by age 70, and a risk of breast cancer in male carriers of 6% by age 70 (Table 1). They reported an increased risk of ovarian cancer based on three cases, and also excesses of laryngeal and prostate cancers.

Lower risks have been seen in population-based series. Struewing et al.[16] assessed the prevalence of BRCA1 and BRCA2 mutations in a population-based sample of 5318 Ashkenazi Jewish subjects in Washington, DC, recruited through the media; 120 (2.3%) had a mutation. The risks of cancer, estimated by comparing the family history data for carriers and non-carriers, were similar in BRCA1 and BRCA2 carriers and were substantially less than the earlier estimates based on IBCLC families, reaching only 56% by age 70 (Table 1). No excess of colon cancer was seen. Thirty-one carriers (25%) had no cancer history in first- or second-degree relatives, which was not due simply to small family size. This sample, while community-based, was probably biased by the method of recruitment toward inclusion of subjects with strong family histories, and the reports of cancer in relatives were not verified. Even so, it suggests that the risks estimated from large multicase families referred to major research centres may be substantially higher than the risks in mutation carriers in general.

BRCA1 and BRCA2: Proportion of Cancers due to the Genes

Based on the IBCLC analyses, Ford et al.[5] calculated a gene frequency of 0.0006 for BRCA1. They estimated that around 5.3% of population cases of breast cancer occurring below the age of 40 are related to the BRCA1 gene, compared to 2.2% between ages 40 and 49, and 1.1% from age 50 to 70; the estimates for ovarian cancer were 5.7%, 4.6% and 2.1% respectively. Overall, about 1.7% of all breast cancers and 2.8% of ovarian cancers at all ages up to 70 occur in BRCA1 carriers. The IBCLC studies suggest that in 50% of families having at least four affected members with breast cancer under age 60 and in over 80% of families with both breast cancer and ovarian cancer, the cancers are due to BRCA1.[17] These estimates are lower than earlier estimates from fewer families.[18,19]

More direct estimates come from testing series of patients for gene mutations (Table 2). Several series are based on subjects referred to genetic clinics. Couch et al.[20] reported on women referred to assessment centres in the eastern US who were not members of known large multicase families. BRCA1 mutations were found in 16% of 169 women who attended because of a family history and in 13% of 94 women who had breast cancer diagnosed before age 40. The authors evaluated factors related to BRCA1 carrier status, providing a table of estimated probabilities. The prevalence of BRCA1 mutations increased with a family history of both breast and ovarian cancers, lower age at diagnosis and Ashkenazi Jewish ancestry. It did not vary with the occurrence of bilateral breast cancer or with the number of breast cancers in the family. The results suggest that gene testing in women who have even several relatives with breast cancer would have a low yield (<10%) unless at least one relative has had breast cancer before age 35.

In a recent international study of 798 referred women from suspected high-risk families, Shattuck-Eidens et al. reported that deleterious mutations were found in 12.8% of these women, using complete sequence analysis, and 50 new genetic alterations were found.[21] Factors predicting BRCA1 mutations included the number of relatives with breast or ovarian cancer.

Results from population-based series are of particular value and tend to give lower frequencies of gene disorders. In a study of a hospital series of 73 women with breast cancer diagnosed before age 32 in the Boston area, Krainer et al.[22] found that only 2 (2.7%) had BRCA2 mutations, whereas 9 (12%) had BRCA1 mutations. If these two mutations have similar population prevalences (as they do in Ashkenazi Jews), these results show a lower penetrance for BRCA2 than for BRCA1. This is consistent with other literature showing BRCA2 mutations in only 13% of 75 breast cancer kindreds where BRCA1 linkage had been excluded.[12,23]

Langston et al.[24] studied 80 women identified through a population-based cancer registry in Washington (state), who had breast cancer before age 35. Using DNA sequencing, they found that six women (8%) had BRCA1 mutations, of whom two had no family history of breast or ovarian cancer. Another four women had rare sequence variants of unknown importance. A further study based on the same registries by Malone et al. showed 6% BRCA1 mutations in 193 breast cancer cases under age 35, and 7% in 208 cases with breast cancer before age 45 with a first-degree relative also affected.[25] In the study of Ashkenazi Jews noted earlier, Struewing et al.[16] found a prevalence of 14% BRCA1 or BRCA2 mutations in subjects with breast or ovarian cancer prior to age 50 (Table 2).

TABLE 2

Prevalence of gene mutations found in defined groups of subjects

Study	Place	Criteria	Test	Number tested	Positive	% positive
Women referred to genetic clinics or hospitals						
Couch et al.[20]	Women seen at genetic clinics in US	Breast cancer + family history (FH)	BRCA1	169	27	16
		Breast cancer < age 40	BRCA1	94	12	13
Shattuck-Eidens et al.[21]	Women referred to genetic clinics, several countries	FH of breast or ovarian cancer	BRCA1	798	102	13
Krainer et al.[22]	Boston, hospital series	Breast cancer < age 32	BRCA1	73	9	12
			BRCA 2	73	2	3
Cancer cases from population-based registries						
Langston et al.[24]	Washington (state), registry-based	Breast cancer < age 35	BRCA1	80	6	8
		Subgroup: with FH breast or ovary		41	4	10
		Subgroup: no FH		39	2	5
Malone et al.[25]	Washington (state), registry-based	Breast cancer < age 35, no FH	BRCA1	193	12	6
		Breast cancer < age 45, FH	BRCA1	208	15	7
Results from a population-based survey of Ashkenazi Jews						
Struewing et al.[16]	Washington (DC), survey-based	Ashkenazi Jews, recruited by media: whole population	BRCA1, BRCA2	5318	120	2
		Breast or ovarian cancer < age 50		143	20	14
		Same, > age 50		153	7	5
		No personal history, FH breast or ovarian cancer		786	30	4
		No personal history, no FH		2648	32	1
		Men: FH breast or ovarian cancer		275	14	5
		Men: no FH		1301	17	1

FH = Family history in first-degree relatives

Frequency of Carriers in the Population

Ford et al.[5] estimated the frequency of the BRCA1 gene by assuming that the excess risks of ovarian cancer in first-degree relatives of breast cancer patients, and of breast cancer in first-degree relatives of ovarian cancer patients, were all due to BRCA1: this gave a gene frequency (f) of 0.0006, with 95% confidence limits of 0.0002 and 0.001. The prevalence of BRCA1 mutations in the general population is then $2f\text{-}f^2$, or very nearly $2f = 0.0012$, that is, 1.2 per 1000 population. The prevalence seems similar in the British and US studies.[26] However, in the study of Ashkenazi Jews noted earlier, the prevalence of BRCA1 or BRCA2 mutations was 2.3%.[16] The prevalence of one particular mutation, 185delAG, was 0.9 % in an Ashkenazi Jewish population in the US.[16,27] Population-based screening programs have been developed in this community, despite some reservations.[27]

This high frequency may be due to a founder effect;[9] that is, most of the community may be descended from a few ancestors who had a high frequency of the gene. Extensive studies of BRCA1 and BRCA2 mutations in different populations have now been published. They show considerable variations in the proportion of high-risk families with BRCA1 mutations and in the frequency of particular mutations in European groups, due to founder effects;[28] although some of the variations seen may be due to selection factors related to referral and to sampling variation.

Data on the many ethnically diverse communities within Canada are therefore important. Some data on French-Canadian families have been presented.[12,29] In recent abstracts, Wong et al.[30] report that 10.3% of 117 Ashkenazi Jewish women with breast cancer before age 65 seen in Montreal and Toronto had BRCA1 mutations. Tonin et al.[31] assessed 94 French-Canadian families with breast cancer in women under age 65, ovarian cancer or male breast cancer; mutations have been identified so far

in 34 families (36%), 19 with BRCA1 and 15 with BRCA2 mutations. Seventy-nine percent of the families with mutations had four or more cases of breast or ovarian type cancer.

Looking at other ethnic groups, BRCA1 mutations may be rarer in Japanese families.[32] In Iceland, most families with combined breast and ovarian cancers are linked to BRCA2 and to a specific mutation, 999del5;[33,34] these families may show an excess of pancreatic cancer.

Other Genes Conferring Increased Risk of Breast Cancer

Several studies have found that about 20% of multicase high-risk families show no linkage to either BRCA1 or BRCA2 after extensive testing.[9,35] This could be due to as yet unidentified mutations of these genes, but it is likely that other genes (BRCA3, etc.) will be identified in some of these families. Another dominant gene condition with an increased risk of breast cancer is the Li-Fraumeni syndrome, related to the suppressor gene p53, which may account for up to 1% of breast cancer cases occurring under the age of 35.[9,36] Other rarer conditions include Cowden disease, an androgen receptor mutation that has been linked to male breast cancer, and genes associated with HNPCC (hereditary non-polyposis colorectal cancer).[9]

Several other genes are reasonably common, but have low penetrance, that is, the risk of breast or other cancers is only moderately increased. Ataxia telangiectasia heterozygotes have a moderately increased risk of breast cancer (relative risk of 3.9 in one overview[37]), conferring a cumulative risk of some 20–30% by age 70. Since between 0.5% and 1% of the population may have this genetic risk factor, it may account for roughly 2–8% of breast cancer in the population. There is some evidence that individuals with p53 and AT mutations may be more sensitive to ionizing radiation, and the breast cancer risks in mothers of AT children (who are heterozygous for the gene) are increased by radiation exposure.[38,39]

The HRAS1 gene carries an increased risk of breast cancer of about twice the normal risk; since the carrier frequency is between 5% and 20%, about 3–8% of all breast cancer could be attributed to HRAS1. This association may be greater for black women and for women with estrogen negative tumours.[40] Carcinogen-metabolism loci encode enzymes involved in the metabolism of tobacco, alcohol, occupational solvents and dietary constituents; elevated risks of breast cancer have been reported in association with specific genotypes.[40]

Interactive Effects of Genetic and Environmental Factors

In a case-control study of breast cancer among subjects known to be BRCA1 or BRCA2 carriers, smoking was negatively associated with breast cancer risk, with an odds ratio of 0.46 (95% confidence interval = 0.27–0.80) for subjects who had more than four pack-years of smoking.[41] The authors of this study, co-ordinated from Toronto, suggest that the anti-estrogenic effect of tobacco may be responsible. Previously, smoking in the general population appeared to be a risk factor for postmenopausal breast cancer among slow acetylators but was protective among rapid acetylators, the difference relating to the *N*-acetyltransferase 2 polymorphism.[42]

In a case-control study based on the Nurses' Health Study in the US, smoking was related to an increase in breast cancer risk among subjects with genotypic variants of cytochrome P450 1A1, which affect aryl hydrocarbon hydroxylase activity, suggesting a causal effect of smoking in a genetically susceptible population.[43]

Validity of Laboratory Tests for Genetic Susceptibility

As with any other test, its ability to correctly identify subjects with a genetic susceptibility (the sensitivity) and the risks of the test giving a positive result when a true genetic susceptibility does not exist (the false positive rate, or 1-specificity) are important parameters. They cannot be measured directly, as all subjects with a true genetic susceptibility cannot be identified, but may be inferred from linkage studies. Simpler tests suitable for widespread use can be compared with more extensive and detailed tests (such as DNA sequencing) that may only be applicable in research situations.

For BRCA1, many specific mutations have been shown;[44] only detailed and expensive testing would detect all of these, and in a newly investigated family, there is a high likelihood of finding a previously unrecognized mutation. Families have been found with very strong evidence of linkage to BRCA1 but without an identified mutation, suggesting that further mutations are yet to be found.[9] So the sensitivity of BRCA1 testing is clearly less than perfect. A negative test result is clinically useful in a family in which a specific BRCA1 mutation has been identified, so that failure to find that mutation in an individual can be taken as a valid negative result. Population-based screening is only feasible for specific mutations, for example, the 185delAG mutation in BRCA1 common in Ashkenazi Jews.[27]

A negative test for a gene such as BRCA1 in a subject from a high-risk family could be due to several possible factors: a mutation was missed because the test used did not detect that specific mutation; another known gene

was responsible; another, as yet unidentified, gene was responsible; the familial risk was due to multiple, low penetrance genes; the "familial" aggregation was due to shared environmental risk factors, or to chance; or this was a sporadic case, despite being from a high-risk family.[9] A false positive genetic test can also occur, since sophisticated testing may demonstrate mutations (i.e. differences from the normal gene sequence) that may not be related to increased risk and may not be informative.

A discussion of the different types of genetic tests that can be used is outside the scope of this review. Much of the literature is based on high-quality studies in research centres, using optimum methods such as confirmation sensitive gel electrophoresis and DNA sequencing. Simpler and cheaper tests, such as the protein truncation test, will detect the great majority of mutations, but the risk of a false negative result must be considered when the tests are interpreted.

Interventions for Subjects at High Risk

The assumption (often implicit) behind screening for genetic cancer susceptibility is that, in those individuals identified as mutation carriers, the cancers anticipated can be prevented, or their morbidity and mortality risk can be reduced by earlier diagnosis from surveillance. As in all issues of screening for chronic disease, there is a need for high-quality objective evidence to show the net benefit of the screening modality; this is best founded on population-based randomized trials, since observational studies are open to various biases. There are no randomized trials assessing the value of screening and intervention specifically for people tested for genetic markers. Whether the results of trials in other groups, such as the general population, can be applied without modification to mutation carriers is debatable. Trials, observational studies, and routine data collection and monitoring of the results of interventions in mutation carriers are of major priority.

Clinical Management of Carriers of BRCA1 and BRCA2: Breast Cancer Surveillance

The options available for clinical management include screening, prophylactic surgery and chemoprevention. Recently (1997) the Cancer Genetics Studies Consortium (CGSC), a US-based multidisciplinary group, published consensus statements on the management of BRCA mutation carriers.[45] The CGSC recommends frequent use of screening procedures, starting at early ages but based on only grade 3 evidence (expert opinion only) [Table 3]. Since there are no available randomized trials of gene

TABLE 3

Recommendations for surveillance and prophylaxis for carriers of BRCA1 and BRCA2 mutations, from the Cancer Genetics Study Consortium (US)

Target cancer site	Estimated risk by age 70 (based on multicase families)	Intervention	Recommendation	Quality of evidence	Cautions given
Breast	85%	Breast self-examination (BSE)	Education on monthly BSE	3	Benefit not proven
		Clinical examination	Annually or 2/year, from ages 25 35	3	Benefit not proven
		Mammography	Annually from ages 25 35	3 (1 at ages 50 69)	Risks and benefits not established under age 50
		Prophylactic bilateral mastectomy	Insufficient evidence to recommend for or against	3	Efficacy uncertain; risk not fully eliminated
Ovary	26 85% (BRCA1) < 10% (BRCA2)	Transvaginal ultrasound with colour Doppler and CA-125	Annually or 2/year, from ages 25 35	3	Benefit not proven
		Prophylactic bilateral oophorectomy	Insufficient evidence to recommend for or against	3	Efficacy uncertain; risk not fully eliminated
Prostate	8% (BRCA1)	Rectal exam, prostate-specific antigen	Inform re screening options annually from age 50	3	Benefit not proven
Colon	6% (BRCA1)	Fecal occult blood	Annually, from age 50	1	Relevance of general population data uncertain
		Flexible sigmoidoscopy	Each 3 5 years, from age 50	2	

Levels of evidence: 1. Randomized controlled trial, in general population
2. Case-control study in general population
3. Expert opinion only

Source: Adapted from Reference 45

carriers or other high-risk groups, these recommendations are based on extrapolation from general population results, carrying the implicit assumption that a lower level of evidence of benefit is acceptable for subjects at higher risk.

For example, breast self-examination (BSE) is recommended by the CGSC despite the fact that the evidence for benefit is based on studies open to selection biases; the results from a non-randomized trial in Britain and from randomized trials in Russia and China all suggest no benefit.[46–48] The apparent benefit seen in observational studies is likely due to other characteristics of those who practice BSE, rather than to the examination itself, and any benefit is likely to be lowest in women involved in other intense monitoring.[49,50] Nevertheless, in a case-control study within the randomized Canadian National Breast Screening Study, there was a strong association between the risk of fatal or metastatic breast cancer and the non-performance of particular components of recommended self-examination procedures.[51]

The specific contribution of clinical breast examination is also difficult to assess because the quality of clinical examination is likely to vary greatly. Data from four randomized trials that compared clinical examination plus mammography with mammography alone showed improved cancer detection rates and sensitivity with the use of both methods, although mammography performed better than clinical examination alone.[52]

Mammographic screening for breast cancer is the best justified intervention proposed for carriers of BRCA genes, as several randomized trials have reported reduced mortality in women in the general population over age 50.[53] However, there is considerable controversy about the value of mammography in women under age 50.[53,54] At younger ages, the sensitivity is lower, with mortality benefits appearing later and being smaller. Although some of the most recent analyses do show a useful mortality reduction even at younger ages,[55,56] much of this may be due to screening after age 50.[54,57] There is no evidence on the effects of mammography in women under age 40. Women with a genetic predisposition may be more sensitive to radiation from mammography, although any effect is unlikely to be substantial.[58]

Outcome of Mammographic Screening in High-risk Women

The effects of family history of breast cancer on the results of mammography screening were assessed for 31,814 asymptomatic women aged 30 or older who had a first screening examination between 1985 and 1992 in San Francisco.[59] In women under 50, the false positive rate was increased by about 10% in those with a positive family history, while the cancer detection rate was increased more, giving screening a higher predictive value for those with a family history (8.3%) than for those without (3.9%). For women over 50, the predictive value of screening was 19.6% for those with a family history and 13.5% for those without. The sensitivity of mammographic screening, estimated by documenting interval cancers in a 13-month period after a negative screen, was significantly lower for women under 50 with a family history (69%) than for those with no family history (88%).[60] This effect was not related to breast density. The authors concluded that it was due to a faster tumour growth in women with a family history of breast cancer, and they recommended annual screening for such women. Family history had no effect for women over age 50, where the sensitivity was 95% for those with a family history and 93% for those without.

Surveillance for Other Cancers in BRCA Carriers

In the case of ovarian cancer, there is no good evidence for the benefits of any screening technique, although trials are in progress in the general population.[61–63] The CGSC recommends the use of ultrasound with colour Doppler and CA125 annually or semi-annually beginning at age 25 or 35, again based only on expert opinion.[45]

BRCA carriers appear to be at moderately increased risks of prostate and colon cancers (see above). For prostate cancer, the CGSC recommends only providing information regarding options, given the lack of evidence for any benefit from prostate screening.[64–66] The recommendation for colon cancer is the same as for the general population:[67] the use of annual fecal occult blood testing and flexible sigmoidoscopy every 3–5 years beginning at age 50, which is supported by evidence from randomized trials[68–70] and case-control studies.[71,72]

Prophylactic Surgery

For subjects with very high cancer risks, prophylactic surgery will remove the target organ to prevent the cancer from arising. Such surgery is as extensive (or more so) than that used to treat a cancer if it does occur, and it will be performed many years earlier. Because many mutation carriers will escape disease or die from other causes, a proportion of any prophylactic surgery done will be unnecessary. Moreover, since all the relevant tissue cannot be removed and since mutation carriers may have increased risks of several cancers, the protection given will be only partial.

The CGSC makes no recommendation for or against prophylactic mastectomy or ovarian removal. Breast cancer has been documented in women after prophylactic mastectomy, as residual breast tissue remains and breast tissue also occurs at other sites.[73–75]

A National Institutes of Health (NIH) consensus conference[63] recommended that women with two or more first-degree relatives with ovarian cancer be offered ovarian removal after completion of

child-bearing or at age 35. Ovarian removal will protect against ovarian cancer, and it also may decrease breast cancer risk. However, these benefits need to be compared with the problems of early surgical menopause, the likely increased risks of osteoporosis and cardiovascular disease and the effects of any replacement hormones used.

Schrag et al.[76] have reported a Markov chain-based decision analysis of prophylactic mastectomy and oophorectomy for mutation carriers. They used three levels of cancer risk (penetrance): the highest were the risks based on the multicase family linkage analyses,[5,14] and the others were the estimated risk and the lower 95% confidence limit reported by Struewing et al.[16] The Schrag analysis assumed an 85% reduction in breast cancer risk after prophylactic mastectomy and a 50% reduction in ovarian cancer risk after oophorectomy. No effect on non-cancer outcomes such as heart disease was assumed, nor any effect of hormonal replacement therapy.

The main results of the Schrag analysis[76] are that the gain in life expectancy from prophylactic mastectomy in mutation carriers is substantial if performed before age 40 and that oophorectomy can be delayed until this age without loss of benefit. The estimated gains for a 35-year-old mutation carrier are similar to the benefits from successful reduction of high cholesterol levels and are greater than smoking cessation or the benefits from using adjuvant chemotherapy after breast cancer diagnosis. However, this decision analysis did not assess quality of life. In a decision analysis incorporating utility measures for quality-adjusted life years, using time trade-off methods,[77] prophylactic surgery was shown to be cost-effective in comparison with surveillance for years of life saved, but not for quality-adjusted years.

Chemoprevention: Tamoxifen

Another option for high-risk women is to prevent breast cancer by hormonal or other interventions. The anti-estrogen tamoxifen appeared to reduce breast cancer risk by 49% in a randomized trial with 69 months' follow-up of women at high risk of breast cancer, based on age over 60, age 35–59 with high risk on the Gail et al. predictive model[78] or a history of lobular carcinoma in situ. All the reduction was in estrogen receptor-positive tumours. These women showed no change in ischemic heart disease incidence, but had an increased incidence of endometrial cancer.[79] This study, the US National Surgical Adjuvant Breast and Bowel Project (NSABBP), was therefore closed early in April 1998, so its ability to assess tamoxifen's affect on mortality has been lost.

However, neither a British nor an Italian trial of tamoxifen in high-risk women showed any reduction in breast cancer incidence.[80,81] Since these European studies were smaller and the Italian study had limited compliance, longer follow-up for mortality is needed.[82] Tamoxifen has been approved by the US Food and Drug Administration (FDA) for reduction of short-term incidence of breast cancer in women at increased risk, but it has not been supported for a wider marketing for breast cancer prevention.[83] Although a range of other chemopreventive agents have been considered for breast cancer and other cancers, none has reached a similar stage of having randomized trial results available.[84]

Cancer Prognosis in Mutation Carriers

A Seattle study reported better survival in breast cancer patients aged 21–45 with a first-degree family history compared with women without a family history, after adjustment for disease stage, mammogram history and other major confounders.[85] In a small study in Scotland, 35 breast cancer patients with BRCA1 experienced better-than-expected survival.[86] However, other studies have recorded similar or worse prognosis in mutation carriers.[34,87] A Canadian study of 117 Ashkenazi Jewish women with breast cancer under age 65 (of whom 10% had BRCA1 mutations)[30] and a French series of breast cancer patients under age 36 (of whom 15 were BRCA1 positive)[88] both showed a worse prognosis in the BRCA1 carriers. The pathology of breast cancer, assessed in a large series by the IBCLC, differs among BRCA1 and BRCA2 carriers in several respects,[89] although it is not clear what overall prognostic effect the differences would have. In a small series of Ashkenazi Jewish women, the BRCA1 carriers were less often estrogen receptor-positive and had a higher nuclear grade, implying a worse prognosis.[90]

Discussion

The risks of cancer in gene mutation carriers are substantially lower in more recent, population-based studies than in the older studies based on selected multicase families. The frequency of mutations in series of cancer patients is also lower in more recent, population-based studies. There is a need for further empirical information on risks in carriers that will avoid the biases in the research based on selected multicase families. More information is also needed on the results of testing as the amount of testing increases and the referral criteria for testing change. The technical aspects of genetic testing develop rapidly. Therefore, the sensitivity of tests suitable for routine use, compared with optimal procedures, must be assessed in routine practice. In addition, the impact of tests for newly recognized mutations in known genes and for newly discovered genetic markers requires continual review.

The guidelines for the clinical management of mutation carriers are based largely on older estimates of risk, which are likely to be too high. None of the interventions recommended for mutation carriers is supported by randomized trial evidence, which is often regarded as essential, or at least highly desirable, to support interventions for the general population or for individual therapy.[91] Indeed, for several of the CGSC

recommendations, the best evidence suggests that a net benefit for general population groups is unlikely. The CGSC recommendations are made on a "best case" argument; it is implied that, although there is only weak evidence for benefit, the use of all these modalities is justified for high-risk women. If a screening modality is effective, its net benefit-to-harm ratio will be greater for high-risk subjects. However, if it is not effective, the risks of both false positive and false negative results may be greater for high-risk subjects than for the general population.

There is no discussion in the CGSC report of the high probability of false positives from using all these screening methods simultaneously or of the potential sequelae in both physical and psychological terms. It may be that the anxiety created by knowledge of the high-risk state is so great that excess examinations and false positives will not increase it, but further assessment of those issues is warranted. Objective consideration of any recommendations is essential, especially for adequate informed consent. The uncertainty of the benefits of surveillance appears to receive relatively little attention in the literature on genetic screening. Current guidelines for management pay little attention to cost and cost-benefit assessments or to quality-of-life issues.

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Public Health Aspects of Breast Cancer Gene Testing in Canada
Part 2: Selection for and Effects of Testing

J Mark Elwood

Abstract

Criteria set by clinical services for referral for counselling and genetic testing are variable and often arbitrary. Empirical data and computer models are available to estimate the probability of being a mutation carrier, based on family and personal history. Surveys show that high proportions of women at risk of cancer and of women in the general population are interested in being tested, but this may be based on inflated perceptions of personal risk and limitations in understanding of the tests used and their implications. A high proportion of women with a positive family history have a greatly overestimated perception of their own risk, and even expert counselling has little impact on this. This risk perception may produce psychological distress and may reduce participation in screening programs. Counselling, while improving understanding, may also have little impact on prior interest in being tested. Interest in being tested relates to a wish to assess the risk for children, and hazards include potential health insurance discrimination. Testing may result in a reduction of psychological disturbance in those shown to be non-carriers, with little change in those shown to be carriers, but unwillingness to be tested may be related to psychological distress. The impact of publicity concerning genetic testing on perceptions of risk and on psychological disturbance, and the subsequent impact of counselling and intervention, require further assessment.

Key words: *attitude to health; breast neoplasms; decision making; genetic counselling; genetic screening; ovarian tumours; risk*

Introduction

This is the second of three related papers; the methods are described in the first.[1,2] The use of genetic markers to identify families and individuals at high risk of breast cancer involves many scientific, ethical and economic issues.[3–5] It has been widely accepted that families with a history suggesting a BRCA1 or BRCA2 mutation should be tested within a research protocol and encouraged to participate in intervention and prevention trials.[6–8]

Testing for genetic susceptibility has many limitations. Knowledge of carrier status could lead to psychosocial harm and altered family relationships. Genetic testing has limitations in sensitivity and specificity.[9] A negative result may be due to the limitations of the test, and a positive result may be due to a variation in gene structure that is not related to disease risk. The existence of many relevant genes and mutations with variable risk implications, the difficulty in interpreting results in small families, problems in communicating the results well, the uncertainty of benefit from most management options, the costs of testing, counselling and follow-up and the possible impacts on insurance and employment all have to be considered.

Selection Criteria for Genetic Testing

Most clinics have defined criteria for genetic testing, which are based, explicitly or intuitively, on the prior probability of identifying a gene mutation.[10] Thus, subjects who are in families that show multiple cancer cases, a young age at incidence or combinations of cancers, such as breast and ovarian cancers, are likely to be eligible. There are several estimates of the probability of finding a relevant mutation given a certain personal and family history.[9,11–14] Many authorities have suggested a 10% prior probability as a useful cut-off; for the BRCA genes this would mean testing families with

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two or more breast cancer cases under age 50 or two or more ovarian cancer cases under age 60; a threshold of 50% would include only families with at least four cases of breast cancer and one of ovarian cancer.[15] These estimates relate to selecting for gene testing from an already selected group: those who have sought counselling and assessment on the basis of their family and personal history. The criteria for this first level of referral from the general population also require attention.

Computer Models of Prior Probabilities

Several models have been developed to estimate prior probabilities of carrying a BRCA gene, most of them using Bayes' theorem. The logic behind one well-described model will be given as an example. Berry et al.[16] computed likelihood ratios for being a carrier of BRCA1 based on the observed family history. For a given family history H, the probability of being a gene carrier, P(M | H), is given by P(M | H) = LR / (LR + O), where LR is the likelihood ratio based on the family history and O is the prior odds against being a gene carrier.

Given the prevalence of the carrier state as 0.0012,[17] O is (1- 0.0012) / 0.0012 = 832. The LR is taken from data on observed cancer risks with and without the gene. For a subject with breast cancer at age *x*, the LR is the ratio of the cumulative risk of breast cancer by age *x* in BRCA1 carriers to the risk in the general population. For an unaffected subject, the LR is the ratio of the probabilities of not being affected (1 - cumulative risk) in gene carriers and in the general population.

These ratios can be developed for a range of personal and family histories, and the probability of being a BRCA1 carrier can be calculated. If gene testing is done, the probabilities of carrying the gene are then estimated again, taking into account the sensitivity and specificity of the test. The model has been extended to include BRCA2 and is being used in a randomized trial to compare the use of the model's results with standard printed material in counselling.[18]

Other predictive models are available.[19] These prior probabilities depend on data from multicase families; as noted in Part 1,[1] penetrance estimates based on representative series of cases from the population are considerably lower, and future models will need to allow for this.

Interest in Genetic Testing in Various Groups

Relatives of Cancer Patients

In a US telephone survey of women who were unaffected first-degree relatives of patients with breast or ovarian cancer,[20] 75% stated that they would "definitely want to be tested" and 20% said they would "probably want to be tested" after being given information about the BRCA1 gene. Interest in testing was positively related to perceived risk. Women did not understand that a negative test did not exclude the possibility of being at high risk, despite having been informed that only 5% of all breast and ovarian cancers are linked to the BRCA1 gene. These authors commented on barriers to adequate informed consent: most individuals overestimate their personal risk of severe events such as cancer occurrence, have difficulty making a decision based on probability and may be unable to process the information they receive because of stress and anxiety.

In a similar study of 105 women aged 30**S**75 who were unaffected first-degree relatives of patients with breast or ovarian cancer, de Silva et al.[21] showed that 91% wanted to be tested. The most common reason given was to assess their children's risk. Most women expected that a positive test result would give them increased anxiety, depression and a reduced quality of life, and 72% felt that a negative result would not prevent anxiety. Another survey of 238 women with a first-degree relative with breast or ovarian cancer concentrated on consent issues: only 57% thought that written consent was necessary before results were given to the immediate family, but most (87%) thought that written consent was needed before results were given to insurers or employers.[22] Lerman et al.[23] summarized the situation, concluding that over 90% of women with a family history of breast or ovarian cancer want to be tested, but that this interest is linked to a "grossly overestimated sense of personal risk, heightened breast cancer anxiety, and misunderstanding of the benefits, limitations, and risks of genetic testing."

General Population

Tambor et al.[24] surveyed 473 women over age 50 in a health maintenance organization in the US in 1994/95, using a telephone interview; the response rate was 53%. In all, 10% of these women had a mother or sister with breast cancer, 51% had heard of the breast cancer gene and 69% were interested in being tested, an interest that was greater in women who were younger, white, more educated, more affluent and supportive of mammography. However, there was no exploration of what benefits were assumed to come from the test, and what actions would result. Some older studies using general population samples have also shown levels of interest of over 80% in testing for genetic susceptibility to breast[25] or colon cancer.[26,27]

Relation Between Interest in Testing and Participation

A high level of interest in testing does not, of course, mean an equivalent demand in actuality. In a study noted earlier,[23] 50% of first-degree relatives of breast cancer patients gave blood samples for testing, whereas over 80% had given affirmative answers to questions on wanting to be tested. Past experience with Huntington's disease (a more complex situation, as there is no preventive action that can be taken) showed that over 60% of relatives expressed interest in testing, compared with less than 15% who later underwent testing.[28]

Public Health Aspects of Breast Cancer Gene Testing in Canada Part 3: A Model of Potential Need and Demand

J Mark Elwood

Abstract

Centres offering expert counselling and genetic testing are already experiencing high levels of demand, and yet the potential demand is much greater. There have been few attempts to estimate the potential demand created by particular guidelines for referral or testing. A model of need and demand for genetic services is presented, and research questions are identified that should assist in better prediction of future requirements for genetic counselling and testing. The value of integrated routine data on referral criteria, demand and clinical service load is considerable. Attention needs to be paid to referral at primary care and general specialist levels as well as to expert centres.

Key words: *Canada; genetic counselling; genetic screening*

Introduction

This is the third of three related papers; the methods are described in the first.[1,2] The current literature on testing for genetic susceptibility to cancer, reviewed in parts 1 and 2,[1,2] is very limited with regard to the assessment of potential need and demand for services. This is partially because many genetic testing centres do not have a population perspective. Often, they were developed primarily from expertise in the laboratory aspects of testing, dealing with those subjects referred to them through varied and largely unrecorded referral processes. Although criteria for testing have been developed, there has been little work done to relate such selection criteria to the population base and to consider issues of demand, need and equity of access.

Current Services and Demand in Canada

In 1997, genetic testing for BRCA1 and BRCA2 and other major cancer-related genes was being offered in research centres in Montreal, Toronto, Vancouver, Victoria and Winnipeg (J Beauvais, Laboratory Centre for Disease Control, personal communication). Several of the centres had long waiting lists, and the demand for counselling exceeded available resources. The guidelines for referral for counselling and for gene testing vary among centres and, in general, represent criteria based on an informal assessment of the likelihood of mutation detection in subjects and families referred, using the available data (as reviewed in Part 2 of this series). The relation between the criteria used and the potential demand defined by those criteria has not been explored in any detail.

A Model of Need and Demand for Genetic Assessment

There appear to be no published data on demand for screening services in Canada; the potential demand is, however, very large. The BRCA1 carrier prevalence of 0.0012[3] equates with 1200 mutation carriers per million population. Testing for breast and ovarian cancer susceptibility genes has tended to be concentrated in women aged 20**S**59. Given the age and sex structure of the Canadian population, there will be some 320 such women carriers per million total population. If (as shown in Part 2) genetic counselling and testing are warranted for women with a 10% risk of being a carrier, then some 3200 women per million population would be eligible for testing. To this needs to be added the numbers of men and women needing testing for other genes, such as those for colon cancer susceptibility, and men may also require testing for BRCA carrier status. Of course these are prevalence figures, whereas the demand on services

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relates to annual numbers of subjects coming for counselling.

At present, only a small fraction of eligible subjects are seeking testing; the concern is that if this changes the demand could increase greatly. At a later point saturation could be reached, when all carriers in a defined population have been identified. The period over which all mutation carriers in a population can be identified and the criteria (age, sex and any other) used to target assessment and testing are therefore critical in determining the demand on screening services. None of these issues has received much attention in the published literature; although a full assessment is impossible with the data available, a general model of the situation may be helpful.

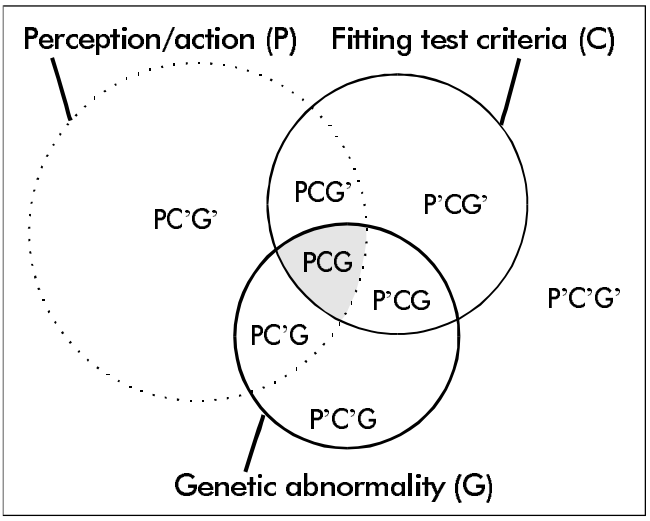
To be identified as a gene carrier by a normal clinical service, three criteria must be met: the subjects must be aware of their increased risk, so that they seek advice about it; they must meet the criteria for testing used by the agency to whom they go for advice; and they must actually have a detectable genetic abnormality. To consider this issue further, it is useful to distinguish different subgroups that would apply in a total population or in a subpopulation defined by sex, age, ethnic group or other criteria.

1. *Genetic abnormality (G)*: The number of subjects in the population with detectable relevant genetic mutations, that is, the prevalence of relevant gene alleles. At this point, the sensitivity of testing will be ignored and the prevalence taken as being that of detectable abnormalities.
2. *Criteria for testing met (C):* The number of subjects who are eligible for testing and expert counselling, based on the criteria of personal and family history used by the clinical service. This number will be larger than G, probably much larger. For example, many criteria suggest that testing is justified if the predictive value of the family history is 10%: that is, up to 10 subjects will be tested for each one found to have a carrier state (see Part 2).
3. *Perception/action (P):* The number of subjects who come forward to seek advice. This is likely to be only a small fraction of all subjects at increased risk since it depends on motivation, knowledge of the services available and access to them. Many people will be aware of their risk and may be concerned about it, but will not take any action because they either do not know of available services or find the services to be inaccessible, expensive, of unknown quality or of unknown value to them. However, many people will overestimate their risk, and many, perhaps most, in this category may not have a strong family history on objective criteria. The quantity P, unlike G and C, will change quickly as the services available vary and public perceptions change. Increasing the provision of services and knowledge about them is likely to increase the demand.

FIGURE 1

Venn diagram showing the interactions of perception (P), meeting criteria for testing (C) and carrying a genetic susceptibility (G)

(Simplified to assume perception = perception sufficient to initiate action, and that the genetic susceptibility is detectable by the tests used)



These three criteria—having a detectable genetic alteration (G), fitting objective criteria (C) and perceiving risk enough to lead to action (P)—can be represented in a Venn diagram, which shows eight sets of subjects in the population (Figure 1). P', C', and G' indicate those groups who do not meet these criteria.

Those people who perceive themselves at risk and are sufficiently concerned to seek advice (group P) will come to the attention of a genetic service provided through clinics, phone contact or other means, and then the following subject groups should fall into place.

i. Group PCG will be correctly identified.

ii. Group PCG' will be tested, but the result will be negative. The balance between PCG and PCG' is determined by the criteria set for testing.

iii. Group PC'G' perceive themselves at risk, but do not meet the criteria for testing and do not have the genetic condition. They require good advice and counselling, without testing, in a cost-efficient way; the challenge is to correctly and successfully reassure this large group.

iv. Group PC'G perceive themselves at risk, but do not meet the criteria for testing; however, they do have the gene state. They are the false negatives of the testing criteria. This number will increase if the testing criteria are narrowed.

Other groups (P') will not come forward to a clinical service that depends on the subjects taking the initiative.

v. Group P'CG do not perceive themselves at risk, but meet the criteria for testing and carry the gene abnormality. This group represents the (probably large) number of gene carriers not identified because of the incomplete use of available services by those eligible for them, although some may be identified through another family member (by outreach investigation) or by a population-based screening program.

vi. Group P'CG' do not perceive themselves at risk, and, although they do meet the criteria for testing, they do not carry the gene abnormality. If referred, they would be unnecessarily tested. It could be said that they benefit from the incomplete access to testing.

vii. Group P'C'G do not perceive themselves at risk, and if surveyed do not meet the criteria for testing, although they do carry the gene abnormality; they will be identified only by a less selective screening system.

Finally, the rest of the population are P'C'G': they do not have the genetic state and correctly do not perceive their risk as high, nor do they meet the criteria for testing. However, many such people will be alerted by publicity on this issue and will need information to avoid being misled into thinking they may be at high risk.

In principle, the number of subjects in a defined population with a well-developed genetic service who fall into each of the different sets depicted in Figure 1 can be ascertained by a combination of good routine data collection and special surveys. Routine data would identify all subjects in groups P, PC, PCG and PCG'. A well-constructed population sample survey could supply a number for group C, and a calculation based on known gene frequency plus knowledge of the sensitivity of the test used could estimate group G.

The number in group PC'G could be calculated by a special survey of gene tests carried out on a sample of subjects who attend for counselling because of perceived high risk but do not fit the normal criteria. The subgroup P'CG could be ascertained by genetic testing of a sample of subjects identified in the community survey as fitting the normal criteria for gene testing, but who have not perceived this risk and taken action themselves.

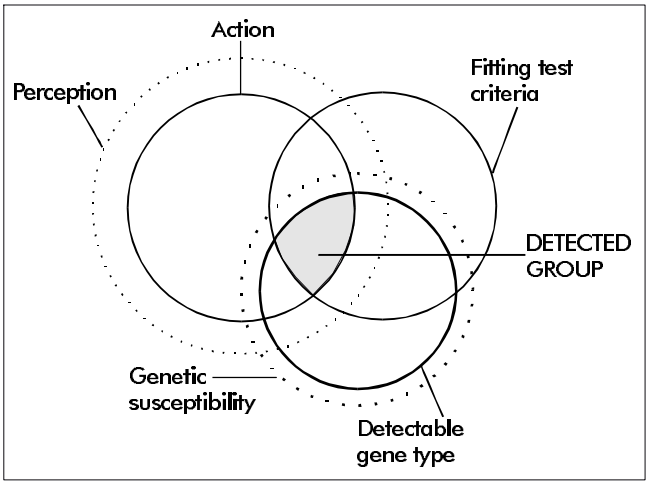
From these steps, the numbers of subjects in all eight categories could be ascertained. In practice, such work would pose many difficulties, one being how to ensure that the responses to questions used in a population survey to assess criteria for testing were consistent with those given by the normally more intensive interview methods used in the clinical service. The results will be specific to the time and place they are generated, as the total P group (representing perception and action) will change quickly, whereas, in principle, the total G and C groups will be fairly constant.

The situation can be explored further, more realistically, by introducing more complexity. To avoid the two main simplifications in the scheme set out above, it is necessary to distinguish perception of risk (in response to some systematic inquiry) from perception that is strong enough to initiate action. The balance between perception and initiation of action will depend, of course, on the ease with which clinical services can be accessed. Thus we can consider the perception group as two concentric circles, the outer one relating to perception of risk and the smaller inner circle to perception of risk followed by initiation of action.

Similarly, the genetic circle can be considered as an outer circle representing the presence of a genetic abnormality and a concentric inner circle representing the presence of a detectable genetic abnormality, to emphasize the lack of total sensitivity of the genetic tests. This model ignores any possible false positives. Introducing these two situations makes the Venn diagram much more complex (Figure 2), since there are now 18 rather than 8 subgroups. Of these 18 groups, only one represents those subjects whose genetic susceptibility will be recognized by the clinical service ("detected group"). As before, this is the PCG group, the intersection of perception plus action, fitting testing criteria and having a detectable genetic abnormality.

Figure 2

Expanded Venn diagram, with perception separated from action and detectable genetic states separated from having a genetic high-risk state



In estimating the demand and need for genetic testing, a number of approaches seem worth consideration.

1. Taking consistent standardized family histories from patients with newly diagnosed breast, ovarian, colon or other cancers, who are a representative or total sample from a defined population (perhaps limited by age), would give the numbers of families fitting various criteria of strength of family history,

identified by a family member having an incident cancer in a given time period. These numbers are directly relevant to the guidelines for family interventions based on the strength of family history in newly incident cancer patients. This is a useful and fairly easily measured indicator of an annual number of families needing investigation. However, it identifies only a fraction, perhaps a small fraction, of all high-risk families in the population because of the limitation of requiring a newly incident case in a certain time period.

2. A population survey will give a direct estimate of the numbers of people who can identify themselves as having specified degrees of family history for specified cancers. Such a survey should be based on a representative series of subjects, limited or stratified by age and sex, and should inquire about relatives affected, type of cancer and the date of diagnosis of the cancer. It would be valuable to compare these results with the investigation of newly incident cancer patients in the same population, as that would show if the results of studying new cases (which would be easier to continue) could be used to estimate the population numbers derived by the survey. Results from self-completed questionnaires suggest that family history data, at least on first-degree relatives, can be collected with reasonable accuracy.[4]

Such a population survey should identify a much larger number of high-risk families than the patient-based method if the data are equally accurate, because there is no narrow time restriction on cancer incidence. However, because of the recent diagnosis, the patient-centred method may produce more detailed and more accurate data. The relation between the numbers of high-risk families identified by these two methods could be estimated from an analysis of extensive data on high-risk families from existing sources, in terms of the probability of having at least one member with a cancer incident in a given time.

3. Such a population survey could also be used to estimate the number of subjects who perceive themselves at high risk, and the number who want advice, counselling or testing. It would be necessary to measure this self-perception of risk independently from collecting data on actual family history, since the process of collecting family history data may change the perception. This could be achieved by a well-constructed telephone interview or by serial data collection methods. The link between perception of risk and the desire to seek help will vary with the services available and with the knowledge and perceptions of the services.

Referral Criteria and Counselling in Primary Care

In a community, the number of subjects whose family history is strong enough to warrant genetic testing is relatively small, but a larger number may benefit from expert counselling, even if they do not require gene testing. However, there are likely to be much larger numbers of subjects who have a concern, perhaps considerable anxiety, about their risk state, but who do not have a strong enough family or personal history to make referral for expert counselling appropriate. Consideration has to be given to how advice and support will be given to these people. It may be through impersonal media or voluntary organizations. In this case the development and testing of educational materials for direct use by the public or to assist relatively unskilled counsellors is important. The family physician is likely to be the first health professional to be consulted. The development of good management plans, materials, support and training for family physicians is also an important issue.

A triage approach developed in Australia[5] for breast cancer risk defined three groups: 95% of women with no family history or only a weak history who could be advised by family physicians alone; up to 4% with a moderately increased risk who could be advised by family physicians using guidelines from expert centres, with consultation if required; and up to 1% with a strong history who required a referral for expert counselling and perhaps testing. Evaluation of this model is in progress.

Economic Issues

Major economic assessments of BRCA testing have yet to be published. In England, the cost per mutation detected has been estimated, but only in an approximate manner.[6] An economic analysis of testing for HNPCC (hereditary non-polyposis colorectal cancer)[7] shows that the major determinants of cost-effectiveness are the prevalence of the gene and the assumptions about the benefits of interventions for gene carriers. For BRCA genes, the benefits of interventions are far from established.

Discussion and Recommendations

Some recommendations for activities to co-ordinate and develop Canadian work on genetic testing for cancer susceptibility can be made. In Canada, as in other countries, the pace of development of laboratory expertise in genetic testing has been greater than that of expertise in counselling and studies of its effectiveness. There is only limited information on the current provision of genetic services, and there has been relatively little attention paid to population-based issues of demand and need. There is little information on the relation between the criteria used for referral and gene testing and the potential demand created if those criteria are applied on a population basis. The model of need and demand for services presented here and the research questions identified may assist in developing better estimates of future requirements for genetic counselling and testing. There is little information on costs and cost-benefit aspects of genetic testing.

Although there is good communication among different centres with similar expertise, for example, in laboratory techniques, there is less communication between groups from different disciplines and perspectives, for example, those with expertise in family medicine or in health economics. The workshops on cancer genetics organized by the Canadian Collaborative Group for Cancer Genetics (CCGCG) have shown the strengths of Canadian research in this area and the value of a forum for discussion. Further efforts to combine disciplinary strengths through networks, meetings or task forces would be valuable. A data monitoring system with adequate attention to issues of confidentiality would be useful in establishing a core data set to monitor counselling and genetic testing in different centres in Canada.

Acknowledgments

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Risk Perception and the Effects of Counselling and Gene Testing

Risk Perception

Understanding personal risk is a complex area, and major problems arise when individuals need to make important decisions based on their understanding of risk. For example, it has been pointed out that a woman who is told that she has a 1 in 4 risk of developing breast cancer may consider herself to be at lesser risk if her sister had been given that diagnosis, believing her sister to be the unlucky one.[29] Most testing centres stress the need for prior information on the limitations as well as potential benefits of testing and the need for adequate informed consent. The content and organization of consent forms vary greatly.[30]

There have been several excellent studies carried out in the US, including randomized trials, which relate to the evaluation of very intensive one-on-one counselling by experts (reviewed later). Studies are also needed on less intensive and less direct methods of providing information, for example by mail or telephone or through family physicians. There is little information on whether the concerns of anxious subjects who do not meet the criteria for referral are adequately dealt with. The socio-behavioural issues involved in genetic counselling and genetic testing have been reviewed in a Canadian context,[31] and a report on communicating risk with regard to familial cancer has been produced in British Columbia.[32]

Women's perceptions of their risk of breast cancer may vary considerably from the reality. In the United States, a study of 145 women aged 40**S**50 with no personal history of breast cancer compared respondents' estimate of their 10-year risk of breast cancer with that calculated from the predictive model developed by Gail et al.[33] The respondents overestimated their risk of death from breast cancer by more than 20 times and greatly overestimated the reduction conferred by screening.[34] In another study of women identified as first-degree relatives of breast cancer patients, over three quarters of women aged under 30 thought they were likely to develop breast cancer, and one third of women at all ages had breast cancer worries that impaired their daily functioning. Although half of the women aged 35**S**39 had undergone mammography within the previous year, psychological distress was associated with a reduction in the use of mammography and with both infrequent and excessive use of breast self-examination.[35]

In another US study, 75% of women with a first-degree relative affected believed that their risk of breast cancer was "higher or much higher" than the risk among other women, while the other 25% believed that their risk was the same or lower. Heightened awareness of breast cancer risk was associated with a higher educational level.[36] In a study evaluating breast cancer risk counselling for high-risk women, the women most likely to participate were those aged 40**S**49, those who had greater levels of education, those who were married and those who perceived their risk as high and were worried about it. The factors influencing participation differed between women with higher and lower levels of education, and the authors suggested that recruitment strategies need to be tailored to the women's educational levels.[37]

In a US study of 672 twin sisters of women with breast cancer diagnoses[38] (mean age 63 years), 35% thought their risk of getting breast cancer some time in their life was the same as among other women, 10% thought it was less, 51% thought it was somewhat or much higher and 4% thought it was "almost inevitable."

Effects of Counselling on Risk Perception and Behaviour

Studies have shown that women with family members affected by breast cancer who show increased levels of anxiety are *less* likely to participate in screening, both in the US and the UK.[29,35,39] One study reported that 27% of such women had a level of psychological distress consistent with the need for counselling.[40] The same authors[41] found that barriers to screening included lack of knowledge, erroneous beliefs about breast cancer and, most important, anxiety and emotional stress. They recommended counselling designed to deal with such barriers, and reported positive results in reducing perception of risk and increasing adherence to screening recommendations in a small pilot study; a randomized trial is planned.

Lerman et al.[42] performed a randomized trial of psychological counselling in high-risk breast cancer patients (Table 1). This study involved 200 women aged 35 and older with a history of breast cancer in a first-degree relative. At recruitment, around 65% of subjects greatly overestimated their own breast cancer risk. Women were randomly assigned to participate in either a general health counselling program (the comparison group) or a specific program involving a 1.5-hour counselling session with a trained nurse educator, which dealt with the provision of individualized risks according to the Gail et al. model,[33] stressed the uncertainty of these risk data and provided both absolute and relative risks. The results showed a technically significant improvement in risk comprehension due primarily to a move of women in the counselled group from overestimation to accurate estimation; however, the counselling made no substantial impact on the two thirds of all women who greatly overestimated their risk at the beginning of the study. Thus, this study shows that, among women with a family history of breast cancer, the majority have a greatly exaggerated estimate of their own risk, and this is not substantially modified even by a thorough and detailed counselling session by a trained educator.

TABLE 1

Effect of counselling on perceived risk of breast cancer: randomized trial

	% of control subjects $n = 110$		% of intervention subjects $n = 90$		Change (%)	
Estimation of actual risk	**Before**	**After**	**Before**	**After**	**Control**	**Intervention**
Underestimate	2.7	0.9	0.0	3.4	-1.8	3.4
Accurate	11.0	9.4	6.6	14.6	-1.6	8.0
Overestimate	23.0	26.0	26.4	18.0	3.0	-8.4
Extremely overestimated	64.0	63.0	67.0	64.0	-1.0	-3.0

Source: Compiled from data of Lerman et al. (Reference 42) [Control data are as in original, although they do not add to 100%]

A somewhat different result has been reported from the United Kingdom[43] in a study of women referred to a family history clinic. The questions are posed in terms of lifetime risk expressed as odds, whereas it would be more appropriate to present risks related to the current age of the individuals. The results suggest that, whereas a quarter of women substantially underestimated their risk initially, a quarter substantially overestimated it, and that the counselling system used at the clinic improved personal risk assessment when re-evaluated at a one-year follow-up.

Most of the published work relates to counselling by experts and in centres of excellence. Expert counsellors cannot be available for all subjects who seek advice. The attitudes of women at risk, physicians and nurse practitioners to different information and consent issues vary considerably.[44] A survey of 98 high-risk women showed that more preferred pre-test information to be given by a genetic counsellor than by an oncologist, with the opposite result for post-test counselling.[45] The appropriate role of others, such as family physicians, who may be able to deal with many more subjects, needs to be further explored. The effectiveness of their counselling, ways in which it could be optimized and the development of effective support materials are all important topics. Approaches to these issues include group therapy[46] and interactive computer programs.[47] The issues of exchange of information within families are complex. In a Minnesota study of 544 high-risk breast cancer families,[48] nearly all first-degree relatives of probands knew of the positive family history before notification, but only 74% of second-degree relatives and 46% of third-degree or more distant relatives knew about it. Small proportions of subjects had concerns about confidentiality issues or about participating in a family genetic study.

Effects of Counselling on Choice of Genetic Testing

Lerman et al.[23] conducted a randomized trial among 400 women who had a first-degree relative with breast or ovarian cancer, to compare the effects of an educational approach with an educational/counselling approach on the women's decision to use genetic testing. Both interventions were substantial and personal: the educational approach involved a 45**S**60-minute individual session, and the educational/counselling approach used a 75**S**90-minute session with a trained oncology nurse or a genetic counsellor supervisor. Both interventions increased knowledge, and the counselling approach improved understanding of the limitations and the risks of testing; but neither affected the choice itself: 52% of subjects provided a blood sample for testing, a proportion that was similar to intent before intervention and not affected by either intervention. These participants were at generally low risk: 80% had only one first-degree relative with breast cancer. The main objective of this study was to use counselling to produce a more balanced view of the risks and limitations of genetic testing and so to reduce the demand for testing. In this objective, the counselling failed. The authors concluded that the counselling process may only reinforce and validate the subjects' prior intentions, as has been noted in other contexts, such as bone marrow transplantation. In this study, a blood sample was more likely to be provided for testing the stronger the family history was, but there was no effect of strength of family history on the results of counselling. The effects of counselling were reduced among African-Americans.

Consequences of Gene Testing

In a further study, Lerman et al.[49] offered genetic counselling and BRCA1 testing to 279 members of 13 previously identified BRCA1 carrier families in the US and Canada. Overall, 43% participated fully and requested results; 31% declined any involvement in the study; and the rest (26%) took part in the interviews and

counselling but did not want results. Of those given results, 46% were BRCA1 carriers. The desire to be tested increased with strength of family history, knowledge about the test and having health insurance; sex and education were not significant. The main reason for testing (92%) was to assess children's risk; 34% gave possible loss of health insurance as a major risk of testing. Between baseline and one month, those identified by testing as carriers showed no increase in psychological morbidity, assessed in terms of depression, role impairment or sexual impairment, whereas non-carriers showed significant decreases in all these. After testing, 17% of carriers planned prophylactic mastectomy and 33%, prophylactic oophorectomy. In an extension to the study with 327 male and female family members and six months' follow-up,[50] among those with high baseline levels of stress, depression rates fell in non-carriers, did not change in carriers, but increased in those who declined testing.

This study suggests that gene testing has psychological and quality-of-life benefits for those who test negative and no detriments for those who test positive. It was based on subjects who were already known to be members of multicase, BRCA1 carrier families, who would have had a very high prior level of knowledge and likely anxiety about their situation. Nine women tested had already had prophylactic mastectomy, and 15 had had prophylactic oophorectomy, of whom five and four, respectively, were carriers. The applicability of these results more widely is doubtful. Subjects with a much weaker family history or even those with a strong family history who have not been alerted and informed of the family situation may have a much lower prior level of anxiety, and therefore have less to gain and more to lose from the results of testing. It is important that studies like this are carried out in other contexts.

A four-year study of the behavioural and psychological effects of testing has been started in a large Utah kindred with BRCA1 carriers.[51] Frequent screening for breast, ovarian and colon cancers is advised, and information is given on prophylactic surgery and involvement in prevention trials. Of the first 170 subjects counselled, 92% requested testing. Short-term results showed higher distress levels in carriers than non-carriers after testing, particularly in carriers with no personal cancer history.[52]

In a study of members of high-risk families who received BRCA1 results,[53] 78 tested positive; of these, over one third reported sadness, anger or guilt, 35% considered prophylactic mastectomy and 76% prophylactic oophorectomy as options. Of 100 subjects who tested negative, 80% felt emotional relief. For all subjects, concerns about the risks to children and about surveillance and prevention were the main reasons for testing; 25% were concerned about discrimination in insurance.

Discussion

Different expert groups vary considerably in their criteria for genetic testing and for referral to expert counselling. There are few data on the potential numbers of subjects or families who would meet these different criteria. The different criteria used should be compared and monitored, along with data on outcome. Criteria for appropriate referral to different levels of service provision need to be developed and assessed; for example, referral processes from the community to family physicians have been little studied. There is a high level of interest in testing among the public, often not closely related to actual risk, and there is evidence from randomized trials that the desire for testing, once set, may be little changed by further information.

The literature reviewed here suggests that some women, perhaps a high proportion, who have an increased risk of breast cancer due to a family history will have a greatly exaggerated impression of their absolute risk, and randomized trials suggest that expert counselling may have little effect on these perceptions. The high perception of risk may result in substantial psychological disturbance, which may reduce participation in early diagnosis programs. This implies that publicity given to genetic factors conferring very high risks could have some detrimental effects, and reinforces the importance of evaluating the consequences of publicity and screening procedures. Good randomized trials are being carried out on the effects of expert counselling at leading referral centres, although there is little work on the effects of counselling by less intensive or skilled methods at the community or family physician level.

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Deaths Due to Dementia: An Analysis of Multiple-cause-of-death Data

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Abstract

This study analyzes multiple-cause-of-death information from over 113,000 death certificates of Canadians aged 65+ and identifies causes that are significantly likely and significantly unlikely to combine with dementia to cause death. For dementia as a mentioned cause and as the underlying cause of death, frequencies and rates of death were calculated. Dementia was mentioned on death certificates 2.4 times as often as it occurred as the underlying cause of death. Among the causes least associated with dementia were some cancers, chronic respiratory diseases and rheumatoid arthritis. Causes of death that rarely occur with dementia should be further investigated in terms of their potential role in preventing or delaying the onset of dementia. In particular, further study of the role of anti-inflammatory drugs and nicotine in reducing the risk of dementia is indicated. Causes positively associated with dementia largely reflect the physical deterioration it confers.

***Key words**: aging; Canada; cause of death; death certificate; dementia*

Introduction

With the aging of the Canadian population, the number of people affected by dementia is increasing substantially. The prevalence of dementia in Canadians aged 65 and over has been estimated at 8%, amounting to over 250,000 people.[1] The economic cost of dementia in Canada is estimated to be over $3.9 billion annually, or about $14,000 per patient per year.[2]

Athough the significance of dementia in terms of its prevalence, debilitating effects and caretaker burden is increasingly appreciated, its contribution to causing death is less well understood. Dementia, characterized by confusion, disorientation and intellectual impairment, would not by itself seem to be a life-threatening disorder. However, as it advances, dementia gives rise to complications that result in loss of physical function, and thus it is the consequences of the initial disease that cause death.

When dementia is the disorder that has initiated the sequence of events leading to death, it is considered to be the *underlying* cause of death, and, according to the international conventions that govern the medical certification of death, it is entered as such on the death certificate.[3] Dementia might also be *mentioned* (but not as the underlying cause) on the death certificate if it is considered to have "unfavorably influenced the course of the morbid process, and thus contributed to the fatal outcome," even though it was "not related to the disease or condition directly causing death."[3] A dementia code can thus be given as either the underlying cause or a non-underlying cause. However, for a person with dementia whose death is considered to have been caused by other conditions or circumstances, dementia will not necessarily be included on the death certificate.

Conventionally, published mortality statistics identify only a single, underlying condition as the cause of death. However, this practice results in a loss of information, because most deaths result from *several* disorders, especially in the elderly. By virtue of their age, people with dementia are often afflicted with other diseases as well. Causes of death that appear on the death certificate with dementia may be complications of dementia, or they may reflect other pathology. The analysis of

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multiple-cause-of-death data, which include all causes of death entered on the death certificate, permits a more accurate characterization of death than does analysis of single-cause data.[3–5] The availability of such data in Canada is increasing, although few analyses have yet been published.

In countries other than Canada, studies of multiple-cause-of-death data have been reported for some time, and a number of them have focused on dementia. For example, multiple-cause data have been used to illustrate the deficit in the frequency with which dementia is certified as a cause of death, as compared with its presence as a cause of morbidity before death.[6–13] Other analyses of multiple-cause data have focused on the causes of death that are positively associated with dementia.[14,15]

The purpose of this paper is to extend current knowledge of the role of dementia as a reported cause of death using multiple-cause-of-death data from Canada and the United States. Comparisons are made between the frequencies with which dementia is certified as the underlying cause of death and as a mentioned cause. Using Canadian data, we report the causes of death that are positively linked to dementia, as well as those that are negatively associated.

Methods

The development of the data for analysis has been described previously.[5] Briefly, multiple-cause records (produced by automated processing of medical information from death certificates) were edited using software designed for this purpose,[16] and then linked with death records for corresponding individuals from the Canadian Vital Statistics Data Base maintained by Statistics Canada. Thus, data on age at death, sex and other variables were added to each record on the multiple-cause file.

After further edits, 113,144 records of decedents aged 65 and over were retained for analysis. These represented 19% of all deaths of people aged 65 and over in Canada from 1990 to 1993. For the provinces of Quebec and Ontario, random samples of 3% of all death records for the years 1992 and 1993, respectively, were analyzed. For Alberta, New Brunswick, Newfoundland, Nova Scotia, Prince Edward Island, Saskatchewan, Northwest Territories and Yukon, nearly complete data were used. Multiple-cause data were not available for British Columbia or Manitoba. Complete 1993 multiple-cause-of-death data for the United States, available on CD-ROM from the National Center for Health Statistics,[17] had undergone the same type of processing as the Canadian data.

The integrity of the Canadian multiple-cause file was verified using comparisons with other sources. The percentage distribution of the age at death on the records in the multiple-cause file was compared with the same distribution for all deaths in Canada in 1991. As well, the median ages at death and the percentage of deaths with dementia as the underlying cause for age groups 45+, 75+ and 45**S**74 in the multiple-cause records were compared with the corresponding results reported for all deaths.[18] These comparisons showed only negligible differences.

Dementia was defined in this study as either senile and presenile organic psychotic conditions (ICD-9 code 290) or Alzheimer's disease (ICD-9 code 331.0). Frequencies, rates and proportions of all Canadian and US deaths for which dementia was mentioned as a cause were tabulated by sex and age group. For the Canadian data, calculations by sex and age were made for rates of dementia (as a mentioned cause and as the underlying cause of death), mentioned-to-underlying-cause ratios (i.e. the number of times dementia was mentioned at all on the death certificates divided by the number of times it was selected as the underlying cause of death) and rate ratios. Age-standardized rates were calculated by the direct method using the 1991 Canadian population counts in the age groups 65–69, 70–74, 75–79, 80–84, 85–89 and 90+.

To estimate bivariate associations between dementia and every other cause on the same death certificate, odds ratios (ORs) were calculated by sex and age group. These are the odds of dementia being mentioned given that another specific cause is mentioned, divided by the odds of dementia being mentioned given that the other cause is not mentioned. ORs were calculated for all causes at the level of the first three digits in the ninth revision of the International Classification of Diseases (ICD-9).[3] For the mentioned-to-underlying-cause ratios and ORs, dementia was counted at most once per death certificate, as was any other cause. Note, however, that when a code is entered on a death certificate to indicate the nature of an injury that is a cause of death (i.e. the N-code), a corresponding code is always entered to indicate the external cause of the injury (i.e. the E-code). For the calculations of ORs, both N- and E-codes were included from each record containing such entries.

Two-tailed tests at the 0.05 significance level were used to determine whether ORs were significantly different from 1.00. This is equivalent to testing for independence in a two-by-two contingency table of frequencies of dementia being mentioned or not mentioned on the death record, versus the other cause being mentioned or not mentioned. To increase the likelihood of clinical significance of observed associations, only ORs for which each frequency in the two-by-two table was at least 10 were analyzed. The large samples conferred high power on the significance tests, allowing the tests to detect a large number of significant results.

Results

Dementia was given as the underlying cause of death in 2% of all the Canadian death records of people aged 65 and over, and it was mentioned in 6% of these records. Although the pattern of the US data was strikingly similar, the proportions of Canadian death records that mentioned dementia were consistently slightly higher than in the US data (Tables 1, 2; Figures 1, 2). As well, the mentioned-to-underlying-cause ratio was slightly lower for the Canadian death certificates than for the US death certificates—2.4 and 2.5, respectively.

Death rates for dementia increased sharply with age, irrespective of whether rates were based on the underlying or mentioned cause of death (Table 3, Figure 1). Among Canadians aged 85 and over, the rate of death for which dementia was the underlying cause (525 per 100,000 population) was about 26 times as high as among those aged 65**S**74 (20 per 100,000 population). This compares with an approximately 32-fold increase in the corresponding age groups (1348 and 42 per 100,000 population respectively) when dementia was mentioned on the death certificate. In comparison, the 1992 rate of all-cause mortality for the age group 85+ was only seven times as high as the rate for the age group 65–74.[19] That is, dementia death rates increase with age more rapidly than all-cause mortality rates.

The proportion of death certificates giving dementia either as the underlying cause or as a mentioned cause was higher among women than men (Tables 1 and 2, Figures 1 and 2). The age-standardized rate of death due to dementia, however, was higher among men (Table 3).

To identify causes that were positively or negatively associated with dementia on death certificates, odds ratios were tested for significance (see Methods). A total of 153 tests were conducted for all ages combined (65+), both sexes and all three-digit ICD codes. Of these tests, 70% were significant at the 0.05 level, which overwhelmingly exceeds the figure of 5% that would be expected due to chance alone. Similarly, 231 tests were conducted for three separate age groups (65–74, 75**S**84 and 85+), of which 56% were significant.

TABLE 1

Number and percentage of total of deaths with dementia mentioned or given as the underlying cause, by age group and sex, ages 65+, Canada, 1990 1993

Age group	Men			Women			Both sexes			
	Total deaths	Deaths with dementia as underlying cause (%)	Deaths with dementia mentioned (%)	Total deaths	Deaths with dementia as underlying cause (%)	Deaths with dementia mentioned (%)	Total deaths	Deaths with dementia as underlying cause (%)	Deaths with dementia mentioned (%)	Ratio of mentioned to underlying causes
65 74	20,269	125 (0.6)	298 (1.5)	12,474	157 (1.3)	305 (2.4)	32,743	282 (0.9)	603 (1.8)	2.1
75 84	24,699	555 (2.2)	1,331 (5.4)	20,589	635 (3.1)	1,434 (6.9)	45,288	1,190 (2.6)	2,765 (6.1)	2.3
85+	13,793	391 (2.8)	1,082 (7.8)	21,320	862 (4.0)	2,137 (10.0)	35,113	1,253 (3.6)	3,219 (9.2)	2.6
65+	58,761	1,071 (1.8)	2,711 (4.6)	54,383	1,654 (3.0)	3,876 (7.1)	113,144	2,725 (2.4)	6,587 (5.8)	2.4

Note: Records were not available for all jurisdictions. See Methods.

TABLE 2

Number and percentage of total of deaths with dementia mentioned or given as the underlying cause, by age group and sex, ages 65+, United States, 1993

Age group	Men			Women			Both sexes			
	Total deaths	Deaths with dementia as underlying cause (%)	Deaths with dementia mentioned (%)	Total deaths	Deaths with dementia as underlying cause (%)	Deaths with dementia mentioned (%)	Total deaths	Deaths with dementia as underlying cause (%)	Deaths with dementia mentioned (%)	Ratio of mentioned to underlying causes
65 74	279,606	1,459 (0.5)	3,399 (1.2)	208,213	1,403 (0.7)	3,167 (1.5)	487,819	2,862 (0.6)	6,566 (1.3)	2.3
75 84	313,559	4,712 (1.5)	11,807 (3.8)	324,479	6,695 (2.1)	16,482 (5.1)	638,038	11,407 (1.8)	28,289 (4.4)	2.5
85+	172,778	3,924 (2.3)	10,569 (6.1)	355,659	11,747 (3.3)	29,928 (8.4)	528,437	15,671 (3.0)	40,497 (7.7)	2.6
65+	765,943	10,095 (1.3)	25,775 (3.3)	888,351	19,845 (2.2)	49,577 (5.6)	1,654,294	29,940 (1.8)	75,352 (4.6)	2.5

Causes Positively Associated with Dementia

For 36 causes of death, the ORs were significantly elevated in at least one age group, for at least one of the sexes (Table 4). The causes of death that were positively associated with dementia fell into several general categories, as follows: pneumonia and influenza; conditions that are symptomatic of dementia; conditions that arise from the debilitating effects of advanced dementia (e.g. difficulty eating, incontinence, immobility); and cerebrovascular disease. Within these categories, the specific causes of death for which ORs were significantly elevated for both men and women aged 65 and over are shown in Table 5. The causes of death with the most consistently elevated ORs over the age groups and within the two sexes included bronchopneumonia, organism unspecified (ICD-9 485); pneumonia, organism unspecified (ICD-9 486); and pneumonitis due to solids and liquids (ICD-9 507).

Conditions Negatively Associated with Dementia

Forty-one causes of death were significantly negatively associated with dementia (Table 6). These causes could be generally categorized as cancer, heart disease, chronic respiratory diseases and other causes. Within these groupings, the specific causes of death for which the ORs were significantly low for both males and females in the age group 65+ are shown in Table 7. Consistently low ORs were noted for acute myocardial infarction (ICD-9 410), other forms of chronic ischemic heart disease (ICD-9 414) and cardiac dysrhythmias (ICD-9 427). Although relatively rarely certified as a cause of death, rheumatoid arthritis and other inflammatory polyarthropathies (ICD-9 code 714) achieved statistical significance (OR = 0.32) among women in the age group 65+. Among men, the OR for this cause of death was 0.39, significant at level 0.06.

Discussion

This study, based on analyses of multiple-cause-of-death data, reveals new information about the total frequency with which dementia is certified as a cause of death, as well as the causes of death that most frequently and most infrequently occur with dementia. The benefit of multiple-cause data compared with conventional single-cause mortality data is particularly pertinent in the study of dementia, for which a full epidemiologic understanding has not yet been gained.

The finding that a higher proportion of Canadian than US records mentioned dementia might reflect one or both of the following: 1) a more comprehensive identification of dementia cases before death in Canada than in the US, perhaps because of universal access to free diagnostic services and medical care in Canada; 2) a higher proportion of deaths caused by dementia in Canada than in the US.

FIGURE 1

Age-sex-specific rates of mention of dementia and of dementia as the underlying cause, by sex, Canada, 1990-1993

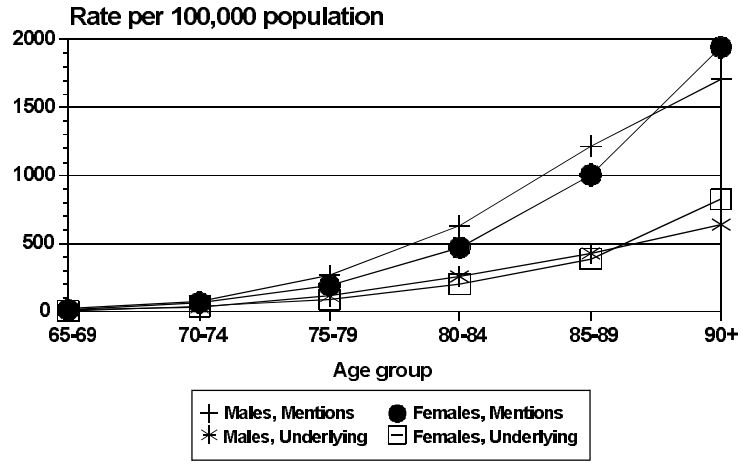
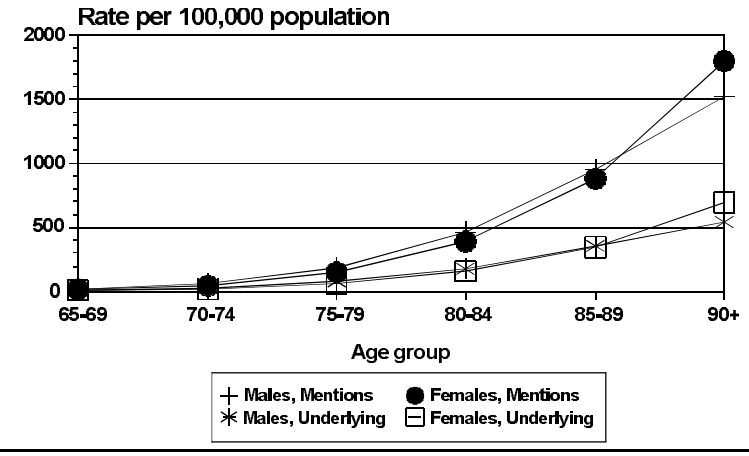


FIGURE 2

Age-sex-specific rates of mention of dementia and of dementia as the underlying cause, by sex, United States, 1993



The increase with age of the mentioned-to-underlying-cause ratio in both countries suggests that when dementia is entered on the death certificate at lower ages, it is more likely to be recorded as the underlying cause of death than when it is entered at higher ages. This may reflect the assumption that dementia in old age is "normal," and thus less likely to initiate the sequence of events leading to death. Increases with age of dementia as a mentioned cause of death can be compared with increases with age in the reported prevalence of dementia in the population. For example, according to the results of a population-based prevalence study, dementia (of all types) was estimated to occur in 2.4% of the Canadian population aged 65**S**74, rising to 34.5% of those aged 85 and over, an increase by a factor of about 15.[1] In comparison, the death rate based on the mention of dementia increases by a factor of 32 between the two age groups. This difference in the two ratios occurs presumably because people aged 65**S**74 who have dementia are less likely to die from it than are people at older ages.

The higher death rates among men than women contrast with prevalence estimates showing a higher rate of dementia in women.[1] This difference probably reflects the longer survival time of women with dementia, for which there is ample evidence.[13,14,20,21]

TABLE 3

Rates of death with dementia mentioned (M) or given as the underlying (U) cause of death, and ratios of mentioned rate to underlying-cause rate, by sex, ages 65+, Canada,[a] 1990 1993

		Men		Women		Both sexes	
Type of rate and ages covered	U or M	Rate[b]	M rate/ U rate	Rate[b]	M rate/ U rate	Rate	M rate/ U rate
Ages 65 74	U	19	2.4	20	2.0	20	2.1
	M	45		40		42	
Ages 75 84	U	167	2.4	135	2.3	148	2.3
	M	401		304		344	
Ages 85+	U	492	2.8	541	2.5	525	2.6
	M	1361		1341		1348	
Ages 65+	U	100	2.5	118	2.3	111	2.4
	M	253		277		267	
Age-standardized[c]: 65+	U	109	2.5	101	2.3	104	2.4
	M	277		234		252	
Age-sex-standardized[c]: 65+	U					104	2.4
	M					251	

[a] Records were not available for all jurisdictions. See Methods.

[b] Rate per 100,000 population

[c] Standardized to the 1991 Canadian population aged 65+

Beginning at about the age of 86, however, the death rates among women surpass those among men (Figures 1 and 2). A variety of reasons could account for this crossover. Although people of both sexes over age 85 represent a very select population, men at that age may be generally healthier than women if a greater proportion of less healthy men have previously been removed from the cohort by death. Or, at these highest ages, women who have a longer life expectancy are more likely to develop "severe" dementia, which is thus more likely to be recorded on death certificates for women than for men.

One explanation of the consistently higher mentioned-to-underlying-cause ratio among men than women is that co-morbid conditions such as coronary heart disease are more often lethal in men than women, even though women generally have more reported co-morbid conditions (unpublished data, National Population Health Survey, 1994/95). Causes of death other than dementia would thus be more frequently designated as the underlying cause among men than among women.

Positively Associated Causes

The strong, consistent association of dementia with bronchopneumonia, pneumonia and influenza has been observed previously[14] and probably reflects the opportunistic nature of these illnesses. People whose general health is compromised by the physical effects of dementia are presumably less resistant to ailments that might otherwise not result in death. As well, pharmaceutical and other treatments for these conditions might be prescribed with less stringency to people with dementia than to those not so affected.

Some causes of death positively associated with dementia on the death certificate arose as part of the symptomatology of dementia. Depression, for example, may be the presenting feature or an early symptom of dementia. Similarly, other causes of death positively associated with dementia reflect the physiological deterioration, such as difficulty eating, incontinence, motor dysfunction and eventual immobility, that occurs as dementia progresses. For example, difficulty with eating could result in malnutrition, disorders of fluid, electrolyte and acid**S**base balance, pneumonitis and symptoms involving the digestive system (e.g. difficulty in swallowing).

TABLE 4

Significant positive associations between mention of dementia and mention of other causes of death, by sex and age group, ages 65+, Canada,[a] 1990 1993

		Odds ratio							
		Men, by age group				Women, by age group			
ICD-9 code	Other causes[b]	65 74	75 84	85+	65+	65 74	75 84	85+	65+
038	Septicemia	1.91*	1.34	0.86	1.20	1.33	1.15	1.06	1.09
263	Other and unspecified protein-calorie malnutrition	3.22	2.34*	0.90	1.91*	5.06*	2.14*	2.10*	2.40*
276	Disorders of fluid, electrolyte and acid-base balance	1.65	2.76*	1.48	2.33*	1.34	2.13*	2.40*	2.49*
307	Special symptoms or syndromes not elsewhere classified		2.93	5.90	6.04		2.43	4.05	4.22*
311	Depressive disorder, not elsewhere classified		1.84	1.77	1.72*	3.29	1.94*	1.10	1.61*
332	Parkinson s disease	5.24*	2.78*	1.41	2.67*	3.38	2.20*	0.96	1.70*
345	Epilepsy	2.59	2.74	3.93	2.81*	4.74	1.46	2.32	1.96*
435	Transient cerebral ischemia	4.48	0.90	1.75	2.05*	5.00	1.62	2.19*	2.57*
436	Acute but ill-defined cerebrovascular disease	2.08*	1.17	0.72*	1.18*	1.91*	0.88	0.67*	0.89*
437	Other and ill-defined cerebrovascular disease	1.82	1.31	1.17	1.52*	2.12	1.00	1.02	1.25*
438	Late effects of cerebrovascular disease	1.38	1.44	1.06	1.40*	1.64	1.23	1.07	1.27
440	Atherosclerosis	1.16	1.18	1.22	1.37*	2.12*	1.21	0.92	1.21*
485	Bronchopneumonia, organism unspecified	3.69*	2.62*	1.73*	2.64*	3.50*	2.66*	1.64*	2.26*
486	Pneumonia, organism unspecified	4.88*	2.59*	1.54*	2.60*	3.44*	1.93*	1.42*	1.87*
487	Influenza	3.95	6.89*	1.62	4.40*		1.87	1.50	1.82*
507	Pneumonitis due to solids and liquids	4.17*	3.12*	2.58*	3.17*	5.02*	3.22*	2.49*	3.05*
514	Pulmonary congestion and hypostasis	1.25	1.48*	1.05	1.36*	2.17*	0.97	1.12	1.19
553	Other hernia of abdominal cavity without mention of obstruction or gangrene		1.76	1.96	1.92		1.84	1.89	2.06*
590	Infections of kidney	3.20	2.44	1.38	2.28*		0.87	0.22	0.47
595	Cystitis		2.70	4.87	1.65			3.60	4.21*
599	Other disorders of urethra and urinary tract	6.84	3.24*	1.34	2.93*	6.78	2.74*	1.62*	2.45
600	Hyperplasia of prostate	2.40	1.31	1.45	1.88*	N/A	N/A	N/A	N/A
707	Chronic ulcer of skin	6.76	3.24	0.78	2.51*	1.90	2.35*	1.30	1.87*
715	Osteoarthrosis and allied disorders	1.60	2.62*	1.65*	2.65*	2.11	1.77*	1.73*	2.18*
780	General symptoms	0.99	1.78*	0.66	1.26	3.37	1.78*	1.22	1.64*
787	Symptoms involving digestive system	9.36	1.87	3.94	3.53*	5.35	3.52*	2.69*	3.45*
797	Senility without mention of psychosis	5.33	1.39	0.72*	1.40*	7.50	1.46*	0.56*	0.95
799	Other ill-defined and unknown causes of morbidity and mortality	0.94	1.03	1.04	1.05	1.41*	1.39*	1.05	1.20*
N-820	Fracture of neck of femur	4.53	2.94*	0.98	2.34*	5.26	2.33*	0.98	1.72*
N-905	Late effects of musculoskeletal and connective tissue injuries	11.20	7.54	5.05	7.25	13.34		4.51*	3.26*
N-933	Foreign body in pharynx and larynx	4.78	1.82	2.19*	2.24*	3.58	2.69*	1.68	2.18
E-887	Fracture, cause unspecified	4.41	2.43*	0.90	2.05*	4.46	2.09	0.88	1.53*
E-888	Other and unspecified fall	5.02	2.65*	0.70	1.86*	1.74	1.78	0.86	1.36
E-911	Inhalation and ingestion of food causing obstruction of respiratory tract or suffocation	7.53	2.20	4.21	3.29*	2.10	2.97	3.60	2.40
E-912	Inhalation and ingestion of other object causing obstruction of respiratory tract or suffocation	3.77	1.55	1.89*	2.02*	3.35	2.38	1.41	1.98*
E-929	Late effects of accidental injury	5.86	2.51	2.94	2.96	16.06		4.70*	3.45*

[a] Records were not available for all jurisdictions. See Methods.

[b] Includes all 3-digit ICD-9 codes with a significant odds ratio greater than 1.00 in at least one age group and with frequencies of at least 10 in each cell of the 2-by-2 table.

* Odds ratio is significant. Significance tests were two-tailed and at level 0.05.

N/A: Not applicable in cases of sex-specific conditions

TABLE 5

Broad categories and specific causes of death positively associated with dementia mentioned on the death certificate, ages 65+, Canada,[a] 1990 1993

ICD-9 code	Cause of death
	Pneumonia and influenza
485	Bronchopneumonia, organism unspecified
486	Pneumonia, organism unspecified
487	Influenza
	Conditions symptomatic of dementia
311	Depressive disorder, not elsewhere classified
332	Parkinson s disease
	Conditions arising from effects of dementia
263	Other and unspecified protein-calorie malnutrition
276	Disorders of fluid, electrolyte and acid-base balance
507	Pneumonitis due to solids and liquids
707	Chronic ulcer of skin
787	Symptoms involving digestive system
820	Fracture of neck of femur
E-887	Fracture, cause unspecified
E-912	Inhalation and ingestion of other object causing obstruction of respiratory tract or suffocation
	Vascular disease
440	Atherosclerosis
435	Transient cerebral ischemia
437	Other and ill-defined cerebrovascular disease
	Other
345	Epilepsy
715	Osteoarthrosis and allied disorders

[a] Records were not available for all jurisdictions. See Methods.

Causes of death that arose from vascular or cerebrovascular disorders were inconsistently associated with dementia. Positive associations were observed between dementia and other or ill-defined cerebrovascular disease, but intracerebral hemorrhage was significantly negatively associated with dementia among both sexes. Acute but ill-defined cerebrovascular disease was positively associated with dementia among men, but negatively associated among women.

The results of the analysis pertaining to cerebrovascular as well as cardiovascular diseases (see discussion below) should be interpreted with caution. Because the death certificate often contains the more general "dementia" diagnosis rather than a specific subtype, all elements of senile and presenile organic psychotic conditions, together with Alzheimer's disease, were treated as one disease in the analysis. However, it is likely that associations with other disorders are not constant across subtypes of dementia. For example, arteriosclerotic dementia and Alzheimer's disease are likely to have quite different associations with stroke and hypertension-related diseases.

Negatively Associated Causes

The negative associations observed between dementia and causes of death for which smoking is a risk factor, particularly cancers of the trachea, bronchus and lung, and chronic respiratory diseases, are consistent with the hypothesis that nicotine can reduce the development of Alzheimer's disease. The negative associations with respiratory cancers might also be partially explained by their rapidly fatal course, however, which may lower the likelihood of certification of dementia as a cause of death.

Although the evidence is equivocal, some epidemiologic studies suggest that nicotine may protect against Alzheimer's disease[22–25] by increasing the number of nicotinic cholinergic receptors.[26–29] In addition, nicotine may enhance cognition in normal individuals,[30] in patients who already have Alzheimer's disease[31–32] and in animals.[33]

Findings from the multiple-cause-of-death data also indicate a negative association between dementia and heart disease, another cause of death for which smoking is a risk factor. Although previous research has suggested a physiologic association between the formation of senile plaques in the brain and coronary artery disease,[34] the negative association observed in the present study is consistent with the results of a study of deaths among dementia patients in Finland: among these patients, cardiovascular disease was less often certified as a cause of death than in the general population.[14] However, as with lung cancer, the rapid and dramatic course of some types of heart disease might partially account for the negative association observed with dementia. For example, dementia might be certified less frequently for patients who die suddenly from an acute myocardial infarction than from other, more lingering causes.

The negative association observed between essential hypertension and dementia corroborates the findings of other research showing a lower prevalence of Alzheimer's disease among people with hypertension than among those without.[35] Dementia was also negatively associated with other causes of death for which hypertension is a risk factor, including aortic aneurysm and kidney failure.

A recent review of the literature indicates that at least 20 studies suggest that the use of anti-inflammatory drugs for the treatment of rheumatoid arthritis is associated with a lower prevalence of Alzheimer's disease.[36] The significantly low OR observed in the present study for rheumatoid arthritis and other inflammatory polyarthropathies (ICD-9 714) among women aged 65 and over is consistent with the

TABLE 6
Significant negative associations between mention of dementia and mention of other causes of death, by sex and age group, ages 65+, Canada,[a] 1990 1993

		Odds ratio							
		Men, by age group				Women, by age group			
ICD-9 code	Other causes[b]	65 74	75 84	85+	65+	65 74	75 84	85+	65+
153	Malignant neoplasm of colon	0.24	0.46*	0.23	0.33*	0.38	0.28*	0.29*	0.27*
159	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum		0.62	0.09	0.34*	0.19	0.24	0.23	0.21*
162	Malignant neoplasm of trachea, bronchus and lung	0.24*	0.22*	0.20	0.17*	0.16	0.19*	0.38	0.15*
174	Malignant neoplasm of female breast	N/A	N/A	N/A	N/A	0.33	0.47*	0.68*	0.42*
185	Malignant neoplasm of prostate	0.34	0.34*	0.58*	0.49*	N/A	N/A	N/A	N/A
188	Malignant neoplasm of bladder	0.29	0.34	0.57	0.45*		0.66	0.09	0.32
197	Secondary malignant neoplasm of respiratory and digestive systems	0.18	0.12	0.13	0.11		0.13	0.21	0.10
198	Secondary malignant neoplasm of other specified sites	0.90	0.18	0.10	0.11		0.24	0.33	0.14
199	Malignant neoplasm without specification of site	0.11	0.15*	0.22*	0.14*	0.21	0.17*	0.22*	0.15*
250	Diabetes mellitus	1.15	0.96	0.80	0.89	0.72	0.59	0.65	0.59*
285	Other and unspecified anemias	0.38	0.59	0.92	0.90	0.38	0.69	0.55*	0.66*
303	Alcohol dependence syndrome	1.24	0.59	1.22	0.56*	0.59		2.24	0.27
310	Specific non-psychotic mental disorders following organic brain damage	0.94	0.79	0.26	0.63	0.85	0.55	0.28*	0.44*
401	Essential hypertension	0.96	0.60*	0.79	0.67*	0.54	0.66*	0.73*	0.67*
402	Hypertensive heart disease	1.15	0.78	0.98	0.86	0.53	0.39	0.76	0.64*
403	Hypertensive renal disease	0.62	0.56	0.70	0.63	0.77	0.32	0.20	0.29*
410	Acute myocardial infarction	0.40*	0.40*	0.51*	0.40*	0.27*	0.33*	0.43*	0.35*
414	Other forms of chronic ischemic heart disease	0.53*	0.57*	0.63*	0.59*	0.55*	0.49*	0.61*	0.60*
415	Acute pulmonary heart disease	0.42	0.29	0.44	0.33*	0.16	0.86	0.44*	0.54*
424	Other diseases of endocardium		0.19	0.69	0.35*	0.36	0.35	0.37*	0.38*
427	Cardiac dysrhythmias	0.67*	0.79*	0.84*	0.81*	0.90	0.84*	0.77*	0.85*
428	Heart failure	0.71	0.60*	0.61*	0.74*	0.73	0.40*	0.50*	0.56*
429	Ill-defined descriptions, complications of heart disease	0.14	0.53*	0.55*	0.47*	1.14	0.80	0.95	0.92
431	Intracerebral hemorrhage	0.32	0.24	0.93	0.41*		0.66	0.45	0.45*
434	Occlusion of cerebral arteries	0.98	0.63	0.69	0.73		1.08	0.42*	0.68*
436	Acute but ill-defined cerebrovascular disease	2.08*	1.17	0.72*	1.18*	1.91*	0.88	0.67*	0.89*
441	Aortic aneurysm		0.29	0.06	0.17*	0.25	0.38	0.74	0.52*
492	Emphysema	0.36	0.61*	0.28	0.46*	0.27	0.10	0.13	0.11*
493	Asthma		0.53	1.45	0.73		0.54	0.64	0.49*
496	Chronic airways obstruction, not elsewhere specified	0.84	0.55*	0.60*	0.62*	0.59	0.42*	0.56*	0.45*
518	Other diseases of lung	0.27	0.80	0.38	0.57*	0.26	0.75	0.66	0.61*
557	Vascular insufficiency of intestine		0.12	0.33	0.18	0.34	0.51	0.45	0.46*
560	Intestinal obstruction without mention of hernia	1.28	0.51	0.65	0.70	0.53	0.64	0.74	0.70*
584	Acute renal failure		0.89	0.75	0.75	0.35	0.34	0.46	0.38*
585	Chronic renal failure		0.43*	0.63	0.54*	0.70	0.23	0.50*	0.38*
586	Renal failure, unspecified	0.61	0.74*	0.45*	0.66*	0.16	0.24*	0.58*	0.43*
714	Rheumatoid arthritis and other inflammatory polyarthropathies	0.76	0.36	0.40	0.39	0.27	0.25	0.50	0.32*
785	Symptoms involving cardiovascular system		0.31*	0.96	0.47*	0.63	0.44*	0.73	0.57*
797	Senility without mention of psychosis	5.33	1.39	0.72*	1.40*	7.50	1.46*	0.56*	0.95
N-997	Complications affecting specified body systems, not elsewhere specified		0.61	0.38	0.46	0.47	0.51	0.61	0.51*
E-878	Surgical operation and other surgical procedures as the cause of abnormal reaction of patient, or of later complication, without mention of misadventure at the time of operation	0.24	0.48	0.45	0.41*	0.24	0.37	0.43	0.34*

[a] Records were not available for all jurisdictions. See Methods.

[b] Includes all 3-digit ICD-9 codes with a significant odds ratio greater than 1.00 in at least one age group and with frequencies of at least 10 in each cell of the 2-by-2 table.

* Odds ratio is significant. Significance tests were two-tailed and at level 0.05. N/A: Not applicable in cases of sex-specific conditions

TABLE 7

Broad categories and specific causes of death negatively associated with dementia mentioned on the death certificate, ages 65+, Canada,[a] 1990 1993

ICD-9 code	Cause of death
	Cancer
159	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum
162	Malignant neoplasm of trachea, bronchus and lung
199	Malignant neoplasm without specification of site
	Heart disease
410	Acute myocardial infarction
414	Other forms of chronic ischemic heart disease
427	Cardiac dysrhythmias
428	Heart failure
785	Symptoms involving cardiovascular system
	Respiratory disease
492	Emphysema
496	Chronic airways obstruction, not elsewhere specified
518	Other diseases of lung
	Other
401	Essential hypertension
431	Intracerebral hemorrhage
441	Aortic aneurysm
585	Chronic renal failure
586	Renal failure, unspecified
E-878	Surgical operation and other surgical procedures as the cause of abnormal reaction of patient, or of later complication, without mention of misadventure at the time of operation

[a] Records were not available for all jurisdictions. See Methods.

hypothesis that anti-inflammatory drugs can delay or prevent the onset of Alzheimer's disease.

Limitations

In interpreting the results of the analysis of multiple-cause data, one must be mindful of the data's limitations.[4] First, certification practices may affect some of the observed associations between causes of death and dementia. For example, previous research suggests that, for people with dementia, the likelihood of certification of particular causes of death, including Alzheimer's disease, pneumonia, heart disease and stroke, varies with the level of the patient's cognitive impairment before death.[15]

It is also important to note that mortality statistics, including multiple-cause-of-death data, do not fully reflect disease prevalence in those who died. This is because the causes that a person dies *from* do not necessarily include all the diseases that he or she dies *with*. As well, a decedent's medical history may not be fully known to the authority who certifies the death, and so a condition that was involved in the sequence of events leading to death may not be entered on the death certificate. Clearly, the greatest limitation to the present study is the potential for misclassification bias. If undercertification of dementia is randomly distributed relative to other causes of death, then the effect will be to decrease the magnitude of the observed associations. More likely, however, certification of dementia relates somewhat to the presence of specific other causes of death, which will result in some amount of differential misclassification and error in the results.

Nonetheless, the analysis of multiple-cause-of-death data provides added insight into the particular combinations of conditions that are fatal, as well as conditions that rarely combine to cause death. Research done to date, mostly involving case-control comparisons, has revealed relatively little regarding the etiology of the major dementias. Multiple-cause data provide a low-cost means of studying cases in which dementia causes death, and also the causes of death with which dementia occurs most rarely.

In conclusion, multiple-cause-of-death data reveal that dementia contributes to death more than twice as often as it is identified as the underlying cause of death. Many of the causes of death that are positively linked to dementia on the death certificate are attributable, directly or indirectly, to the dementing illness, a finding that is consistent with current knowledge. Causes that are negatively associated with dementia may involve treatments that help to prevent or delay the onset of dementia. For example, the negative associations observed between dementia and smoking-related cancers and arthritis are supportive evidence of possible protective effects of nicotine and anti-inflammatory drugs. Further study of the roles of these substances in preventing or delaying the onset of dementia is indicated. Other negative associations observed, such as those between dementia and hypertension, aortic aneurysm and renal failure, suggest a variety of hypotheses that warrant further investigation.

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Short Report

Health Consequences of Smoking Among Canadian Smokers: An Update

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Abstract

The expected number of deaths in four hypothetical Canadian cohorts (male current smokers, male never-smokers, female current smokers and female never-smokers) was examined by constructing abridged life tables. The expected number of premature deaths (before age 70) among lifelong smokers was found to be about twice that expected among lifelong never-smokers for both males (2.3) and females (1.9). The higher number of premature deaths in the smoking cohorts resulted mainly from cancer and coronary heart disease. The results of this paper highlight the dramatic impact that smoking has on premature mortality.

Key words: *Canada; coronary disease; life table; mortality; neoplasms; smoking*

Introduction

Premature death due to tobacco use is the most important public health problem facing Canadians today. It has been estimated that at least one quarter of all deaths among persons aged 35–84 in Canada are attributable to tobacco use.[1] An estimated 45,000 deaths in Canada in 1991 were caused by smoking.[2]

This study was designed to update and refine previous work[3,4] exploring premature mortality (before age 70) attributable to smoking. The most recent Canadian study modelling such mortality[4] has become outdated, in part because of changes in mortality rates, particularly for coronary heart disease. We modelled the expected number of deaths in four hypothetical cohorts (male current smokers, male never-smokers, female current smokers and female never-smokers), starting from age 15.

Methods

Age-specific prevalence rates of current smokers were estimated from the 1996 National Population Health Survey.[5] Relative risk estimates for smoking-related diseases were derived from data from the American Cancer Society's Cancer Prevention Study II (American Cancer Society, personal communication, 1998), which is examined in detail elsewhere.[6] Mortality rates according to age, sex and cause were calculated using death counts retrieved from the Canadian Mortality Database of Statistics Canada and Canadian population data, adjusted for census undercount, also obtained from Statistics Canada. It was assumed that the cohorts would be subject to these mortality rates over the course of their lifetime.

The method outlined by Mattson et al.[7] was used to calculate mortality rates for current smokers and never-smokers using the aforementioned relative risk, prevalence and mortality rates. Abridged life tables were constructed[8] for each of the four cohorts (i.e. male current smokers, male never-smokers, female current smokers and female never-smokers). From these life tables, the probabilities of dying in each age interval were retrieved. Expected numbers of deaths were then estimated by multiplying age-specific probabilities of death by the number of surviving members of the respective cohort, a figure taken from the constructed life tables. The expected total number of deaths for each

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cohort was based on an initial population of 100,000 persons aged 15 years. Those in the smoking cohorts were assumed to be smokers for the duration of their lives. Deaths attributable to smoking were calculated by subtracting the number of deaths among never-smokers from the number of deaths among current smokers.

For each cause of death, probabilities of death for each age interval were calculated in a similar fashion to that already described. Expected numbers of deaths were estimated by multiplying age- and cause-specific probabilities of death by the number of surviving members of the respective cohort. Risks to smokers were assumed to be equivalent to never-smokers for homicide, motor vehicle traffic accidents, HIV/AIDS and suicide. To form a direct basis of comparison, the process was repeated using smoking prevalence rates[9] and mortality figures from 1990.

Results

More than a third of the cohort of 100,000 male smokers aged 15, and almost a quarter of a similar group of females, were anticipated to die before age 70 (Table 1). The expected number of premature deaths among smokers was found to be about twice that expected in similar cohorts of never-smokers for both males (2.3) and females (1.9). The higher number of premature deaths among the smoking cohorts resulted mainly from cancer and coronary heart disease.

Smoking accounted for 56% and 48% of premature mortality among male and female smokers respectively. Among male smokers, approximately 3.5% of premature deaths were due to suicide, 2.1% to motor vehicle accidents, 1.4% to HIV/AIDS and 0.4% to homicide. Similarly, among female smokers, 1.5% of premature deaths were due to motor vehicle accidents, 1.6% to suicide, 0.3% to homicide, and 0.2% to HIV/AIDS.

Table 2 presents the same type of information as Table 1 but uses 1990 rather than 1996 smoking prevalence and mortality data. The number of premature deaths attributable to smoking was 5.5% lower using 1996 compared with 1990 data. The largest decreases were observed for cardiovascular disease; coronary heart disease was 18% lower, and cerebrovascular disease was 8% lower. For chronic obstructive pulmonary disease and cancer, particularly the former, the number of premature deaths attributable to smoking declined among males but increased among females.

Discussion

The results of this paper highlight the dramatic impact that smoking has on premature mortality. Compared with non-smokers, the risk of premature death is more than double among males and almost double among females who begin smoking by age 15. Over half of the expected premature deaths would be attributable to smoking as compared with less than 6% from suicide, motor vehicle traffic accidents, HIV/AIDS and homicide combined. Like other researchers,[3,4] we observed that the higher number of premature deaths among the smoking cohorts resulted mainly from cancer and coronary heart disease.

The estimate of the expected premature mortality attributable to smoking was over 10% lower than that previously reported in a similar hypothetical study[3] using 1990 smoking prevalence and mortality data. However,

TABLE 1

Expected number of deaths before age 70 in four cohorts of 100,000 individuals now aged 15, based on 1996 Canadian mortality and smoking prevalence data

Cause of death	ICD-9 code	Deaths among males			Deaths among females		
		Current smokers	Never-smokers	Number attributable to smoking	Current smokers	Never-smokers	Number attributable to smoking
Smoking-related diseases							
Coronary heart disease	410 414	7,726	3,589	4,137	3,436	1,334	2,102
Cerebrovascular disease	430 438	1,570	632	938	1,370	444	926
Cancer	140 195, 199 208	13,895	4,809	9,086	10,814	6,230	4,584
Chronic obstructive pulmonary disease	490 492, 496	948	82	866	955	85	870
Selected other causes[a]							
Homicide	E960 969	141	145		61	61	
Motor vehicle accidents	E810 819	786	810		349	354	
Suicide	E950 959	1,303	1,345		381	385	
HIV/AIDS	177	510	521		46	47	
ALL CAUSES		36,801	16,263	20,538	23,414	12,105	11,309

[a] Estimated deaths from selected other causes were lower for the smoking cohort than for the non-smoking cohort because of competing mortality. The same risks by sex and age were assumed for smokers and non-smokers.

TABLE 2

Expected number of deaths before age 70 in four cohorts of 100,000 individuals now aged 15, based on 1990 Canadian mortality and smoking prevalence data

Cause of death	ICD-9 code	Deaths among males			Deaths among females		
		Current smokers	Never-smokers	Number attributable to smoking	Current smokers	Never-smokers	Number attributable to smoking
Smoking-related diseases							
Coronary heart disease	410 414	9,372	4,391	4,981	4,276	1,666	2,610
Cerebrovascular disease	430 438	1,776	727	1,049	1,474	492	982
Cancer	140 195, 199 208	14,577	5,116	9,461	10,833	6,263	4,570
Chronic obstructive pulmonary disease	490 492, 496	1,031	93	938	825	77	748
Selected other causes[a]							
Homicide	E960 969	153	157		81	81	
Motor vehicle accidents	E810 819	1,042	1,074		444	450	
Suicide	E950 959	1,205	1,245		337	340	
HIV/AIDS	177	442	451		20	20	
ALL CAUSES		39,892	17,910	21,982	24,336	12,608	11,728

[a] Estimated deaths from selected other causes were lower for the smoking cohort than for the non-smoking cohort because of competing mortality. The same risks by sex and age were assumed for smokers and non-smokers.

methodologic differences between these two studies made a direct comparison problematic. Accordingly, we duplicated our analysis using data from 1990. Our 1996 estimates represent a 6% lower number of smoking-attributable premature deaths than the 1990 estimates. Differences between the two sets of estimates can be explained largely by changes in mortality rates that have occurred between 1990 and 1996, and they may reflect improved survival for such conditions as coronary heart disease and cerebrovascular disease. While the mortality rate for chronic obstructive pulmonary disease has decreased over this period among men, it has increased among women, particularly women aged 65–69.

We observed nearly twice as many smoking-attributable deaths among males than among females. This is, in part, the result of sex differences in age-specific mortality rates and relative risk estimates. The relative risk estimates used in this analysis partially reflect past differences in patterns of smoking (e.g. age at initiation, number of cigarettes smoked daily) between men and women.[10] Although forecasting changes in the prevalence of smoking, mortality rates and underlying relative risks was beyond the scope of this report, it is reasonable to assume that if sex-specific patterns of smoking were similar then differences in smoking-attributable death counts between males and females would be considerably narrowed.

A range of interventions, from educating the public about the adverse health effects of tobacco use to advertising restriction and other legislative initiatives (e.g. taxation), contributed to significant decreases in the prevalence of tobacco use during the 1980s.[10,11] Nevertheless, 30% of Canadians 15 years and older still smoke, and teen smoking rose sharply during the early 1990s.[12–14] Since most smokers start this highly addictive habit during adolescence,[10] the pattern of smoking among youth will shape the future health care burden and the number who will prematurely die. A comprehensive approach to preventing youth smoking is necessary to reduce the number of Canadians who will die from smoking-related diseases.[10,15]

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Book Reviews

Population Health: Concepts and Methods

By T Kue Young
New York: Oxford University Press, 1998; ix + 315 pp; ISBN 0-19-511972-X; $63.95 (CAN)

This beautifully crafted textbook fills a long-empty niche in public health training. It provides between one set of covers a comprehensive introduction to all the quantitative methods for the assessment of population health status that the average health professional needs to know. Perhaps there's even enough for the non-epidemiologist Master's level student in programs designed to train health administrators, health promoters or occupational/environmental health specialists. Full-fledged epidemiologists may also find it useful in teaching basic concepts—especially to undergraduates or non-specialist graduate students. However, they would generally find the depth of methodological matters covered to be inadequate for training graduate students aiming for a career in epidemiologic research.

The best thing about the book is its clear, simple explanation of almost every basic idea in epidemiology, and quite a few in demography and health economics as well as several other core public health sciences. The author has included (unusually but very helpfully in this era of multidisciplinary work) brief sections on complementary social science and qualitative approaches to public health, including the area in which he has graduate training—cultural anthropology (although he is better known as an epidemiologist). The whole effect is very refreshing and holistic—this is a book that can really be used to give a broad, if introductory, picture of how we know what we do about the health of populations.

Another great strength of the book is the rich, up-to-date examples of all the main ideas presented, making use of text boxes and many fine figures and tables that please the eye. Furthermore, there are well thought-out exercises for each chapter, complete with model answers at the back of the volume. Not since Mausner and Kramer's book[1] of 14 years ago has there been such a useful introductory text in this field. And the examples are not only current but also frequently Canadian—a great credit to the publishers, who are clearly aware that copies must be sold in the USA to recoup their investment!

One word of warning—those expecting the title to imply that the entire book is a treatment of the ideas that have come to be associated with the term *population health* in Canada in the last decade will be disappointed. The author has covered these ideas, with appropriate citations of key works such as *Why Are Some People Healthy and Others Not?*[2] But these sections only stretch to a few paragraphs here and there. Essentially the author uses the term *population health* to mean "the health of populations."

However, this is not a failing: the book sets out to acquaint the student with a broad and comprehensive view of all the factors that influence the health of societies, as well as the basic methods for assessing it. In this, the author succeeds admirably. The big question is whether undergraduates in the health sciences would be given the timetable space to cover this essential material in most universities ... I doubt that most medical schools would do so. Yet a strong case can be made that all the ideas and techniques covered in this book are the *bare minimum* required for the intelligent practice of a clinical discipline in the early 2000s.

Indeed, one cannot even read a general medical journal, let alone critically appraise research reports, without a mastery of the ideas in this book. Perhaps the very fact that these ideas have been so skilfully and attractively brought together by Kue Young in this volume will provoke a long overdue reappraisal of what core training of health professionals in public/community health should be. If so, then the author will have done us all a great service.

Overall rating:	Excellent—as a *basic* text of community health/epidemiology
Strengths:	Fresh, comprehensive and up to date, with many Canadian examples—it fills an empty textbook niche
Weaknesses:	Treatment of quantitative epidemiologic topics is too superficial for students proceeding to the MSc level or preparing to do research
Audience:	1. Undergraduates in the health sciences (rather pricey for them!) 2. First-semester Master's level grad students in general community/public health graduate programs or non-epi-specialist programs (such as health administration, health promotion or occupational/environmental health)

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Public Health and Preventive Medicine in Canada, Fourth Edition

By Chandrakant P Shah
Toronto: University of Toronto Press, 1998; xx + 458 pp; ISBN 0-9694044-3-3 (French version not yet available)

The fourth edition of the best known Canadian textbook of public health states that it has two purposes. The first one is to help readers learn about their role as health care professionals, administrators or policy makers within the health care system. Second, it is intended for anyone interested in participating in the ongoing debate on health care issues by providing the fundamentals of health and health care of Canadians.

A glance through the table of contents shows that the book is meant to be comprehensive. For instance, it ranges from epidemiologic methods to the regulation of health professionals, from environmental health to the evolution of national health insurance. In particular, it attempts to give both methods and content: to describe the structure and function of subsystems within the health care system and, at the same time, give content information on the health problems that the subsystem faces. Not only is occupational health in Canada described as a system, but major workplace health hazards (of which there are a bewildering number) are then discussed in some detail. This pattern is repeated in several other sections.

Compiling a book like this is a difficult task. The range of potential salient facts and observations is huge, and the information is changing rapidly enough in some areas to be outdated by the time publication occurs. Yet, with the comparatively small Canadian audience, it is important for the book to be as broad as possible. This means that the author must become a master of areas that are rarely considered together and where a detailed understanding of current issues in one area does not necessarily give insight into the others. Because the intended audience is made up of a wide range of different interests within the health care system, the author cannot easily sacrifice depth for breadth. On the other hand, when a book is in its fourth edition, the author may well have learned how to refine each section, paring it down to its essentials without loss of important detail. How well has this task been achieved in *Public Health and Preventive Medicine in Canada*?

To answer this question, I took three stabs at accessing the book from the index backwards. My first try was not promising. The index heading "socioeconomic links to health" led me back to a discussion on the health effects of child poverty, called "psychosocial environment." The labels "psychosocial" and "socioeconomic" were used interchangeably here, with no discussion of the distinctions that are usually made between them or their complex interplay. On my second try, however, I hit pay dirt. Under "regional health boards — functions in Canadian provinces," I found a wonderful four-page summary table of the structure and function of boards by province. Although the information will change over time, it is an excellent entry point to the subject of similarities and differences in the decentralization of health care by jurisdiction in Canada and a very efficient vehicle for doing so. Finally, under "periodic health examinations," there was a four-page section that went to the heart of Canadian thinking in this area.

In general, when the book is accessed in this way, the "hit rate" for getting the most pertinent information in the most efficient way is very high. When one table on a subject is given, it is a useful one and often the most relevant one. This was especially true in the areas of funding of health care and health care organization. My conclusion is that this is a book that has benefited from its author's accumulated experience over four editions. It is a refined and helpful resource.

Perhaps the most difficult question to answer, though, is "helpful to whom?" Although the book is meant for a Canadian market of health professionals and general Canadian audiences, I think that it ought to be considered for international audiences as well. First, it could serve as a basic text in American schools of public health and health administration, where Canadian approaches are widely admired but often not understood in any detail. Second, it ought to be promoted among the

24 Canadian studies programs in other parts of the world, as a case study of how we organize our largest and most sophisticated public endeavour. Finally, it would be an excellent introductory reference for all the international visitors who come through on work-study tours.

In this context, the most awkward problem with *Public Health and Preventive Medicine in Canada* may be found in its handling of the difference between how systems are officially said to work in Canada and how they work in practice. For instance, the section on occupational health describes a system with a great many more options and access points than the one that workers face on a day-to-day basis. The section on the evolution of health care in Canada does not adequately convey the degree to which political struggles between the federal and provincial governments actually steer the realities of the health care system. The danger here is in exacerbating something I would call the "Lalonde syndrome," which is the strongly held belief in other parts of the world that Canada's achievements in producing health are as great as the conceptual frameworks we create are imaginative. Yet, with this caveat in mind, *Public Health and Preventive Medicine in Canada* does provide an accurate portrait of a system about which we ought to be proud.

Overall rating:	Very good
Strengths:	Comprehensive, broad, efficient for reference
Weaknesses:	Content quality uneven; tends to idealize systems
Audience:	Could be broadened to a more international audience

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Calendar of Events

June 3–6, 1999 **Winnipeg, Manitoba**	1st International Conference on Diabetes and Cardiovascular Disease Presented by the Diabetes Research and Treatment Centre, Winnipeg, and the Institute of Cardiovascular Sciences, University of Manitoba	Maureen Carew Bureau of Cardio-Respiratory Diseases and Diabetes Laboratory Centre for Disease Control Jeanne Mance Bldg, AL: 1918C3 Health Canada, Tunney's Pasture Ottawa, Ontario K1A 0K9 Tel: (613) 941-1293 Fax: (613) 954-8286
June 5–9, 1999 **Toronto, Ontario**	AIHCCE 1999: American Industrial Hygiene Conference & Exposition "goes global"	Dr Ugis Bickis Consultants in Occupational and Environmental Health 500 – 837 Princess Street Kingston, Ontario K7L 1G8 Tel: (613) 544-1740 Fax: (613) 544-3104 E-mail: uib@phoenix-ohc.on.ca <www.aiha.org/aihce99/info.html>
June 6–9, 1999 **Winnipeg, Manitoba**	"Public Health in the New Millennium" Canadian Public Health Association 90th Annual Conference Co-sponsored by the Manitoba Public Health Association	CPHA Conference Department 400 – 1565 Carling Avenue Ottawa, Ontario K1Z 8R1 Tel: (613) 725-3769 Fax: (613) 725-9826 E-mail: conferences@cpha.ca <www.cpha.ca>
June 26–29, 1999 **Moncton, New Brunswick**	"Practice and Education of Health Professionals Responsive to the Needs of Individuals and Communities" International Francophone Conference in Health Sciences Co-sponsored by the World Health Organization Organized in conjunction with the Francophone Summit 1999	Secrétariat Conférence Acadie-Sherbrooke 1999 PO Box 946 Moncton, NB E1C 8N8 Tel: (506) 861-6341 *or* 1-800-964-7070 Fax: (506) 855-1646 E-mail: secretariat@confacadie-sherbrooke.org <www.confacadie-sherbrooke.org>
July 11–30, 1999 **Ann Arbor, Michigan** **USA**	34th Annual Graduate Summer Session in Epidemiology University of Michigan School of Public Health	Administrative Co-ordinator: Jody Gray Department of Epidemiology Tel: (734) 764-5454 Fax: (734) 764-3192 E-mail: umichgss@sph.umich.edu <http://www.sph.umich.edu/epid/GSS>

July 26–31, 1999 **Ottawa, Ontario**	2nd World Conference on Breast Cancer	World Conference on Breast Cancer 841 Princess Street Kingston, Ontario K7L 1G7 Tel: (613) 549-1118 Fax: (613) 549-1146 E-mail: brcancer@kos.net <www.brcancerconf.kos.net>
August 1–4, 1999 **Turku** **Finland**	"From Epidemiology to Clinical Practice" 1999 Symposium of the World Psychiatric Association's Section of Epidemiology and Public Health	Mrs Leena Kekoni, STAKES PO Box 220 FIN-00531 Helsinki, Finland Tel: 358-9-3967-2183 Fax: 358-9-3967-2155 E-mail: leena.kekoni@stakes.fi
August 31–Sept 4, 1999 **Florence** **Italy**	"Epidemiology for Sustainable Health" 15th International Scientific Meeting of the International Epidemiological Association	Organizing Secretariat IEA Florence '99 c/o SINEDRION Via G. Marconi, 27 50131 Firenze, Italy Tel: 39-55-570502 Fax: 39-55-575679 E-mail: iea99@stats.ds.unif.it <http://iea99ds.unifi.it>
October 1–3, 1999 **Toronto, Ontario**	"Closing the Loop: Evidence into Health Practice, Organization and Policy" 3rd International Conference on the Scientific Basis of Health Services Sponsors: Canadian Foundation for Health Services Research, Health Canada and Medical Research Council of Canada	3rd Intl Conference on the Scientific Basis of Health Services c/o Alysone Will, CMP The Paragon Conference & Event Group Inc. 704 – 205 Richmond Street West Toronto, Ontario M5V 1V3 Tel: (416) 979-1300 Fax: (416) 979-1819 E-mail: info@paragon-conferences.on.ca <www.paragon-conferences.on.ca/health99.html>
October 18–20, 1999 **Chilton, Oxfordshire** **United Kingdom**	International Workshop on UV Exposure, Measurement and Protection Sponsors: National Radiological Protection Board (NRPB), World Health Organization and International Commission on Non-Ionizing Radiation Protection	Dr Colin Driscoll NRPB (UV Workshop) Chilton, Didcot, OX11 0RQ United Kingdom Tel: 44-1235-822724 Fax: 44-1235-831600 E-mail: colin.driscoll@nrpb.org.uk <http://www.nrpb.org.uk/WHO-uv.htm>
November 11–13, 1999 **Halifax, Nova Scotia**	Fourth National Conference on Asthma and Education (ASED 4) Presented by the Canadian Network for Asthma Care (CNAC) *Call for abstracts—deadline:* ***June 30, 1999***	A Les McDonald Executive Director, CNAC 1607 – 6 Forest Laneway North York, Ontario M2N 5X9 Tel: (416) 224-9221 Fax: (416) 224-9220 E-mail: ased@cnac.net

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